Vall d'Hebron Institut de Recerca (VHIR)

ANNUAL REPORT 2010

Vall d'Hebron
Institut de Recerca
VHIR

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ANNUAL REPORT 2010

VHIR is accredited as a Health Care Research Institute
by the Carlos III Health Institute

Vall d'Hebron Institut de Recerca (VHIR)

ANNUAL REPORT 2010

Generalitat de Catalunya

Institut Català de la Salut

Vall d'Hebron Institut de Recerca VHIR

UAB Universitat Autònoma de Barcelona

ISC Instituto de Salud Carlos III

Edifici Mediterrània, 2nd floor
Passeig Vall d'Hebron, 119-129
08035 Barcelona
www.vhir.org

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Presentation

This scientific report, the first in which I have the honour to make the presentation as General Director for Regulation, Health Planning and Resources at the Health Department of the Catalonian Government explains the increase in the quantity and quality of scientific output of Vall d'Hebron Research Institute (VHIR), the center that coordinates all the research at the Vall d'Hebron University Hospital, one of the leaders of the Catalan Institute of Health (ICS).

A center that has experienced the second year of the new direction that has seen coming true expansion of its facilities with the new Building Collserola and that, with the collaboration of the Government of Catalonia, has faced a major investment in operation and equipment to accomplish its objectives.

VHIR has been recognized by its efforts and leadership in translational research with the setting up of EATRIS, a European infrastructure for translational research in which acts as the scientific coordinator of the Spanish health sciences centers that belong to it.

The interrelationship between research done in laboratories and patient diaries problems, translational research and clinical research, is one of the objectives of this and other Catalan centers, leading this task in Spain and fighting for a place among the international reference centres.

From this Department we congratulate VHR for the quality of its research, with increases in its impact factor, publications, clinical trials and projects despite the complications of the economic situation. We also celebrate the achievements in innovation, a very successful movement and very necessary in these difficult times.

Vall d'Hebron, one of the hospitals that had to apply the economic adjustments that we had to implement to improve the viability of the Catalan health system, has therefore with VHIR a reason to feel proud and a success flag to add to the work and effort of all the professionals.

Dr. Carles Constante i Beitia
General Director for Regulation, Health Planning and Resources at the Health Department of the Catalonian Government

Presentation

Antoni Castellà i Clapé
Research and University Secretary
Economy and Knowledge Department
Catalonian Government

2010 has been a relevant year to Vall d'Hebron Research Institute (VHIR), a leading center of scientific and health care excellence. It has been significant in many ways: in basic research and a growing number of publications and scientific impact index. In recognition and prestige with the awards received throughout the year, and funding for new research lines. It's been a year of progress in the struggle against serious diseases such as diabetes, Alzheimer, cancer or multiple sclerosis. A year of awards for researchers, research units and programs, as well as an intensive period of knowledge transfer, value and pursuit of opportunities in the market.

VHIR is a good example of the successful policies developed in recent years. It stands out as an example of biomedical research in Catalonia. We excel in biomedicine and biotechnology, for which we are recognized as the knowledge reference regional cluster. VHIR is a leading center for biomedical research because of its privileged relationship with Vall d'Hebron University Hospital, the first hospital complex in Catalonia, and its relationship with the Universitat Autònoma de Barcelona (UAB).

This model of university hospital, in which teaching, research and patient care services are connected, contributes to making of VHIR one of the main reference of our excellence. The fact that VHIR was chosen in 2010 as coordinator of a great European project is a prime example, amongst others, of the success of a research institute that fosters, moreover, that all members participate in the biomedical and clinical research in an integrated manner.

VHIR's demonstrated willingness to network collaboration, internationalization and bringing innovation to the market is fully aligned with the values of CERCA, the research consortium of the Government of Catalonia. CERCA has opted to include the research institutes linked to the referral hospitals. VHIR is also a good example of the governance model and operation of CERCA centers, which promotes flexibility, efficiency in management and strategic planning.

The will showed by VHIR to network collaboration, internationalization and bring innovation to the market, it fits perfectly within the values of institution CERCA of the Government of Catalonia, which has opted to include in the center system the research institutes of referral hospitals. VHIR is also a good example of the model of governance and operation of CERCA centers, which promotes flexibility, efficiency in management and strategic planning.

For all the above, I am honoured to invite you to discover in the next pages the activities that, during the year 2010, have helped to bring this center to a position of leadership in biomedical research.

Antoni Castellà i Clapé
Research and University Secretary
Economy and Knowledge Department
Catalonian Government

Presentation

Ana Ripoll Aracil
Second Vice President of the VHIR Board of Trustees

Rector of Universitat Autònoma de Barcelona

The Vall d'Hebron Research Institute (VHIR) annual report once again reveals the excellent research being carried out by the research groups created to date in different scientific areas. VHIR has a clear vocation to serve the general public, and understands that its research is aimed at transferring knowledge to society. In other words, the research institute knows that its mission is to improve the health of the citizens, not only of this country, to whom it dedicates great effort, but of the world as a whole, given that its increasing internationalisation aims to share the results of research with as many people as possible.

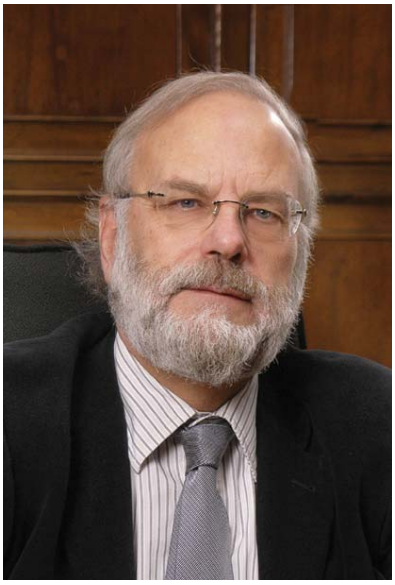
The activities carried out by the institute demonstrate that VHIR is succeeding in what was one of its founding principles: to become one of Europe's leading centres in biomedical research. To my understanding, this is possible because VHIR is strongly committed to quality results based on combining the efforts of scientists from multiple disciplines. This means that groups are formed by researchers with diverse scientific profiles, as well as by clinical experts and academics working at the prestigious first-rate university hospital Vall d'Hebron, and teaching or carrying out research at the Universitat Autònoma de Barcelona.

For this reason I wish to congratulate all the people at VHIR for the magnificent work being done, for its scientific rigour and commitment to society. I hope this ability to innovate and transfer will not be lost, not only for the benefit of the research institute itself and a better future for society, but also for the benefit of this country, which is in need of reorienting its productive model towards the industry of knowledge. And the Vall d'Hebron Research Institute is a clear example of successfully achieving this goal.

Ana Ripoll Aracil
Second Vice President of the VHIR Board of Trustees

Rector of Universitat Autònoma de Barcelona

Presentation



José Luis de Sancho
Former General Manager
of Vall d'Hebron University Hospital

The continued growth of Vall d'Hebron Research Institute (VHIR) is reflected in the data that we present in this scientific report. As manager of Vall d'Hebron University Hospital (HUVH), and because of its significance to the hospital, I am proud of the steady increase in VHIR's activity and quality, bearing in mind that its purpose is simply to improve the care of patients treated in this hospital and the care of society in general.

The excellent scientific results of VHIR compete with top Catalan and Spanish centers. All the researchers and their teams work with unceasing energy to make important breakthroughs towards its internationalization.

Despite the complexities and trends of this year, 2010, I specially value and appreciate the efforts of all professionals involved, those who are devoted exclusively to research and those who combine it with clinical patient care. They are all are the architects of this determined evolution of HUVH and VHIR.

This year's difficulties have meant that VHIR received 6% less funding as compared to 2009. Nonetheless it should be emphasized that good management of these resources has allowed it to go ahead with major projects with a smaller budget, to which the hospital has contributed 3.8 million Euros.

With regard to funding, in 2010 VHIR obtained 36.3 million Euros, primarily from the private sector, and particularly from agreements with industry, clinical trials and donations.

The data illustrate economic effort, but it is talent, dedication and ability to overcome obstacles displayed by our researchers and staff that make our Hospital and the Research Institute a clear example and an inspiration for the future.

This document reflects the work of all those who have given and give much of their time to research. They have my trust and full support for what this collective effort brings to society. To all, I offer my deepest appreciation.

José Luis de Sancho
Former General Manager
of Vall d'Hebron University Hospital

Introduction

Joan X. Comella
VHIR's Director

2010 has been a fruitful year for Vall d'Hebron Research Institute (VHIR). The general economic situation has not been an impediment to achieving new milestones. As a research center we have achieved our goals through the efforts of our researchers and the support staff of all the different units. We have improved on most of the challenges that we set every day, we have achieved many advances in research and have made strategic decisions that strengthen us as an institution.

In 2010 we have increased more than 27% the impact factor of our scientific production over the previous year. We've gone from 540 to 595 publications and from a total impact factor of 2,474.71 to one of 3,149.5. With respect to the average impact factor per paper, we have grown from 4.58 to 5.29. 55% of our publications are in the first quartile and 27.2% in the first decile. With a slight increase in human capital in the management structure and around 1,200 people dedicated to research we have also managed to increase the number of active clinical trials (428, an increase of 3.6%), as well as the number of research projects (242, an increase of 5.2% since 2009). In 2010, 16 of our 17 research team groups were part of the Thematic Network of Health Centers (RETICS) of the Instituto de Salud Carlos III (ISCIII). We have received external funding for 242 projects and 28 of our groups have been granted recognition from the Generalitat de Catalunya.

But beyond the positive scientific production data, 2010 was the year of the inauguration of a new space, the Collserola Building, for which we were granted a FEDER fund of 2 million Euros. Following an agreement, the Department of Health of the Generalitat de Catalunya provided us with a grant of 1.5 million Euros for operating expenses, plus 500,000 Euros for equipment. The Collserola Building is a step forward but not the end of the journey, since our potential drives us to seek new horizons and more space to continue growing, despite the economic context.

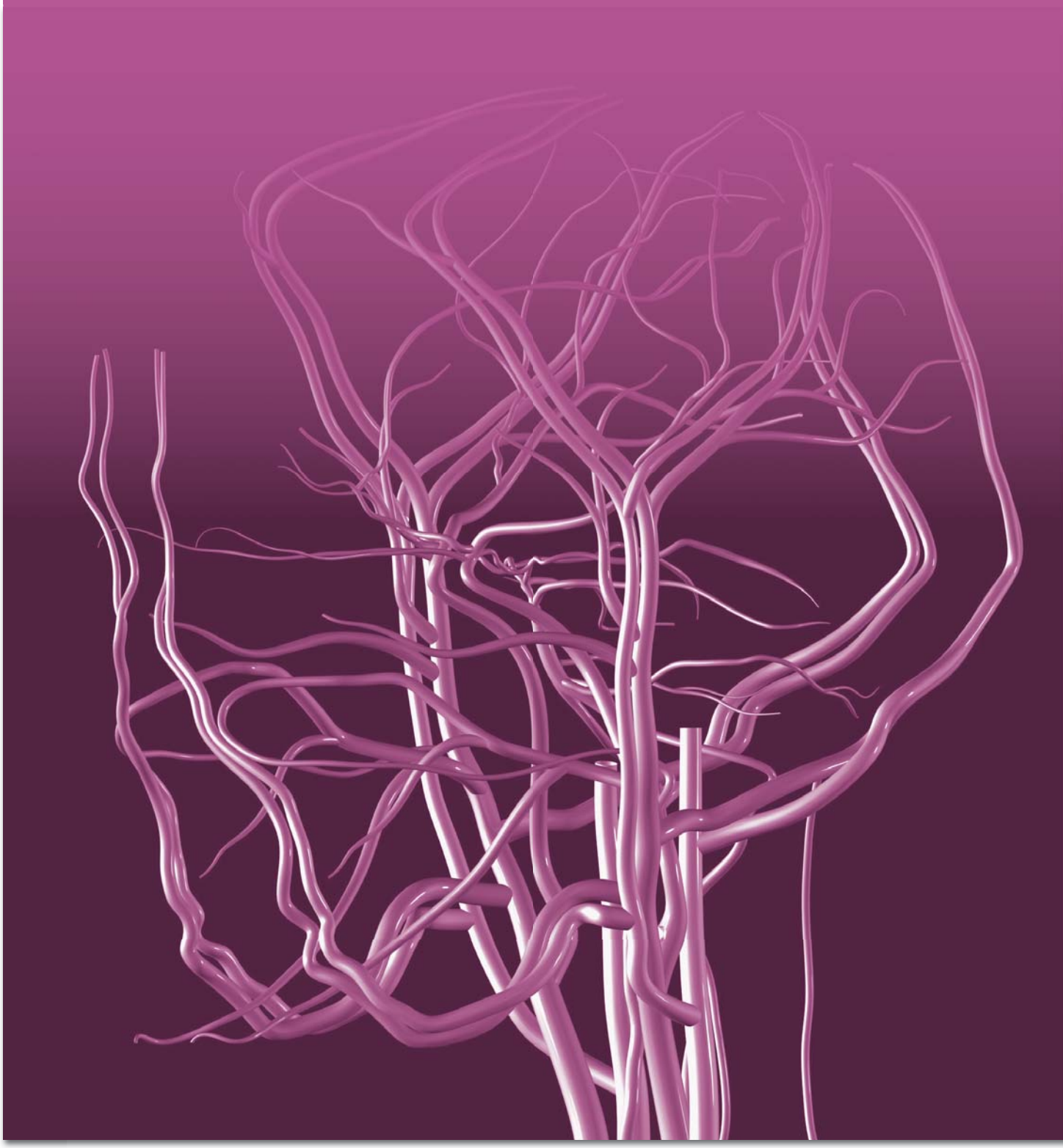
2010 has also been the year of our commitment to innovation. Including the creation of a new unit dedicated to looking for opportunities to exploit the results of our research and transfer our knowledge, creating partnerships with companies from different sectors in order to become a benchmark. VHIR, a brand established in the biomedical world, has opened up to other productive sectors of Catalonia, the rest of Spain and beyond our borders, because if our researchers come from anywhere in the world our strategic movements must also be worldwide.

Along with innovation, we strongly believe in communication, because we are in the era of communication and nothing one does is fully recognized if it is not known about. We have explained in an increasingly thorough manner what we do, internally and externally, and reached more audiences, beyond the boundaries of biomedicine and the healthcare environment. But it is only a beginning, because there is still a long way to go. Always serving society, we strive to explain to our stakeholders what we do, to ask for their support, to this end we have also created a development unit, which has recently started operating and must also represent a step forward in our goals.

The quality of our research and the dedication of the support units have been recognized by the Spanish and the European scientific community. And so we have been chosen as Spain's scientific coordinators, along with the institutional coordination of ISCIII, and the European translational research project EATRIS, of which we will be proud to be part once it has been launched. During 2010, the second year under this direction, many of the challenges outlined in 2009 have come to pass, others have evolved and a few new ones have emerged and will become reality in the near future, as part of the strategic plan 2011-2015 currently being developed. Nothing will stop us, not even the economic difficulties.

Joan X. Comella
VHIR's Director

VHIR Information



Vall d'Hebron Institut de Recerca (VHIR)

MISSION

The Vall d'Hebron Research Institute - VHIR - is a public sector institution that promotes and develops innovative biomedical research at the University Hospital Vall d'Hebron. VHIR is oriented towards finding solutions to the health problems of citizens and aims to contribute to scientific, educational, social and economic development within its area of competence.

VISION

We want our research and innovation, carried out by the people who make up the institution, to expand the frontiers of knowledge and become an active and important reference for our society, our health system and our citizens, attracting talent and ensuring that our activities correspond in terms of excellence, quality and translation, with the leading position that the Hospital Vall d'Hebron deserves.

GOVERNING BODIES

The Management and decision making infrastructure of VHIR is located in the Foundation University Hospital Vall d'Hebron Research Institute, where the governing bodies include:

TRUSTEES

The Board is the Foundation's governing body, it represents, manages, and assumes all powers and functions necessary to achieve the aims of VHIR.

Trustees to 16th December 2010

President
Marina Geli Fàbrega
Catalonian Regional Minister of Health

1st Vice President
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Director Catalonian Institute of Health (ICS)

2nd Vice President
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Rector Universitat Autònoma de Barcelona (UAB)

3rd Vice President
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General Manager Vall d'Hebron University Hospital (HUVH)

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Deputy Director Professional Development Catalonian Institute of Health (ICS)

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President Health, Innovation & Society Foundation (Novartis)

José Baselga Torres
Chief of Service Medical Oncology (HUVH)

Joan Berenguer i Maimó
Chief Executive Officer Imaging Diagnostic Institute (IDI)

Antoni Esteve Cruella
President Blood and Tissue Bank (HUVH)

Pedro Fontana i García
President Advisory Council Banco Bilbao Vizcaya Argentaria (BBVA)

David García-Dorado
Coordinator Research Group in Cardiocirculatory Pathology (VHIR)

Francesc Gòdia i Casablancas
Appointee by the Rector for Biotechnology and Biomedicine. Universitat Autònoma de Barcelona (UAB)

Joan-Ramon Laporte Roselló
General Director Catalonian Institute of Pharmacology Foundation (ICF)

Carles Miquel i Colell
Coordinator of Health-care Research and Innovation Programme Department of Health

Ramon Pau Pla Illa
Managing Director Blood and Tissue Bank (HUVH)

José Sánchez de Toledo Codina
Chief of Service Pediatrics Oncology (HUVH)

Oriol de Solà-Morales Serra
Director Agència d'Avaluació de Tecnologia i Recerca Mèdiques

Joaquim Tosas i Mir
President CIMA Clinic

Miquel Vilardell i Tarrés
Chief of Service Internal Medicine (HUVH)

Concepció Violán Fors
Manager Research Institute Jordi Gol

Attendee
Joan X. Comella Carnicé
Director
Vall d'Hebron Research Institute (VHIR)

Secretary
Lluís Massó i Guitart
Manager
Vall d'Hebron Research Institute (VHIR)

Current Trustees from December 16th

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Boi Ruiz i Garcia
Catalonian Regional Minister of Health

1st Vice President
Andreu Mas-Colell
Catalonian Regional Minister of Economy and Knowledge

2nd Vice President
Ana Ripoll Aracil
Rector of Universitat Autònoma de Barcelona

Members
José Luis de Sancho Martín
General Manager Vall d'Hebron University Hospital (HUVH)
(until July 2011)

Jaume Raventós i Monjo
General Manager Vall d'Hebron University Hospital (HUVH)
(from July 2011)

Enric Argelagués Vidal
Managing Director Catalonian Health Institute (ICS)
(until July 2011)

Joaquim Casanovas
Managing Director Catalonian Health Institute (ICS)
(from July 2011)

Manuel Armengol Carrasco
Coordinator of the Educational Unit (HUVH)

Joaquim Esperalba Iglesias
General Director of Regulation, Planning and Health Resources at the Catalonian Regional Minister of Health

Manel López Béjar
Vice Chancellor for Research. Universitat Autònoma de Barcelona (UAB)

Josep Maria Martorell i Rodón
General Director of Research. Catalonian Government.

Ramon Pau Pla Illa
Manager Blood and Tissue Bank (BST)

Lluís Rovira Pato
Director Research Centers of Catalonia (ICERCA)

Josep Tabernero Caturla
Clinical Research Director. Vall d'Hebron Institute of Oncology (VHIO)

Attendee
Joan X. Comella Carnicé
Director
Vall d'Hebron Research Institute (VHIR)

Secretary
Lluís Massó i Guitart
Manager
Vall d'Hebron Research Institute (VHIR)

Governing Board / Executive Committee

On December 16th, 2010 the Governing Board became the Executive Committee, with the following functions:

a) To carry out the resolutions adopted by the Board that this body may require.

b) To periodically monitor the tasks of leadership and school management.

c) To develop the proposed agenda for meetings of the Board and review the documentation to be submitted, if applicable.
d) To propose to the Board the adoption of agreements that apply to this body.

e) To monitor the covenants and agreements subscribed by the Foundation.

f) To report on the borrowing requirements of the Foundation.

g) To carry out the leadership and management tasks of the Foundation, especially with regard to its relationships with the founding institutions.

Governing Board (until December 2010)

President
José Luis de Sancho Martín
General Manager, Vall d'Hebron University Hospital

Vice President
Joan X. Comella Carnicé
Director, VHIR

Members
Manuel Armengol Carrasco
Coordinator of the Educational Unit, HUVH

Joan Fernández Náger
Director of Medical Processes, HUVH

David García-Dorado García
President, Internal Scientific Committee VHIR

Vicenç Martínez Ibáñez
Director of Surgical Processes, HUVH

Joan Montaner Villalonga
Vicepresident, Internal Scientific Committee VHIR

Ana Ochoa de Echaguen Aguilar
Director of Mother&Child Processes

Rafael Simó Canonge
Clinical Trials Unit (UCICAC) Scientific Responsible, HUVH

Pilans Solans Julián
Director of Health Care, HUVH

Miquel Vilardell i Tarrés
Chief of Service Internal Medicine, HUVH

Secretary
Lluís Massó i Guitart
VHIR Manager

Executive Committee (from December 2010)

President
Joaquim Esperalba Iglesias
General Director of Regulation, Planning and Health Resources at the Catalonian Regional Minister of Health
(until July 2011)

Members
Lluís Rovira Pato
Director Research Centers of Catalonia (ICERCA)

Josep Maria Martorell i Rodón
General Director of Research. Catalonian Government.

Manel López Béjar
Vice chancellor for research. Universitat Autònoma de Barcelona (UAB)

Secretary
José Luis de Sancho Martín
General Manager Vall d'Hebron University Hospital (HUVH)
(until July 2011)

Jaume Raventós i Monjo
General Manager Vall d'Hebron University Hospital (HUVH)
(from July 2011)

Management

Director

Joan X. Comella
direccio@vhir.org

The Director is responsible for developing the executive management of the Foundation. He has the following functions:

a) To direct, organize and manage the research activities of the Foundation.

b) To propose the Foundation's schedule of activities to the Board, specifying the research, cost and anticipated funding sources.

c) To present the Foundation's proposed annual budget to the Board.

d) To propose the appointment of individuals to fill management and consulting posts to the Board

and, if necessary:

e) To coordinate obtaining the necessary resources to be able to carry out the Foundation's objectives.

f) Reporting the development of the Foundation's research activities and programs to the Board.

g) To manage the selection process of researchers and research support staff.

h) To propose services that may be required for the Foundation to develop assigned activities and functions.

i) To propose rules of procedure to the Board.

j) To formalize collaboration agreements with public or private institutions, below the maximum amount expressly authorized by the Board.

k) Other duties as may be expressly assigned or delegated by the Board, under the terms provided in the Bylaws.

Assistant Director in Clinical Research
Joan Genescà
joan.genesca@vhir.org

Direction Secretariat
Irene Sendiu Gubianes
Tel. 93 489 38 63
irene.sendiu@vhir.org

Manager

Lluís Massó Guitar
lluis.masso@vhir.org

The duties of the Management:

a) To direct financial and accounting management, the management of funds from other institutions or agencies, the preparation of annual accounts and to ensure the Foundation's administrative tasks are carried out properly, the processing of documents and preparation of the management report.

b) To run works, services and supply contracts on behalf of the Foundation, as delegated by the Board.

c) To manage, in accordance with the guidelines set by the Board, the Foundation's human resources, staffing, incidents, separation and termination of labour and services contracts, as well as the management of grants.

d) To provide the necessary administrative support for meetings of the Board and other bodies of the Foundation.

e) To ensure the proper condition and operation of the Foundation's assets and tracking the goods inventory. To run treasury borrowing operations. To conduct all required legal matters and management transactions for all property and securities, in accordance with guidelines approved by the Board.

f) Anything that may be assigned or delegated by the bodies of the Foundation.

Secretary
Trinidad Gutiérrez Morente
Tel. 93 489 41 01
trini.gutierrez@vhir.org

From Internal Scientific Committee to Internal Scientific Council

On December 16th, 2010, the Internal Scientific Committee became the Internal Scientific Council. The Board names, proposed by the Director, an Internal Scientific Council with a minimum of three and a maximum of twenty researchers from Research Groups of the Foundation, which aims to advise the direction in the performance of its functions. This body does not represent the Foundation nor hold management functions of any kind.

Internal Scientific Committee (until December 2010)

President
David García-Dorado
Coordinator Research Group in Cardiocirculatory Pathology

Vice President
Joan Montaner Villalonga
Research Group in Neurovascular Diseases

Members
Antònia Andreu Domingo
Research Group in Microbiology

Antoni Andreu Périz
Research Group in Neuromuscular and Mitochondrial Pathology

Joaquín Arribas López
Research Group in Growth Factors and Cancer

Laura Audí Parera
Research Group in Pediatric Endocrinology

Joan X. Comella Carnicé
General Director, FIR-HUVH
(From September 2009)

María Jesús Cruz Carmona
Research Group in Pneumology

Joan Genescà Ferrer
Research Group in Hepatic Diseases

Francisco Guarner Aguilar
Research Group in Physiology and Digestive Physiopathology

Monserrat Martínez Muñoz
Deputy Director Nursing, Continuing Education, HUVH

Francina Munell Casadesús
Research Unit in Biomedicine and Translational and Pediatric Oncology

Rosanna Paciucci
Research Unit in Biomedicine and Translational and Pediatric Oncology

Simó Schwartz Navarro
Research Group in Nanomedicine

Internal Scientific Council (from December 2010)

President
Joan X. Comella Carnicé
Director, VHIR

Members
Antoni Andreu Périz
Director of Program in Molecular Medicine

Joaquín Arribas López
Chief of Research Group in Growth Factors and Cancer

José Antonio Barrabés Riu
Research Group in Cardiovascular Diseases

Enric Cáceres Palou
Chief of Service Department of Orthopedics and Rehabilitation, HUVH

Miquel Casas Brugué
Chief of Psychiatry Service and Chief of Research Group in Psychiatry and Mental Health

María Jesús Cruz Carmona
Research Group in Pneumology

Carmen Fuentelsaz Gallego
Chief of Research Group in Health Care Research

David García-Dorado García
Clinical Director of Heart Cardiology Area and Chief of Research Group in Cardiocirculatory Pathology

Joan Gavaldà Santapau
Research Group in Infectious Diseases

Joan Genescà Ferrer
Deputy Director of Research and Research Group in Liver Diseases

Francisco Guarner Aguilar
Research Group in Physiology and Digestive Physiopathology

Xavier Montalban Gairín
Clinical Director of Neuroscience Area and Chief of Research Group in Clinical Neuroimmunology

Joan Montaner Villalonga
Chief of Research Group in Neurovascular Diseases

Josep Ordi Ros
Research Group in Systemics Diseases

Ricard Pujol Borrell
Chief of Immunology Service and Chief of Research Group in Immunology

Santiago Ramón y Cajal Agüeras
Chief of Pathology Service and Chief of Research Group in Molecular Pathology

Jaume Reventós Puigjaner
Chief of Research Unit in Biomedicine and Translational and Pediatrics Oncology

Simó Schwartz Navarro
Coordinator of CIBBIM

Joan Seoane Suárez
Chief of Research Group in Gene Expression and Cancer

Rafael Simó Calonge
Chief of Research Group in Diabetes and Metabolism

From External Scientific Committee to External Scientific Council

On December 16th, 2010 External Scientific Committee became the External Scientific Council. The External Scientific Council is the body responsible for advising on the scientific activities of the Foundation and for ensuring its scientific quality. This body does not represent the Foundation nor hold management functions of any kind.

The External Scientific Council is comprised of a minimum of three and a maximum of twenty internationally renowned scientists who are widely recognized in the Foundation's fields of research. In no case can any member of the External Scientific Council engage in research linked to, or collaborate regularly with, the Foundation.

External Scientific Committee (until December 2010)

Jesús Ávila de Grado
Director, Severo Ochoa Molecular Biology Center, Universidad Autónoma de Madrid

María Blasco Marhuenda
Director Molecular Oncology Program, National Oncology Research Center (CNIO)

Carlos Diéguez González
Professor Physiology, Medical School University of Santiago de Compostela

Francisco Fernández Avilés
Director Institute of Heart Sciences (IDICOR), Valladolid

José López Barneo
Professor Physiology, University of Sevilla

Carlos López Otín
Professor Biochemistry and Molecular Biology, University of Oviedo

José María Martín Moreno
Professor Public Health, University of Valencia

José María Mato de la Paz
Director Bioscience Operational Research Center (CIC Biogune) Vizcaya Technological Park

External Scientific Council (from December 2010)

Dr. Ernest Arenas
Chief of Department of Medical Biochemistry and Biophysics. Chief of Molecular Neurobiology Research in Karolinska Institute in Stockholm

Dr. Jesús Ávila de Grado
Research Professor in CBM (CSIC-UAM)

Dra. María Blasco Marhuenda
Director of Molecular Oncology Programme of the National Center for Cancer Research

Dra. Barbara Casadei
Professor in Cardiovascular Medicine Department of John Radcliffe Hospital, Oxford

Dr. Carlos Diéguez González
Chairperson in Physiology of Faculty of Medicine, Santiago de Compostela University

Dra. Ruth Duncan
Emeritus *Chairperson, Cardiff*

Dr. Stanislav D. Ehrlich
Macrobiotics Genetics Unit Director, National Institute for Regional Research, Paris

Dr. Francisco Fernández Avilés
Director of Institute of Heart Sciencies (ICICOR), Hospital Clínico Universitario de Valladolid, and Head of Cardiology, Hospital Universitario Gregorio Marañón, Madrid

Dr. Jay A. Fishman
Director of Transplant, Infectious Diseases and Program in immunologically compromised patients, Massachusetts General Hospital, Boston

Dr. Seija Grénman
President of Obstetrics and Gynecology Department, Turku University Hospital, Turku

Dra. Nancy Hynes
Senior Group Leader of Friedrich Miescher Institute for Biomedical Research, Basel

Dr. José López Barneo
Chairperson in Physiology, University of Seville

Dra. Catherine Lubetzki
Chairperson and Neurology, Hôpital Pitié-Salpêtrière, Paris

Dr. Michael Manns
President of Gastroenterology, Hepatology and Endocrinology Department in Medical School of Hannover

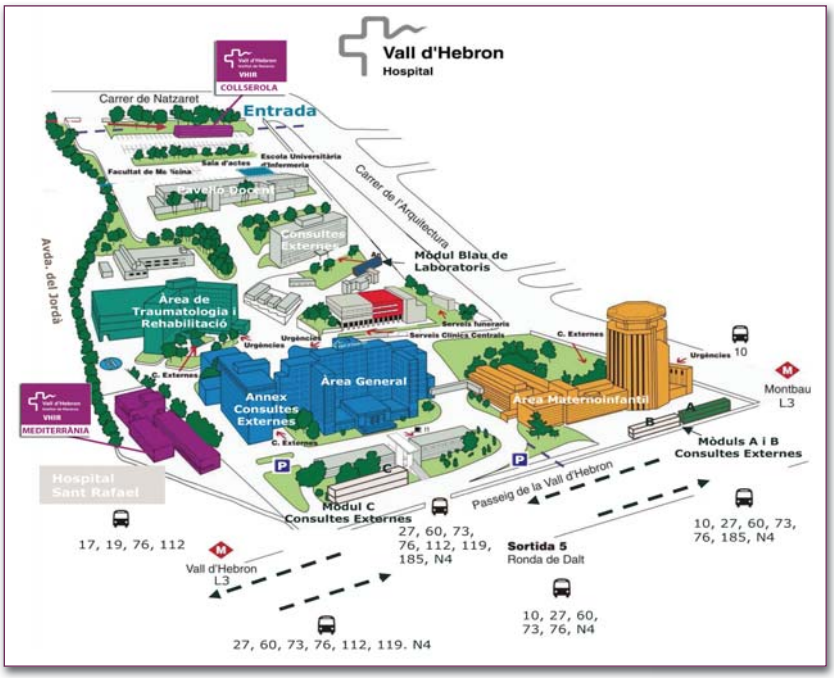
Dr. José María Mato de la Paz
Director of Center for Cooperative Research in Biosciences (CIC Biogune). Technology Park of Bizkaia

Dr. Benoit Nemery
Chairperson, Occupational Medicine and Toxicologists. President of Public Health Department, Leuven

Dra. Marina Pollán
President of Cancer Epidemiology Unit, National Center of Epidemiology, Madrid

Dra. Sylvie Robine
President of Morphogenesis and Cell Signaling Unit, Institute Curie, Paris

Dr. Martin Wehling
Director of Institute of Experimental and Clinical Pharmacological and Toxicology, Mannheim



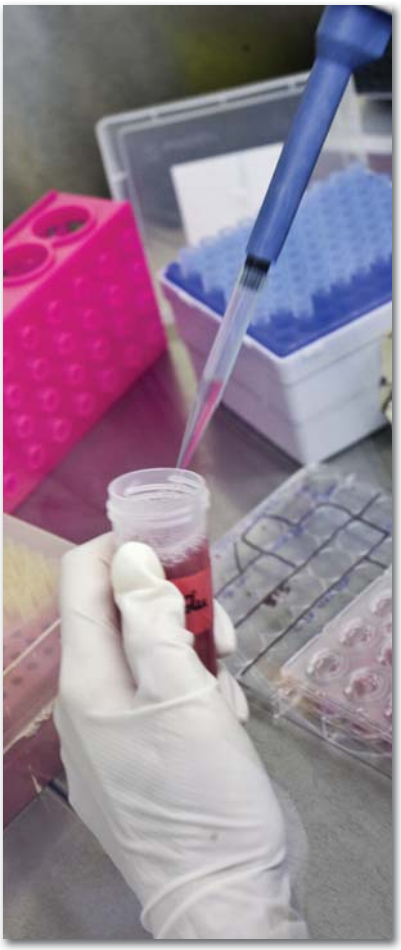
WHERE WE ARE

Vall d'Hebron Research Institute
Passeig Vall d'Hebron, 119-129
08035 Barcelona

www.vhir.org
twitter.com/@VHIR_
facebook.com/VHIR.org

Research Support Units

Everyone at VHIR works together to support our research effort. Innovative new technologies, services and administrative staff are always available to support and advance the work of our researchers.



Innovations

Head of Unit
Francesc Iglesias García
Tel. 93 489 4523
francesc.iglesias@vhir.org

Innovations Secretary
Ana Lucía Román Mora
Tel. 93 489 4187
ana.roman@vhir.org

Advice Coordinator
Raquel Egea Martínez
Tel. 93 274 61 00 (ext. 6426)
raquel.egea@vhir.org

Legal Advisor
Lourdes Salomón Sancho
Tel. 93 489 30 00 (ext. 4945)
lourdes.salomon@vhir.org

Business Development & Marketing
Cecília López García
Tel. 93 489 30 00 (ext. 4947)
cecilia.lopez@vhir.org

Financial Advisor
Frederic Horta Sellarès
Tel. 93 489 30 00 (ext. 4882)
frederic.horta@vhir.org

Innovation Model

The Vall d'Hebron University Hospital has created its own model of innovation in the Vall d'Hebron Institut de Recerca (Research Institute), with the joint goals of promoting innovation in order to create a more competitive hospital which operates both as an economic development agency and generates research findings that are beneficial to society.
The Innovations team is made up of highly qualified senior personnel with extensive experience in marketing the institute's innovative work results to both the public and private sectors.
Work carried out by this unit includes; advising on strategies to protect intellectual property rights, technological brokering, patent licensing negotiations, assistance in creating spin offs, providing coaching for collaborative projects and "Innovation Initiatives", etc.

Administrative Structure

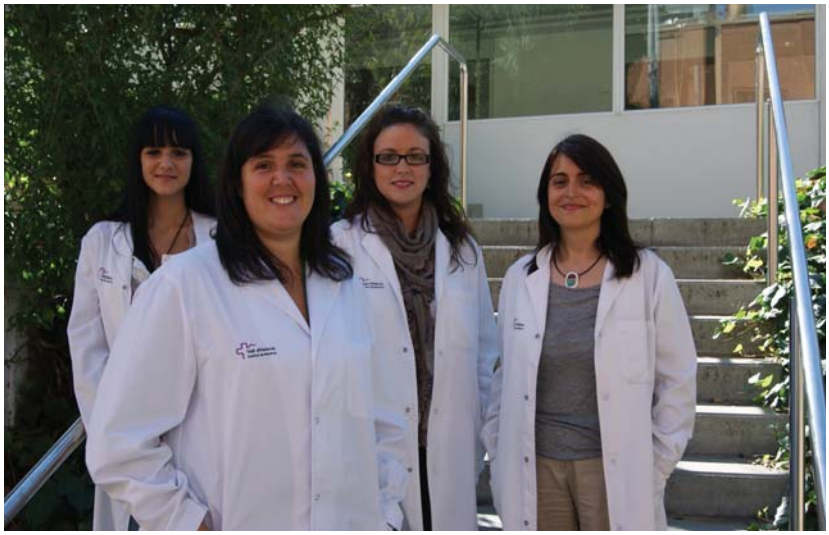
CEIC Support Unit

Head of Unit
Mireia Navarro Sebastián
Tel. 93 489 46 51
mireia.navarro@vhir.org

Research Project Staff
Vanessa Rojas Sotomayor
Tel. 93 489 38 91
vanessa.rojas@vhir.org

Administrative Support Staff
Immaculada Pérez Gladiador
Tel. 93 489 46 51
imma.perez@vhir.org

Montserrat Fernández Recio
Tel. 93 489 40 10
montserrat.fernandez@vhir.org



This unit provides support for clinical trials and post authorization studies involving medicines, medical devices and therapeutic interventions. The unit supports both projects launched by in-house researchers as well as those originating in other public agencies. It focuses on the ethical, methodological and logistical aspects of research. Portfolio of Services.

Management

- Project development, management and protocol design.
- Informed consent forms for subjects taking part in medical research.
- Center for Review and Dissemination CRD (presented on digital or paper formats) design, development and data management (presented as digital CRD or Databases).
- Processing trial results at the CEIC and other public agencies.
- Management of agreements and contracts between centers.
- Monitoring.
- Adverse event management.
- Archive management (Master file).
- Compilation of periodical and final reports.

Communication Management Unit

Head of Unit
Fran García Morales
Tel. 93 489 30 00 (ext. 4835)
fran.garcia@vhir.org

Web and Corporate Image
Elena Casaldàliga Albisu
Tel. 93 489 30 00 (ext. 4668)
elena.casaldaliga@vhir.org

Multimedia and Corporate Image
Roland Peralta Díez
Tel. 93 489 40 59
roland.peralta@vhir.org

Communication
Montserrat Ferrando Pastor
Tel. 93 274 67 28
montse.ferrando@vhir.org

Seminars
Marçal Farrés Juste
marcal.farres@vhir.org

Documentation
Laura Llopart Estrems
laura.llompart@vhir.org

The communication unit is responsible for the following functions:

- Using the broadcast and social media to inform the public about the VHIR's scientific research and related activities.
- Producing communication campaigns to report VHIR research activities at press conferences, in interviews and to the broadcast media.
- Developing and maintaining the institutional website as an essential tool for internal and external communication.
- Internal communication of publications and activities carried out by our researchers. Internal communication, intranet, web 2.0.
- The writing of an annual analytic report of the scientific output of the VHIR.

- Publishing the majority of information in English due to the global nature of scientific research.

Computer Management Unit

Project Manager
Domènec Far Macia
Tel. 93 489 45 64
domenec.far@vhir.org

Systems Manager
Jesús María Vicente Pérez
Tel. 93 489 41 27
jesusmaria.vicente@vhir.org

Programming Technician
Xavier López Soriano
Tel. 93 489 48 07
xavi.lopez@vhir.org

Computer Assistance
Joan Aymà Comas
Tel. 93 274 20 02
joan.ayma@vhir.org

Toni Vega Gala
Tel. 93 274 20 02
toni.vega@vhir.org

VHIR Computer Services support our researchers by managing and coordinating all computer related issues. The unit created a comprehensive centralized database designed to manage the institution's research findings, which covers both internal research processes as well as external agents' research processes. Many useful research tools have been developed from this database: The GIR platform (www.vhir.org/gir) is a dynamic, interactive and participative tool that incorporates online services and allows researchers access to interactive data in real time, wherever they are.

Financial Management Unit

Head of Unit
Montserrat Giménez Prous
Tel. 93 489 41 28
montse.gimenez@vhir.org

Bids and Contracts
Ingrid Feliubadaló Díaz
Tel. 93 489 30 00
ingrid.feliubadalo@vhir.org

Economic Reports
Anna Corominas Ruiz
Tel. 93 489 45 91
anna.corominas@vhir.org

Joaquim Cahors Gómez
Tel. 93 489 30 00
joaquim.cahors@vhir.org

Marta Esteve Costal
Tel. 93 489 41 48
marta.esteve@vhir.org

Invoices/Income
Meri Montero Cueto
Tel. 93 274 60 34
mlmontero@ir.vhebron.net

Laia Batet Candela
Tel. 93 489 40 18
laia.batet@vhir.org

Technical Manager
Xavier Bros Marín
Tel. 93 489 45 91
xavier.bros@vhir.org

Legal Advisors
Marta Pina Martí
Tel. 93 489 30 00
marta.pina@vhir.org

Marta González Barcelò
Tel. 93 489 69 52
marta.gonzalez@vhir.org

Purchasers
Imma Jiménez Ariza
Tel. 93 489 40 27
inma.jimenez@vhir.org

Mercè Garcia Vidal
Tel. 93 489 30 00
merce.garcia@vhir.org

Secretary
Trinidad Gutiérrez Morente
Tel. 93 489 41 01
trini.gutierrez@vhir.org

Treasurer
Montse Abad de la Vega
Tel. 93 489 44 59
montse.abad@vhir.org

The Financial Management Unit aims to optimize the VHIR's economic resources to improve the efficiency and effectiveness of research management. The Financial Management Unit supports the economic management of the various research projects and clinical trials developed at the HUVH and at the VHIR, both through financial tracking and the writing of financial reports.

Development Unit

Head of Unit
Carmen Netzel Riera
Tel. 93 489 30 00 (ext. 4931)
carmen.netzel@vhir.org

The Development Unit is responsible for generating philanthropic support for biomedical research, coordinating external relations and alliances with international groups.
We pay special attention to:

- Raising awareness about the importance of research in the curing of diseases.
- Fostering and nurturing partnerships with corporate contributors, donors and friends of the VHIR.
- Providing support for researchers and clinicians in their relationships with donors and philanthropic partners.

Human Resources Unit

Head of Unit
Roger Verdejo Torras
Tel. 93 489 43 39
roger.verdejo@vhir.org

Human Resources Personnel
Laia Pérez Lasarte
Tel. 93 489 40 08
laia.perez@vhir.org

Miriam Izquierdo Sans
Tel. 93 489 40 26
miriam.izquierdo@vhir.org

Natàlia Tibau Llarden
Tel. 93 489 43 37
natalia.tibau@vhir.org

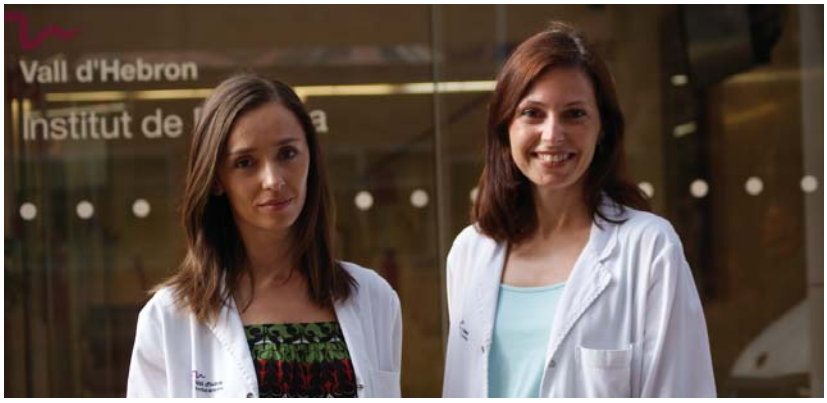
The Human Resources Unit promotes and facilitates working relationships within the VHIR. It provides workforce suited to VHIR requirements and guidelines, respecting existing ethic and legal frameworks.

Occupational Risk Prevention Unit

Safety at Work Team
Ana Elena Ruiz Querol
Tel. 93 489 43 31
ana.elena.ruiz@vhir.org

Mª Teresa de la Campa Alonso
Tel. 93 489 43 31
teresa.delacampa@vhir.org

The Occupational Risk Prevention Unit advises on and works to promote health and safety at work, according to the regulations laid out in Law 31/95 of Occupational Risk Prevention. It assesses and controls risk, producing safety instructions, analyzing work accidents, training and informing employees, promoting healthy work habits and preventing the contraction of occupational diseases.



Project Management Unit

Head of Unit
Laura Casado Castells
Tel. 93 489 40 11
laura.casado@vhir.org

International Projects
Anaïs Le Corvec
Tel. 93 489 40 13
anais.lecorvec@vhir.org

Manuel Morillas Díaz
Tel. 93 489 40 13
manuel.morillas@vhir.org

Project Monitoring
Raquel Fornells Fiestas
Tel. 93 489 30 00
raquel.fornells@vhir.org

Research Grants and Fellowships
Maribel Corral Zabala
Tel. 93 489 40 12
maribel.corral@vhir.org

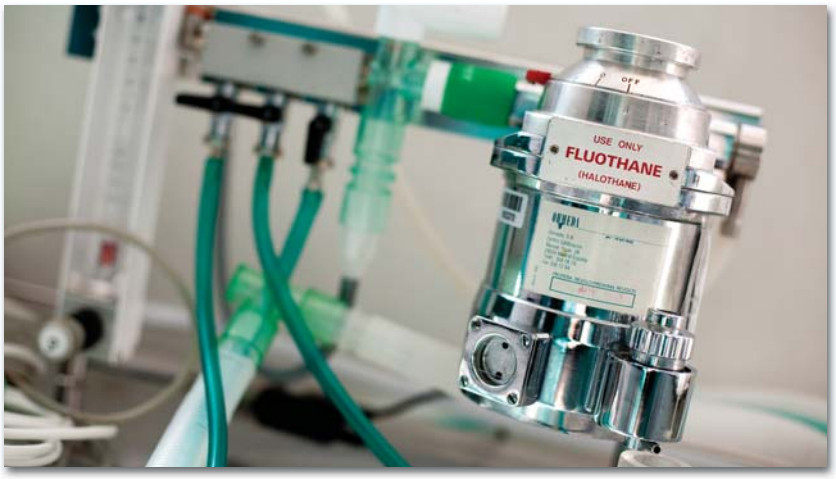
The Project Management Unit provides support to VHIR and HUVH researchers in preparing, presenting, and monitoring research projects, funded by regional, national and international private and public agencies.
Its main functions are:

- The selection and dissemination of information on available resources and financial support.
- The monitoring of resources and funded projects.
- Working towards a more effective use of resources in research project development at VHIR.
- The dissemination and organization of training on resources available for the development of research projects.

Services

Advancing Health Research

The Vall d'Hebron Research Institute has a number of important services whose role is to support research and to provide the complex environments currently required in biomedicine research.
These include the scientific and technical Support Unit (UCTS), the Statistics and Bioinformatics Unit (UEB), the Support Unit for Biomedical Research Methodology (USMIB), the Clinical Research Ethics Committee (CEIC), the Animal Facility and Laboratory Coordination Unit.
The two most recently created services are the biobank and the Central Unit of Clinical Research and Clinical Trials (UCICAC). Which in addition to providing researchers with up-to-date services and technology works towards increasing profitability and improving self-sufficiency.



Scientific and Technical Support Unit (UCTS)

The Scientific and Technical Support Unit (UCTS) offers a range of high-tech services to support teaching and research activities in the field of biomedics. The centralized nature of STSU permits it to offer researchers the most advanced tools available in genomics, bioinformatics, proteomics, cytomics and microscopy at a reduced cost, with frequent updates and specialized advice.

Head of Unit
Fátima Núñez Mangado
Tel. 93 489 41 89
fatima.nunez@vhir.or

Researchers
Francisca Gallego Valadés
Tel. 93 489 41 79
paqui.gallego@vhir.org

Marta Valeri Sala
Tel. 93 489 41 79
marta.valeri@vhir.org

Mª Ángeles Artaza Marino
Tel. 93 489 41 79
maria.angeles.artaza@ vhir.org

Ricardo Gonzalo Sanz
Tel. 93 489 41 79
ricardo.gonzalo@ vhir.org

Àlex Bote Tronchoni
Tel. 93 489 41 79
alex.bote@ vhir.org

Rosa Mª Prieto Sánchez
Tel. 93 489 41 79
rosa.prieto@ vhir.org

Rosa Arjona Martos
Tel. 93 489 41 79
rosa.arjona@ vhir.org

Irene Sales Pardo
Tel. 93 489 41 79
irene.sales@ vhir.org

Àlex Sànchez Pla
Tel. 93 489 40 07
alex.sanchez@ vhir.org

Israel Ortega Serrano
Tel. 93 489 40 07
israel.ortega@ vhir.org

Josep Lluís Mosquera Mayo
Tel. 93 489 40 07
jl.mosquera@ vhir.org

1. Genomics Unit

Real-Time Quantitative PCR System

Head of Unit
Francisca Gallego Valadés
Tel. 93 489 41 78
paqui.gallego@vhir.org

Scientific Advisor
Joan Seoane Suárez
Tel. 93 274 60 26
joan.seoane@vhir.org

Equipment
- 1 Real-Time PCR system PCR ABI PRISM 7000-SDS.
- 1 Real-Time PCR system PCR ABI PRISM 7900-SDS.
- 2 single cell PCR system.

DNA Sequencing Service

Head of Service
Rosa Arjona Martos
Tel. 93 489 41 81
rosa.arjona@ vhir.org

Scientific Advisor
Antoni Lluís Andreu Périz
Tel. 93 489 40 57
toni.andreu@vhir.org

Equipment
- 1 Applied Biosystems ABI PRISM 3100 Automatic sequencer.

Bioanalysis Service

Heads of Service
Ricardo Gonzalo Sanz
Tel. 93 489 41 78
ricardo.gonzalo@ vhir.org

Rosa Arjona Martos
Tel. 93 489 41 78
rosa.arjona@ vhir.org

Equipment
- 1 Agilent Bioanalyzer 2100.

2. Molecular Diagnostic Platform

Ultrasequencing Service

Head of Service
Rosa Mª Prieto Sánchez
Tel. 93 489 41 79
rosa.prieto@ vhir.org

Operator
Francisca Gallego Valadés
Tel. 93 489 41 79
paqui.gallego@vhir.org

Equipment
- 1 Roche/454GS-FLX system.
- 1NimbleGen Microarray Scanner MS 200.
- 1 sequence enrichment system on a solid bracket.
- 1 sequence enrichment system in solution.

Genetic Expression Analysis Service

Head of Service
Ricardo Gonzalo Sanz
Tel. 93 489 41 78
ricardo.gonzalo@ vhir.org

Operator
Francisca Gallego Valadés
Tel. 93 489 41 79
paqui.gallego@vhir.org

Scientific Advisor
Joan Seoane Suárez
Tel. 93 274 60 26
joan.seoane@vhir.org

Equipment
- 1 Affymetrix GeneChip Microarray systems with two fluid stations and an automatic array charger.
- 1 Affymetrix GeneTitan system to process arrays automatically.

Protein Microarray Service

Head of Service
Francisca Gallego Valadés
Tel. 93 489 41 79
paqui.gallego@vhir.org

Staff Team
Marta Valeri Sala
Tel. 93 489 41 79
marta.valeri@vhir.org

Àlex Bote Tronchoni
Tel. 93 489 41 79
alex.bote@ vhir.org

Equipment
- 1 system for high-density microarrays - Zeptosens Reverse Array System (including Zepto Reader Scanner and NanoPlotter).

3. Proteomics Platform

Proteomics Service

Head of Service
Francesc Canals
Tel. 93 489 41 75
fcanals@vhio.net

Researchers
Núria Colomé Calls
Tel. 93 489 4174
ncolome@vhio.net

Joan Josep Bech Serra
Tel. 93 489 41 74
jjbech@vhio.net

Marta Monge Azemar
Tel. 93 489 41 74
mmonge@vhio.net

Equipment
- 1 Amersham Bio -Sciences system for two-dimensional electrophoresis of proteins, composed of:
  - 2 units a pH-gradient strip for isoelectric focusing IPGPHOR.
  - 2 electrophoresis units DALT VI for gels of 26 x 20 cm.
- 1 Amersham BioSciences scanner and imaging analysis Image Master Platinum software.
- 1 GE Healthcare DIGE System (Differential Gel Electrophoresis, Amersham), composed of:
  - 1 Typhoon 9400 scanner to obtain fluorescence images of 2D electrophoresis gels.
  - 1 GE Healthcare DeCyder for quantitative analysis of differences.
  - 1 Nonlinear Dynamics SameSpots software for quantitative analysis of images.
- 1 GE Healthcare Spot Picker robot.
- 1 Bruker Proteineer DP robot.

- 1 Bruker mass spectrometry MALDITOF/ TOF Autoflex Speed.
- 1 Ettan LC system by Amersham of liquid chromatography from micro- to analytical scale.
- 1 LC-Packings nano-HPLC system.
- 1 nano-HPLC Proxeon system.
- 1 Bruker Ionic trap-electrospray mass spectrometry Esquire Ultra-ETD.
- 1 Bruker mass spectrometry Ultra High Resolution Q-TOF Maxis.

4. Metabolomics Science Platform

Metabolomics Service (Cardiocirculatory Pathology)

Head of Service
Ignasi Barba Vert
Tel. 93 489 41 86
ignasi.barba@vhir.org

Group Leader
David García-Dorado
Tel. 93 489 40 38
dgdorado@ir.vhebron.net

Equipment
- 1 RMN Bruker Avance 400 WB spectrometer, with *z*-axis gradient with the following probes:
  - 1 5 mm 1H-BB inverse probe.
  - 1 20 mm 1H-BB probe.
  - 1 HR-MAS 1H-31P-13C probe.
- 1 BCUC05 unit to regulate temperature.
- 1 Equipment Bruker Mini-imaging 0.5 to obtain images.
- 1 Animal monitoring equipment.

Metabolomics Service (STSU)

Head of Service
Mª Ángeles Artaza Marino
Tel. 93 489 41 79
maartaza@ir.vhebron.net

Operator
Ricardo Gonzalo Sanz
Tel. 93 489 41 79
rgonzalo@ir.vhebron.net

Equipment
- 1 Waters ACQUITY UPLC system.
- 1 Waters mass spectometer MS/MS X¬evo TQ.
- 1 nano-HPLC Tempo system.
- 1 Applied Biosystems hybrid mass spectometer triple quadrupole with ionic trap 4000 Q TRAP LC/MS/MS.

5. Citomics Platform

Cytometry Analysis and Cell Sorting Service

Head of Service
Irene Sales Pardo
Tel. 93 489 41 82
irene.sales@ vhir.org

Operator
Àlex Bote Tronchoni
Tel. 93 489 41 77
alex.bote@ vhir.org

Scientific Advisors
Jordi Barquinero Máñez
Tel. 93 489 67 26
jordi.barquinero@vhir.org

Jordi Pétriz González
Tel. 93 489 31 23
jordi.petriz@vhir.org

Equipment
- 3 flow cytometers:
  - 2 Becton & Dickinson FACScalibur flow cytometer analyzers.
  - 1 Becton & Dickinson LSR Fortessa.
- 2 high-speed cell sorters:
  - Becton & Dickinson FacsAria.
  - Beckman Coulter MOFLO.

6. Microscopy Platform

Confocal Microscopy Service

Head of Service
Marta Valeri Sala
Tel. 93 489 41 83
marta.valeri@vhir.org

Operator
Rosa Mª Prieto Sánchez
Tel. 93 489 41 79
rosa.prieto@ vhir.org

Scientific Advisor
Rosanna Paciucci
Tel. 93 489 40 63
rosanna.paciucci@vhir.org

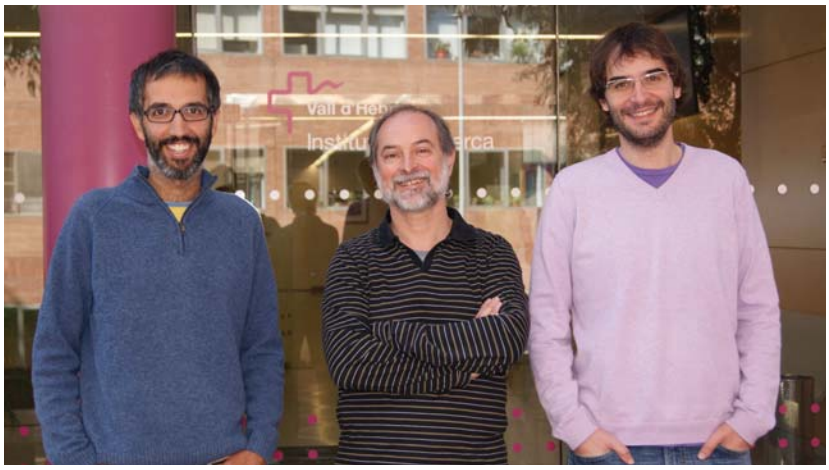
Equipment
- 1 Olympus spectral confocal microscopy FV1000.
- 1 Olympus multidimensional microscopy TIRFM high-speed CellR.
- 1 Olympus conventional fluorescence microscopy BX61.

Microdissection Service

Head of Service
Mª Ángeles Artaza Marino
Tel. 93 489 41 80
maria.angeles.artaza@ vhir.org

Scientific Advisor
Santiago Ramón y Cajal
Tel. 93 274 68 09
santiago.ramonycajal@vhir.org

Equipment
- 1 microdissection microscopy: Leica LMD 6000 with optical tweezers and adapted to microdissect living cells.
- 1 cryostat Leica CM3050 S.



Bioinformatics and Statistics Platform (UEB)

The Bioinformatics and Statistics Platform is part of the Scientific and Technical Support Unit whose main objectives are:

- To provide statistical and bioinformatics support to analyze high performance data (high throughput) generated during the biomedical research carried out at VHIR.
- To develop our own research lines in statistics and bioinformatics; with special emphasis on fields that may enhance the array of services provided by this unit.
- To establish a training program in statistics and bioinformatics for biomedical research.

Head of Service
Àlex Sánchez Pla
Tel. 93 489 40 07
alex.sanchez@vhir.org

Staff Team
Israel Ortega Serrano
Tel. 93 489 40 07
israel.ortega@vhir.org

Josep Lluís Mosquera Mayo
Tel. 93 489 40 07
jlmosquera@ir.vhebron.net

Services offered
- High-performance data analysis.
- Advice when applying for project funding or compiling research protocols.
- To develop and maintain bioinformatics applications.
- To carry out general or specific training activities.

Equipment
- 3 HP workstations with 2 processors and 8/16 Gb RAM.
- 1 server spreadsheet with 4 processors and 16 Gb RAM.
- Free software (R, PHP or mySQL).
- Propietary software (i.e. Partek Genomics Suite or Ingenuity System).

Vall d'Hebron University Hospital Biobank (VHUHBB)

The Vall d'Hebron University Hospital Biobank (VHUHBB) is a research support unit which collects biological samples of human origin for biomedical research projects in compliance with current legislation. Its main objective is to provide the scientific community with the high quality biological material required for research to ensure competitiveness and research excellence.

Scientific Director
Santiago Ramón y Cajal
Tel. 93 274 68 09
santiago.ramonycajal@vhir.org

Technical Director
Fátima Núñez Mangado
Tel. 93 489 41 89
fatima.nunez@vhir.org

Coordinator
Isabel Novoa García
Tel. 93 274 60 00 (ext. 4842)
isabel.novoa@vhir.org

Operator
Maribel Velasco García
Tel. 93 274 60 00 (ext. 4842)
maribel.velasco@vhir.org

Services

- Advice for the proper collection, processing, storage and use of human biological samples for biomedical research.
- Registration, processing and storage of the human biological samples in the biobank collections.

Animal Facility

The animal facility of the Vall d'Hebron Research Institute focuses on teaching related to the use of laboratory animals. Located in the Mediterrània Building, it occupies a single floor of 745 m^2.
The animal facility operates within current legislation. It is registered at the "Departament de Medi Ambient i Habitatge" with number B9900062.
The facility is divided into two areas: The Rodent Area with a standard clean area, a passive quarantine, a barrier area to accommodate immunodeficient mice, six manipulation rooms and the Molecular Imaging Platform; as well as the Big Animals Area with space enough to accommodate rabbits, pigs and sheep with fully equipped experimental operating rooms to carry out teaching and experimental surgical procedures.
The animal facility has an advisory committee composed of Institute research staff, whose role is to create, improve and modify animal testing procedures.

Head of Facility
Marta Rosal Fontana
Tel. 93 489 40 09
marta.rosal@ir.vhebron.net

Veterinarians
Marielle Esteves
Tel. 93 489 43 11
marielle.esteves@vhir.org

Àlex Rojo Amigo
Tel. 93 489 38 97
alex.rojo@vhir.org

Animal Laboratory Technicians (Felasa B)
Raquel García Ontivero
Tel. 93 489 43 10
raquel.garcia@vhir.org

Cristina León Català
Tel. 93 489 43 10
cristina.leon@vhir.org

Animal Caretakers (Felasa A)
Martha Irene Giraldo Sánchez
Tel. 93 489 43 10
martha.irene.giraldo@vhir.org

Sílvia Gil López
Tel. 93 489 43 10
silvia.gil@vhir.org

Daniel Martínez Falconero
Tel. 93 489 43 10
daniel.martinez@vhir.org

Secretary
Montserrat Molano i Flores
Tel. 93 489 38 97
montse.molano@vhir.org

Equipment

- Automatic control system and environmental parameters regulation: ventilation and pressure, temperature, relative humidity and lighting.
- Support structures, cages and accessories for animal maintenance.
- Ventilated racks with positive pressure.
- Biological safety cabinets.
- Bottle and rack cleaners to automatically clean and disinfect shelves, cages and other accessories.
- Autoclave.
- Micronebulizer to disinfect/sterilize all rooms.
- Water treatment: filtration apparatus and ultraviolet radiation.
- Experimental operating rooms:
  - E2 for pigs and sheep.
  - 1 for rabbits.
  - 7 manipulation rooms for rodents: 6 strictly conventional rooms and 1 SPF room.
- Experimental operating rooms equipment:
  - Inhalatory anesthesia equipment.
  - Mono or bipolar Electronic scalpel.
  - Laparoscopy and endoscopy towers.
  - Scopy arch.
  - 4 surgical microscopes.

Animal House Species
Mouse, rat, rabbit, pig, sheep.

Molecular Imaging Platform

The Molecular Imaging Platform (PIM) is an optical imaging system using bioluminescence and fluorescence and was established through the combined efforts of CIBER-BBN, CIBBIM-Nanomedicine and the VHIR as a service provided for research groups and pharmaceutical companies. Its mission consists of providing the capacity to develop non-invasive optical images in vivo at cellular, molecular and functional level, including fluorescence and bioluminescence. The main equipment consists of:

- Xenogen IVIS® Spectrum.
- Leica Macro Fluo: precision macroscope for fluorescence.
- Hammamatsu ORCA-2BT-512.

Head of Service
Yolanda Fernández Amurgo
Tel. 93 489 30 00 (ext. 3375)
yofernan@ir.vhebron.net

Technician
Anna Pujol Esclusa
Tel. 93 489 30 00 (ext. 4661)
apujol@ir.vhebron.net

Location
Mediterrània Building
Ground floor, Vall d'Hebron
Research Institute.
Vall d'Hebron University Hospital

UCICAC

The Central Unit of Clinical Research and Clinical Trials (UCICAC) was established by a professional multidisciplinary team and offers researchers a comprehensive program of services (start-to-finish) to assist them to develop clinical research projects and clinical trials. It guarantees that HUVH biomedical research remains a competitive and appealing proposition.
The UCICAC generates and promotes both projects and instruments to facilitate clinical research. Additionally, the UCICAC promotes training activities in clinical research and clinical trials. In the future, its functions will be offered from a single central location on the 13th floor of the Maternity Hospital, where the following units will be located:

- Research and Clinical Trial Unit (URAC) (link below).
- Methodological Support for the Biomedical Research Unit (USMIB) (link, USMIB new web site or information repetition below).

Head of Unit
Antonio Salgado Remigio
antonio.salgado@vhir.org

Scientific Director CAIBER
Rafael Simó Canonge
rafa.simo@vhir.org

Coordinator
Claudia Cases
claudia.cases@vhir.org

Project Manager
Mònica Anglada Bàguena
monica.anglada@vhir.org

Secretary
Ester Carceller Delgado
ester.carceller@vhir.org

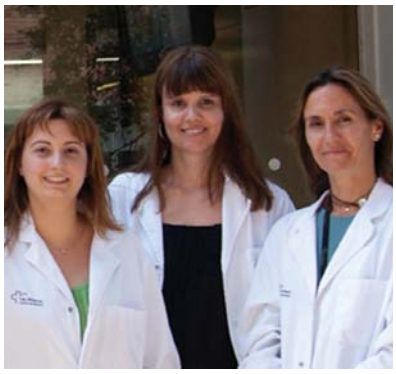
1. URAC

Coordinator
Immaculada Fuentes Camps
inma.fuentes@vhir.org

Nursing
Patricia Fernández Vandellòs
patricia.fvandellos@vhir.org

Instructor
Silvia Garcia Matas
silvia.garcia.matas@vhir.org

The Research and Clinical Trial Unit (URAC) supports clinical trials and post-authorization studies involving medicines, medical devices and therapeutic interventions. It supports both projects launched by in-house researchers as well as those originating in other public agencies. It focuses on the ethical, methodological and logistical aspects of research. Additionally, the Research and Clinical Trials Unit aims to promote continuing training in clinical research and clinical trials.



2. USMIB

Coordinators
Antonio Salgado Remigio
antonio.salgado@vhir.org

Claudia Cases
claudia.cases@vhir.org

Methodologists
Xavier Vidal Guitart
xavier.vidal@vhir.org

Santiago Pérez Hoyos
santi.perezhoyos@vhir.org

Lluis Armadans Gil
larmadans@vhebron.net

Eva López Guerrero
eva.lopez.guerrero@vhir.org

The Biomedical Research Methodological Support Unit (USMIB) was developed by the Vall d'Hebron Research Institute (VHIR) with the institutional support of the Vall d'Hebron University Hospital (HUVH) management and the collaboration of the "Servei de Farmacologia Clínica" - Clinical Pharmacology Service and the "Servei de Medicina Preventiva i Epidemiologia" - Preventive Medicine Service. The USMIB offers scientific methodology services to promote and facilitate biomedical research at the Vall d'Hebron University Hospital, to both primary healthcare providers and independent health service operators requiring advanced research services. One of its tasks is to establish a training program in methodology for biomedical research.

Laboratory Coordination Service

Head of Service
Núria Prim Vilaró
Tel. 93 489 43 23
nuria.prim@vhir.org

Laboratory Technicians
Fátima Jiménez Mamolar
Tel. 93 274 67 99
fatima.jimenez@vhir.org

Eulàlia Joseph Munné
Tel. 93 489 30 00 (ext. 4904)
eulalia.joseph@vhir.org

Secretaries
Anna Pedrol Clará
Tel. 93 274 67 99
anna.pedrol@vhir.org

Rosa Guillén Vidal
Tel. 93 489 49 05
rosa.guillen@vhir.org

Maintenance Staff
María Pilar Alonso Alonso
Tel. 93 489 30 00 (ext. 4902)

Flora Díaz Ramos
Tel. 93 489 40 39

Tao González Zaragoza
Tel. 93 489 30 00 (ext. 4902)

Esther Mateos Mullor
Tel. 93 489 30 00 (ext. 4970)

Raimundo Molina Martínez
Tel. 93 489 30 00 (ext. 4902)

Xavier Pardos Benito
Tel. 93 489 40 39

Joaquim Solà Santesmases
Tel. 93 489 40 39

Pablo Vilalta Gras
Tel. 93 489 40 39

Margarita Ruiz Olivart
Tel. 93 489 40 39

Laboratory Cleaners
Flor Menéndez Parraga
Tel. 93 489 30 00 (ext. 4672)

Patricia Hinojosa Casanova
Tel. 93 489 30 00 (ext. 4669)

Rosario Molano Flores
Tel. 93 489 30 00 (ext. 4948)

The main objectives of the Laboratory Coordination Service are:

– To coordinate the operational aspects of all laboratories at the "Institut de Recerca"

– To manage resources such as nursing personnel, nursing technicians and auxiliary staff supporting biomedical investigation services.

These objectives are achieved by acting as a link between the various laboratories and General Management whilst providing know-how, managing vacancies and facilitating the implementation and monitoring of regulations concerning both hospital and Research Institute areas.

Members
María Antolín Mate
Pharmacist
Researcher at "Unitat de Fisiologia i Fisiopatologia Digestiva"

María Teresa Martín Gómez
Microbiologist doctor
Researcher at the "Malalties Infeccioses" group

José Luis Peiró Ibáñez
Doctor
Pediatric surgery expert

Diego Arango del Corro
Biologist
Researcher at the CIBBIM group

Ramón Gimeno Martínez
Doctor
Researcher at the "Teràpia Cel·lular i Gènica" group

ETHICS COMMITTEES

Animal Experimentation Ethics Committee (CEEA)

The Animal Experimentation Ethics Committee (CEEA) was created on the 8th January 1998 to ensure the care and welfare of animals used in experimentation. Its functions include the following: producing reports on experimental procedures, eliminating unnecessary pain and providing humanitarian euthanasia, assessing the professional profiles of personnel involved in procedures, and assessing the suitability of the procedures used.

President
Carmen Espejo Ruiz
Biologist
"Neuroimmunologia Clínica" group researcher

Secretary
Marta Rosal Fontana
Veterinarian
Animal facility manager. Animal welfare adviser

Clinical Research Ethics Committee (CREC)

The CREC collaborates with and provides support to the VHIR. The CREC is an independent body comprising health and non health professionals. It is responsible for ensuring that the rights, safety and welfare of subjects taking part in clinical trials are protected. It guarantees adequate trial protocols, researcher suitability, the suitability of facilities, as well as ensuring that adequate procedure and documentation is in place to obtain informed consent.

President
Soledad Gallego Melcón
Doctor

Vice President
Joan Bagó Granell
Doctor

Secretary
Mireia Navarro Sebastián
Chemist

Members
Lluís Armadans Gil
Doctor

Fernando Azpiroz Vidaur
Doctor

Arantxa Catalán Ramos
Primary health care pharmacist

Esther Cucurull Folgera
Pharmacologist-doctor

Inés M. de Torres Ramírez
Doctor

Ignacio Ferreira González
Doctor

Carmen Fuentelsaz Gallego
Qualified nurse

Inmaculada Fuentes Camps
Qualified nurse

Jaume Guardia Massó
Doctor

Juan Carlos Hortal Ibarra
University law professor

Francisco de la Torre Arteche
Doctor

Joan-Ramon Laporte Roselló
Pharmacologist-doctor

Isabel Miró Muixi
Doctor

J. Bruno Montoro Ronsano
Hospital pharmacist

Alexis Rodríguez Gallego
Pharmacologist-doctor

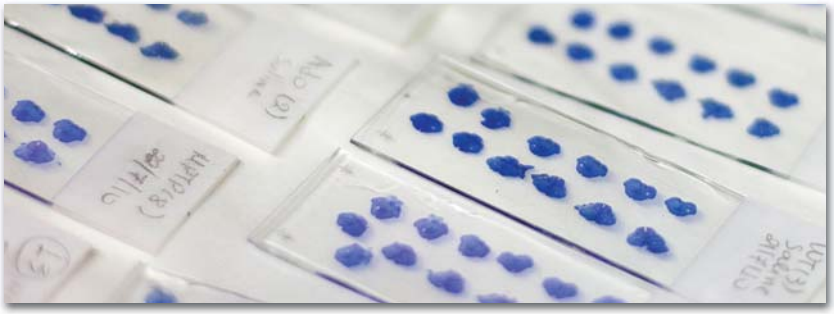
Joan Segarra Sarries
Lawyer

Marta Solé Orsola
Qualified nurse

Pilar Suñé Martín
Hospital pharmacist

Summary of Research Activity

The VHIR's research activities, outlined in this 2010 Annual Report can be summarized as follows.



RESEARCHERS AND TECHNICIANS

Table 1
VHIR researchers and technicians

57 Research Groups		
Research staff (65%)		
Researchers		**489**
Doctors	393	
Biologists	27	
Biochemists	15	
Pharmacists	5	
Psychologists	13	
Chemists	4	
Veterinarians	3	
Others	29	
Postdocs		**77**
Predocs		**213**
Supporting research staff (35%)		
Supporting research staff		**417**
Graduates	143	
Nurses. ATS. DUI	34	
Laboratory technicians	89	
Administrative staff	79	
Others	72	
Total		**1,196**

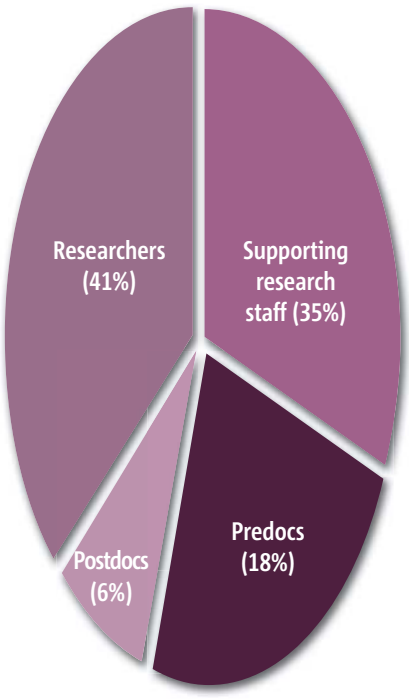


Figure 1
VHIR researchers and technicians

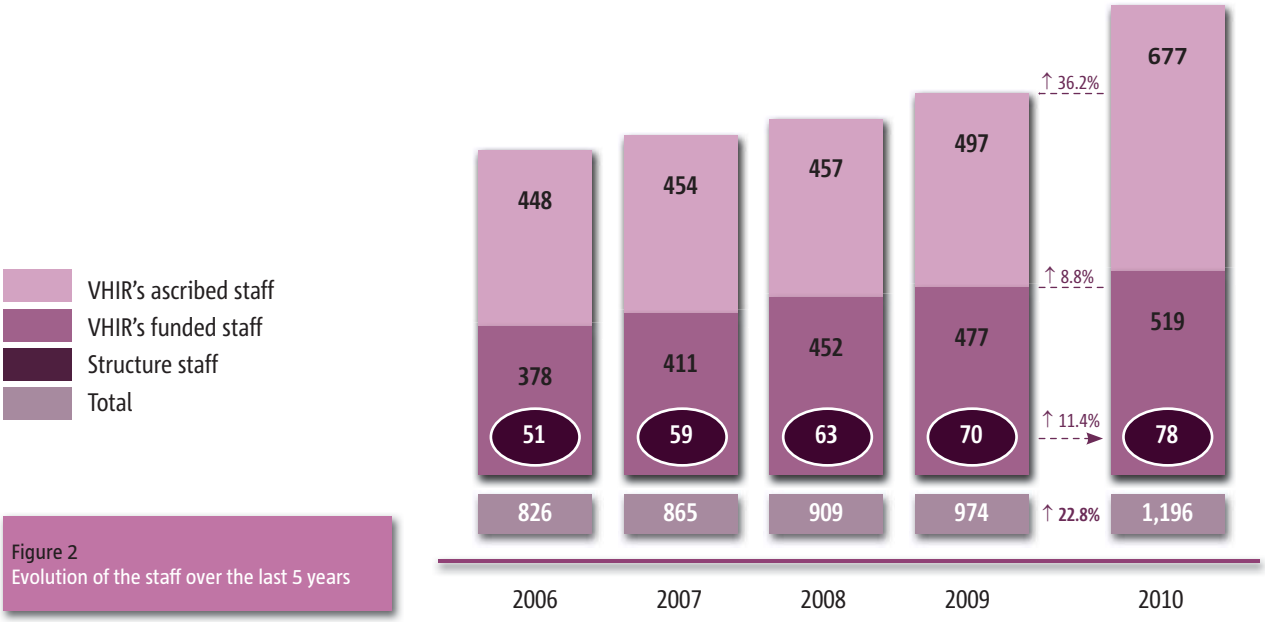


Figure 2
Evolution of the staff over the last 5 years

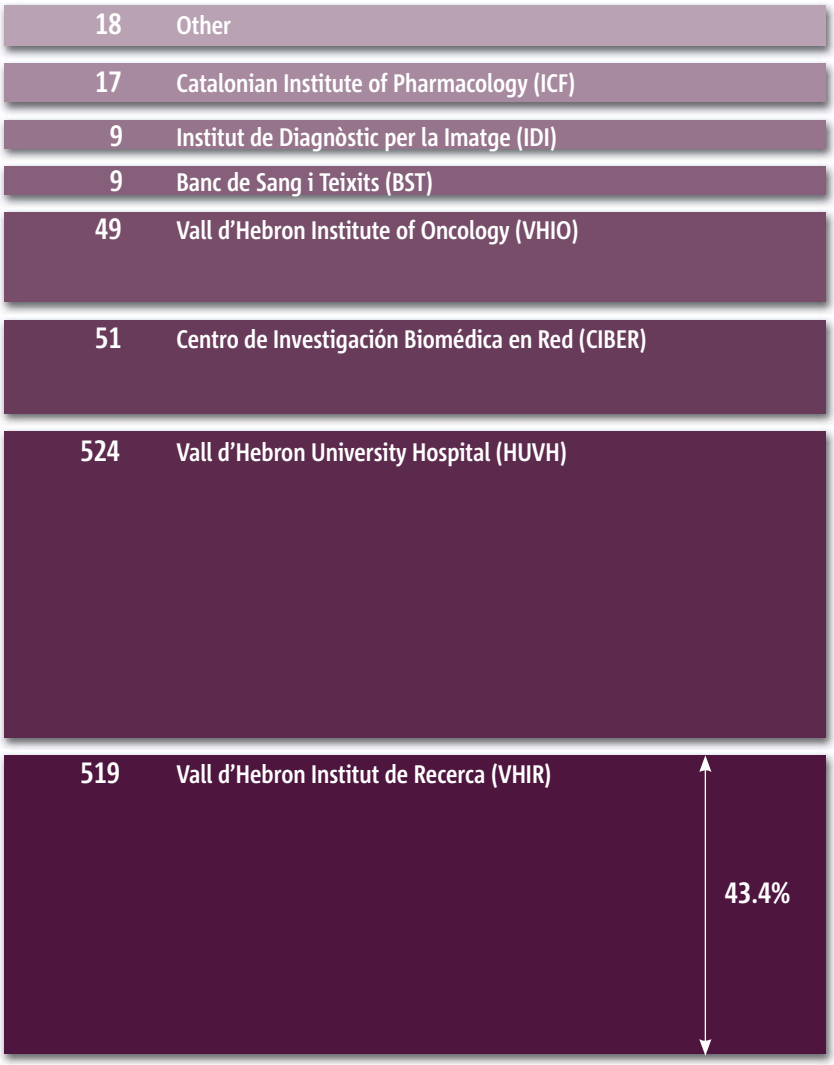


Figure 3
Contracting entities.
Staff funded by the VHIR: 519 (43.4%)

VHIR'S ECONOMIC SUMMARY

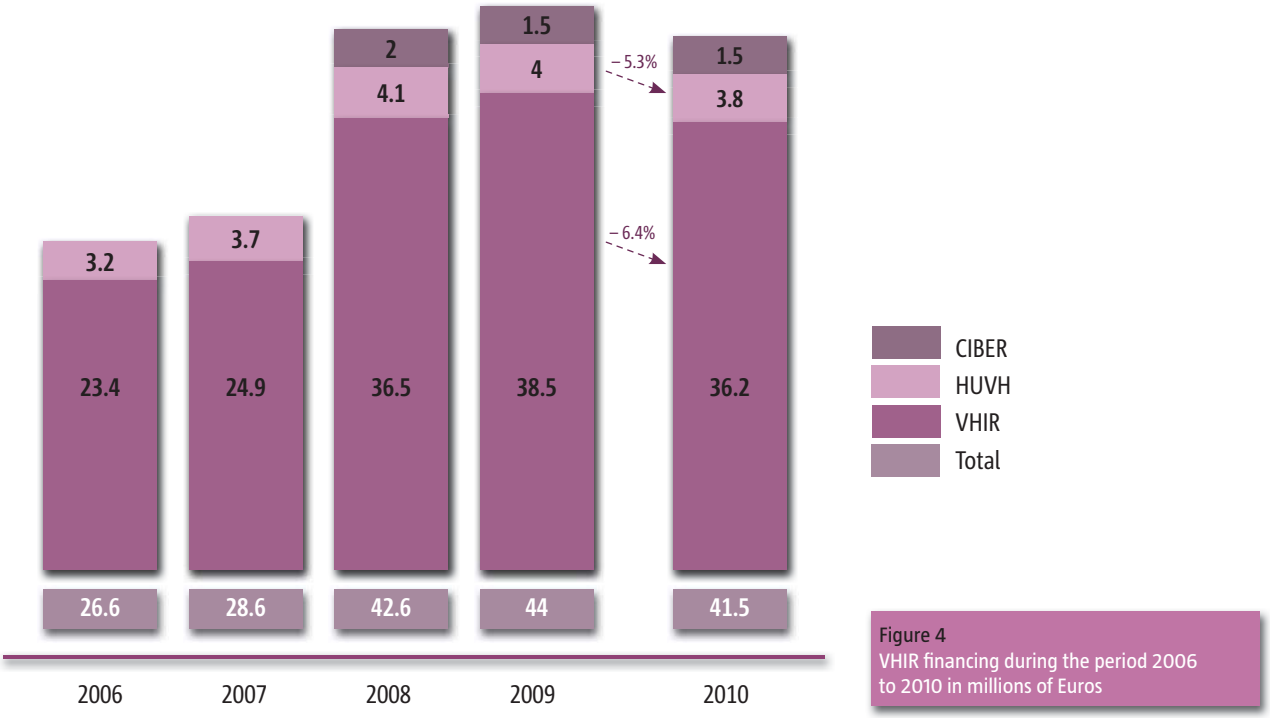


Figure 4
VHIR financing during the period 2006 to 2010 in millions of Euros

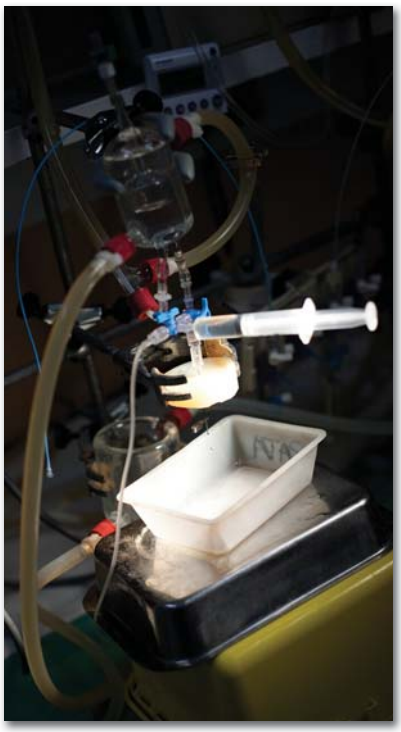


Table 2
2010 VHIR's income breakdown

2010 Income Breakdown	Million of Euros
Projects funded by agencies	13.4
Agreements with industry	6.6
Donations	3.9
Clinical Trials	6.7
Teaching	1.6
Other	4
Total	**36.2**
HUVH contributions (Staff, Goods and Direct Services and other €)	3.8

PRESENCE IN PUBLICATIONS IN NATIONAL AND INTERNATIONAL *JOURNAL CITATION REPORTS* (JCR)

In 2010, 595 papers by VHIR's researchers were published in scientific journals, achieving a combined impact factor of **3,149.576,** with an average impact factor per review of **5.293.**

2010 *Journal Citation Reports (JCR)* was used to calculate the impact factor for 2010. Original papers, reviews and editorials were included, while conference correspondence was excluded.

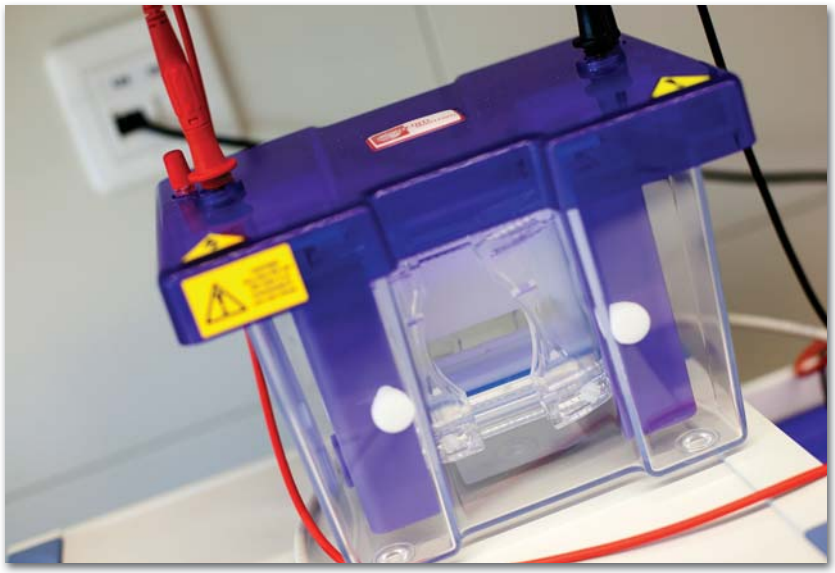


Table 3
VHIR's 2010 international and national publications

	Number	Impact Factor
Papers in international journals	440	2,583.252
Papers in national journals	69	98.314
Reviews in international journals	41	201.615
Reviews in national journals	8	9.205
Editorials in international journals	29	245.902
Editorials in national journals	8	11.288
Total	**595**	**3,149.576**

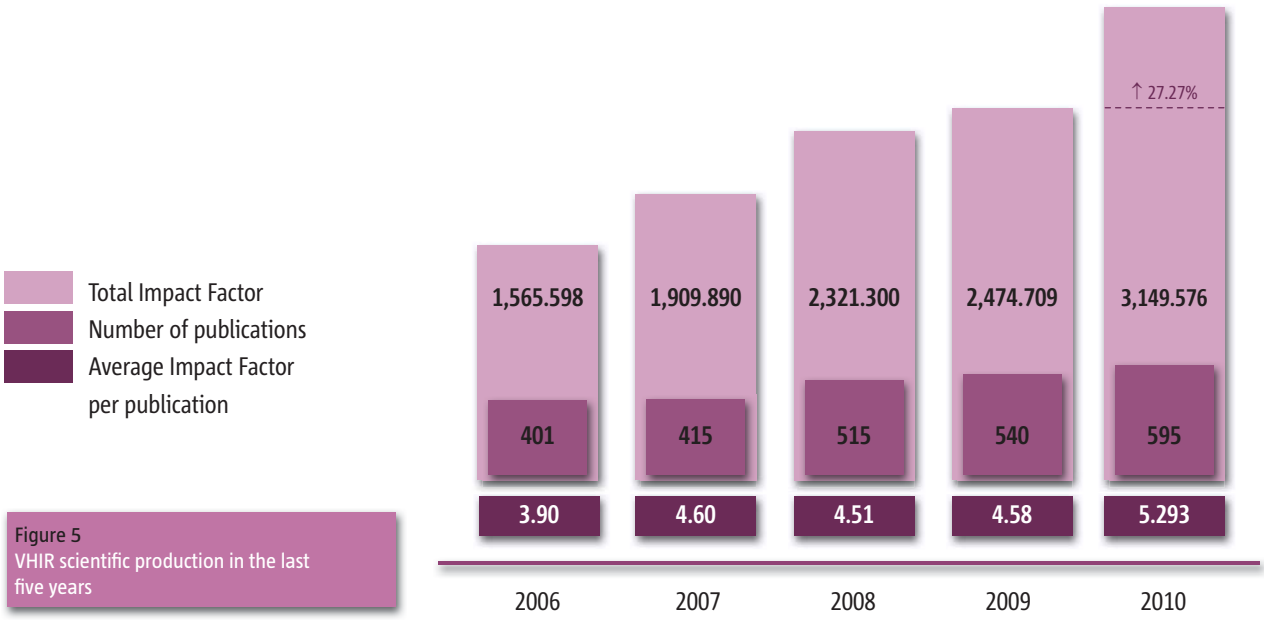


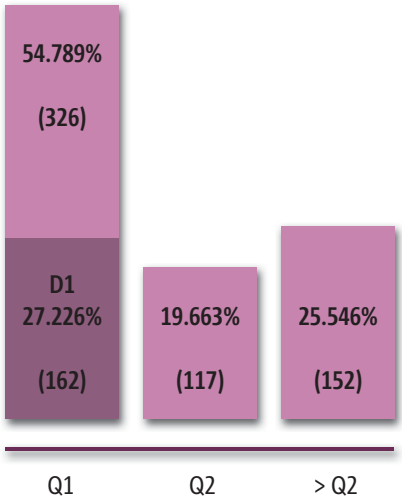
Figure 5
VHIR scientific production in the last five years

It is also significant that 54.789% of publications in scientific journals by VHIR's researchers appear in the first quartile of publication data sets. If we consider the category and impact factor they belong to, 27.226% of these publications belong in the first decile of these data sets.

Table 4
Publications per quartiles

Quartile	Number	%
Q1	326	54.789%
First decile D1	*162*	*27.226%*
Q2	117	19.663%
> Q2	152	25.546%
Total	**595**	**100.00%**

Figure 7
Distribution of publications per quartiles and first deciles according to category and Impact Factor



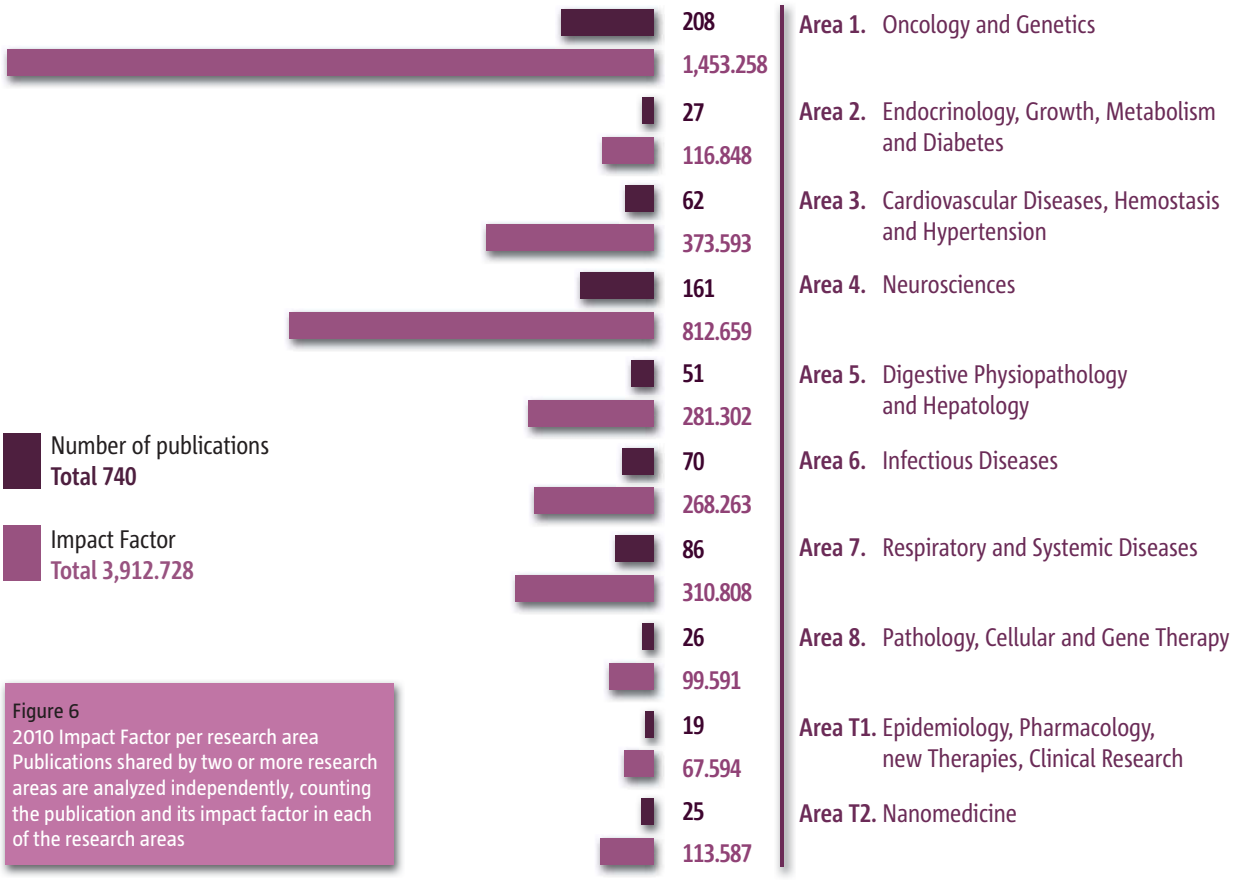


Figure 6
2010 Impact Factor per research area
Publications shared by two or more research areas are analyzed independently, counting the publication and its impact factor in each of the research areas

Table 5
2010 Impact Factor per research area/group

Research Groups	Total Impact Factor	Total Publications	Average Impact Factor
Area 1. Oncology and Genetics	**1,453.258**	**208**	**6.987**
Unit in Biomedicine and Translational and Pediatric Oncology	121.380	28	4.335
Molecular Pathology	216.587	41	5.283
VHIO-Growth Factors	43.500	7	6.214
VHIO-Proteomics	19.941	4	4.985
VHIO-Gene Expression and Cancer	48.851	2	24.426
Animal Models	11.809	3	3.936
VHIO-Experimental Therapeutics	554.055	68	8.148
VHIO-Stem Cells and Cancer	7.135	1	7.135
VHIO-Gastrointestinal Tumors	228.090	28	8.146
VHIO-Radiation Oncology	70.214	13	5.401
VHIO-Tumors Biomarkers	3.570	1	3.570
Experimental Hematology	109.306	10	10.931
Oncology and Molecular Pathology	18.820	2	9.410
Area 2. Endocrinology, Growth, Metabolism and Diabetes	**116.848**	**27**	**4.328**
Diabetes and Metabolism	63.491	16	3.968
Paediatric Endocrinology	14.354	4	3.589
Nephrology	39.003	7	5.572
Area 3. Cardiovascular Diseases, Hemostasis and Hypertension	**373.593**	**62**	**6.026**
Cardiovascular Diseases	364.079	59	6.171
Reparative and Therapy of the Heart	9.514	3	3.171
Area 4. Neurosciences	**812.659**	**161**	**5.057**
Clinical Neuroimmunology	194.695	40	4.867
Pediatric Neurology	24.345	7	3.478
Psychiatry and Mental Health	106.222	25	4.249
Neurovascular Diseases	192.676	34	5.667
Neurotraumatology and Neurosurgery (UNINN)	34.519	9	3,835
Magnetic Resonance and Neuroradiology	82.348	15	5.490
Alzheimer	51.246	9	5.694
Neurodegenerative Diseases	78.772	7	11.253
Neuromuscular and Mitochondrial Pathology	23.480	6	3.913
Cell Signaling and Apoptosis	7.178	1	7.178
Headache and Neurological Pain	3.702	3	1.234
Peripheral Nervous System	13.476	5	2.695

Table 5
2010 Impact Factor per research area/group *(Cont.)*

Research Groups	Total Impact Factor	Total Publications	Average Impact Factor
Area 5. Digestive Physiopathology and Hepatology	**281.302**	**51**	**5.516**
Digestive Transplants	18.298	4	4.575
Liver Diseases	155.762	26	5.991
Physiology and Pathophysiology of the Digestive Tract	107.242	21	5.107
Area 6. Infectious Diseases	**268.263**	**70**	**3.832**
Infectious Diseases	93.304	26	3.589
Microbiology	57.332	17	3.372
Clinical Research and Innovation in Pneumonia & Sepsis	117.627	27	4.357
Area 7. Respiratory and Systemic Diseases	**310.808**	**86**	**3.614**
Systemic Diseases	158.067	39	4.053
Pneumology	122.241	40	3.056
Immunology	28.146	5	5.629
Chronic Fatigue	2.354	2	1.177
Area 8. Pathology, Cellular and Gene Therapy	**99.591**	**26**	**3.830**
Neuro-spinal Pathology Study	7.483	2	3.742
Ophthalmology	24.126	6	4.021
Maternal Fetal Medicine	22.134	9	2.459
Genetics	45.848	9	5.094
Bioengineering, Orthopedics and Surgery in Pediatrics	10.275	4	2.569
Area T1. Epidemiology, Pharmacology, New Therapies, Clinical Research	**67.594**	**19**	**3.558**
Epidemiology and Public Health (EPIDEM)	42.287	10	4.229
Clinical Pharmacology	20.562	8	2.570
Cell and Gene Therapy	4.745	1	4.745
Area T2. Nanomedicine	**113.587**	**25**	**4.543**
CIBBIM-Nanomedicine. Drug Delivery and Targeting	49.014	8	6.127
CIBBIM-Nanomedicine. Molecular Oncology	18.452	3	6.151
CIBBIM-Nanomedicine. Immunobiology	5.328	1	5.328
CIBBIM-Nanomedicine. Lysosomal Storage Diseases and Cell Pathophysiology.	19.774	5	3.955
CIBBIM-Nanomedicine. Renal Pathophysiology	4.351	1	4.351
CIBBIM-Nanomedicine. Basic Research in Aging	16.668	7	2.381
Other Research Units	**53.946**	**18**	**2.997**

Table 6
Number of papers published in relevant scientific journals during 2010

Journal	Published papers	IF
Nejm - New England Journal of Medicine	2	47.050
Nature	2	34.480
Cell	1	31.152
Lancet	5	30.758
JAMA - Journal of the American Medical	2	28.899
Cancer Cell	3	25.288
Cell Stem Cell	1	23.563
Lancet Neurology	1	18.126
Journal of Clinical Oncology	17	17.793
Annals of Internal Medicine	1	16.225
Journal of Clinical Investigation	1	15.387
Molecular Psychiatry	2	15.049
Circulation	7	14.816
Lancet Oncology	2	14.470
Nature Neuroscience	1	14.345
British Medical Journal	1	13.660
Plos Medicine	1	13.050
Gastroenterology	2	12.899
Journal of the American College of Cardiology	1	12.535
Biochimica et Biophysica Acta-Reviews on Cancer	1	11.685
Genome Research	1	11.342
Hepatology	2	10.840
American Journal of Respiratory and Critical Care Medicine	2	10.689
Blood	2	10.555

Table 7
Publications in international journals

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
International journals (*n* = 290)						
Acta Neurochirurgica	1.472	1.472	1	1.472		Q3
Acta Paediatrica	1.768	1.768	1	1.768		Q2
Advances in Clinical Chemistry	3.406	3.406	1	3.406		Q1
AIDS	4.909	19.636	4	4.909	1	Q1
AIDS Patient Care and STDs	2.683	2.683	1	2.683		Q2
AIDS Research and Human Retroviruses	2.178	2.178	1	2.178		Q3
Alimentary Pharmacology & Therapeutics	4.357	4.357	1	4.357		Q1
American Heart Journal	4.357	8.714	2	4.357		Q1
American Journal of Cardiology	3.575	3.575	1	3.575		Q1
American Journal of Gastroenterology	6.012	6.012	1	6.012		Q1
American Journal of Industrial Medicine	1.721	1.721	1	1.721		Q2
American Journal of Medical Genetics Part A	2.404	4.808	2	2.404		Q3
American Journal of Medical Genetics Part B	3.481	10.443	3	3.481		Q2
American Journal of Medicine	4.466	4.466	1	4.466		Q1
American Journal of Neuroradiology	3.296	3.296	1	3.296		Q1
American Journal of Pathology	5.673	11.346	2	5.673	1	Q1
American Journal of Physiology-Cell	4.013	4.013	1	4.013		Q1
American Journal of Respiratory and Critical Care Medicine	10.689	21.378	2	10.689	1	Q1
American Journal of Surgical Pathology	4.062	4.062	1	4.062	1	Q1
American Journal of Transplantation	6.433	19.299	3	6.433	1	Q1
Anesthesiology	5.354	5.354	1	5.354	1	Q1
Angiology	1.097	1.097	1	1.097		Q4
Annals of Allergy Asthma & Immunology	2.457	2.457	1	2.457		Q2
Annals of Internal Medicine	16.225	16.225	1	16.225	1	Q1
Annals of Neurology	9.317	27.951	3	9.317	1	Q1
Annals of Oncology	5.647	135.528	24	5.647		Q1
Annals of Surgical Oncology	4.130	4.130	1	4.130	1	Q1
Annals of the New York Academy of Sciences	2.670	2.670	1	2.670		Q1
Annals of the Rheumatic Diseases	8.111	16.222	2	8.111		Q1
Annual Review of Medicine	9.940	9.940	1	9.940	1	Q1
Antimicrobial Agents and Chemotherapy	4.802	4.802	1	4.802		Q1
Applied and Environmental Microbiology	3.686	7.372	2	3.686		Q1
Archives of Gynecology and Obstetrics	0.912	0.912	1	0.912		Q4
Archives of Internal Medicine	9.813	9.813	1	9.813	1	Q1
Arteriosclerosis, Thrombosis and Vascular Biology	7.235	7.235	1	7.235	1	Q1
Arthritis and Rheumatism	7.332	7.332	1	7.332		Q1

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
Asian Pacific Journal of Allergy and Immunology	0.562	0.562	1	0.562		Q4
Atherosclerosis	4.522	18.088	4	4.522		Q1
Autoimmunity Reviews	6.368	12.736	2	6.368		Q1
Autophagy	6.829	6.829	1	6.829		Q1
Biochimica et Biophysica Acta-Reviews on Cancer	11.685	11.685	1	11.685	1	Q1
Biology of Blood and Marrow Transplantation	3.149	3.149	1	3.149		Q2
Bioorganic & Medicinal Chemistry	2.822	2.822	1	2.822		Q2
BJU International	2.865	5.730	2	2.865		Q2
Blood	10.555	21.110	2	10.555	1	Q1
BMC Bioinformatics	3.428	3.428	1	3.428		Q1
BMC Cancer	2.736	5.472	2	2.736		Q2
BMC Infectious Diseases	2.550	2.550	1	2.550		Q2
BMC Neurology	2.109	6.327	3	2.109		Q3
BMC Psychiatry	1.832	1.832	1	1.832		Q3
BMC Public Health	2.223	2.223	1	2.223		Q2
Bone Marrow Transplantation	2.998	2.998	1	2.998		Q2
Brain	9.490	9.490	1	9.490	1	Q1
Brain, Behavior and Immunity	5.061	5.061	1	5.061		Q1
Breast Cancer Research and Treatment	4.696	23.480	5	4.696		Q1
British Journal of Clinical Pharmacology	3.246	3.246	1	3.246		Q2
British Journal of Haematology	4.597	4.597	1	4.597		Q1
British Journal of Nutrition	3.446	3.446	1	3.446		Q1
British Journal of Ophthalmology	2.917	2.917	1	2.917		Q1
British Medical Journal	13.660	13.660	1	13.660	1	Q1
Burns	1.950	1.950	1	1.950		Q2
Canadian Medical Association Journal	7.271	7.271	1	7.271	1	Q1
Cancer Cell	25.288	75.864	3	25.288	1	Q1
Cancer Journal	3.471	3.471	1	3.471		Q2
Cancer Research	7.543	37.715	5	7.543	1	Q1
Cancer Treatment Reviews	5.295	5.295	1	5.295		Q1
Cardiology in the Young	1.183	1.183	1	1.183		Q3
Cardiovascular and Interventional Radiology	1.949	1.949	1	1.949		Q2
Cardiovascular Research	5.801	23.204	4	5.801	1	Q1
Cell	31.152	31.152	1	31.152	1	Q1
Cell Stem Cell	23.563	23.563	1	23.563	1	Q1
Cellular Physiology and Biochemistry	3.563	3.563	1	3.563		Q2
Cerebrovascular Diseases	3.535	3.535	1	3.535		Q1
Circulation	14.816	103.712	7	14.816	1	Q1

Table 7
Publications in international journals *(Cont.)*

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
Circulation-Heart Failure	3.433	3.433	1	3.433		Q2
Clinica Chimica Acta	2.535	2.535	1	2.535		Q1
Clinical & Translational Oncology	1.146	3.438	3	1.146		Q4
Clinical and Experimental Immunology	3.009	3.009	1	3.009		Q2
Clinical and Experimental Rheumatology	2.396	4.792	2	2.396		Q3
Clinical Breast Cancer	2.065	4.130	2	2.065		Q3
Clinical Cancer Research	6.747	26.988	4	6.747		Q1
Clinical Cardiology	1.602	1.602	1	1.602		Q3
Clinical Infectious Diseases	8.195	8.195	1	8.195	1	Q1
Clinical Microbiology and Infection	4.014	24.084	6	4.014		Q1
Clinical Neurology and Neurosurgery	1.303	1.303	1	1.303		Q3
Clinical Nuclear Medicine	3.915	3.915	1	3.915		Q1
Cochrane Database of Systematic Reviews	5.653	5.653	1	5.653	1	Q1
Comprehensive Psychiatry	2.082	2.082	1	2.082		Q3
Contemporary Clinical Trials	1.506	1.506	1	1.506		Q3
Critical Care	4.931	4.931	1	4.931		Q1
Critical Care Medicine	6.373	19.119	3	6.373	1	Q1
Current Hypertension Reports	2.377	2.377	1	2.377		Q2
Current Opinion in Investigational Drugs	3.549	3.549	1	3.549		Q1
Current Opinion in Rheumatology	4.600	4.600	1	4.600		Q2
Current Pharmaceutical Design	4.414	4.414	1	4.414		Q1
Cytotherapy	2.204	2.204	1	2.204		Q2
Chest	6.360	19.080	3	6.360	1	Q1
Chirurg	0.601	0.601	1	0.601		Q4
Dermatology	2.741	2.741	1	2.741		Q2
Diabetes-Metabolism Research and Reviews	2.762	5.524	2	2.762		Q2
Diabetologia	6.551	6.551	1	6.551	1	Q1
Diagnostic Microbiology and Infectious Disease	2.451	2.451	1	2.451		Q3
Digestive Surgery	1.372	1.372	1	1.372		Q2
Drug and Alcohol Dependence	3.599	3.599	1	3.599		Q2
Drugs & Aging	2.209	2.209	1	2.209		Q2
EJSO	2.564	2.564	1	2.564		Q1
Europace	1.871	1.871	1	1.871		Q3
European Heart Journal	9.800	19.600	2	9.800	1	Q1
European Journal of Applied Physiology	2.047	2.047	1	2.047		Q1
European Journal of Clinical Pharmacology	2.743	5.486	2	2.743		Q2
European Journal of Echocardiography	1.476	2.952	2	1.476		Q3
European Journal of Gastroenterology & Hepatology	1.662	1.662	1	1.662		Q3
European Journal of Gynaecological Oncology	0.614	0.614	1	0.614		Q4

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
European Journal of Human Genetics	3.564	3.564	1	3.564		Q2
European Journal of Neurology	2.510	5.020	2	2.510		Q2
European Journal of Nuclear Medicine and Molecular Imaging	4.531	4.531	1	4.531	1	Q1
European Journal of Obstetrics Gynecology and Reproductive Biology	1.582	3.164	2	1.582		Q3
European Journal of Radiology	2.645	2.645	1	2.645		Q2
European Respiratory Journal	5.527	22.108	4	5.527	1	Q1
European Spine Journal	1.956	1.956	1	1.956		Q2
European Urology	7.667	7.667	1	7.667	1	Q1
Experimental Diabetes Research	2.574	2.574	1	2.574		Q2
Expert Opinion on Pharmacotherapy	2.018	2.018	1	2.018		Q3
Expert Review of Anticancer Therapy	2.493	4.986	2	2.493		Q3
Expert Review of Proteomics	3.570	3.570	1	3.570		Q1
Eye	1.974	1.974	1	1.974		Q2
Familial Cancer	2.189	4.378	2	2.189		Q3
Fertility and Sterility	3.970	7.940	2	3.970	1	Q1
Free Radical Biology and Medicine	6.081	6.081	1	6.081		Q1
Future Microbiology	2.875	2.875	1	2.875		Q2
Gastroenterology	12.899	25.798	2	12.899	1	Q1
Gene Therapy	4.745	4.745	1	4.745		Q1
Genes and Immunity	4.222	8.444	2	4.222		Q1
Genes Brain and Behavior	3.795	3.795	1	3.795		Q1
Genome Research	11.342	11.342	1	11.342	1	Q1
Gerontology	1.661	1.661	1	1.661		Q3
Gut	9.357	18.714	2	9.357	1	Q1
Haematologica-the Hematology Journal	6.416	25.664	4	6.416		Q1
Health and Quality of Life Outcomes	2.456	4.912	2	2.456		Q1
Heart	5.385	10.770	2	5.385		Q1
Hepatology	10.840	21.680	2	10.840	1	Q1
Histopathology	3.855	3.855	1	3.855		Q1
HIV Medicine	2.878	2.878	1	2.878		Q2
Human Brain Mapping	6.256	6.256	1	6.256	1	Q1
Human Genetics	4.523	9.046	2	4.523		Q1
Human Molecular Genetics	7.386	7.386	1	7.386		Q1
Human Reproduction	3.859	15.436	4	3.859		Q1
IEEE Transactions on Medical Imaging	3.540	3.540	1	3.540	1	Q1
Infection	2.051	2.051	1	2.051		Q3
Inflammatory Bowel Diseases	4.643	4.643	1	4.643		Q1
Intensive Care Medicine	5.168	10.336	2	5.168		Q1
International Journal of Antimicrobial Agents	3.032	6.064	2	3.032		Q2

Table 7
Publications in international journals *(Cont.)*

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
International Journal of Cancer	4.722	4.722	1	4.722		Q1
International Journal of Colorectal Disease	2.102	2.102	1	2.102		Q2
International Journal of Geriatric Psychiatry	1.981	1.981	1	1.981		Q2
International Journal of Gynecological Pathology	2.179	4.358	2	2.179		Q2
International Journal of Neuroscience	0.855	0.855	1	0.855		Q4
International Journal of Radiation Oncology	4.592	4.592	1	4.592	1	Q1
International Reviews of Immunology	2.641	2.641	1	2.641		Q3
Investigative Ophthalmology & Visual Science	3.431	3.431	1	3.431		Q1
JAMA-Journal of the American Medical	28.899	57.798	2	28.899	1	Q1
Journal of Affective Disorders	3.763	3.763	1	3.763		Q1
Journal of Alzheimer's Disease	3.832	15.328	4	3.832		Q2
Journal of Allergy and Clinical Immunology	9.165	18.330	2	9.165	1	Q1
Journal of Antimicrobial Chemotherapy	4.352	21.760	5	4.352		Q1
Journal of Biological Chemistry	5.328	21.312	4	5.328		Q1
Journal of Biomedical Materials Research Part A	2.816	2.816	1	2.816		Q1
Journal of Biomedicine and Biotechnology	1.750	1.750	1	1.750		Q3
Journal of Cardiothoracic Surgery	0.737	0.737	1	0.737		Q4
Journal of Cellular Biochemistry	2.935	2.935	1	2.935		Q2
Journal of Clinical Endocrinology & Metabolism	6.202	12.404	2	6.202		Q1
Journal of Clinical Investigation	15.387	15.387	1	15.387	1	Q1
Journal of Clinical Microbiology	4.162	8.324	2	4.162		Q1
Journal of Clinical Oncology	17.793	302.481	17	17.793	1	Q1
Journal of Crohns & Colitis	1.729	3.458	2	1.729		Q3
Journal of Heart and Lung Transplantation	3.541	3.541	1	3.541		Q1
Journal of Hepatology	7.818	23.454	3	7.818	1	Q1
Journal of Hypertension	4.988	4.988	1	4.988		Q1
Journal of Immunological Methods	2.347	2.347	1	2.347		Q3
Journal of Immunology	5.646	5.646	1	5.646		Q1
Journal of Infectious Diseases	5.865	5.865	1	5.865	1	Q1
Journal of Interferon and Cytokine Research	1.627	1.627	1	1.627		Q3
Journal of Lipid Research	4.917	4.917	1	4.917		Q1
Journal of Medical Genetics	5.751	11.502	2	5.751		Q1
Journal of Minimally Invasive Gynecology	1.920	1.920	1	1.920		Q2
Journal of Molecular and Cellular Cardiology	4.965	4.965	1	4.965		Q1
Journal of Molecular Diagnostics	3.413	3.413	1	3.413		Q1
Journal of Neural Transmission	2.259	2.259	1	2.259		Q2
Journal of Neurochemistry	3.999	3.999	1	3.999		Q2

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
Journal of Neuroimmunology	2.841	8.523	3	2.841		Q2
Journal of Neurology	2.903	8.709	3	2.903		Q2
Journal of Neuropathology and Experimental Neurology	4.564	4.564	1	4.564		Q1
Journal of Neuroscience	7.178	14.356	2	7.178	1	Q1
Journal of Neurosurgery	2.594	5.188	2	2.594		Q2
Journal of Nuclear Cardiology	2.777	2.777	1	2.777		Q2
Journal of Nutrition Health & Aging	1.712	1.712	1	1.712		Q3
Journal of Pediatric Endocrinology & Metabolism	0.738	0.738	1	0.738		Q4
Journal of Pediatric Orthopaedics	1.226	1.226	1	1.226		Q3
Journal of Pediatric Surgery	1.430	1.430	1	1.430		Q2
Journal of Physiology-London	4.764	9.528	2	4.764	1	Q1
Journal of Proteome Research	5.132	5.132	1	5.132		Q1
Journal of Psychiatric Research	3.723	3.723	1	3.723		Q1
Journal of Rheumatology	3.854	3.854	1	3.854		Q2
Journal of Sleep Research	3.500	3.500	1	3.500		Q1
Journal of the American College of Cardiology	12.535	12.535	1	12.535	1	Q1
Journal of the Neurological Sciences	2.324	11.620	5	2.324		Q2
Journal of Thoracic and Cardiovascular Surgery	3.063	3.063	1	3.063		Q1
Journal of Translational Medicine	3.407	3.407	1	3.407		Q2
Journal of Trauma-Injury Infection and Critical Care	2.626	2.626	1	2.626		Q2
Journal of Urology	4.016	4.016	1	4.016		Q1
Journal of Viral Hepatitis	3.348	3.348	1	3.348		Q1
Journal of Water and Health	1.469	1.469	1	1.469		Q3
Journal of Womens Health	1.770	1.770	1	1.770		Q2
Lancet	30.758	153.790	5	30.758	1	Q1
Lancet Neurology	18.126	18.126	1	18.126	1	Q1
Lancet Oncology	14.470	28.940	2	14.470	1	Q1
Leukemia & Lymphoma	2.397	4.794	2	2.397		Q3
Life Sciences	2.560	2.560	1	2.560		Q2
Liver International	2.987	8.961	3	2.987		Q2
Lung Cancer	3.140	3.140	1	3.140		Q1
Lupus	2.586	5.172	2	2.586		Q3
Medicine	5.054	10.108	2	5.054	1	Q1
Metabolic Brain Disease	1.959	1.959	1	1.959		Q3
Microvascular Research	3.075	3.075	1	3.075		Q2
Mitochondrion	4.145	4.145	1	4.145		Q1

Table 7
Publications in international journals *(Cont.)*

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
Molecular Biology of the Cell	5.979	5.979	1	5.979		Q1
Molecular Cancer Research	4.162	4.162	1	4.162		Q2
Molecular Cancer Therapeutics	4.953	4.953	1	4.953		Q1
Molecular Genetics and Metabolism	2.897	2.897	1	2.897		Q2
Molecular Psychiatry	15.049	30.098	2	15.049	1	Q1
Movement Disorders	4.014	8.028	2	4.014		Q1
Multiple Sclerosis	3.279	22.953	7	3.279		Q2
Nature	34.480	68.960	2	34.480	1	Q1
Nature Neuroscience	14.345	14.345	1	14.345	1	Q1
Nature Reviews Neurology	0.000	0.000	2	0.000	1	Q1
Nephrology Dialysis Transplantation	3.306	6.612	2	3.306		Q1
Neurobiology of Aging	5.937	5.937	1	5.937		Q1
Neurobiology of Disease	4.518	4.518	1	4.518		Q1
Neurogastroenterology and Motility	3.568	7.136	2	3.568		Q1
Neurology	8.172	40.860	5	8.172	1	Q1
Neuropsychopharmacology	6.993	6.993	1	6.993	1	Q1
Neuroradiology	2.616	2.616	1	2.616		Q2
Neuroscience Letters	1.925	1.925	1	1.925		Q3
New England Journal of Medicine	47.050	94.100	2	47.050	1	Q1
Obesity Reviews	5.086	5.086	1	5.086		Q1
Obesity Surgery	2.934	5.868	2	2.934		Q1
Obstetrical & Gynecological Survey	3.097	3.097	1	3.097		Q1
Oncogene	7.135	21.405	3	7.135	1	Q1
Oncologist	6.701	6.701	1	6.701		Q1
Ophthalmology	5.491	16.473	3	5.491	1	Q1
Pediatric Infectious Disease Journal	2.854	11.416	4	2.854	1	Q1
Pediatric Neurology	1.497	1.497	1	1.497		Q2
Pediatric Radiology	1.186	1.186	1	1.186		Q3
Pediatric Research	2.607	2.607	1	2.607		Q1
Pediatric Transplantation	1.573	1.573	1	1.573		Q2
Pharmacogenomics	3.893	11.679	3	3.893		Q1
PLoS Genetics	9.532	9.532	1	9.532	1	Q1
PLoS Medicine	13.050	13.050	1	13.050	1	Q1
PLoS One	4.351	21.755	5	4.351		Q1
Proceedings of the National Academy of Sciences	9.432	9.432	1	9.432	1	Q1
Prostate	3.081	12.324	4	3.081		Q2
Psychiatric Genetics	2.327	2.327	1	2.327		Q3
Psychiatry Research-Neuroimaging	3.435	3.435	1	3.435		Q1
Respiratory Care	1.524	1.524	1	1.524		Q3
Respiratory Medicine	2.331	9.324	4	2.331		Q2

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
Respirology	1.853	1.853	1	1.853		Q3
Retina-the Journal of Retinal and Vitreous	2.932	2.932	1	2.932		Q1
Rheumatology	4.236	4.236	1	4.236		Q2
Sarcoidosis Vasculitis and Diffuse Lung Diseases	1.056	1.056	1	1.056		Q4
Scandinavian Journal of Rheumatology	2.507	2.507	1	2.507		Q3
Seminars in Arthritis and Rheumatism	4.724	4.724	1	4.724		Q1
Seminars in Liver Disease	5.171	5.171	1	5.171		Q1
Stem Cells	7.747	7.747	1	7.747	1	Q1
Stroke	7.041	77.451	11	7.041	1	Q1
Thorax	7.041	7.041	1	7.041	1	Q1
Thrombosis and Haemostasis	4.451	4.451	1	4.451		Q1
Thyroid	2.602	2.602	1	2.602		Q3
Transfusion and Apheresis Science	0.938	0.938	1	0.938		Q4
Transplant Infectious Disease	2.063	2.063	1	2.063		Q3
Transplant International	3.254	3.254	1	3.254		Q1
Transplantation	3.498	3.498	1	3.498	1	Q1
Tumori	0.863	0.863	1	0.863		Q4
Urologia Internationalis	0.902	0.902	1	0.902		Q4
Urology	2.365	2.365	1	2.365		Q2
Vox Sanguinis	2.585	5.170	2	2.585		Q2
World Journal of Biological Psychiatry	5.564	5.564	1	5.564	1	Q1
World Journal of Surgery	2.696	2.696	1	2.696		Q1
World Journal of Urology	2.629	2.629	1	2.629		Q2
Worldviews on Evidence-Based Nursing	1.944	1.944	1	1.944	1	Q1
Total International Journals		**3,028.152**	**503**	**6.020**		

Table 8
Publications in national journals

Publication	Impact Factor	Total Imp. Fac.	Published Papers	Average Imp. Fac.	Decile (D)	Quartile (Q)
Spanish journals (*n* = 17)						
Actas Españolas de Psiquiatría	0.515	0.515	1	0.515		Q4
Allergologia et immunopathologia	0.630	0.630	1	0.630		Q4
Anales de Pediatría	0.363	1.815	5	0.363		Q4
Archivos de Bronconeumología	2.166	23.826	11	2.166		Q3
Clinical & Translational Oncology	1.146	9.168	8	1.146		Q4
Enfermedades Infecciosas y Microbiología	1.393	12.537	9	1.393		Q4
Gaceta Sanitaria	1.172	3.516	3	1.172		Q3
Medicina Clínica	1.231	23.389	19	1.231		Q3
Nefrología	0.533	0.533	1	0.533		Q4
Neurocirugía	0.247	0.741	3	0.247		Q4
Neurología	0.596	2.980	5	0.596		Q4
Nutrición Hospitalaria	1.065	2.130	2	1.065		Q4
Revista Clínica Española	0.584	0.584	1	0.584		Q3
Revista de Neurología	1.234	13.574	11	1.234		Q3
Revista Española de Cardiología	2.746	21.968	8	2.746		Q2
Revista Española de Enfermedades Digestivas	0.994	1.988	2	0.994		Q4
Revista Española de Medicina Nuclear	0.765	1.530	2	0.765		Q4
Total Spanish Journals		**121.424**	**92**	**1.320**		

Table 9
Total national and international journals

Publication	Total Impact Factor	Published Papers	Average Impact Factor
International Journals	3,028.152	503	6.020
Spanish Journals	121.424	92	1.320
Total National and International Journals	**3,149.576**	**595**	**5.293**

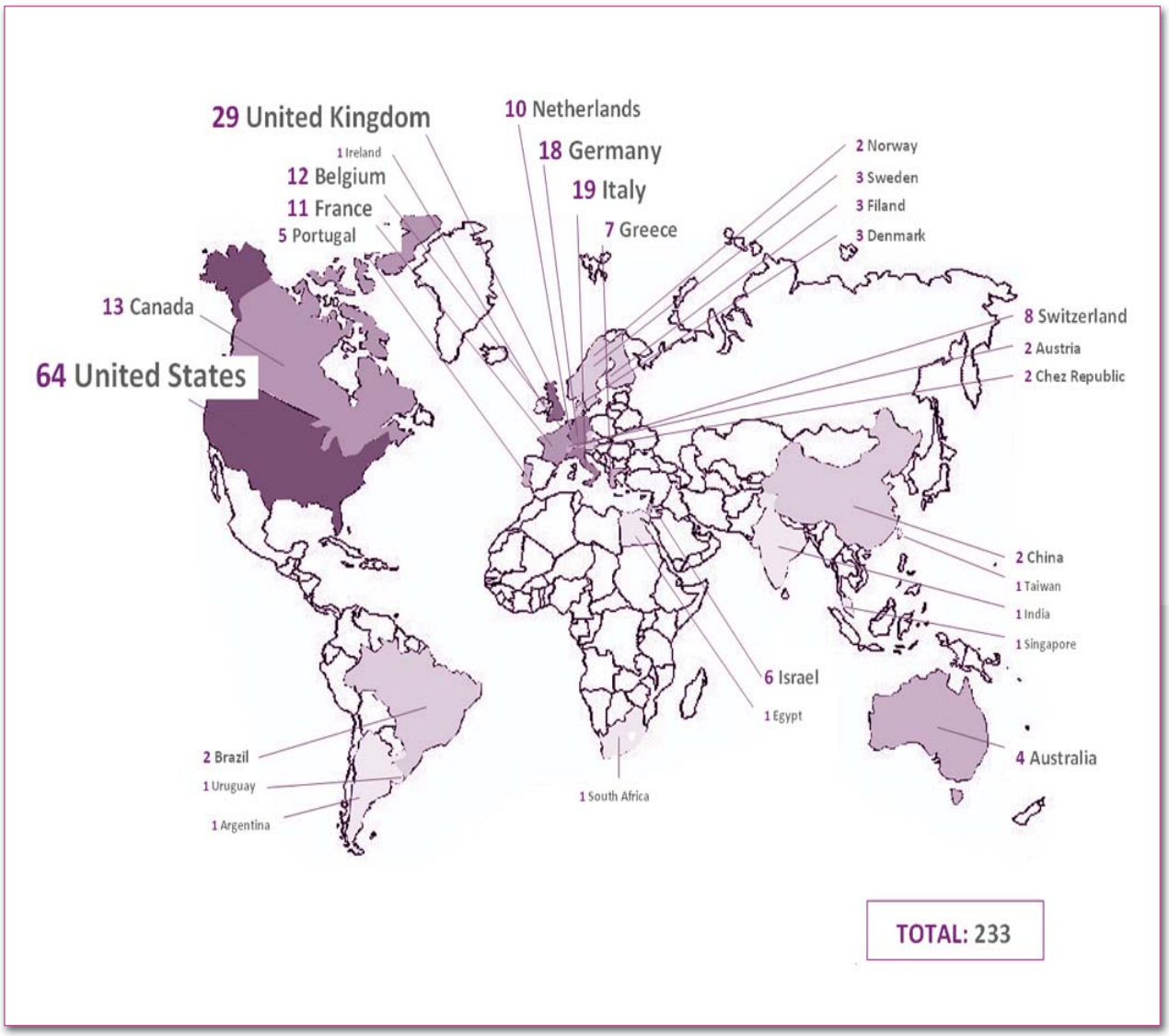
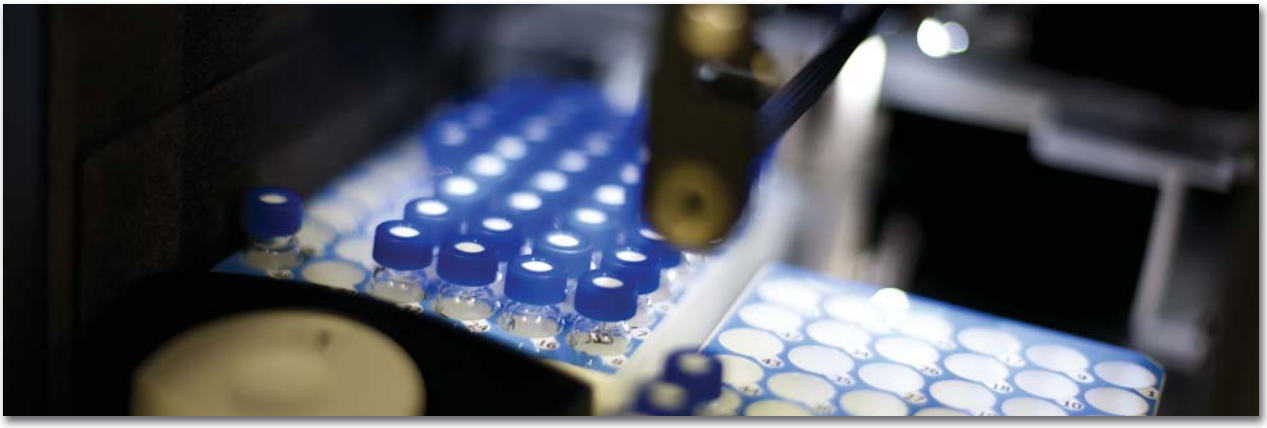


Figure 8
Co-authors international publications



RESEARCH PROJECTS

Active research projects funded by public and private institutions are listed below.

During 2010, 84 projects were awarded funding. On December 31st 2010 there were 242 active research projects and these are listed below.

Table 10
List of active research projects in 2010

Sponsors	Number of active sponsored projects
Fondo de Investigación Sanitaria (FIS) Instituto de Salud Carlos III	121
European Commission	13
Ministerio de Ciencia e Innovación	22
Fundació La Marató de TV3	13
Fundación de la Investigación Médica – Mutua Madrileña Automovilista	13
Agència d'Avaluació de Tecnologia i Recerca Mèdiques (AATRM)	3
Fundación para la Investigación y la Prevención del Sida en España (FIPSE)	2
Fundación Ramón Areces	1
Centro para el Desarrollo Tecnológico Industrial (CDTI)	4
Centro Nacional de Investigaciones Cardiovasculares (CNIC)	2
Asociación Española contra el Cáncer	4
Genoma España	2
Fundación Alicia Koplowitz	2
Fundació Santiago Dexeus Font	3
CIDEM – ACC1Ó	1
Other	36
Total	**242**

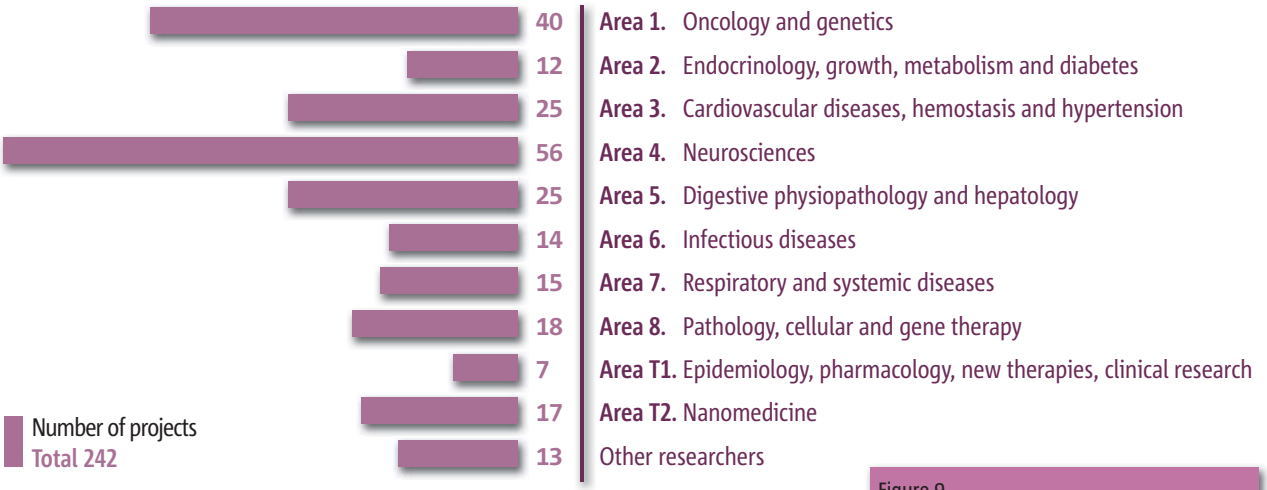


Figure 9
List of active research projects according to research area

CLINICAL TRIALS

In 2010, 238 clinical trials were submitted to the HUVH Clinical Research Ethical Committee (CREC) for approval. 205 (86%) of them were multicenter trials and 33 (14%) unicenter trials. Of these 205 multicenter trials, 85 centers acted as reference groups CREC (41%) and the remaining 120 centers acted as involved CREC (59%). Of these 238 submitted trials, 199 (84%) were sponsored by the pharmaceutical Industry, 8 (3%) were sponsored by VHIR researchers and 31 (13%) were sponsored by other hospitals.
On 31st December 2010, there were 428 active clinical trials.

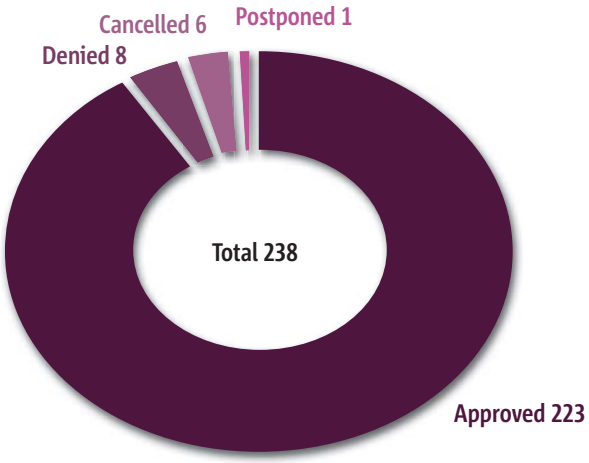


Figure 10
Clinical trials submitted to CREC in 2010

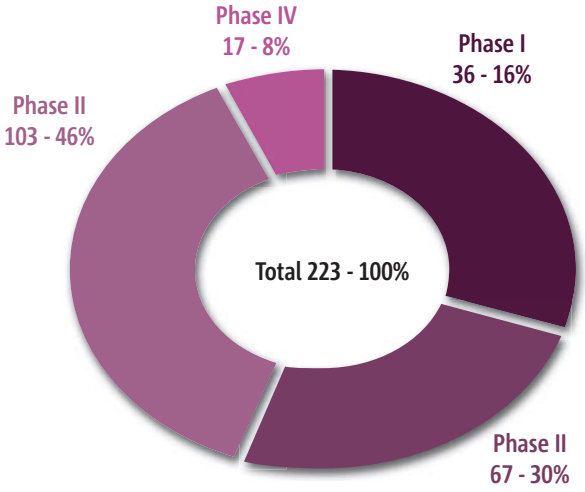


Figure 12
Clinical trials approved by CREC in 2010 classified according to trial phase

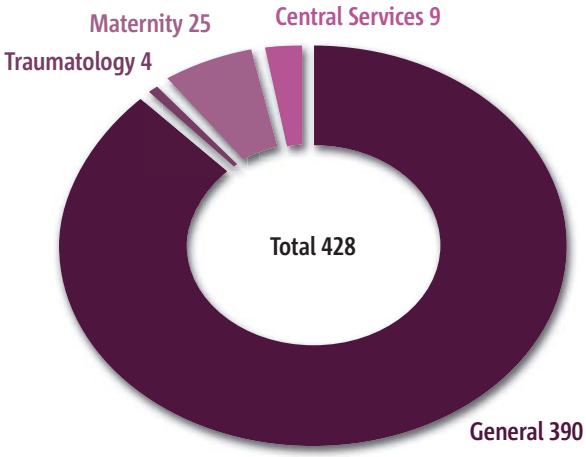


Figure 11
List of active clinical trials on 31st December 2010, classified according to service

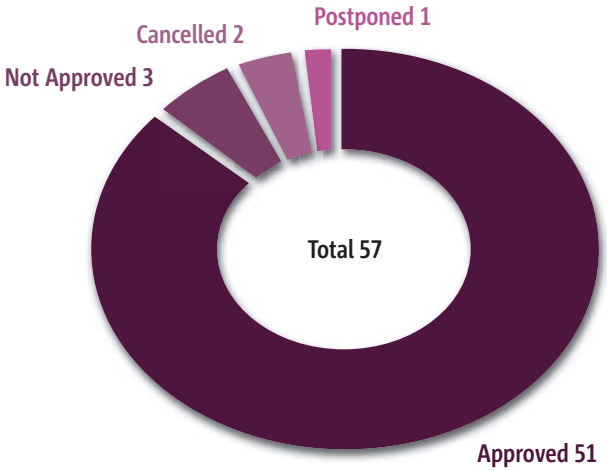


Figure 13
Post-authorization studies submitted to CREC in 2010

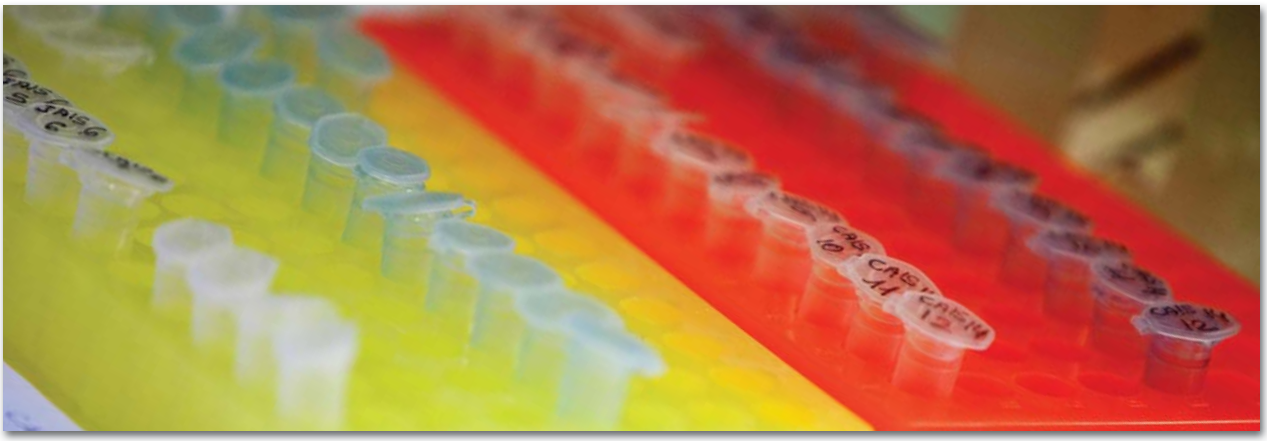


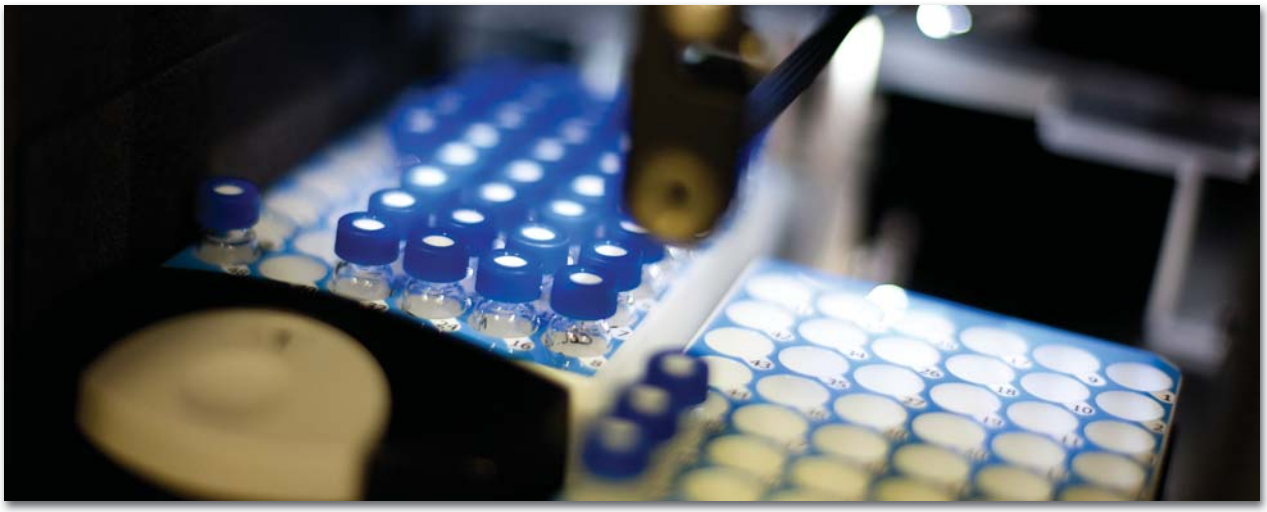
Table 11
List of active clinical trials on 31st December 2010, classified according to service

Hospital Services	Number
General Area	**390**
Oncology	186
Internal Medicine - Hepatology	20
Neurotraumatology	4
Internal Medicine - Infectious Diseases	8
Cardiology	16
Pneumology	19
Internal Medicine	5
Nephrology	7
Hematology	23
General Surgery	3
Endocrinology	14
Digestive Apparatus	5
Urology	5
ICU	2
Haemophilia	6
Neuroimmunology	25
Allergies	2
Internal Medicine - Rheumatology	6
Ophthalmology	7
Neurophysiology. Neurology and Neurosurgery	15
Dermatology	1
Radiotherapy	4
Hemodynamics	4
Resuscitation	1
systemic Diseases	1
"Institut de Diagnòstic per la Imatge"	1
Maternity and Children's Area	**25**
Pediatric Cardiology	1
Pediatric Oncohematology	9
Pediatric Endocrinology	1
Neonatology	1
Pediatric Pneumologya	2
Pediatric Genetics	1
Pediatric Neurology	1
Obstetrics and Gynecology	9
Traumatology Area	**4**
Rehabilitation	1
Anesthesiology	2
Burn Unit	1
Central services	**9**
Psychiatry	9
Total	**428**

NEW CONTRACTS AWARDED TO RESEARCHERS AND TECHNICIANS FUNDED BY DIFFERENT ORGANIZATIONS AND PROGRAMS

Table 12
New VHIR contracts for researchers

New contracts for researchers		Number
Senior Researchers		**10**
Miguel Servet Programme	3	
Intensification Programme contracts – *Instituto de Salud Carlos III*	6	
Research Retainment Programme – *Instituto de Salud Carlos III*	1	
Postdoc Researchers		**11**
Rio Hortega Programme	5	
Juan de la Cierva Programme	1	
Beatriu de Pinós - Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)	3	
Contracts stemming from Research Projects	2	
Predoc Researchers		**16**
Instituto de Salud Carlos III	4	
Fundació VHIR	2	
Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)	1	
Contracts stemming from Research Projects	9	
Support Staff		**8**
Instituto de Salud Carlos III	3	
Contracts stemming from Research Projects	5	
Total		**45**



ONLINE BIOMEDICAL RESEARCH CENTER (CIBER)

The Online Biomedical Research Center (CIBER) is a research organization with its own legal entity. Its main objective is conducting highly specific research into pathologies or concrete health disorders. CIBER is an amalgam of various independent research groups operating in the public and private sector with their own research lines and objectives. CIBER aims to generate larger translational research centers of a multidisciplinary and multi-institutional character to carry out basic clinical and population research.

CIBER aims to develop a single common research program, focusing on pathologies which are considered strategic or relevant to the National Health System due to their prevalence or social impact.

The VHIR is involved in the following CIBER projects:

CIBER: *Bioenginyeria. biomaterials i nanomedicina*
CIBER: *Malalties respiratòries*
CIBER: *Malalties hepàtiques i digestives*
CIBER: *Malalties neurodegeneratives*
CIBER: *Malalties rares*
CIBER: *Epidemiologia i salut pública*
CIBER: *Diabetis i malalties metabòliques*

Table 13
List of CIBER projects with VHIR involvement

CIBER File	Title	Project Manager
CB06/01/0012	CIBER: *Bioenginyeria, biomaterials i nanomedicina*	Simó Schwartz Navarro
CB06/06/0030	CIBER: *Malalties respiratòries*	Ferran Morell Brotad
CB06/04/0021	CIBER: *Malalties hepàtiques i digestives*	Fernando Azpiroz Vidaur
CB06/04/0025	CIBER: *Malalties hepàtiques i digestives*	Rafael Esteban Mur
CB06/04/0028	CIBER: *Malalties hepàtiques i digestives*	Juan Ignacio Esteban Mur
CB06/04/0062	CIBER: *Malalties hepàtiques i digestives*	Francisco Guarner Aguilar
CB06/04/0007	CIBER: *Malalties hepàtiques i digestives*	Juan Córdoba Cardona
CB06/05/0017	CIBER: *Malalties neurodegeneratives*	Miquel Vila Bover
CB06/07/0015	CIBER: *Malalties rares*	Antonio Luis Andreu Périz
CB06/07/0063	CIBER: *Malalties rares*	Antonio Carrascosa Lezcano
CB06/02/0009	CIBER: *Epidemiologia i salut pública*	Gaietà Permanyer Miralda
CB06/07/0027	CIBER: *Malalties rares*	Mari Carmen Domínguez Luengo
CB07/08/0024	CIBER: *Diabetis i malalties metabòliques*	Rafael Simó Canonge

COLLABORATIVE RESEARCH THEMATIC NETWORKS AT THE *INSTITUTO DE SALUD CARLOS III*

Thematic Networks are organizational structures sponsored by the *Instituto de Salud Carlos III* (ISCIII) composed of different biomedical centers and multidisciplinary research groups, whose aim is to conduct collaborative research projects of general interest. The networks were set up in response to the priorities of the *Plan Nacional* (2000-2003) in the field of healthcare and are composed of different research projects as a strategy to reduce the distance that currently exists between new knowledge generated and its transfer and application to medical practice.

The VHIR takes part in the following Thematic Network Centers:

- *Red Temática de Investigación Cooperativa de Centros de Cáncer.*
- *Factores de Riesgo. Evolución y Tratamiento de las Enfermedades Cardiovasculares* (RECAVA).
- *Red Española de Investigación en Patología Infecciosa* (REIPI).
- *Red Neurovascular* (RENEVAS).
- *Red de Investigación en Sida* (RIS).
- *Patología ocular del envejecimiento. calidad visual y calidad de vida.*
- *Red Española de Esclerosis Múltiple* (REEM).
- *Red de Salud Materno-Infantil y del Desarrollo.*
- *Red de Innovación en Tecnologías Médicas y Sanitarias.*
- *Red Tematica de Investigación Cooperativa de Biobancos.*

Table 14
List of ISCIII Thematic Network Centers that the VHIR is involved in

Nets of Centers File	Title	Project Manager
RD06/0020/0022	*Red Temática de Investigación Cooperativa de Centros de Cáncer*	Joaquin Arribas López
RD06/0020/0075	*Red Temática de Investigación Cooperativa de Centros de Cáncer*	José Baselga Torres
RD06/0014/0025	*Factores de Riesgo. Evolución y Tratamiento de las Enfermedades Cardiovasculares (RECAVA)*	David García-Dorado
RD06/0008/0030	*Red Española de Investigación en Patología Infecciosa (REIPI)*	Antoni Julià Font
RD06/0026/0010	*Red Neurovascular (RENEVAS)*	Joan Montaner Villalonga
RD06/0008/0026	*Red Española de Investigación en Patología Infecciosa (REIPI)*	Albert Pahissa Berga
RD06/0020/0104	*Red Temática de Investigación Cooperativa de Centros de Cáncer*	Santiago Ramón y Cajal Agüeras
RD06/0020/0058	*Red Temática de Investigación Cooperativa de Centros de Cáncer*	Jaume Reventós Puigjaner
RD06/0006/0039	*Red de Investigación en Sida (RIS)*	Esteban Ribera Pascuet
RD06/0020/1021	*Red Temática de Investigación Cooperativa de Centros de Cáncer*	Josep Sánchez de Toledo Codina
RD06/0014/1014	*Factores de Riesgo. Evolución y Tratamiento de las enfermedades cardiovasculares (RECAVA)*	Rafael Simó Canonge
RD07/0062/0010	*Patología ocular del envejecimiento. calidad visual y calidad de vida*	José García Arumí
RD07/0060/0020	*Red Española de Esclerosis Múltiple (REEM)*	Xavier Montalban Gairín
RD08/0072/0034	*Red de Salud Materno-Infantil y del Desarrollo*	Lluís Cabero Roura
RD09/0077/00090	*Red de Innovación en Tecnologías Médicas y Sanitarias*	Francesc Iglesias García
RD09/0076/00066	*Red Tematica de Investigación Cooperativa de Biobancos*	Santiago Ramón y Cajal Agüeras

RESEARCH GROUPS RECOGNIZED BY THE GENERALITAT DE CATALUNYA

One of the objectives of the research program of the "Generalitat de Catalunya" is to provide support to research groups based in Catalan universities and research centers which are articulated around a stable group of researchers with convergent paths. This support is provided by taking part in collaborative research projects publications and common activities promoting training for junior researchers. The VHIR has 28 groups recognized by the "Generalitat de Catalunya".

Table 15
List of VHIR research groups recognized by the "Generalitat de Catalunya"

Area	File	Title	Project Manager
Oncology and genetics	2009 SGR 604	*Oncologia i patologia molecular*	Matilde Lleonart Pajarín
	2009 SGR 756	*Patologia molecular*	Santiago Ramón y Cajal Agüeras
	2009 SGR 487	*Oncologia traslacional*	Jaume Reventós Puigjaner
Endocrinology, growth, metabolism and diabetes	2009 SGR 31	*Fisiopatologia del creixement*	Antonio Carrascosa Lezcano
	2009 SGR 739	*Grup de recerca en Diabetis i Metabolisme*	Rafael Simó Canonge
Cardiovascular diseases, hemostasis and hypertension	2009 SGR 802	*Patologia cardiocirculatòria*	David García-Dorado
Neurosciences, mental health and senescence	2009 SGR 1520	*Patologia neuromuscular i mitocondrial*	Antonio Luis Andreu Périz
	2009 SGR 346	*Senyalització cel·lular i apoptosi*	Joan Xavier Comella Carnicé
	2009 SGR 78	*Grup de recerca en neurologia infantil de l'HUVH*	Alfons Macaya Ruíz
	2009 SGR 793	*Unitat de Neuroimmunologia Clínica (UNic)*	Xavier Montalban Gairín
	2009 SGR 432	*Grup de recerca en malalties neurovasculars*	Joan Montaner Villalonga
	2009 SGR 495	*Unitat d'Investigació de Neurotraumatologia i Neurocirurgia (UNINN)*	Joan Sahuquillo Barris
	2009 SGR 664	*Grup de recerca en malalties neurodegeneratives*	Miquel Vila Bover

Table 15
List of VHIR research groups recognized by the "Generalitat de Catalunya" *(Cont.)*

Area	File	Title	Project Manager
Digestive physiopathology and hepatology	2009 SGR 219	*Unitat de recerca del sistema digestiu*	Fernando Azpiroz Vidaur
	2009 SGR 383	*Unitat de recerca en malalties hepatobiliars*	Joan Genescà Ferrer
	2009 SGR 256	*Grup de recerca en patologia pancreàtica exocrina*	Francesc Xavier Molero Richard
Infectious diseases and AIDS	2009 SGR 86	*Malalties infeccioses*	Albert Pahissa Berga
Immunology: respiratory, systemic and genetic disorders	2009 SGR 257	*Unitat de recerca en pneumologia*	Ferran Morell Brotad
	2009 SGR 296	*Grup d'investigació en Microbiologia de l'Hospital Vall d'Hebron*	Guillem Prats Pastor
	2009 SGR 661	*Autoimmunitat i malaltia trombòtica*	Miquel Vilardell Tarrés
Pathology, cellular and gene therapy	2009 SGR 157	*Grup d'oncologia molecular*	Diego Arango Corro
	2009 SGR 75	*Patologia cel·lular*	Anna Meseguer Navarro
	2009 SGR 758	*Direccionament i alliberament farmacològic*	Simó Schwartz Navarro
	2009 SGR 493	*Immunobiologia*	Joan Sayós Ortega
R+D, new technologies and experimental surgery	2009 SGR 384	*Grup de recerca en oftalmologia Vall d'Hebron*	José García Arumí
	2009 SGR 130	*Ortopèdia pediàtrica*	César Galo García Fontecha
Other	2009 SGR 537	*Grup de recerca en medicina materna i fetal*	Lluís Cabero Roura
	2009 SGR 412	*Fundació Institut Català de Farmacologia*	Joan-Ramon Laporte Roselló

THESIS

The doctoral thesis read in 2010 by VHIR's researchers was 62: of which, 55 were read in several departments of the Autonomous University of Barcelona (UAB), 6 at the University of Barcelona (UB), and 1 at the University of Navarra.

Table 16
Doctoral thesis read in 2010 or supervised by VHIR's staff

Phd	Title	Directors	Department	University	Qualification
Albert Brotons, Dimpna Calila	*Ecocardiografía Doppler y Doppler tisular en recién nacido pretérmino: influencia del ductus arterioso y foramen oval en el llenado ventricular izquierdo y su correlación con la evolución clínica*	Salvador Salcedo Abizanda	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent *CumLaude*
Almeida Prado Nino, Joel Eduardo	*El cáncer de laringe en mujeres en Cataluña*	Juan Lorente Guerrero, Enrique Perelló Scherdel	Cirurgia	UAB	Excellent *CumLaude*
Alonso Cotoner, Carmen	*Disfunción e inflamación de la mucosa intestinal inducida por el estrés psicosocial crónico y su relevancia translacional para el síndrome del intestino irritable*	Juan Ramon Malagelada Benaprés, Javier Santos Vicente	Medicina	UAB	Excellent *CumLaude*
Álvarez Bulnes, Olga	*Descripción y análisis del grosor de la capa de fibras nerviosas retinianas obtenidas mediante tomografía de coherencia óptica en pacientes sometidos a cirugía combinada de glaucoma*	José García Arumí	Cirurgia	UAB	Excellent
Álvarez-Uria Miyares, Gerardo	*Factores asociados al éxito del tratamiento del virus de la hepatitis B y C*	Manel Crespo Casal, Vicente Falcó Ferrer	Medicina	UAB	Excellent *CumLaude*
Balbuena Delgado, Jana	*Implicación de células madre tumorales de la Side Population e hipoxia en la resistencia a fármacos en líneas celulares de astrocitomas*	Jordi Pétriz	Unidad de Biología de Tumores Cerebrales	Universidad Navarra	Excellent *CumLaude*

Table 16
Doctoral thesis read in 2010 or supervised by VHIR's staff *(Cont.)*

Phd	Title	Directors	Department	University	Qualification
Bielsa Carrafa, Ana	*Estudio neurofisiológico por neuroimagen del trastorno por déficit de atención e hiperactividad (TDAH). Comparación pre y postratamiento con metilfenidato*	Isabel Roca Bielsa, Óscar Vilarroya Oliver	Psiquiatría i de Medicina Legal	UAB	Excellent *CumLaude*
Boerno, Rafael Luis	*Relación entre el haplogrupo del DNA mitocondrial y el grado de pérdida auditiva en la presbiacusia*	Ana María García Arumí, Enrique Perelló Scherdel	Cirurgia	UAB	Excellent *CumLaude*
Calbo Sebastián, Esther	*Resposta inflamatòria en la pneumònia neumocòcica greu*	Vicenç Falcó Ferrer, Xavier Garau Alemany	Medicina	UAB	Excellent *CumLaude*
Camilotti Gasperin, Alexandre	*El triángulo luminoso de la laringe. Los pliegues vocales no son blancos, se ven blancos*	Juan Lorente Guerrero, Enrique Perelló Scherdel	Cirurgia	UAB	Excellent *CumLaude*
Coll Loperena, Maria del Mar	*Inhibició i atròfia simpàtica: nou mecanisme implicat en la vasodilatació esplàncnica associada a la hipertensió portal*	Juan Genescà Ferrer, Maria Martell Pérez-Alcalde, Joaquín Ariño Carmona	Bioquímica i de Biologia Molecular	UAB	Excellent *CumLaude*
Corominas Casti, Roser	*Avaluació de gens de susceptibilitat a formes comunes de migranya*	Alfons Macaya Ruíz	Genètica	UB	Apte *CumLaude*
Corona Gutiérrez, América Aime	*Índice de masa corporal previo al embarazo y resultados perinatales*	Lluís Cabero Roura	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent
Corripio Collado, Raquel	*Niños obesos prepuberales: efecto de una intervención dietética y en el estilo de vida sobre las lipocalinas y el brain-derived neurotrophic factor. Estudio longitudinal de dos años de duración*	Diego Yeste Fernández	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent *CumLaude*
Domingo Sábat, Montserrat	*Genética de la butirilcolinesterasa en les sinucleïnopaties: establiment d'una eina per all diagnòstic diferencial de la demència amb cossos de Lewy*	Katrin Beyer, Catalina Casas Louzao	Biologia Cel·lular, de Fisiologia i d'Immunologia	UAB	Excellent *CumLaude*

Table 16
Doctoral thesis read in 2010 or supervised by VHIR's staff *(Cont.)*

Phd	Title	Directors	Department	University	Qualification
Domingues, Sophie	*Identification of genetic risk factors for ischemic stroke*	José Álvarez Sabín, Israel Fernández Cadenas, Joan Montaner Villalonga	Medicina	UAB	Excellent *CumLaude*
Dopeso González, José Higinio	*Papel funcional de los receptores EPH en el cáncer colorrectal*	Diego Arango del Corro	Genètica	UB	Excellent *CumLaude*
Estrada Cuxart, Josep Oriol	*Anàlisi dels indicadors de seguretat i eficàcia per a l'avaluació del programa de tractament antibiòtic endovenós d'una unitat d'hospitalització a domicili*	Vicente Fonollosa Pla, Alfons Cuxart Melich	Medicina	UAB	Excellent *CumLaude*
Ferrer Menduiña, Maria Queralt	*Función cardíaca fetal en casos afectos de restricción de crecimiento intrauterino y/o preclampsia y evolución postnatal: Fetal Programming*	Jaume Casaldàliga	ACOR-Cardiologia pediàtrica	UAB	Excellent *CumLaude*
Ferrer Oliveras, Raquel	*Prevalencia y valor clínico de los anticuerpos antifosfolípido y antifactor en la preeclampsia*	Jaime Alijotas Reig, Elisa Llurba Olivé	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent *CumLaude*
Gallofré López, Miquel	*Els audits com a mètode d'avaluació de l'atenció hospitalària a una malaltia prevalent a Catalunya: la malaltia vascular cerebral*	Gabriel Sampol Rubio	Medicina	UAB	Excellent *CumLaude*
Giné Soca, Eva	*Estudi del fenomen de la tranformació histològica en síndromes limfoproliferatius indolents*	Francesc Bosch	Medicina	UB	Excellent *CumLaude*
Gómez Lanza, Esther	*Análisis de la concentración sérica de vitamina D como factor de riesgo de cáncer de próstata y agresividad tumoral*	Juan Morote Robles	Cirurgia	UAB	Excellent *CumLaude*
Hernando Martínez, Víctor	*Activación de calpaínas durante la reperfusión miocárdica. Importancia como sistema efector de muerte celular y como diana terapéutica*	David García-Dorado, Javier Inserte Igual	Departament de Bioquímica i de Biologia Molecular	UAB	Excellent *CumLaude*

Phd	Title	Directors	Department	University	Qualification
Hernecki, Jaroslaw Jerzy	*Programa de cribaje de la retinopatía diabética en el Vallès Oriental mediante cámara no midriática. Estudio de 5228 pacientes diabéticos tipo 2*	José García Arumí	Cirurgia	UAB	Excellent *CumLaude*
Julia Cano, Antonio	*Genomic approaches for the indentification of risk loci for Rheumatoid Arthritis*	Sara Marsal, Joaquín Ariño Carmona	Bioquímica i Biologia Molecular	UAB	Excellent *CumLaude*
Leal Blanquet, Juan	*Influència del suport audiovisual sobre les expectatives preoperatòries del malalt candidat a una artroplàstia total de genoll*	Enric Cáceres Palou	Cirurgia	UAB	Excellent *CumLaude*
López Fauqued, Marta	*Estudio preclínico de inhibidores de PI3K y BRAF en melanoma maligno*	Juan A. Recio Conde	Bioquímica i Biologia Molecular	UB	Excellent *CumLaude*
López Peig, Cristina	*Análisis de un programa de deshabituación de benzodiazepinas destinado a ser aplicado por enfermería en las consultas de atención primaria*	Eduard Diogene Fadini	Medicina	UAB	Excellent *CumLaude*
López Vicente, Laura	*Estudi de l'expressió d'RSK4 en tumors humans i la seva implicació amb senescència*	Santiago Ramón y Cajal Agüeras, Gemma Armengol Rosell, Anna Meseguer Navarro	Bioquímica i de Biologia Molecular	UAB	Excellent *CumLaude*
Malagelada Prats, Carolina	*Evaluación de la motilidad intestinal mediante análisis de imágenes endoluminales*	Fernando Azpiroz Vidaur	Medicina	UAB	Excellent *CumLaude*
Manso García, Begoña	*Evaluación de función coronaria mediante resonancia magnética de perfusión miocárdica en pacientes con transposición de grandes arterias (TGA) intervenidos con cirugía tipo Switch arterial*	Jaume Casaldàliga	ACOR-Cardiologia pediàtrica	UAB	Excellent *CumLaude*

Table 16
Doctoral thesis read in 2010 or supervised by VHIR's staff *(Cont.)*

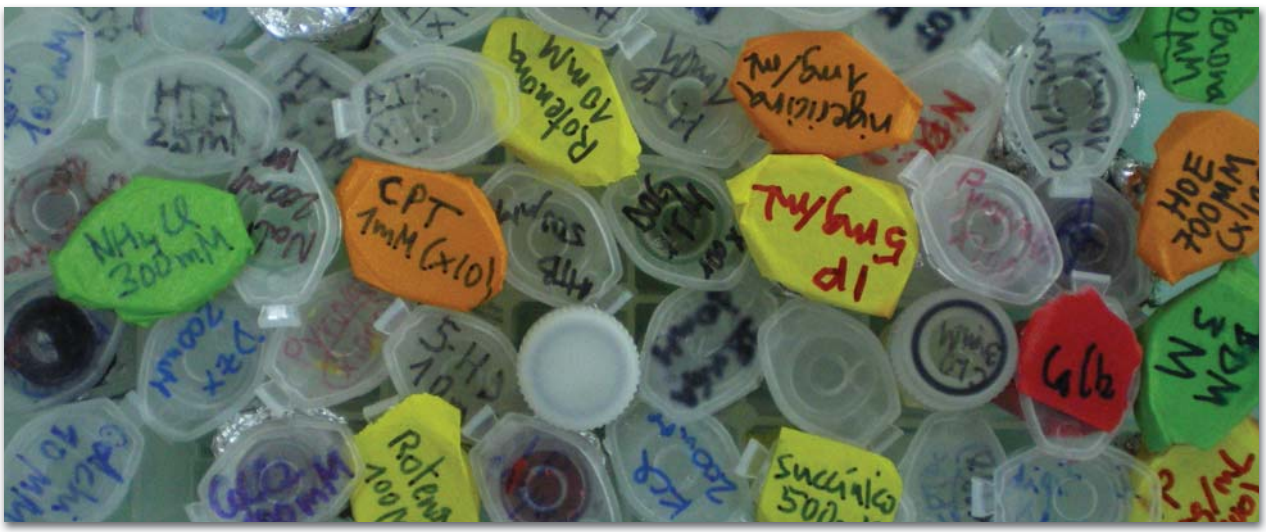
Phd	Title	Directors	Department	University	Qualification
Martín Begué, Nieves	*Tratamiento de la retinopatía del prematuro con láser de diodo: correlación de la retinopatía grave y la presencia de enfermedad plus con factores clínicos de riesgo predictivo*	José García Arumí	Cirurgia	UAB	Excellent *CumLaude*
Martínez Alonso, Mónica	*Engineering and Production of Quality Viral Proteins in Prokaryotic and Eukaryotic Systems*	Neus Ferrer Miralles, Antonio Pedro Villaverde Corrales, Rob Noad	Genètica i de Microbiologia	UAB	Excellent *CumLaude*
Mendioroz Iriarte, María Tere	*Utilidad de los biomarcadores plasmáticos en el diagnóstico, tratamiento y pronóstico de la enfermedad cerebrovascular aguda*	Joan Montaner, Israel Fernández Cadenas, José Álvarez Sabín	Cirurgia	UAB	Excellent *CumLaude*
Monteagudo Jiménez, Manuel	*Las plaquetas reticuladas medidas por citometría de flujo: un marcador indirecto de la actividad trombocitopoyética*	Vicente Fonollosa Pla	Medicina	UAB	Excellent *CumLaude*
Monteserín Nadal, María Rosa	*Ensayo clínico aleatorizado sobre la eficacia de una intervención tras una valoración geriátrica integral en el ámbito de la atención primaria*	Antonio San José Laporte, Carlos Brotons Cuixart	Medicina	UAB	Excellent *CumLaude*
Navarro Sobrino, Miriam	*Influència de les cèl·lules endotelials progenitores sobre la modulació espaial i temporal de l'angiogènesi i la vasculogènesi després de l'ictus isquèmic humà*	Joan Montaner, Anna Rosell, José Álvarez Sabín	Medicina	UAB	Excellent *CumLaude*
Olloquequi González, Jordi	*Cèl·lules inflamatòries en la malaltia pulmonar obstructiva crònica*	Jaume Ferrer Sancho, José García Valero, Juan Francisco Montes Castillo	Biologia cel·lular	UB	Excellent *CumLaude*
Pagola Pérez Blanca, Jorge	*Trombosis de la arteria basilar. Tolerancia isquémica, respuesta a la sonotronolisis potenciada y transformación hemorrágica postratamiento*	José Álvarez Sabín, Marc Ribó Jacobi, Carlos Molina Cateriano	Medicina	UAB	Excellent *CumLaude*

Phd	Title	Directors	Department	University	Qualification
Pascual Angulo, Gloria	*Generación de modelos transgénicos para el estudio fisiopatológico de la proteína KAP en el riñón murino*	Anna Meseguer Navarro	Departament de Genètica	UB	Excellent *CumLaude*
Pidemunt Molí, Gemma	*Factores determinantes en el deterioro de la función y la calidad de vida del anciano afecto de fractura de cadera*	Enric Cáceres Palou	Cirurgia	UAB	Excellent *CumLaude*
Pons López, Berta	*Estudi de 4E-BP1 i la seva regulació en càncer de mama*	Santiago Ramón y Cajal, Gemma Armengol	Bioquímica i de Biologia Molecular	UAB	Excellent *CumLaude*
Porta Balanyà, Rut	*La vía del receptor EP4 de la prostaglandina E2 y de la 15-hidroxiprostaglandina deshidrogenasa en el cáncer de pulmón de célula no pequeña: relevancia clinicopatológica*	Antonio González Fernández, Joan Brunet i Vidal	Medicina	UAB	Excellent *CumLaude*
Puig Verdie, Lluís	*Estudi comparatiu entre el cultiu de la sonicació de l'implant i el teixit del voltant en el diagnòstic d'infecció postquirúrgica en cirurgia ortopèdica*	Enric Cáceres Palou	Cirurgia	UAB	Excellent *CumLaude*
Ramos Terrades, Natalia	*Marcadores bioquímicos de lesión endotelial, sistema fibrinolítico y microalbuminuria en HTA esencial*	Alfons Segarra Medrano, Vicente Fonollosa Pla	Medicina	UAB	Excellent *CumLaude*
Roca Gas, Oriol	*Qualitat de vida i alteracions morfo-funcionals en supervivents a una síndrome del destret respiratori agut*	Joan Ramon Masclans Enviz, Xavier Muñoz Gall	Medicina	UAB	Excellent *CumLaude*
Roca Tey, Ramón	*Diagnòstic precoç de l'estenosi de l'accés vascular per hemodiàlisi mitjançant la determinació no invasiva del flux sanguini*	Vicente Fonollosa Pla	Medicina	UAB	Excellent *CumLaude*
Rodríguez Diez, Basilio	*Artritis idiopática juvenil: estudio de la incidencia y prevalencia en Catalunya*	Consuelo Modesto Caballero, A. Selva O' Callaghan	Medicina	UAB	Excellent *CumLaude*

Table 16
Doctoral thesis read in 2010 or supervised by VHIR's staff *(Cont.)*

Phd	Title	Directors	Department	University	Qualification
Romero Cullerés, Georgia	*Aplicació de toxina botulinítica tipus A via transperineal en la hipertonia esfínter uretral extern en la retenció urinària crònica secundaria a una lesió medul·lar*	Joan Nardi Vilardaga, Joan Conejero Sugrañes, Miguel Ángel González Viejo	Cirurgia	UAB	Excellent *CumLaude*
Ruiz Riol, Marta	*Análisis de los mecanismos de tolerancia central y periférica implicados en la patogénesis de las enfermedad de Graves-Basedow*	Ricardo Pujol Borrell	Biologia Cel·lular, de Fisiologia i d'Immunologia	UAB	Excellent *CumLaude*
Ruiz Romance, María del Mar	*Valor clínico de las micropartículas circulantes en las pérdidas gestacionales, en la preeclampsia y en el retraso de crecimiento intrauterino*	Jaume Alijotas Reig	Medicina	UAB	Excellent
Saltor Pons, Manuel	*Estudio de la torsión femoral en la vida prenatal. Evolución de las rotaciones de la cadera entre los 7 y 14 años*	Joan Nardi Vilardaga	Cirurgia	UAB	Excellent *CumLaude*
Sánchez, Antonio	*Correlación clínico-ecocardiográfico, hemodinámica del derrame pericárdico*	Jaume Sagristá	ACOR-Cardiologia pediàtrica	UAB	Excellent *CumLaude*
Soler Palacín, Pere	*Hiperlactacidèmia en fills de mare VIH i exposats a antiretrovirals (2004-2007). Estudi de cohorts, obert i prospectiu*	Concepció Figueras Nadal	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent *CumLaude*
Sordia Hernández, Luis Humberto	*Menopausia: La severidad de su sintomatología y depresión*	Lluís Cabero Roura	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent
Trasovares Navarrete, María Victoria	*Condicionament clàssic aversiu i al context: el paper de la conciència de contingència i l'ansietat tret*	Miguel Casas Brugué	Departament de Psiquiatria i de Medicina Legal	UAB	Excellent *CumLaude*

Phd	Title	Directors	Department	University	Qualification
Treviño Salinas, Emilio Modesto	*Valor de la estereotaxia en el diagnóstico de neoplasia en las lesiones no palpables de mama, de acuerdo a las diferentes imágenes mamográficas*	Jordi Xercavins Montosa	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent
Vázquez Suárez, Ana	*Equilibrio entre las citoquinas pro y antiinflamatorias en los derrames pleurales infecciosos*	José Alegre Martín	Medicina	UAB	Excellent *CumLaude*
Vélez Villa, Roberto	*Estimulación de la regeneración ósea mediante células madre en un modelo preclínico de osteonecrosis de la cabeza femoral*	Marius Aguirre, Vicenç Martínez Ibáñez, Joan Nardi	Departament de Cirurgia	UAB	Excellent *CumLaude*
Vidaur Tello, Loreto	*Patrones de resolucion clínica de neumonía asociada a ventilación mecánica*	Jordi Rello Condomines	Medicina	UAB	Excellent *CumLaude*
Vizmanos Lamotte, Gerardo	*Tipificación del fenotipo inflamatorio en el asma bronquial en niños de 7 a 14 años, mediante recuento celular y determinación de citoquinas en esputo inducido*	Antonio Moreno Galdo, Antonio Carrascosa Lezcano	Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva	UAB	Excellent *CumLaude*



Scientific Report

The scientific activities organized during 2010 by VHIR were 148, stressing the great importance of teaching in our institute.

Table 17
VHIR's activities

Activities		
Extraordinary Conferences		**3**
XIV Conferència Anual HUVH	1	
4th Scientific Meeting VHIR	1	
Jornada "Papel de los virus y la respuesta"	1	
Seminars		**109**
VHIR	28	
Oncology	4	
Cardiology	26	
Gastroenterology	21	
Neuroscience	6	
Neurosurgery	19	
Nano Seminars CIBBIM-Nanomedicina	2	
VHIR briefing (3)		
Courses		**36**
USMIB	7	
UEB	6	
UCTS	9	
Other courses	14	

One thing that stands out in comparison with 2009 is the increase in the number of VHIR Seminars held (75%), and a further increase in the number of courses offered (140%).
The VHIR website is available in **www.vhir.org** to consult the list of scientific activities by a search by date and type of activity. In 2010, VHIR opened a YouTube Channel where further scientific activities can be viewed on video. Visit us at:

www.youtube.com/user/VHIRtv

For further information consult the online version of the scientific report.

VHIR Research Activity

Area 1 Oncology and Genetics

Vall d'Hebron Institute of Oncology (VHIO)

VHIO: ADVANCING PERSONALIZED AND TARGETED THERAPIES AGAINST CANCER

With the explosion of novel genomic and pathway data and the stunning advancement in new diagnostic and therapeutic options, there has never been a more exciting time in oncology. But research progress can only be translated into genuine benefit for cancer patients within an environment that provides the appropriate infrastructure, expertise, and essential interconnectivity between all oncology specialists *en force*.

Since it was established in 2006, the Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, has been organized and structured to do just that. By adopting a purely translational research model, VHIO is proof of the bench-bedside-bench principle – a term describing the process by which research from the laboratory is directly applied to patients and from the clinical side, patient samples are analyzed in the laboratory.

The translational approach is nothing new and clearly facilitates the detailed and direct study of each patient and each tumor. The strength of the VHIO is that it can 'translate' more swiftly and dynamically. With direct access to our patients at the Vall d'Hebron University Hospital, one of the largest hospitals within Spain, our multidisciplinary teams strive to improve survival and quality of life for all our patients today, and in so doing turn research into more effective, personalized treatments and better practice for the future.

2010 Impact Factor:
778.818

AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.1 VHIO-Experimental Therapeutics

Group Leader
José Manuel Baselga Torres
Tel. 93 274 60 85
jbaselga@vhio.net

Researchers
Maurizio Scaltriti, PhD
Violeta Serra, PhD
Pieter Eichhorn, PhD
Yasir Ibrahim, PhD
Celina García-García, PhD

Research Associates
Marta Guzmán
Olga Rodríguez
Pilar Antón

Administrative Staff
Susana Muñiz

OBJECTIVES

The Experimental Therapies Program aims to develop novel breast cancer targeted therapies along with phase I clinical trials at VHIO. Our program works in close collaboration with the Growth Factors Group as well as the Molecular Pathology Group.

RESEARCH LINES

Truncated p95HER2 receptor and novel anti-HER2 therapies

We previously showed that the expression of truncated forms of the HER2 receptor, p95HER2, correlate with a lack of response to the anti-HER2 antibody trastuzumab. Lapatinib, a HER2 tyrosine kinase inhibitor, has proven to be efficacious in p95HER2-expressing cells in our preclinical models. We have now interrogated clinical samples from patients treated with lapatinib and found that patients with p95HER2-overexpressing tumors were as sensitive to this agent as p95HER2 negative tumors. This finding represents an additional step towards a rational subclassification of HER2-positive disease and a better selection of therapy for these patients. We have also explored new combinations of anti-HER2 therapies. Indeed, the combination of trastuzumab and lapatinib has already shown enhanced efficacy in the neoadjuvant setting for patients with metastatic breast cancer. We had previously identified the potential mechanism for the enhanced clinical activity of this combination, namely an enhanced immune-mediated trastuzumab dependent cytotoxicity as a result of the lapatinib induced HER2 accumulation at the plasma membrane.

Additional mechanisms of resistance to targeted therapy against the HER2/PI3K pathway

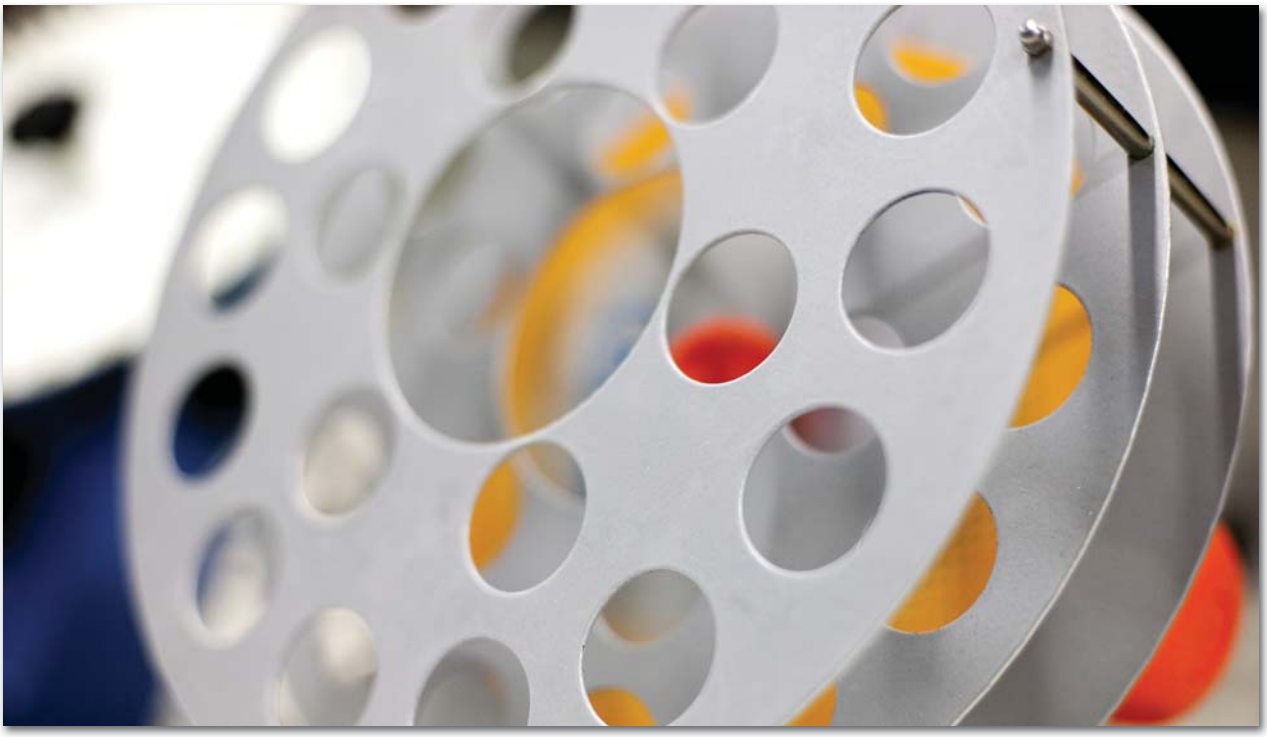
As with the majority of anticancer agents, acquired resistance to anti-HER2 agents becomes an unavoidable phenomenon. Therefore, identifying potential "escape" mechanisms could lead to im-

proved therapeutic strategies. In the light of these considerations, and in order to identify resistance mechanisms, we used a molecular barcode-screen approach to identify mediators of lapatinib resistance. We showed that deregulation of the PI3K pathway, either through PTEN down-modulation, or through overexpression of the two most frequent breast cancer mutations in PI3KCA (E545K and H1047R), confers resistance to trastuzumab and lapatinib. We then confirmed these observations by showing that PI3K-mediated trastuzumab and lapatinib resistance can be abrogated with the PI3K/mTOR inhibitor NVP-BEZ235. We understood that the enhanced efficacy of combining anti-HER2 compounds with PI3K/mTOR inhibitors is due to prevention of compensatory pathway activation. Such combinations are presently under investigation in phase Ib clinical trials.
Using a different approach, we also generated cells with acquired resistance to either trastuzumab or lapatinib. These cells represent a powerful tool in gaining a better understanding of the molecular mechanisms responsible for the resistant phenotype and, hence, the testing of new compounds that may overcome it. We explored the genetic aberrations in trastuzumab-resistant cell lines, by both microarray (Luminex) and genome-wide single nucleotide polymorphism (SNPs) analysis (Affymetrix 500K SNP array).

These analyses have shown that cyclin E gene is amplified and its protein product upregulated in our resistant cell lines. We then confirmed these findings by FISH and IHC in a cohort of 50 HER2 positive patients where cyclin E amplification/overexpression was found in approximately 30% of the cases. We reasoned that deregulation of cyclin E expression may play a causative role in the acquisition of trastuzumab resistance, and we have tested this hypothesis both preclinically and in trastuzumab treated breast cancer patients. In cell lines with cyclin E overexpression we found that CDK2 inhibitors were very effective in inducing cell death and slowing down tumor growth.

In the clinical setting we confirmed that presence of cyclin E amplification/overexpression negatively correlates with clinical benefit rate and progression-free survival of patients treated with trastuzumab-based therapy. We plan to confirm these results in a larger cohort of patients and, if these data are in line with the previous findings, design ad hoc clinical trial with CDK inhibitors together with anti-HER2 agents.

Finally, with the help of a cDNA library we have identified novel kinases that mediate resistance to PI3K inhibition. We are further elucidating the precise mechanism by which these kinases confer resistance to PI3K-targeted therapy, with the aim of improving the clinical efficacy of these agents upon overexpression of the given kinases.



AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.2 VHIO-Breast Cancer

Group Leader
Javier Cortés
Tel. 93 274 60 85
jacortes@vhio.net

Attending Physicians
Meritxell Bellet
Serena di Cosimo
Patricia Gómez
José Pérez
Cristina Saura

Fellows
Eva Muñoz
María Vidal
Vanesa Ortega
Leticia de Mattos

Clinical Trials Coordinators
Susana Muñoz
Raquel Espallargas
Violeta Esteban
Beatriz García
Olga Vidal

OBJECTIVES

- Implement sequencing of tumors in patients with breast cancer.
- Study the efficacy of inhibitors of the *PI3K/mTOR* pathway and their relationship with the mutational state.
- Continue investigating the factors involved in resistance to anti-*HER2* treatments and strategies aimed at reversing them.
- Study the efficacy of PARP inhibitors in breast cancer.
- Implement therapeutic strategies and clinical trials differentiated by tumor subtype.
- Study new chemotherapeutic agents in metastatic breast cancer.
- Study new therapeutic approaches to patients with luminal b and triple negative metastatic breast cancer.

RESEARCH LINES

Optimization of the treatment of breast cancer with the incorporation of new drugs aimed at biological targets

Optimization of multidisciplinary treatment in patients with stage I-III breast cancer, incorporating studies with translational objectives

Participation in the development of new chemotherapy drugs

Incorporation of proteomic and genomic platforms as well as platforms of circulating tumor cells in breast cancer studies

Area 1 Oncology and Genetics

Vall d'Hebron Institute of Oncology (VHIO)

1.3 VHIO-Gastrointestinal Tumors

Group Leader
Josep Tabernero Caturla
Tel. 93 489 43 01
jtabernero@vhebron.net

Researchers
Jaume Capdevila Castillón
María Elena Elez Fernández
Teresa Macarulla Mercadé
Maria Alsina Maqueda

Researchers in Training
Irene Braña García
Guillem Argilés Martínez

OBJECTIVES

The Medical Oncology Department's Gastrointestinal Tumors Program is an integral component of the multidisciplinary team of the Vall d'Hebron Gastrointestinal Tumors Project which consists of gastrointestinal surgeons, medical oncologists, radiation oncologists, pathologists, molecular biologists, radiologists, palliative care and clinical trials specialists.

The program is dedicated to patient care, research, training and education in gastrointestinal tumors. As a clinical academic unit, it is committed to clinical excellence, clinical and translational research, and a broad range of teaching (to undergraduates, medical trainees and fellows, nurses, clinical researchers, and others).The Gastrointestinal Tumors Program's approach is based on the principle that clinicians provide the best quality cancer care when they are members of a multidisciplinary cancer institute, meeting regularly to discuss the most appropriate management of each individual patient.

RESEARCH LINES

Clinical Research
The clinical trials conducted by this group can be classified in three different major areas:

- Phase II and III clinical trials aimed to demonstrate clinical benefit with new chemotherapy schedules and targeted agents in gastrointestinal malignancies.
- Phase I pharmacokinetic and pharmacodynamic studies with targeted agents directed to different critical signal transduction pathways.
- Phase I pharmacokinetic and pharmacodynamic studies with cytotoxic agents.

Translational Research
Translational research devoted to improving knowledge of prognostic and predictive biomarkers in the different gastrointestinal malignancies.

Basic Research
Basic research in collaboration with the VHIO Stem Cells, Gene Expression, Tumor Biomarkers, Experimental Therapeutics and Growth Factors Groups as well as other international research groups (University of Michigan, Vanderbilt University, Harvard University, Broad Institute-MIT, Weizmann Institute, and Leuven University).

AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.4 VHIO-Gene Expression and Cancer

Group Leader
Joan Seoane Suárez
Tel. 93 489 41 67
joan.seoane@vhir.org

Researchers
M. Àngels Carmona Heredia
Anna Cascante Cirera
Andrea Sáez Borderías
Joan Seoane Suarez

Researchers in Training
Gerard Folch Codera
Alba González Junca
Laura Rodón Ahnert

Nursing, Technical and Administrative Staff
Alexandra Arias Piñeiro
Mª Isabel Cuartas Maza
Rosa Gil Villaverde
Eva Paradell Salinas
Carolina Raventós Bernal

OBJECTIVES

Our group's research focuses on the study of glioma, the most common and aggressive brain tumor, and works with cell cultures and with mouse models of glioma. Gliomas are the most common primary tumors of the brain and the most malignant form of glioma (glioblastoma multiforme) is one of the most aggressive human cancers. Treatment for these malignancies remains elusive and progress in this area of research is still needed.

Gliomas have morphologic and gene-expression characteristics similar to glia, the support cells of the brain. Gliomas can be divided into four clinical grades on the basis of their histology and prognosis. Grade IV gliomas (glioblastoma multiforme, GBM) are highly malignant, usually recalcitrant to radio- and chemotherapy and have a median survival of 1-2 years. Until recently, radiation has been the main standard-of-care treatment with a minimal role for systemic chemotherapy. However in a recent study, concurrent treatment with temozolomide with radiation improved median survival by 2.5 months compared with radiation therapy alone. Thus, temozolomide has become a standard adjuvant therapy for gliomas although providing modest clinical benefits.

Novel molecularly-targeted therapies against these devastating tumors are required. Our studies are mostly based on the study of cells obtained from patient-derived tumors. We obtain tumor samples 30 minutes after surgery and we set up primary cultures and isolate cell populations from the tumor such as the cancer stem-cell-like pool. The study of the cells gives us more reliable information about the original tumor than the study of established cell

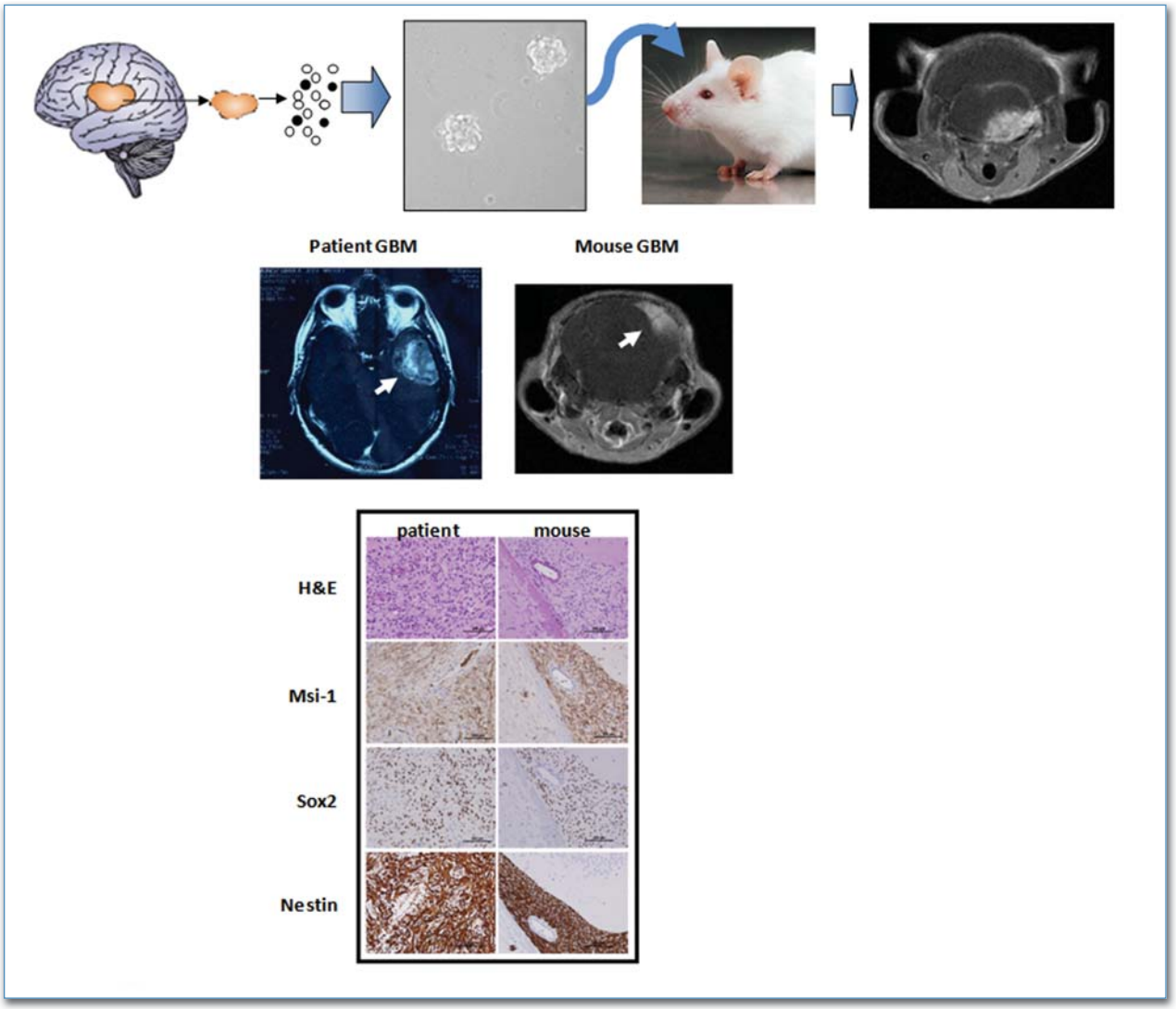


Figure 14
Patient-derived mouse model of glioma

lines. Moreover, we inoculate the patient-derived glioma stem cells into the brain of immunocompromised mice and we are able to generate tumors with the same characteristics as the original human tumor which we can monitor by MRI.

This mouse model for human glioma is of great interest in studying the molecular mechanisms involved in cancer as well as evaluating the efficiency of pharmacological compounds.

RESEARCH LINES

Patient-derived glioma stem cells

Recently, a subpopulation of tumor cells with stem-cell-like properties was identified in gliomas. This pool of cells, known as glioma stem cells, is considered to be responsible for the initiation, propagation and recurrence of tumors indicating that more effective therapies will result from approaches aimed at targeting the stem-cell-like component of gliomas. Glioma stem cells are characterized by their self-renewing capacity, their multilineage differentiation properties, their high oncogenic potential, and their ability to generate detached spherical cellular structures (neurospheres) when cultured in a serum-free medium.

Several markers, most of them previously described for neuroprogenitor cells, have been reported to identify glioma stem cells. Specifically, it has been shown that a glioma subpopulation of cells expressing the cell surface protein, CD133, is enriched for cancer stem cells. Little is known however regarding the molecular characteristics, and

regulatory mechanisms that control glioma stem cell biology. We have studied glioma stem cells derived from patients, comparing their molecular characteristics with the rest of the tumor cells in order to obtain biomarkers of glioma stem cells and elucidate the oncogenic aberrations present in this type of cells.

The TGF-beta signal transduction pathway in glioma

The best-characterized pathways involved in glioma are the tyrosine kinase receptor pathways (EGFR, PDGFR) and many reports have shown that these pathways tend to be hyperactive and promote glioma genesis. However, other pathways such as the TGF-beta pathway have recently been shown to play a relevant role in glioma progression. Little is known about the mechanisms of signal transduction of the TGF-beta pathway and its role in oncogenesis. We are characterizing the activity and function of the TGF-beta pathway in human glioma and how it is interconnected with other pathways. We are studying how this pathway regulates glioma cell proliferation, invasion, motility, angiogenesis and differentiation. We aim to understand why and how the TGF-beta pathway is aberrantly regulated in cancer and we expect our results to contribute to the knowledge of the signal transduction mechanisms of TGF-beta in the context of cancer and normal development. Our work is based on the study of patient-derived tumor cells and biopsies.

Role of the forkhead transcription factor FoxG1 in glioma

We are studying a transcriptional factor that may have a crucial role in the genesis of glioma. FoxG1 (previously known as BF1) is a transcription factor of the forkhead family and is the cellular homolog of Qin, the oncogene of the avian sarcoma virus 31. Importantly, FoxG1 is expressed in the neuroprogenitors of the telencephalon but not in differentiated cells and is essential for forebrain formation. Its ablation causes premature differentiation and cell cycle arrest of neuroprogenitors, impairing the development of the telencephalon.
Interestingly, data from our laboratory have shown that FoxG1 is expressed in human high grade gliomas as well as in glioma cell lines and we have some indications that FoxG1 might be relevant in glioma genesis and progression as a putative new oncogene. We are studying FoxG1 transcriptional regulation and determining why FoxG1 is aberrantly expressed in gliomas. We are studying the regulation of its activity identifying FoxG1 post-transcriptional modifications. In addition, we are identifying the set of genes regulated by FoxG1.

AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.5 VHIO-Genitourinary, Central Nervous System (CNS), Sarcoma and Cancer of Unknown Primary Site

Group Leader
Joan Carles Galcerán
Tel. 93 274 62 73
jcarles@vhio.net

Medical Oncologists
Jordi Rodón
Cristina Suárez
Claudia Valverde

Clinical Fellows
Rafael Morales
César Serrano

OBJECTIVES

- Design and development of clinical trials for genitourinary malignancies with the active participation of investigators from the Urology, Radiation Therapy and Medical Oncology Departments.
- Creation of a translational research platform for Urologic Cancer.
- Collaboration of physicians from the different disciplines involved in the Urologic cancer Board for the carrying out of doctoral theses of fellows belonging to each department.
- Collaboration with the Spanish Oncology Genitourinary Group (SOGUG) in order to conduct clinical trials at different stages of the disease with emphasis on a histologic-tailored design.
- Consolidation of the CNS Committee with the development of several multidisciplinary clinical trials.
- Consolidation of a translational research platform for Glioblastoma, in collaboration with the lab of Joan Seoane.
- Collaboration with the Spanish Sarcoma Group (GEIS) in order to conduct clinical trials at different stages of the disease with emphasis on a histologic-tailored design.
- Creation of a translational platform for Sarcomas and Basic Research in close collaboration

with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Center of Salamanca (CIC).

- The option for every member of the group to spend a minimum of 3 months in centers of acknowledged prestige in a specific area. In the following years, the program will promote shorter stays for the development of joint projects.

RESEARCH LINES

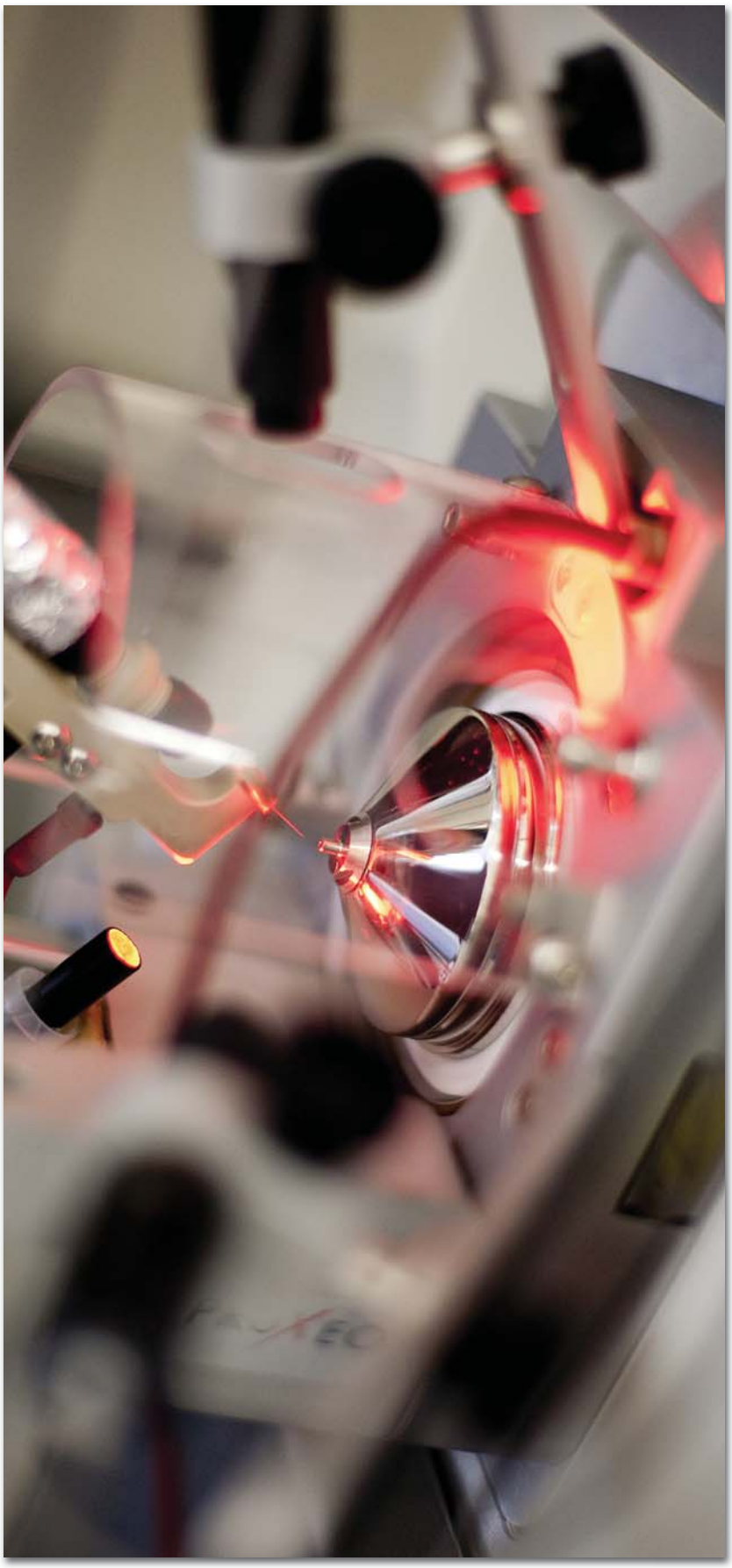
Implementation of a Urologic Oncology Functional Unit (Vall d'Hebron Urologic Tumors Center)

Development of a translational platform in prostate cancer in parallel with the development of innovative clinical trials, with special focus on the androgen receptor

Consolidation of the Committee on Nervous System Tumors, with the development of several multidisciplinary clinical trials, with special focus on drugs in early development (phase I and early phase II) with TGFβ inhibitors and PI3K inhibitors

Our main focus surrounds innovative trial designs in first line in combination with radiation therapy and in second/third line of treatment.

Consolidation of the Bone and Soft Tissue Sarcoma Committee



Area 1 Oncology and Genetics

Vall d'Hebron Institute of Oncology (VHIO)

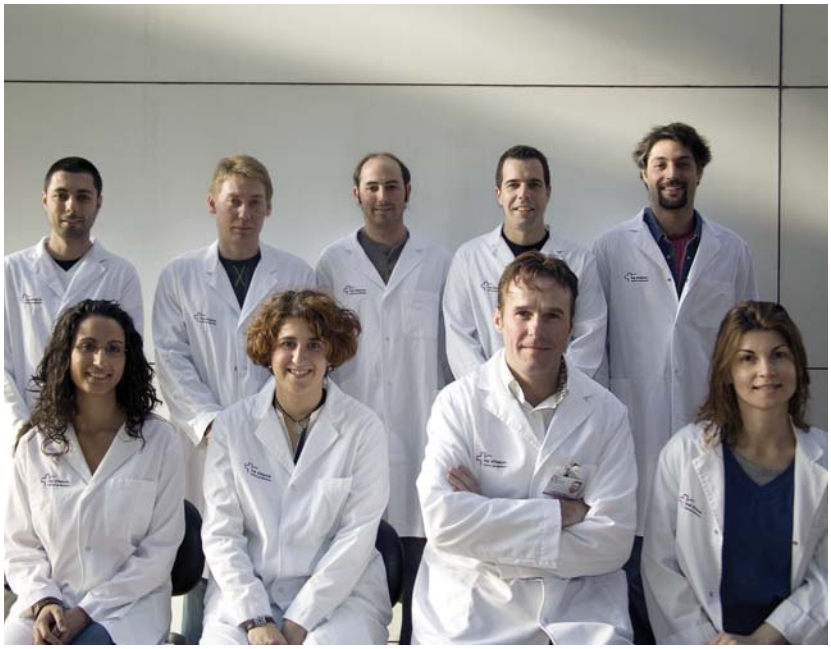
1.6 VHIO-Growth Factors

Group Leader
Joaquín Arribas López
Tel. 93 274 68 60
joaquin.arribas@vhir.org

Researchers
Joaquín Arribas López
Kim Pedersen
Josep Lluís Parra Palau
Mariano Zacarias Fluck
Beatriz Morancho Armisen
Aniello Cerrato

Researchers in Training
Pier David Angelini
Cristina Bernadó Morales

Nursing, Technical and Administrative Staff
Marta Escohiruela Baez
Maria Cristina Ferrer Ramon
Antonio Luque García
Elena Guzmán Guerrero



OBJECTIVES

The Growth Factors Laboratory explores the role of certain signal transduction pathways in the progression of breast cancer. Breast cancer is the most common cancer among women; according to the World Health Organization, more than 1.2 million women will be diagnosed with breast cancer each year worldwide and over 500,000 will die from the disease.

Approximately 30% of patients with breast cancer express excessive levels of the tyrosine kinase receptor HER2. The prognosis of these patients is clearly worse than that of patients with normal levels of the receptor. HER2 (ErbB2) belongs to the family of the epidermal growth factor receptor (EGFR), which also includes HER3 (ErbB3) and HER4 (ErbB4). We are currently investigating the relevance of novel isoforms of HER2 in tumor progression and treatment.

RESEARCH LINES

The HER signaling pathway

Dimerization of the extracellular domains leads to interaction between the intracellular kinases of the HER receptors and subsequent transphosphorylation of certain tyrosine residues in the C-terminal tail. These phosphotyrosines act as docking sites for a group of intracellular phosphotyrosine-binding proteins that transduce signals from the plasma membrane to the nucleus via different signalling pathways, including the mitogen activated protein kinases (MAPKs), PI(3)K-activated Akt, Src and phospholipase C gamma (PLCgamma) pathways. These signalling circuits control the expression of target genes that act in coordination to modify key aspects of cellular biology, including proliferation, migration, survival and differentiation.

Novel signaling abilities of HER receptors and their fragments

In addition to the canonical mode, HER receptors, or fragments of them, seem to be endowed with

direct signalling abilities. HER2 is a substrate of metalloproteases collectively known as alpha-secretases, which release the extracellular domain, leaving behind the transmembrane-cytoplasmic fragment, known as P95. By analogy with other transmembrane proteins also cleaved by alpha-secretases, it has been suggested that the cleavage of P95 can also be achieved by gamma-secretases, which release the intracellular domain in a process known as RIP (regulated intramembrane proteolysis).

Although P95 has been poorly characterized, partly because it is produced at very low levels in cultured cell lines, it has been suggested that it is active. However, since P95 lacks the extracellular domain, it is not predicted to form hetero- or homodimers. Thus, the mechanism of activation of P95 remains unexplained. We have recently identified alternative initiation of translation as an additional mechanism that generates CTFs of HER2 similar, but not identical, to P95. Initiation of translation from methionine codons, located upstream or downstream of the transmembrane domain, leads to the generation of two different CTFs. Although preliminary evidence suggests that CTFs generated by translation are active, as in the case of P95, the mechanism of activation is unknown. In summary, at least four different HER2 CTFs are generated by two independent mechanisms: proteolytic processing and alternative initiation of translation. Two HER2 CTFs contain the transmembrane and cytoplasmic domains while two are predicted to be soluble intracellular proteins encompassing most of the cytoplasmic domain.

HER2 fragments and breast cancer progression and treatment

Breast cancer patients expressing CTFs of HER2 are more likely to develop nodal metastasis and have a worse prognosis than those expressing predominantly the full-length receptor. Furthermore, the presence of CTFs seems to be relevant for tumor treatment. Currently, two types of drugs targeting HER2 are used in clinical practice: monoclonal antibodies against the extracellular domain and small-molecule inhibitors that block the kinase activity of the receptor. We have recently shown that approximately 90% of breast cancer patients expressing CTFs are resistant to treatment with the anti-HER2 antibody Herceptin (trastuzumab). However, the CTFs expressed in tumors have not been characterized in detail and it is not known if these fragments arise in tumors by proteolysis and/or alternative initiation of translation. Furthermore, since the activity of the different CTFs has not been analyzed individually, their relative contribution to the malignant phenotype has not been determined.

Development of specific antibodies against HER2 CTFs

In 2010 we finished a comprehensive analysis of the different CTFs of HER2 expressed in breast cancers. In addition we were able to generate and characterize monoclonal antibodies that recognize epitopes exposed in the fragments but masked in full-length HER2. These antibodies constitute a useful tool to identify p95HER2-positive tumors and to find a better treatment for this subtype of patients.

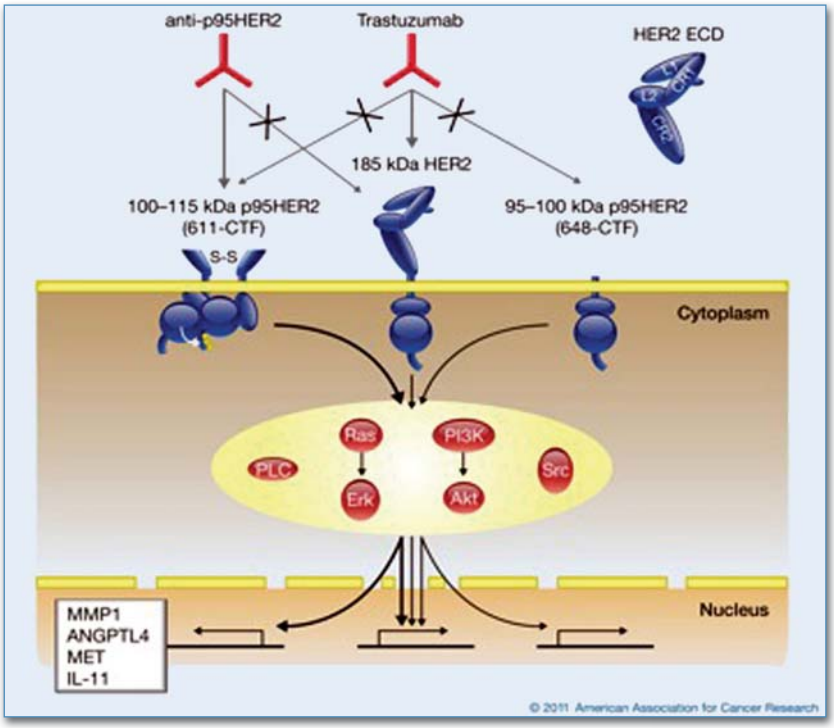


Figure 15
Full-length HER2 (middle, blue), the 100- to 115-kDa p95HER2 fragment generated by alternative initiation of translation from the AUG codon in position 611 (left) and the 95- to 100-kDa p95HER2 generated by proteolytic cleavage of full-length HER2 (right). Note that the names of different domains are marked in the soluble extracellular domain of HER2 (HER2 ECD). Top, the antip95HER2 antibodies recognize epitopes in 100- to 115-kDa p95HER2 that are masked in fulllength HER2 and absent in 95- to 100-kDa p95HER2. Within the cytoplasm, the red globes represent selected components of signaling pathway activated by HER2 and p95HER2. Bottom, gene expression is regulated by the different HER2 forms. Note that a group of genes specifically regulated by 100- to 115-kDa p95HER2, such as MMP1, ANGPTL4, MET, and IL-11, have been causally involved in the metastatic progression

AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.7 VHIO-Head, Neck and Gynecological Tumors

Group Leader
Josep Maria del Campo
Tel. 93 489 48 25
jmcampo@vhebron.net

Attending Physicians
Isabela Díaz de Corcuera
Ana Oaknin
Victor G.Freixinos

Clinical Trials Coordinators
Cristina González
Mireia Sanchis
Olga Padros

OBJECTIVES

Our team aims to consolidate itself as a reference center by creating high-level multidisciplinary teams. To this end, we encourage training of specialists involved in gynecological and head and neck tumors through a Fellowship in hospitals of international reference.

- Create a regional network of hospitals to facilitate patient access to novel treatment in clinical trials that are currently limited to centers of reference.
- Form part of the Management structures of the cooperative groups of the utmost International relevance (ENGOT, GCIG) and strengthen relations with highly specialized centers in our areas of interest (NCIC, Peter McCallum CC, Irvine MC, HSK Wiesbaden).
- Develop our own database for each disease to facilitate exhaustive reviews of practical interest and publishing potential.
- Increase dissemination via international forums and impact factor publications.

RESEARCH LINES

Reference Center in Patient Care and Clinical Research

Highly specialized in treatment

Training in Gynecological Oncology

Fellowships

International projection

Potentiate scientific activity

Publications in high impact factor journals

Presenting at International conferences

AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.8 VHIO-High Risk and Cancer Prevention

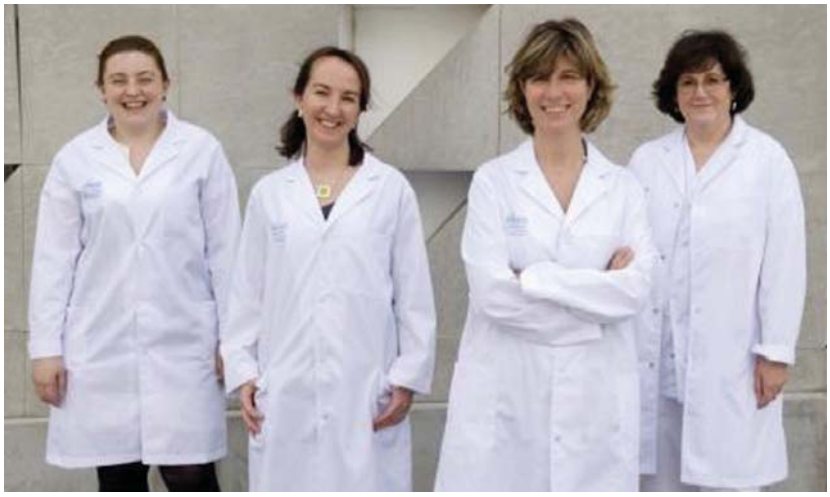
Group Leader
Judith Balmaña
Tel. 93 274 60 00 (ext. 4713)
jbalmana@vhebron.net

Staff Scientist
Nina Bosch

Clinical Nurse Specialist
Neus Gadea

Research Fellow
Begoña Graña

Graduate Student
Maria Coma



OBJECTIVES

We are continuing to develop specific new therapies for patients with hereditary cancer and patients with sporadic cancer who share molecular abnormalities similar to those of hereditary cancer. We are also participating in several clinical trials with these new compounds, from phase I to II, in patients with early and advanced cancer.

We are performing in-depth analysis into the long-term psychosocial impact of genetic studies in hereditary syndromes, specifically after BRCA disclosure and in the male population. We are also analyzing the intake of prophylactic surgeries among BRCA mutation carriers.

At international level, we are participating in a study aimed at analyzing the efficacy of early detection of prostate cancer in patients with a mutation in the *BRCA1 or a BRCA2* gene, and we are also taking part in a national study to determine the role of breast density as a risk factor for breast cancer in women with mutations in the *BRCA1/2* genes.

We have started to run next generation studies to search for mutations in new genes conferring predisposition to hereditary breast cancer.

We are participating in an international collaboration to validate and compare the PREMM1,2,6 predictive model for identification of Lynch syndrome patients with a mutation.

RESEARCH LINES

Development of clinical and molecular tools to identify people with Lynch syndrome or hereditary breast and ovarian cancer syndrome associated with BRCA1 or BRCA2, or P53 mutations

Analysis of the medical and psychosocial impact of genetic studies in hereditary cancer syndromes (BRCA and Lynch syndrome)

Development of specific therapeutic strategies for tumors associated with hereditary genetic alterations

Identification of new genes causing predisposition to hereditary breast cancer

Evaluation of the risk of cancer and follow up strategies for adult patients with Fanconi anemia and survivors of other childhood hereditary cancer syndromes with genetic predisposition to late-onset cancer

Area 1 Oncology and Genetics

Vall d'Hebron Institute of Oncology (VHIO)

1.9 VHIO-Oncogenetics

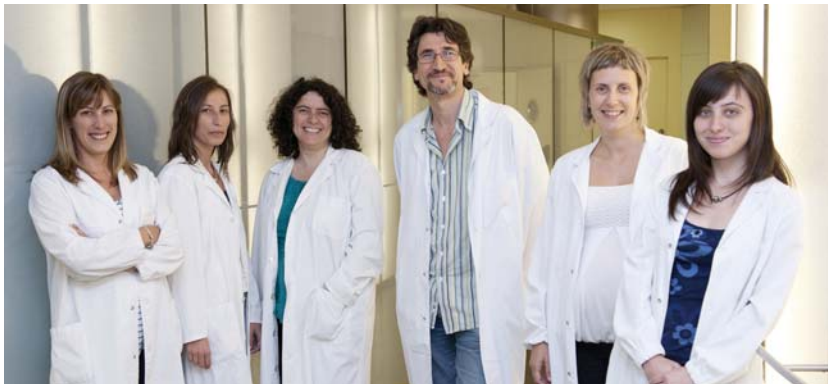
Group Leader
Orland Díez
Tel. 93 489 48 26
odiez@vhebron.net

Staff Scientists
Sara Gutiérrez Enríquez

Post-Doctoral Fellow
Sandra Bonache Real

Graduate Student
Gemma Montalbán Canudas

Technicians
Miriam Masas Castro
Anna Tenés Felipe



OBJECTIVES

- Molecular analysis of the genetic predisposition to hereditary cancer (breast/ovarian cancer syndrome, Li-Fraumeni syndrome).
- Application of massively parallel sequencing for the study of cancer predisposition genes.
- Molecular analysis of the genetic predisposition to side effects of radiotherapy.

RESEARCH LINES

Identification and characterization of new germ line sequence variants in BRCA1, BRCA2, and TP53 in cancer families

Development of probability models for predicting BRCA1 and BRCA2 mutations in 3.500 Spanish families with breast/ovarian cancer

Collaboration in the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) International Consortium for the analysis of variants with potential splicing effects, unknown biological significance, and transcriptional isoforms in BRCA1 and BRCA2

Molecular analysis of other DNA repair genes related to breast/ovarian cancer predisposition (CHEK2, RAD51C, RAD51D, PALB2, ATM, etc.)

Analysis of genetic modifiers of risk in BRCA1/BRCA2 breast/ovarian cancer families. Collaboration in the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)

Identification of new genes of predisposition to familiar breast/ovarian cancer by targeted capture and massively parallel sequencing

Characterization of transcriptional profiles induced by ionising radiation in cells with mutations in BRCA1 or BRCA2 genes

Identification of genes for susceptibility to radiotherapy side-effects by genetic association studies. Collaboration with the International Radiogenomics Consortium

Transcriptional profiles and apoptosis analysis as biomarkers for radiotherapy toxicity in breast cancer patients

AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.10 VHIO-Proteomics

Group Leader
Francesc Canals Suris
Tel. 93 489 41 75
francesc.canals@vhir.org

Researchers
Joan Josep Bech Serra
Francesc Canals Suris
Marta Monge Azemar

Nursing, technical and administrative staff
Adelina Acosta Martín
Núria Colomé Calls

OBJECTIVES

The Proteomics Laboratory provides services to research groups on latest-generation proteomics methodologies. The importance of the interaction between tumor cells and their microenvironment in malignant progression has been recently highlighted. Different metalloproteases play a crucial role in the regulation of the tumor microenvironment by mediating the remodeling of the extracellular matrix and the processing of extracellular and membrane proteins. Knowledge of the substrate repertoire (degradome) of these proteases is needed to elucidate their role in tumor growth and metastasis, in order to evaluate their potential use as therapeutic targets. We have demonstrated the utility of proteomic techniques to explore these degradomes. The present focus of our research is to extend these studies, incorporating new proteomic analysis techniques, to study metalloproteases known to play key roles in tumor progression. Metalloproteases of the ADAM family (ADAM10, ADAM17/TACE), and of the ADAMTS family (ADAMTS1) will be the object of study. TACE and ADAM10 are involved in the proteolytic cleavage of the transmembrane forms of EGFR ligands (shedding), required for the activation of the receptor, and are also involved in regulation of cell migration and adhesion. Several metalloproteases of this family are overexpressed in different types of tumors. The thrombospondin-domain containing protease ADAMTS1 has been recently found to be highly overexpressed in highly invasive mammary tumor cells, suggesting a major role for this protease in metastatic processes. The proposed proteomic studies aim for the identification and characterization of new substrates of these proteases in the context of cancer cells. The putative substrates identified will then be validated through characterization in vitro. The importance of the newly identified substrates in tumor development will be analyzed in preclinical models and their expression and shedding will be determined in mammary tumor samples.

RESEARCH LINES

Identification of substrates of ADAM10 and ADAM17 proteases using SILAC analysis

In order to search for substrates of the ADAM10 and ADAM17 metalloproteases, we have used model breast cancer cells in which conditional expression has been introduced, using the tet-off system, of either the protease or siRNA to knock down specifically the protease of interest. The comparison between conditions where the protease is either inactive or active can be then carried out in the same cell clone. Differential proteomic analysis of the conditioned culture media of these cells has been performed using a SILAC (stable isotope labeling through aminoacids in culture) approach, and an analytical workflow comprising 1D-SDS-PAGE fractionation followed by liquid-chromatography coupled to electrospray mass spectrometry (LC-MS). Labeling is accomplished supplying specific labeled amino acids in the cell culture medium, thus allowing the labeling of all the proteins in the cell through its own metabolic processes. In this way, quantitative information can be obtained for all the proteins detected in the analysis. A number of known substrates of both proteases were identified as such in the analysis, showing the expected decrease of the shed extracellular domain abundance in the medium upon knock down of the protease. In addition, several new candidate substrates of both proteases were identified. Among them, the GPI-anchored protein C4.4A, was identified and further validated as substrate of both ADAM10 and ADAM17 proteases. According to the identified peptides, both proteases cleave this protein close to the juxtamembrane region, releasing a soluble form devoid of the GPI-anchor. C4.4A protein, homologous to the urokinase-type plasminogen activator receptor, has been related to tumor invasion and metastasis. Cleavage of this protein by ADAMs constitutes a previously unknown level of regulation of its function. Work is in progress to validate and further characterize other proteins identified as potential substrates of these proteases.

Identification of ADAMTS1 substrates using DIGE and SILAC proteomic analysis

We have applied two complementary proteomic approaches, 2D electrophoresis DIGE and SILAC LC-MS analysis, to the search for substrates of the metalloprotease ADAMTS1, in a model breast cancer cell line where conditional overexpression of the protease was introduced. Glycoproteins of the conditioned media from parental and ADAMTS1 overexpressing cells were purified and analyzed using a 2D-DIGE electrophoresis approach (Figure 2) and a SILAC methodology similar to the one described above for the ADAM10 and ADAM17 experiments. Both approaches led to the identification of thrombospondin-1 as a substrate of ADAMTS1, which has been reported recently by others, and shown to play a role in modulating angiogenesis. Semaphorin 3C was also identified by both methodologies, and further validated as a substrate of both ADAMTS1 and ADAM17. This family of extracellular matrix proteins plays different roles in cell axon guidance in the nervous system, as well as in angiogenesis and tumor progression. The role of Semaphorin 3C in cancer cell migration is currently being investigated.

Other collaborative projects with VHIO groups

- *Signaling through C-terminal fragments of HER-2 in breast cancer* (with J. Arribas Lab.): SILAC proteomic analysis was used to analyze protein-protein interaction partners of HER-2. Several potential mediators of HER-2 signalling, as well as previously unreported phosphorylation sites have been identified.
- *Screening for surface marker proteins of glioma-initiating stem-cells* (with J. Seoane Lab.): Several candidate proteins have been identified as putative surface markers of glioma neurosphere forming cells through cell-surface proteome analysis.
- *Biomarkers to monitor response to Hsp-90 inhibitor IPI-504 treatment* (with M. Scaltriti- J.Baselga Lab.): Several candidate biomarkers of IPI-504 action have been identified by SILAC proteomic analysis of model cells.

Facility and Collaborative Work

The Proteomics Laboratory has continued providing services as a member of the "Instituto de Salud Carlos III" Cancer Research Network, and of the "Instituto Nacional de Proteómica ProteoRed", funded by "Fundación Genoma España". This year, the laboratory has provided services to more than 30 research groups, not only from the Vall Hebron Hospital, but also to the main hospitals, research centers and universities in the area. In summary, the analyses performed include 40 2D-DIGE gels, 20 quantitative ICPL or SILAC experiments, representing a total of more than 450 LC-MS runs, and around 500 protein identifications by peptide mass fingerprint. In conjunction with the services provided, the laboratory has actively participated in several projects involving proteomic analysis. In collaboration with Dr. R. Simó, of the Endocrinology Unit at the VHIR we have continued to apply DIGE technology to study alterations in the protein content of vitreous fluid of proliferative diabetic retinopathy patients subjected to vitrectomy. Together with the Department of Immunology at the Universitat Autònoma, Barcelona, led by Dr. Dolores Jaraquemada, we have been working on the analysis of repertoires of HLA associated peptides of cell lines related to autoimmune diseases or cancer. In the framework of the ProteoRed network, the laboratory has coordinated a multicentric study to evaluate reproducibility of a 2D-DIGE differential proteomic experiment. The results of the study show the robustness of the methodology used, and demonstrate the feasibility of across-lab validation schemes, pointing towards development of inter-lab QC strategies for proteomics research. The results were presented at the ABRF'09 Meeting, the 3rd SEPROT-LAHUPO Congress, and at the HUPO special meeting on reproducibility studies as preliminary requirements to launch the HUPO Human Proteome Project.

Area 1 Oncology and Genetics

Vall d'Hebron Institute of Oncology (VHIO)

1.11 VHIO-Radiation Oncology

Group Leader
Jordi Giralt
Tel. 93 274 60 86
jgiralt@vhebron.net

Radiation Oncologists
Manel Altabas
Sergi Benavente
Xavier Maldonado
Meritxell Molla
Begoña Navalpotro
Mónica Ramos
Victoria Reyes
Ramona Vergés

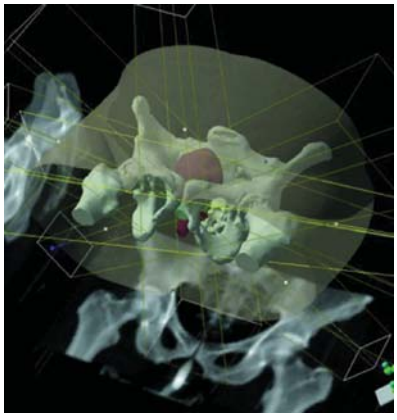
OBJECTIVES

- Continuation of the IMRT program in pediatric, gynecological and gastrointestinal tumors.
- Development of the extracranial stereotactic radiotherapy program in lung cancer and liver metastases.
- To improve quality control programs and develop new techniques.
- Study new therapeutic combinations with radiotherapy and EGFR inhibitors in head and neck cancer and gastrointestinal tumors.

RESEARCH LINES

Technology developments: Highly conformal Radiotherapy

Translational research: EGFR inhibitors plus Radiotherapy



AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.12 VHIO-Stem Cells and Cancer

Group Leader
Héctor García Palmer
Tel. 93 274 49 25
hgpalmer@vhio.net

Researchers
Héctor García Palmer
Isabel Puig Borreil
Stephan Tenbaum

Nursing, Technical and Administrative Staff
Irene Chicote Ramos

OBJECTIVES

The main interest of our laboratory is to understand the molecular mechanisms that control the initiation and progression of epithelial tumors. In particular, we are focused on the study of the intra-tumoral cell heterogeneity inherent to colon cancer and its consequences for the progression of the disease. Among the different cell populations present in colon carcinomas we are currently identifying those responsible for drug-resistance and relapse as well as those with enhanced metastatic capacity. Relapse and metastasis frequently occur and patients at these advanced stages present short life expectancy. Some cells among drug-resistant and metastatic populations retain properties similar to stem cells and have been termed "cancer stem cells". In colon cancer, they represent rare populations with long-term self-renewing capacity that perpetuate tumors and give rise to all types of malignant cells present in the cancerous tissue.

At the molecular level, we are analyzing the relevance of Wnt/β-catenin and PI3K/AKT pathways controlling the fate of colon cancer stem cells. We have recently discovered that these oncogenic pathways play a central role promoting metastasis and resistance to a new generation of drugs directed to inhibit PI3K or AKT signalling. Our results could impact directly on treatment with these target-directed drugs which are currently being tested in numerous clinical trials worldwide.

We are specifically interested in novel mechanisms of gene transcription-dependent on these pathways and their relevance in driving stem cell decisions: self-renewal vs. differentiation, apoptosis vs. survival, proliferation vs. quiescence.

Our technical approaches include cellular and molecular biology, mouse models of cancer and, most importantly, the analysis of cells directly derived from patients with colon carcinomas directly upon surgery. This line of work is extremely exciting since it allows us to work with human cancer stem cells - a privileged opportunity in the field of cancer research.

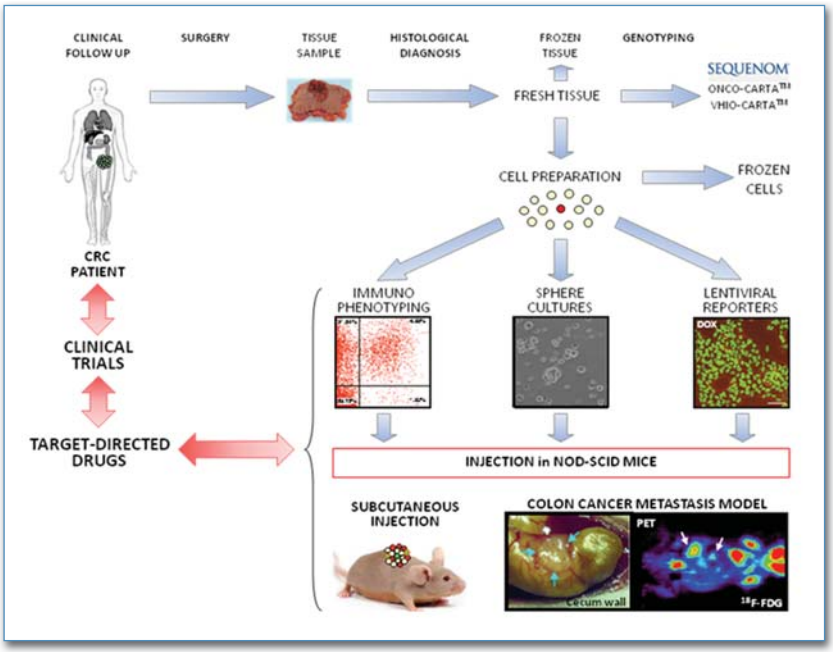


Figure 16
Working circuit to study colon cancer patient-derived cells. Cells are derived from patients immediately after surgery. Cell suspension is obtained and different analyses in vivo and in vitro are performed. Particular target-directed drugs are tested in the laboratory and the results are translated to oncologists to design safer and more personalized clinical trials for colon cancer patients

RESEARCH LINES

To study the role of cancer stem cells in the initiation, progression and self-renewal of epithelial tumors

To investigate the enhanced capacity of colon cancer stem cells to resist target-directed drugs and their contribution to patient relapse and metastasis

Characterization of new molecular features of Wnt/beta-catenin and PI3K/AKT signalling pathways and their relevance in normal and cancer stem cells physiology

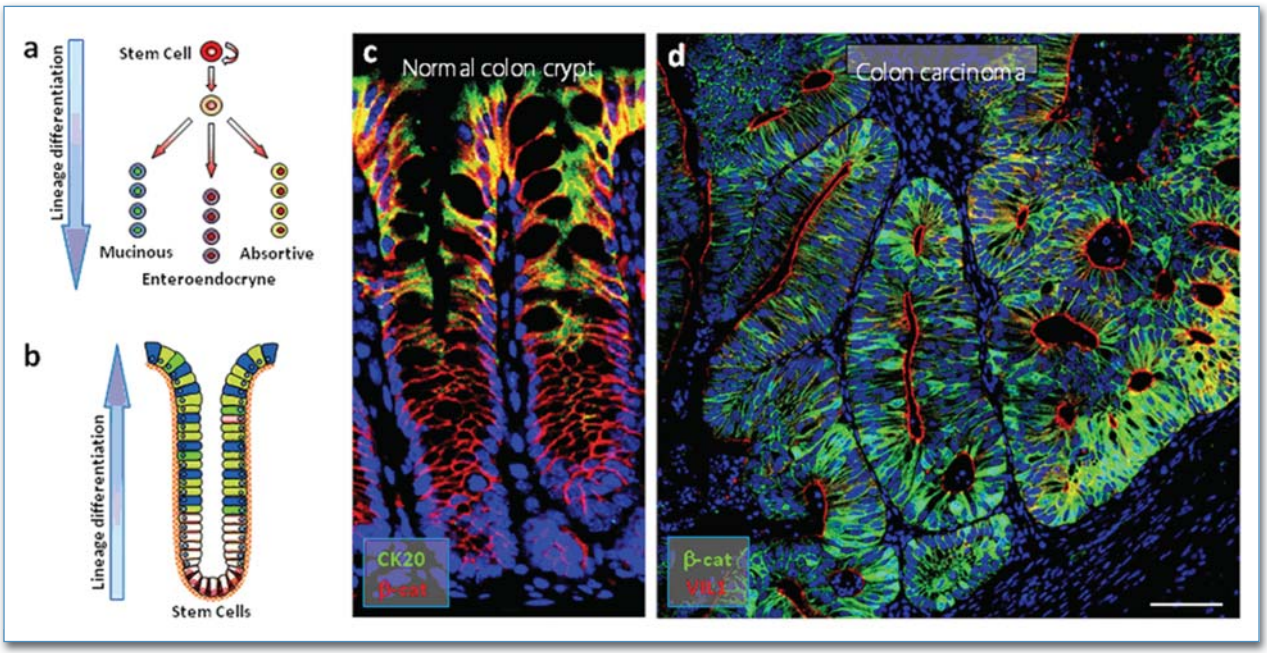


Figure 17
Normal and Cancer Stem Cells are the source of cell heterogeneity in human colon epithelium and carcinomas. (a) Programmed mechanisms that drive lineage selection in normal colon crypts are retained in carcinomas. (b) Normal colon crypt with stem cells at the bottom (red), proliferative cells in the middle (white) and differentiated cells in the upper part (green, yellow and blue). (c) Immunofluorescence and confocal microscopy showing differentiated cells positive for Cytokertatin 20 (CK20) in green and the expression of beta-catenin in red. (d) Immunofluorescence and confocal microscopy showing differentiated cells positive for Villin1 (VIL1) in red and heterogeneous expression of beta-catenin in green. (c,d) Nuclei were stained with Hoechst 33342. Scale bar, 100 μm

AREA 1 ONCOLOGY AND GENETICS

Vall d'Hebron Institute of Oncology (VHIO)

1.13 VHIO-Thoracic Tumors

Group Leader
Enriqueta Felip
Tel. 93 274 60 98
efelip@vhebron.net

Attending Physicians
Susana Cedrés
Pablo Martínez
Alex Martínez
Victor Freixinós

Head of Study Coordinator
Irene Marimón

Clinical Trials Coordinators
Oriol Nualart
Meritxell Soler
Marta Beltrán

OBJECTIVES

- Implement the determination ALK translocation.
- Study the efficacy of PI3K/mTOR inhibitors in patients with lung cancer resistant to EGFRTKIs.
- Research the efficacy of PARP inhibitors in lung cancer.
- Analyze the epidemiologic/clinical characteristics of women diagnosed with lung cancer.
- Play an active role in organizing a European consensus meeting on lung cancer.

RESEARCH LINES

Optimization of multidisciplinary treatment in patients with stage IIII Cancer

Early integration of genetic determinations to personalize treatments

Participation in the development of new drugs

Active intervention in the fight against smoking

Area 1 Oncology and Genetics

Vall d'Hebron Institute of Oncology (VHIO)

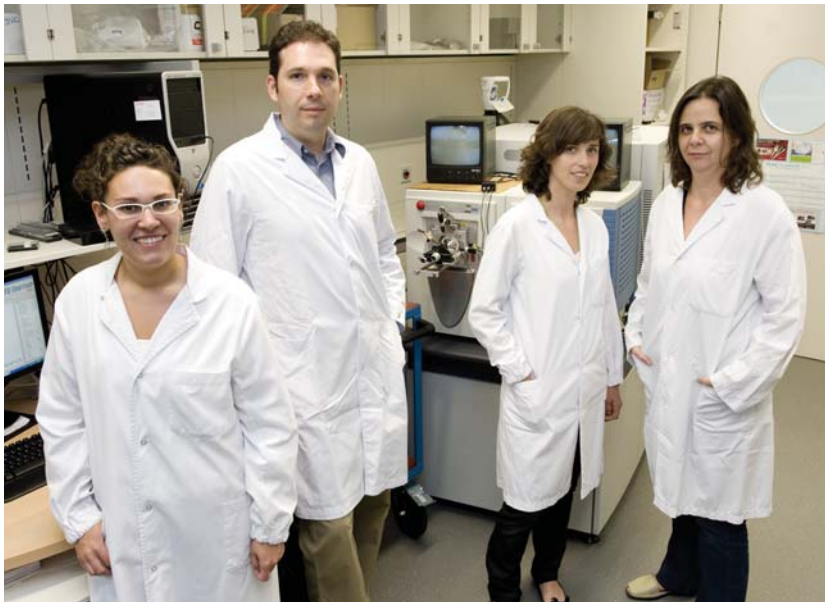
1.14 VHIO-Tumors Biomarkers

Group Leader
Josep Villanueva Cardús
Tel. 93 489 41 75
josep.villanueva@vhir.org

Researchers
Olga Méndez Fernández
Josep Villanueva Cardús
Laura Villarreal Tolchinsky

Researchers in Training
Cándida Salvans Gorjon
Sílvia Torrents Zapata

Nursing, Technical and Administrative Staff
Laura Córcoles Pujadas



OBJECTIVES

The aim of this group is to discover new tumor-specific biomarkers and therapeutic targets using proteomic methodologies to improve cancer diagnostics and therapeutic treatment. Our specific goals are:

- The characterization of the mechanisms used by tumor cells to communicate with their microenvironment during tumorigenesis, and its exploitation for biomarker discovery.
- The discovery of secreted signaling pathway-based tumor biomarkers and therapeutic targets using quantitative proteomics.
- The discovery of secreted response/resistance biomarkers to targeted drug therapy measurable through non-invasive methods.

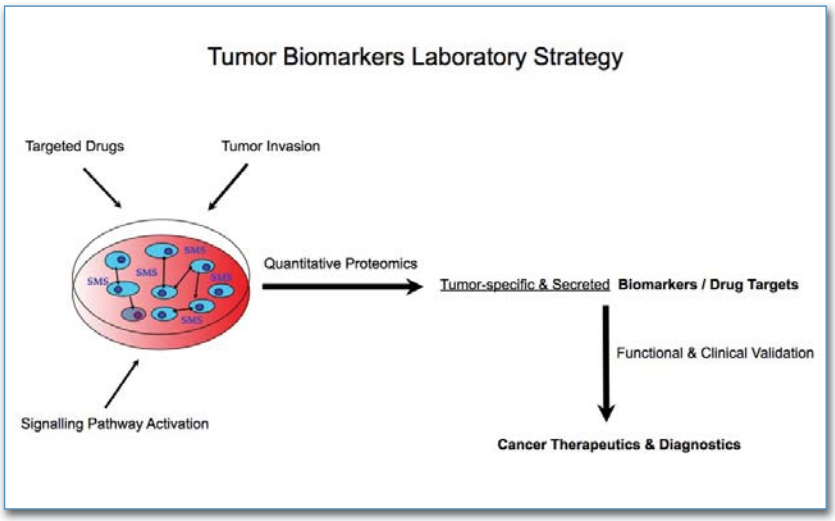


Figure 18
Scientific strategy of the Tumor Biomarkers Laboratory

RESEARCH LINES

Tumor cell communication with its microenvironment plays a key role in tumor initiation and progression

Tumor cells hijack the tumor microenvironment ecosystem via paracrine signaling to promote a pro-oncogenic microenvironment that is critical for the establishment of primary and metastatic tumors. The working hypothesis of the laboratory is that cellular signaling pathways are altered during the tumorigenesis process, and that these alterations are translated into differential protein secretion, which potentially can be exploited to discover secreted markers. Furthermore, some of the differentially regulated proteins could be direct extracellular messengers of intracellular signaling pathways contributing to key steps in cancer initiation and progression, therefore becoming potential therapeutic targets.

The aim of the laboratory therefore is to discover secreted tumor-specific biomarkers and therapeutic targets to improve cancer diagnostics and therapeutic treatment

Proteomic technologies offer the advantage of a genome-scale search for tumor-specific biomarkers and drug targets and could revolutionize early detection and molecular characterization of cancer through non-invasive methods. However, the field of cancer proteomics has encountered problems with reproducibility and limitations related to the massive complexity of biological samples.

The laboratory will consequently focus on the discovery of biomarkers and drug targets using the proteomic profiling of subproteomes, rather than whole tissues or plasma/serum

By using a new proteomics approach capable of the quantitative profiling of the secreted subproteome ("secretome") of cells, we will generate secretome signatures in different cancer model systems, as well as from clinical samples. We are confident that the discovery of secreted tumor-specific biomarkers will play a key role in cancer therapeutics and diagnostics.

CURRENT RESEARCH PROJECTS INSTITUT DE RECERCA – VHIO

PI: José Manuel Baselga Torres
Targeting PI3K in Women's Cancer
Funding Agency: AACR- American Association for Cancer Research
Reference: SU2C-AACR-DT0209
Funding: 954,250 $
Duration: 2009 to 2012

PI: José Manuel Baselga Torres
Overcoming resistance to anti-HER2 therapy with PI3K inhibitors. Anticipating emerging resistance to PI3K pathway inhibition
Funding Agency: Novartis
Reference: Novartis-CIBOT2009
Funding: 699,000 €
Duration: 2009 to 2012

PI: José Manuel Baselga Torres
Novel Cancer Therapies to overcome resistance to anti-HER2 and PI3k inhibitors in breast cancer
Funding Agency: BCRF-Breast Cancer Research Foundation
Reference: BCRF2009
Funding: 200,000 $
Duration: 2009 to 2010

PI: José Manuel Baselga Torres
Inhibiting the PI3K pathway as a therapeutic strategy in breast cancer
Funding Agency: BCRF-Breast Cancer Research Foundation
Reference: BCRF2010
Funding: 223,000 $
Duration: 2010 to 2011

PI: José Manuel Baselga Torres
Estrategias de Reversión de la Resistencia
Funding Agency: ISCIII-Instituto de Salud Carlos III
Reference: PS09/00623
Funding: 714,505 €
Duration: 2010 to 2014

PI: José Manuel Baselga Torres
RTICC - Red Temática de Investigación cooperativa de cáncer
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0020/0075
Funding: 324,898.82 €
Duration: 2007 to 2012

PI: José Manuel Baselga Torres
Ajuts de Suport a la Recerca. Grup de Recerca Consolidat
Funding Agency: AGAUR- Agència de Gestió d'Ajuts Universitaris i de Recerca
Reference: 2009SGR342
Funding: 42,640 €
Duration: 2010 to 2014

PI: Josep Tabernero
RD06/0020/0075. ISCIII. Red Temática de Investigación Cooperativa en Cáncer (RTICC) del Instituto de Salud Carlos III, MSC. Co-Principal Investigator. 2006-2010, renewed 2011.

PI: Josep Tabernero
Genentech 09/001. "In vitro and in vivo activity of the AKT inhibitor GDC-0068 in breast and colon cancer cells". Co-Principal Investigator. 2009-2010.

PI: Josep Tabernero
Fidelity UK Foundation. "Towards Personalized Medicine in Cancer: Acquisition of a Sequenom MassARRAY Platform to match the right patient with the right anticancer therapy". Co-Investigator. 2009-2010.

PI: Josep Tabernero
Rafael del Pino Foundation "Circulating Tumor Cells". Co-Principal Investigator. 2009-2010, renewed 2011.

PI: Josep Tabernero
FP7-HEALTH-2010 (COLTHERES). "Modelling and predicting sensitivity to targeted therapies in colorectal cancers". Co-Principal Investigator 2010-2013.

PI: Joaquín V. Arribas
Functional characterization of novel factors mediating the oncogenic activity of HER2. Role in the progression of breast cancer
Funding Agency: Breast Cancer Research Foundation
Funding: 230,000 $
Duration: 2010 to 2011

PI: Joaquín V. Arribas
Red Temática de Investigación Cooperativa del Cáncer
Funding Agency: Instituto de Salud Carlos III
Reference: RD06/0020/0022
Funding: 272,000 €
Duration: 2011

PI: Joaquín V. Arribas
Fragmentos C-terminales (CTFs) de HER2 en la progresión y el tratamiento de tumores de mama
Funding Agency: Instituto de Salud Carlos III (Proyecto Intrasalud)
Funding: 794,970 €
Duration: 2008 to 2011

PI: Joaquín V. Arribas
SGR Suport a Grups d'Investigació de Qualitat
Funding Agency: AGAUR Generalitat de Catalunya
Funding: 44,720 €
Duration: 2009 to 2014

PI: Joan Seoane Suárez
Mecanismos moleculares implicados en la génesis del glioma y estudio de las células madre tumorales. Identificación de nuevas dianas terapéuticas y marcadores para la estratificación de pacientes y respuesta a fármacos
Funding Agency: Asociación Española contra el Cáncer – AECC
Duration: 2010

PI: Joan Seoane Suárez
EMBO YIP (European Molecular Biology Organization Young Investigator Programme)
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-04778-E
Duration: 2009 to 2013

PI: Joan Seoane Suárez
An Integrated approach to post-transcriptional regulation of gene expression and its role in human disease
Funding Agency: Ministerio de Ciencia e Innovación
Reference: Consolider RNAREG
Duration: 2009 to 2012

PI: Joan Seoane Suárez
SGR Suport a Grups de Recerca de Qualitat
Funding Agency: Agencia de Gestió d'Ajuts Universitaris i de Recerca
Reference: 2009SGR504
Duration: 2009 to 2014

PI: Joan Seoane Suárez
Molecular mechanisms of glioma genesis and progression (Glioma) Grant No 205819ERC Starting Grant
Funding Agency: European Commission
Reference: GLIOMA-205819
Duration: 2008 to 2013

PI: Josep Villanueva
Proteómica cuantitativa de perfiles de secretomas para el descubrimiento de biomarcadores
Funding Agency: ISCIII (Miguel Servet)
Duration: 2009 to 2011

PI: Josep Villanueva
Secretomas de cáncer de mama basados en vías de señalización para el descubrimiento de biomarcadores
Funding Agency: ISCIII (FIS)
Duration: 2010 to 2012

PI: Joan Seoane Suárez
Pathway based secretomes in breast cancer biomarker discovery
Funding Agency: European Union IRG Marie Curie
Duration: 2010 to 2012

PI: Joan Seoane Suárez
Modelling and predicting resistance to molecular therapies in colorectal cancer
Funding Agency: European Union FP7
Duration: 2011 to 2014

PI: Héctor G. Palmer
Human Colon Cancer Stem Cells and Wnt pathway
Funding Agency: Fundació Vall d´Hebron Institut d´Oncología (VHIO)
Duration: 2008 to 2011

PI: Héctor G. Palmer
Human Colon Cancer Stem Cells and Wnt/β-catenin pathway
Funding Agency: Instituto de Salud Carlos III
Reference: FIS - PI081356
Duration: 2009 to 2012

PI: Héctor G. Palmer
Human Colon Cancer Stem Cells
Funding Agency: Olga Torres Foundation
Duration: 2009 to 2011

PI: Héctor G. Palmer
Colon Cancer Stem Cells and Wnt/β-catenin pathway
Funding Agency: Fundación de la Asociación Española Contra el Cáncer (AECC)
Duration: 2010 to 2013

PI: Francesc Canals Suris
Identificación mediante análisis proteómico de nuevos sustratos de metaloproteasas implicadas en cáncer y caracterización de su papel funcional
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/1058
Funding: 286,770 €
Duration: 2008 to 2010

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Adam R, Haller DG, Poston G, Raoul JL, Spano JP, Tabernero J, Cutsem E van. Toward optimized front-line therapeutic strategies in patients with metastatic colorectal cancer – an expert review from the International Congress on Anti-Cancer Treatment (ICACT) 2009. *Ann Oncol* 2010 Aug; 21 (8): 1579-84. ➲ IF: 5.647.

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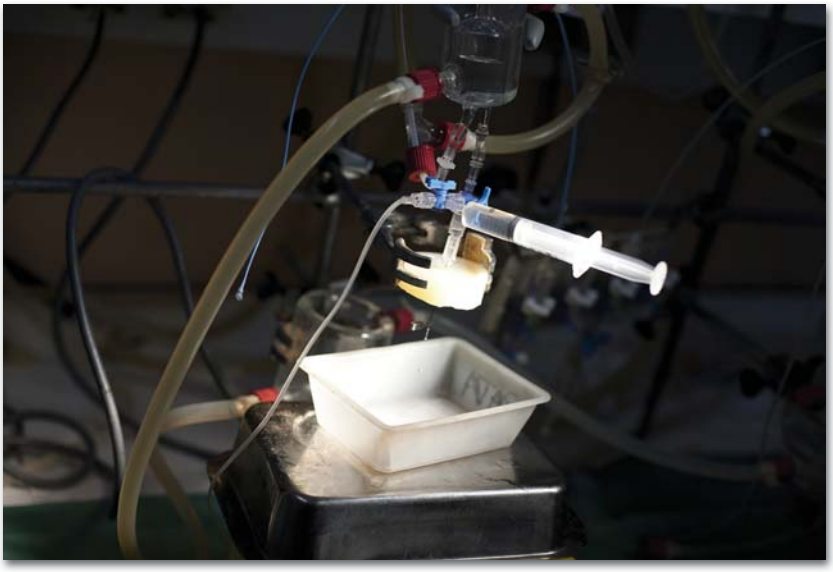

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AREA 1 ONCOLOGY AND GENETICS

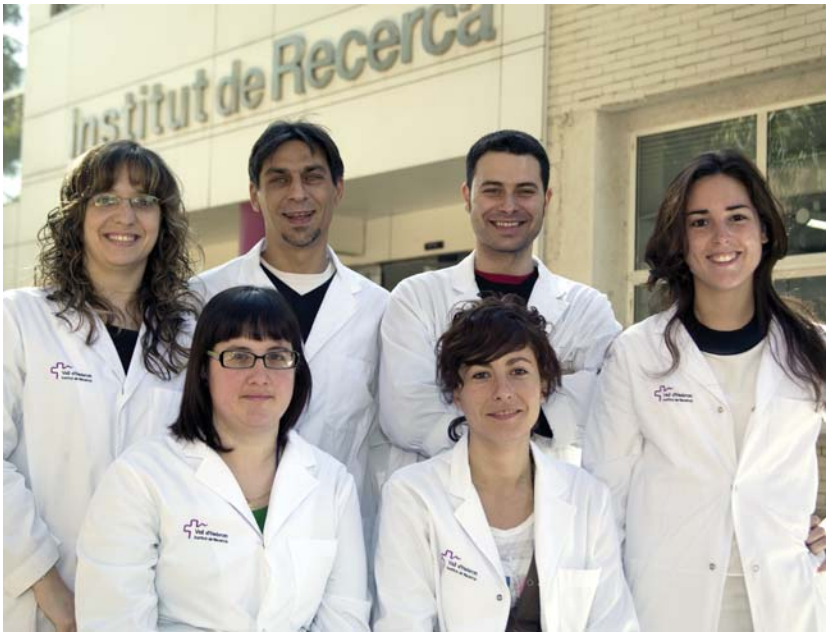
1.15 Animal Models

Group Leader
Juan Ángel Recio Conde
Tel. 93 489 40 75
juan.recio@vhir.org

Researchers in Training
Pedro A. Andreu Pérez
Rosaura Esteve Puig
Ana Carolina Rhodes Cabrerizo

Animal Work Technician
Rosa Gil Villaverde

Lab technician
Judit Grueso



OBJECTIVES

Our main interest is to investigate the genetic and molecular mechanisms underlying tumor development and progression. More precisely, our research is directed to understand melanoma. Melanoma represents the most deadly form of skin cancer. If it is not recognized and treated early, the cancer can advance and spread to other parts of the body, where it becomes hard to treat and can be fatal.

2010 Impact Factor:
11.809

RESEARCH LINES

Discovery of novel molecules involved in melanoma

Using proteomic screenings (DIGE, SILAC) applied to tumor cell lines obtained from primary tumors raised on relevant animal models that recapitulate the human disease (such as: HGF mouse melanoma model), we isolated and identified 56 novel phospho-proteins in response to growth factors that participate in the tumor behavior and maintenance. Among the molecules identified was the LKB1 energy sensor kinase. This molecule is deleted or mutated in different type of tumors (lung, colon, melanoma...). Our results indicated an important link between RAS pathway activation and the LKB1 kinase that belongs to the energy sensor pathway. Importantly, BRAF is mutated in 70% of melanomas. BRAF mutant melanoma cell lines showed constitutive levels of LKB1 phosphorylated, indicating the crosstalk between RAS and LKB1 pathways, and an unusual resistance to energy stress conditions. Further investigations lead us to discover that BRAF signaling was mediating the uncoupling of LKB1

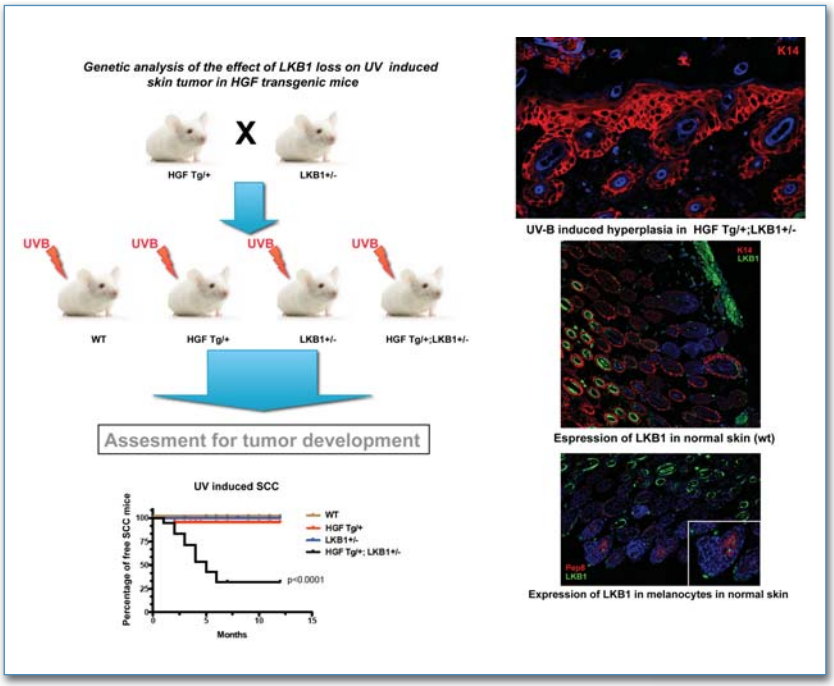


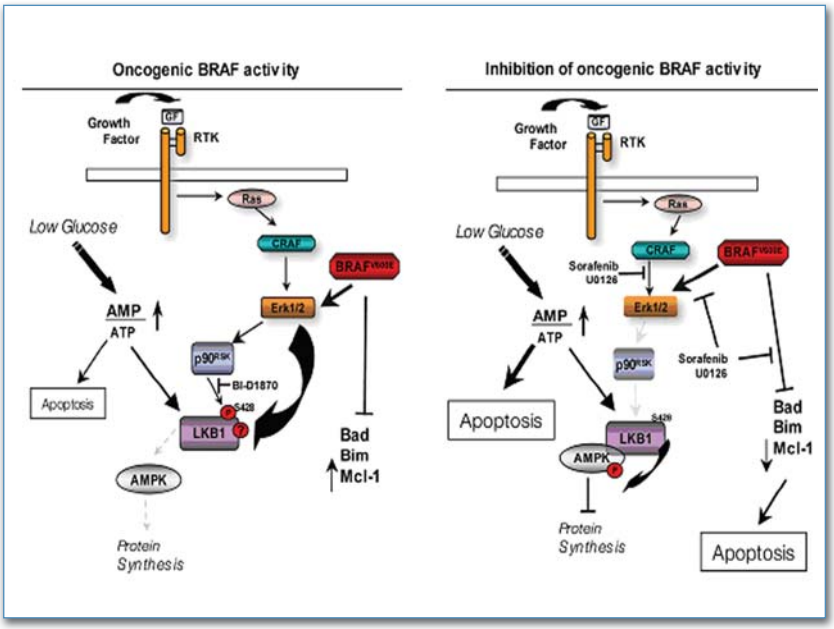
Figure 19
Crossing strategy to generate the HGF Tg/+;LKB1+/- mice to investigate tumor development in response to UVB. Representative images of UVB induced skin hyperplasia, expression of LKB1 in normal skin and nuclear localization of LKB1 in melanocytes within the hair follicle

and its downstream target AMPK disconnecting the energy sensor pathway, making these mutant cells resistant to low energy conditions. Importantly, the inhibition of BRAF signaling in combination with metabolic stress or activators of AMPK, lead the cells to apoptosis (Esteve-Puig *et al. PLoS ONE* (2009) 4 [3]: e4771).

Role of LKB1 in tumor biology. LKB1 role in UVB-induced DNA damage response

Our own results and the previous literature revealed the role of LKB1 as a tumor suppressor involved in cell cycle control, and transcription regulation. In view of this, we wanted to investigate the possible interaction of LKB1 with proteins involved in the cell cycle and in the response to DNA damage. We have discovered a novel LKB1 binding protein involved in the cell cycle and DNA damage responses. The aim is to elucidate the role of LKB1 in DNA damage responses in skin cancer and it mutational status in human tumors as a predictor of risk factor.

Figure 20
A model of the metabolic stress response regulation by oncogenic BRAF in melanoma cells. Resistance to stress conditions is essential for melanoma cell survival.
We propose that oncogenic BRAFV600E signaling (left panel) protects from apoptosis by regulating BH3-family members and confers resistance to low energy conditions promoting the uncoupling of LKB1 and AMPK through Erk1/2 and p90Rsk. Under this condition BRAF mutant cells have a limited response to low energy conditions. On the right panel the inhibition of BRAF signaling allows the formation of the LKB1-AMPK complexes restoring the energy stress pathway and promoting the down-regulation of anti-apoptotic proteins such as Mcl1. The activation of AMPK by metabolic stress conditions and the inhibition of BRAF signaling would have synergistic effects promoting apoptosis



Novel therapeutic strategies for melanoma treatment

Preclinical study using PI3K/mTOR dual inhibitors and sorafenib in melanoma treatment. We have also assessed the in vitro and in vivo inhibition potential of the dual PI3K/mTOR inhibitor, PI-103 and sorafenib, as single agents and in combination in primary melanoma cell lines. Although PI-103 and sorafenib inhibited melanoma in vitro cell proliferation and viability, the inhibition of RAS pathway appeared to be more effective. The combination of the two agents in vitro showed a synergistic effect inhibiting RAS and PI3K pathways in a cell line dependent manner. However, no cooperative effect was observed in blocking in vivo tumor growth in immunocompetent mice. Contrary to what was expected, the data indicate that PI-103 induced immunosuppression by inducing thymus atrophy and the upregulation of IL6, IL10 and VEGF, promoting in vivo tumor growth and inhibiting apoptosis. Furthermore, in vitro studies examining the effects of the PI3K/mTOR inhibitor in tumor derived cell lines indicated that PI-103 induced the activation of STAT3 and the upregulation of the anti-apoptotic BH3 family proteins Mcl1, Bcl2 and BclxL favoring, the in vitro survival of sorafenib treated melanoma cells. These data certainly make an argument for investigating unexpected effects of rational drug combinations on immunocompetent animal models prior to conducting clinical studies (López-Fauqued *et al. Int J Cancer* 2009; 126 [7]: 1549-1561).

CURRENT RESEARCH PROJECTS

PI: Juan Ángel Recio Conde

Papel de LKB1 en melanoma maligno

Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/12/2006
Funding: 61,000 €
Duration: 2007 to 2010

PI: Juan Ángel Recio Conde

Papel de LKB1 en respuesta a factores de crecimiento y en el desarrollo y progresión del melanoma

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080653
Funding: 225,907 €
Duration: 2009 to 2011

PUBLICATIONS
(Impact Factor: 11.809)

Andreu-Pérez P, Hernández-Losa J, Moliné T, Gil R, Grueso J, Pujol A, Cortés J, Avila MA, Recio JA. Methylthioadenosine (MTA) inhibits melanoma cell proliferation and in vivo tumor growth. *BMC Cancer* 2010 Jun 8; 10 (1): 265. ➲ IF: 2.736.

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López-Fauqued M, Gil R, Grueso J, Hernández J, Pujol A, Moliné T, Recio JA. The dual PI3K/mTOR inhibitor (PI-103) promotes immunosupression, in vivo tumor growth and increases survival of sorafenib treated melanoma cells. *Int J Cancer* 2010 Apr 1; 126 (7): 1549-61. ➲ IF: 4.722.

AREA 1 ONCOLOGY AND GENETICS

1.16 Unit in Biomedicine and Translational and Pediatrics Oncology

Group Leader
Jaume Reventós Puigjaner
Tel. 93 489 40 52
jaume.reventos@vhir.org

Researchers
Maria Antònia Arbós Via
Pilar Bastida Vila
Silvia Cabrera Díaz
Lluís Cecchini Rosell
Jose Luis Dapena Díaz
Maria Cristina Díaz de Heredia Rubio
Andreas He Doll
Izaskun Elorza Álvarez
Soledad Gallego Melcón
Antonio Gil Moreno
Luis Gros Subias
Anna Llort Sales
Joan Morote Robles
Ma Teresa Olivé Oliveras
Rosanna Paciucci Barzanti
Jordi Petriz González
Ma Teresa Quiles Pérez
Jaume Reventós Puigjaner
Ma Victoria Ribera Canudas
Josep Roma Castanyer
Ana Ruiz Nel·lo
Constantino Sábado Álvarez
Josep Sánchez de Toledo Codín
Marta Sesé Faustino
Enric Trilla Herrera
Jorge Xercavins Montosa

Researchers in Training
Ana Almazan Moga
Angélica Betancourt Suárez
Eva Colas Ortega
Tugce Sevgi Ertekin
Marta García López
Marta Llauradó Fernández
Guillermo López Torrents
Blanca Majem Cavaller
Lorena Marín Buera
Neus Marques Bescos
Anna Masià Fontana
Melania Montes Pérez

Jesús Planagumà Valls
Verónica Pons Escoll
Noelia Purroy Zuriguel
Pablo Velasco Puyó
María del Mar Zardoya Ávila

Nursing, Technical and Administrative Staff
Oriol Abelló Ramia
Meritxell Cucurell Bigas
Luna Martín Castel
Raúl Morales Alarcón
Nuria Pedrola Montero
Marta Rebull Santamaria

OBJECTIVES

Our group is focused on the molecular and translational research of several cancers including those of the prostate, the endometrium, the ovary, the pancreas as well as the pediatric neuroblastoma and rhabdomyosarcoma. We aim to identify and characterize new molecules which might play relevant roles in the neoplastic cell transformation, and/or growth, progression or dissemination of those tu-

2010 Impact Factor:
121.380

mors. All of our projects are based on unresolved clinical needs. Using experimental models, we develop new research strategies that could lead to preclinical validation. We are also studying several molecules of extracellular matrix and their roles in tissue injury and reparation as well as their interactions with biomaterials. Our final aim is to identify new and valuable molecules and biomarkers to improve diagnosis, prognosis and therapy.

RESEARCH LABORATORIES

A) Laboratory of Translational Urological Research

Group Leaders
Jaume Reventós
Joan Morote
Andreas Doll

Principal Investigators
Jaume Reventós (MD, PhD)
Joan Morote (MD, PhD)
Andreas Doll (PhD)
Maite Quiles (PhD)
Maria Antònia Arbós (MD, PhD)

Research Team
Marta García (Graduate Student)
Marina Rigau (Graduate Student)
Jacques Planas (Clinical Associated Investigator)
Enrique Trilla (Clinical Associated Investigator)
Carlos Raventós (Clinical Associated Investigator)
José Placer (Clinical Associated Investigator)
Carlos Salvador (Resident)
Jordi Ropero (Resident)
Marta Alué (Resident)
María Carmen Mir (Resident)
Luis Castro (Resident)
Geisy Delgado (Resident)
Juan M. Bastarós (Resident)

Research Focus

Our overall goal focuses several aspects of translational urology mainly based on the knowledge of the molecular bases of prostate cancer, in particular, but also on the role of inflammatory mechanisms as critical regulators of tumor progression. Our central hypothesis is that a deeper understanding of these pathways will advance the development of preventive treatment strategies.

Research Lines in Prostate Cancer (PC)

Development of non-invasive methods for the early detection of PC in biological fluids

We have determined the specific, differential proteomic profiles to be found in the urine of patients with PC, as compared to age matched controls, with the ultimate goal of settling on a non-invasive diagnostic tool using urine that could help to circumvent the low specificity of the currently-used PSA serum measurements. We use liquid chromatography, mass spectrometry and triple quadrupole mass spectrometry (LC/MS-MS SRM). The Selected Reaction Monitoring technique (SRM) is an emerging technology that ideally complements the discovery capabilities of shotgun strategies through its unique potential for the reliable quantification of low abundance analytes in complex mixtures, such as urine samples. Using this technique we quantify and detect different selected proteins with high sensitivity and a good chromatographic separation within the complex biological samples. The final goal of this research is the establishment of a reliable diagnostic test, which can be used in hospitals and outpatient routines.

Identification of the molecular markers of bone metastases in prostate cancer

We have developed humanized animal models for metastatic prostate cancer able to mimic the human dissemination of PC cells to bones. We use immunocompromised mice transplanted with human bone. Human prostate cancer cells, which over-express luciferase, are injected, allowing metastasis detection and the continued monitoring of the living animals. This permits the identification of bone metastasis markers, patients with a high risk of recurrence and could define new therapeutic targets that will act to block bone lesions through conventional therapies

Development of improved bone metastasis animal models, very close to the clinics, in order to monitor the process of in vivo metastasis

We use an animal model of immunocompromised mice with a transplantation of human bone fragments. Subsequently, human PCa cell lines, over-expressing luciferase, are injected. This allows the detection and monitoring of metastasis in the living animal, since the implanted bone fragments maintain their human microenvironment.

Identification of the molecules responsible for the formation of human bone metastasis

By analyzing the changes in protein expression levels by proteomics in the metastases obtained from this animal model, we examine whether the reinjection of bone metastasis cells affects the specificity or phenotype, due to reprogram-

ming. We attempt to identify the factors that attract human prostate cancer cells to human bone and the mechanisms that are involved in the process of metastasis. This is accomplished by proteomics, using a fluorescence-based differential gel electrophoresis (DIGE) with mass spectrometry (MALDI / TOF), as well as isotope-based techniques (iTRAC etc.) and LC-MS/MS with SRM.

Efficacy of new adjuvant therapies for PC bone metastasis

We use intra-tibial injection of prostate cancer cells overexpressing luciferase in immunocompromised balb/c nude mice, a straightforward method to induce local growth in bone marrow. This Bioluminescent Imaging (BLI)-based metastasis model allows us a regular monitoring of the development and progression of experimental bone metastases in living animals with high sensitivity. Fewer laboratory animals are needed as due to the noninvasive nature of the methods repetitive measurements can be taken from the same animal, which also increases the reliability of observed effects. This approach will enable us to include the micro-environmental growth support system of the bone for the treatment of metastatic disease.

Extracellular matrix and inflammatory mechanisms regulated by prostate cancer-associated fibroblasts

We are interested in understanding extracellular matrix and inflammatory mechanisms regulated by cancer-associated fibroblasts (CAFs) as promoting forces for prostate cancer progression. Cancer-associated fibroblasts support tumorigenesis by stimulating angiogenesis, cancer cell proliferation, invasion and tumor-enhancing inflammation. Using primary cell cultures, we have learned that prostate CAFs display significant phenotypic and transcriptional differences from their normal associated fibroblast (NAF) counterparts:

i) an invasive and migratory phenotype,

ii) expression of epithelial-mesenchymal transition genes and

iii) enhanced expression of inflammatory molecules.

Currently we are studying the differential response of the monocytic cell line THP1 in front of CAFs/NAFs (cell-cell adhesion, chemotaxis, gene and protein expression, matrix metalloproteinase activation).

Molecular analysis of "proliferative inflammatory atrophy" (PIA) as a premalignant condition in prostate cancer development

We also focus our research on the potential importance of chronic inflammatory microenvironments as premalignant condition in prostate cancer development. Currently we are studying a common lesion, often associated with inflammation, termed "proliferative inflammatory atrophy" (PIA), which has been postulated to represent an intermediate step between normal tissue and cancer. It may, therefore, serve as a risk factor lesion for prostate cancer. Using microdissection and microarray technology we have performed paired comparative analysis of gene expression in the following prostatic tissues: benign, PIA, high grade prostatic intraepithelial neoplasia (HGPIN) and cancer lesions. Our objective is to test whether:

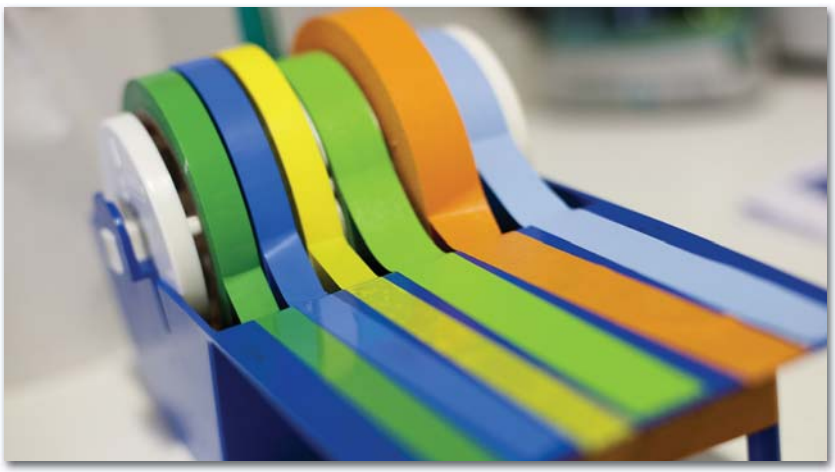
i) our data support the notion that PIA may be considered a premalignant lesion, and

ii) we can detect and characterize common transcriptionally altered pathways among these pathologies.

These studies have implications for prevention and chemoprevention of prostate cancer.

Decrease of bone mass during androgen deprivation in prostate cancer

Decrease of plasmatic levels of testosterone produced by androgen deprivation indirectly alters the mineral bone metabolism and produces loss of bone mass and there is increased the risk of fractures and mortality. This research line contains studies of prevalence of osteoporosis and osteopenia, prediction of the pace of bone mass loss, study of the molecular mediators, specifics diagnosis methods and prevention.



Dyslipemia and metabolic syndrome during androgen deprivation in prostate cancer

Cardiovascular mortality is the leading cause of death in patients with prostate cancer and it is believed that androgen deprivation is the intermediate reason. This research line includes studies of metabolic syndrome prevalence and dyslipemia as the most frequent cause of cardiovascular mortality, molecular mediators analysis, early diagnosis methods of cardiovascular risk and prevention.

Cognitive alterations during androgen deprivation in prostate cancer

Androgen suppression in prostate cancer patients produces cognitive alterations that are not well studied despite being very important for quality of life. The purpose of this research line is to study the cognitive alteration profile that produces androgen deprivation, the mediators who generate these alterations at central level, early diagnosis and possible forms of prevention.

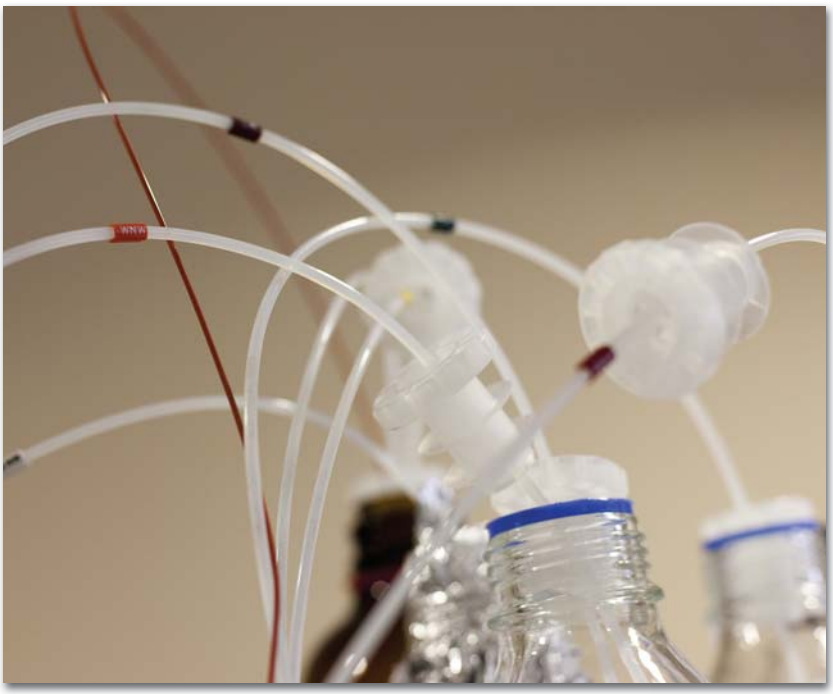
High grade intraepithelial neoplasia and prostate cancer

High grade intraepithelial neoplasia is preneoplasics prostate cancer damage. Nevertheless, it is unknown the molecular mechanisms who define his neoplasic transformation or his persistence as high grade intraepithelial neoplasia isolated. High grade intraepithelial neoplasia detection in a prostatic biopsy entails a repeat biopsy strategy that has not yet been clearly established. This research line integrates the analysis of molecular predictors of neoplasic transformation (genomics and proteomics), the analysis of metabolic image (RNM and spectroscopy) and possible prevention mechanisms of prostate cancer chemoprofilaxis.

Research Lines in Kidney Diseases

Pneumoperitoneum impact of laparoscopic surgery on renal function

Analysis of molecular mechanisms of renal oncogeny



B) Laboratory of Gynecological Oncology

Group Leaders
Jaume Reventós
Anna Ruiz,
Antonio Gil

Principal Investigators
Jaume Reventós (MD, PhD)
Anna Ruiz (PhD)
Antonio Gil (MD)
Jordi Xercavins (MD, PhD)

Research Team
Marta Llauradó (Graduate Student)
Eva Colás (Graduate Student)
Núria Pedrola (Graduate Student)
Sílvia Cabrera (Clinical Associated Investigator)
Assumpció Pérez (Clinical Associated Investigator).

Research Focus

We are focused on the understanding of the molecular bases of endometrial and ovarian cancers. In particular, in new molecules involved in progression and dissemination. Our search also includes new molecular biomarkers of precocious diagnosis as well as molecular therapeutic targets.

Research Lines in Endometrial Cancer (EC)

Differential gene expression in endometrial cancer: analysis of the roles of transcription factors Runx1 and ETV5 in the progression and dissemination of tumors

Previous research in our lab has identified ETV5 and RUNX1 proteins as key determinants of myometrial invasion and dissemination. The main objective of the project is the investigation of the molecular mechanisms regulated by the ETV5 and RUNX1 transcription factors that are responsible for endometrial cancer cell invasion and dissemination. To achieve these objectives we have already developed some

tools such as endometrial cancer cell lines with ETV5 overexpression or downregulation. The identification of proteins involved in the invasion and dissemination processes will lead to the design of new experimental therapies that will be evaluated (tumor growth, metastasis) in the orthotopic animal models that we have developed for endometrial cancer.

Development of highly-sensitive and highly-efficient molecular tools for the diagnosis of endometrial cancer in uterine aspirates

Through a proteomic approach, our lab has identified and validated new robust biomarkers for endometrial carcinoma using human samples obtained from uterine aspirates. Our objective is to develop a reliable tool for screening EC risk using endometrial biopsies, which will enhance sensitivity and specificity, as well as preclude unnecessary hysteroscopy.

Development of endometrial orthotopic murine models to test new therapies

We have developed two different orthotopic endometrial cancer murine models that might be useful tools in endometrial cancer preclinical studies. The generation of these murine models for endometrial cancer has been achieved by inoculation of either a tumor cell line or human tumor tissue intra-uterus. The Hec-1A endometrial cancer cell line derived model represents advanced disease and can be used to test the efficacy of antimetastastic drugs. In this model, the follow-up of disease progression is performed using bioluminescence in vivo and correlating bioluminescence ex vivo with metastasis generation. The human tissue derived model maintains the histological pattern and represents local and locally-advanced disease, and can be used to test drugs against specific targets of endometrial cancer.

Characterization by proteomics and genomics of markers expressed differentially at the EC invasion front and in metastasis

Using an orthotopic mouse model we have shown the involvement of RUNX1 in distant metastasis in endometrial cancer. Using proteomics, we have also shown a series of promising proteins involved in myometrial invasion that are differently expressed between cancer and age-matched uterine tissue. Our goal is to identify the gene clusters involved in invasion and metastasis and to study their therapeutic potential using preclinical mouse models.

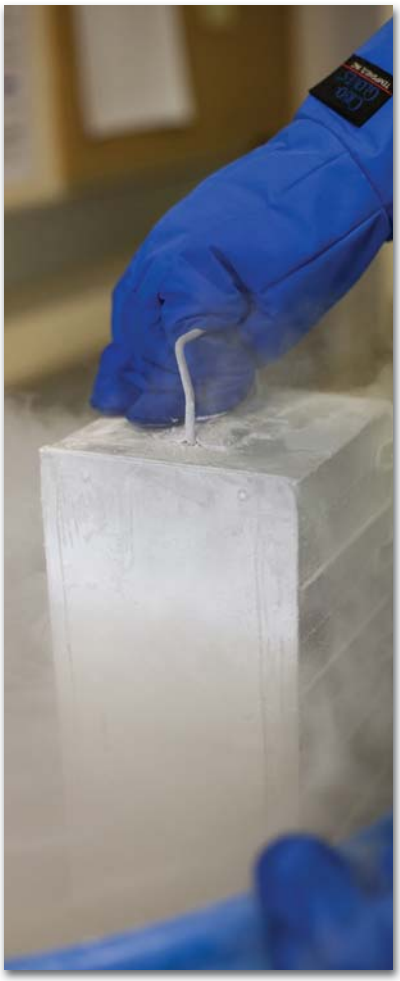
Research Lines in Ovarian Cancer (OC)

New biomarker identification for ovarian cancer diagnosis, prognosis and drug treatment

This project proposes the identification of new molecular biomarkers for the diagnosis and prognosis of ovarian cancer. Microarray technology has been used to identify molecules differentially expressed between tumoral tissue and control samples. The final goal is to identify a panel of biomarkers that can distinguish the presence or absence of ovarian cancer.

Mechanisms of cancer cell dissemination regulated by ETV5 in ovarian cancer

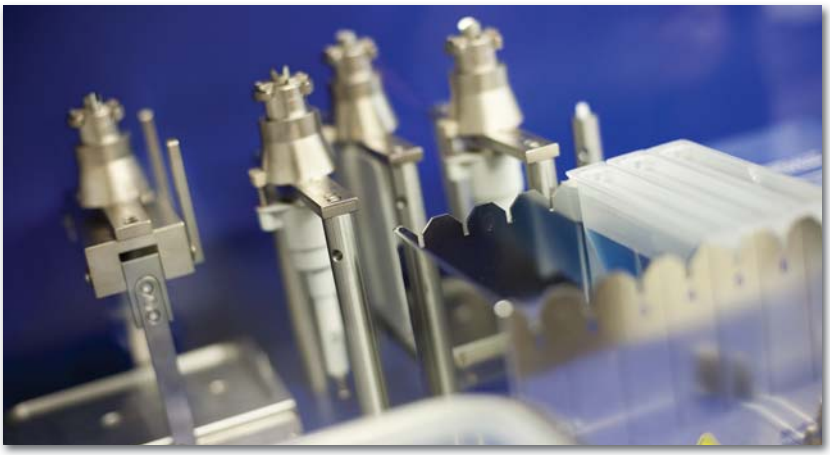
Previous research in our lab has identified ETV5 as a protein overexpressed in ovarian cancer. We have characterized its role in ovarian tumour progression. Currently, we are characterizing ETV5 target genes involved in ovarian cancer dissemination through the peritoneal cavity. The final goal is to design new therapies to stop ovarian cancer cell dissemination.



Molecular pathways involved in ovarian cancer cell dissemination

Ovarian cancer disseminates to secondary sites through the peritoneal cavity. Ovarian cancer cells are shed from the ovarian primary tumor, aggregate as spheroids within the abdominal cavity and subsequently attach to the peritoneal wall. We are interested in the identification of those molecular pathways involved in ovarian cell dissemination through the peritoneal cavity in order to design new therapies that target ovarian cancer dissemination and therefore ovarian cancer spread to secondary sites.

Cohort study comparing surgical vs laparoscopic staging and treatment in primary endometrial cancer (clinical stage I)



C) Laboratory of Cell Signalling and Cancer Progression

Group Leader
Rosanna Paciucci

Principal Investigators
Rosanna Paciucci (PhD)
Marta Sesé (postdoct, PhD)
Neus Marqués (PhD student)
Lide Alaña (PhD student)
Raul Morales (Technician)

Research Interests

The primary interests of the group are the identification of new and selective targets for anti-cancer therapy and markers potentially useful to identify aggressive tumors from non-aggressive. Our studies aim to broaden our knowledge on the biology of aggressive cancer cells and shed light on the molecular circuits that are established in aggressive tumors. We have been approaching our aims studying carcinomas of the exocrine pancreas and, more recently, prostate cancer by:

i) the identification of mis-expressed genes in tumors versus normal tissues using different methodologies to analyze gene expression;

ii) the selected genes are being studied for their contribution to tumor aggressiveness through the analysis of phenotypes obtained with the gain-of-function/knockdown in vitro and in vivo;

iii) the relevant targets are further studied to understand their function and mechanisms of action on major cellular signaling pathways implicated in cancer progression.

Other Clinical Research Projects

- Prospective study of validation of sentinel lymph node detection technique in cervical cancer in initial stages.
- Prospective study of validation of sentinel lymph node detection technique in vulvar cancer in initial stages.
- Prospective comparative study of laparoscopic versus laparotomic radical hysterectomy approach in initial cervical cancer treatment.
- Prospective study of validation of extra-peritoneal aortic laparoscopic or robotic assisted lymphadenectomy in locally advanced or bulky cervical cancer.
- Prospective comparative study of robotic assisted versus laparoscopic versus laparotomic approaches in endometrial cancer (supported by AATRM, Technology and Medical Research Evaluation Agency).
- Pre-neoplasic vaginal and vulvar pathology: VIN and VAIN.
- Study of p-16 as a progression marker in cervical pre-invasive lesions.
- Follow-up in women with HPV 16 infection.
- CIN and pregnancy.
- Follow-up of women treated for H-SIL cervical cancer lesions.
- Endocervical sample as a marker of relapse in cervical intraepithelial neoplasia.
- Results of neo-adjuvant concomitant chemo-radiotherapy in the treatment of locally advanced cervical cancer.
- Validation of robotic assisted and laparoscopic aortic extraperitoneal lymphadenectomy in recurrences of gynaecologic malignancies.
- Evaluation of robotic surgery in the treatment of gynaecologic malignancies.
- Borderline ovarian tumours.
- Endoscopic treatment of ovarian cancer in initial stages.
- Ressecability predictive value of laparoscopic approach in advanced ovarian cancer.
- Results of neo-adjuvant chemotherapy in the treatment of advanced ovarian cancer.

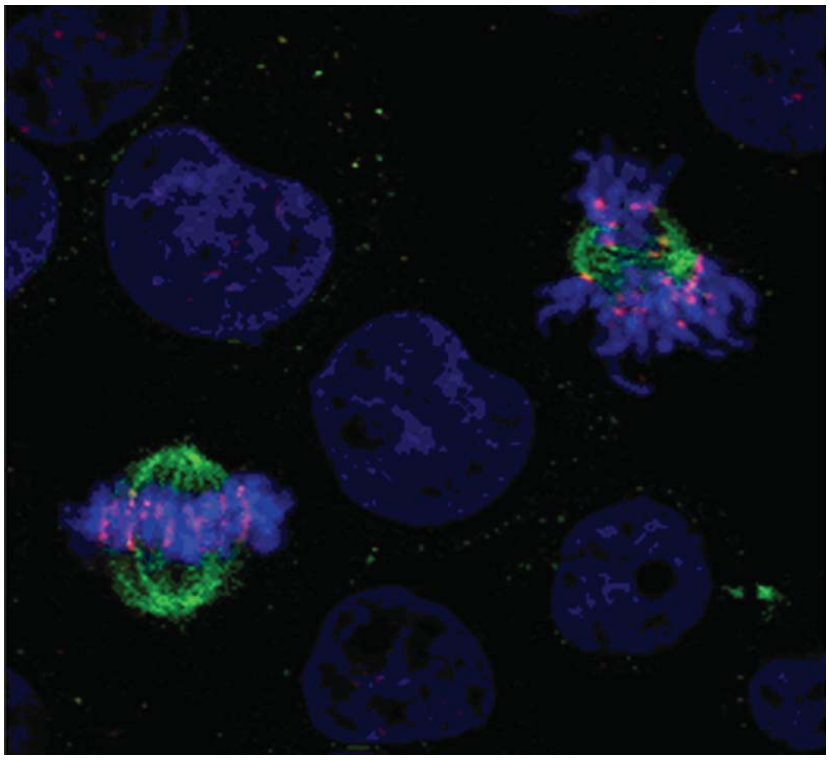


Figure 21
HeLa cells depleted of Flotillin-1 by specific siRNA were stained for tubulin (green), kinetochores (red) and DNA (blue) and the images captured by confocal microscopy

Specific Lines of Research

In pancreas cancer, we are studying tissue plasminogen activator (tPA) specifically overexpressed in cancer cells (Paciucci *et al.,* 1998). Our findings indicate that tPA activates cell proliferation in vitro and in vivo, in immuno-deficient mice, and contributes to pancreas cancer growth and progression (Díaz *et al.,* 2002). tPA is a serine protease that specifically activates plasminogen to plasmin. In pancreas cancer cells we identified specific binding sites for tPA on the membrane of tumor cells (Díaz *et al.,* 2004.). tPA bound to these receptors induces a proteolytic cascade with the consecutive activation of plasmin and the pro-MMP9. The latter allows heparin-bound EGF to engage the epidermal growth factor receptor (EGFR) producing its activation (Hurtado *et al.,* 2007). This activation event is required for the mitogenic action of tPA on pancreas cancer cells. Using specific substrates to detect the activity of tPA in cancer cells, we are screening for specific inhibitors.

In prostate cancer, we are studying the newly identified protein Prostate Tumor OVerxpressed-1 (PTOV1), a protein well conserved in mammals, flies and simpler eukaryotes, the protein defines a new family of proteins containing a structurally unknown new domain (PTOV), also encountered in other mammalian proteins (i.e. PTOV2/MED25) (Benedit *et al.,* 2001). PTOV1 is overexpressed in

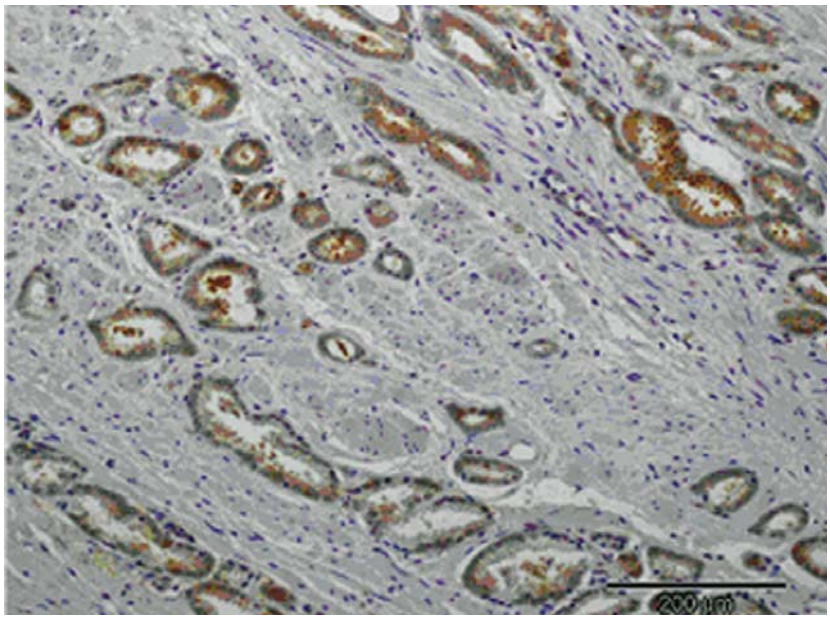


Figure 22
The image shows the expression of the protein PTOV1 in a prostate carcinoma

D) Laboratory of Translational Research in Paediatric Cancer

Group Leaders
Josep Roma
Josep Sánchez de Toledo
Soledad Gallego

Principal Investigator
Josep Roma (PhD)

Research Team
Anna Almazán (Researcher in training)
Anna Masià (Graduate Student)
Pablo Velasco (Graduate Student)
Marta Rebull (Technician)
Josep Sánchez de Toledo (Clinical Associated Investigator)
Soledad Gallego (Clinical Associated Investigator)

Research Focus

Malignant neoplasms in children and adolescents are rare diseases with different prognoses and biologic behaviour. The prognosis of childhood cancer has improved considerably in recent decades and survival is approximately 70% in western countries. However, even with the current multimodal therapies, a considerable number of these patients still relapse and eventually die due to progressive or refractory ne-

pre-malignant lesions of HGPIN and in prostate cancer, where it promotes cell proliferation and invasion (Santamaría *et al.,* 2003). Its detection in prostate biopsy is useful to predict the presence of cancer (Morote *et al.,* 2008). PTOV1 interacts with Flotillin-1 and both proteins are required for cell proliferation (Santamaría *et al.,* 2005). Our results show that Flotillin-1, a major component of lipid-rafts compartments of cellular membranes, is required for Aurora kinase B function in mitosis (Gómez *et al.,* 2010). PTOV1 protein is overexpressed in numerous other human cancers, including bladder and renal cell carcinoma, colon carcinoma, endometrial and ovary carcinomas. We are studying the mechanisms implicated in the PTOV1-promoted cell proliferation and invasion. With this aim in mind, are following three major strategies:

- We are studying the interactions of PTOV1 with known cellular proteins implicated in tumor progression obtained by yeast-two-hybrid assays. One such interaction, the PTOV1-RACK1, stimulates the specific translation of several proteins required for the PTOV1-mediated cell invasion effect. We are now defining the mechanisms implicated in this action.

- In the second approach, we are analyzing the functional interaction of PTOV1 with major cellular pathways implicated in cancer progression. We are presently studying the interference of PTOV1 with the signaling of Notch and its importance in prostate cancer establishment and progression.

- Finally, we are using the D. melanogaster model to study and confirm the function of the protein PTOV1 in the signaling circuits identified in cancer cells that might be active during development.

In colon cancer, we are studying the contribution of the alteration of protein translation in the expression of genes associated with oncogenesis and progression of carcinomas.

oplasms. Consequently, paediatric oncologists need new approaches to improve the efficacy of anticancer therapies. Molecular diagnosis, detection of microdisseminated disease and the search for new therapeutic strategies would help to improve the results of the current treatments of paediatric cancer. Our research group is focused on:

- Molecular diagnosis of malignant tumors in children: neuroblastoma, Ewing's sarcoma, soft tissue sarcomas, nephroblastoma, brain tumors.
- Analysis of the prognostic impact of minimal disseminated disease (MDD).
- Search for new molecular therapeutic targets in children with cancer.

Research Lines

Molecular diagnosis

We systematically perform molecular characterisation using PCR of the most common types of cancer in children i.e. neuroblastoma, soft tissue sarcomas, bone sarcomas, non-Hodgkin lymphomas, nephroblastoma and brain tumors. Our laboratory is the National Reference Centre for Biological Studies in soft tissue sarcomas, receiving tumor material from most of the cases included in the current therapeutic protocols in Spain.

Minimal disseminated disease (MDD)

The presence of occult rhabdomyosarcoma cells in peripheral blood and bone marrow is systematically analysed by testing the expression of multiple genes using real-time RT-PCR. In collaboration with Dr. A Rosolen (University of Padua) and Dr. J Stutterheim (AMC, Amsterdam) and under the auspices of the EpSSG (European Pediatric Soft Tissue Sarcoma Group) we have developed the European consensus protocol for the study of MRD in RMS. In neuroblastoma, MDD study is performed by analysing tyrosine hydroxylase gene expression in peripheral blood, and bone marrow using real-time RT-PCR.

Therapeutic targets

- *NOTCH pathway and rhabdomyosarcoma:* The main objective of this line is to ascertain the effects of NOTCH pathway inhibition using in vitro models as well as a murine xenograft model of RMS in an attempt to establish new molecular targets for treating patients with RMS. Our studies in vitro suggest that inhibition of the NOTCH pathway by gamma-secretase inhibitors produces a significant decrease in the invasiveness of rhabdomyosarcoma cells. Moreover, NOTCH pathway activation seems to play a crucial role in sustaining the rare population of tumor-initiating cells in some neoplasms and it has recently been reported that RMS cells positive for the fibroblastic growth factor receptor 3 (FGFR3) are able to generate tumors from a single cell. The main objective of this line is to identify and separate tumor-initiating cells in rhabdomyosarcoma tumors and characterise the NOTCH pathway in this subpopulation as a possible candidate for the development of targeted therapies.
- *Cancer stem cells in paediatric cancers:* We attempt to isolate progenitor cancer cells (stem cells) in soft tissue sarcomas, bone sarcomas, neuroblastoma, high-grade non-Hodgkin lymphomas and brain tumors. The analysis of the expression profiles of this putative stem cell population could permit us to identify new therapeutic targets that will overcome resistance to chemotherapy.

E) Laboratory of Bioengineering and Cellular Interactions

Group Leaders
Maria Antònia Arbós
María Teresa Quiles
Manel Armengol

Research Team
Maria Antònia Arbós (MD, PhD, Researcher)
María Teresa Quiles (PhD, Researcher)
Manuel Armengol (MD, PhD, Clinical Associated Investigator)
Manuel López-Cano (MD, PhD, Clinical Associated Investigator)
Marta Rebull (Technician)

Research Focus

Our laboratory is interested in the role of cell-extracellular matrix (ECM) interactions in the fields of tissue repair and inflammation, with a special focus on abdominal wall defects. Our studies are mostly based on patient-derived tissue samples and primary cells, as well as on surgically-induced

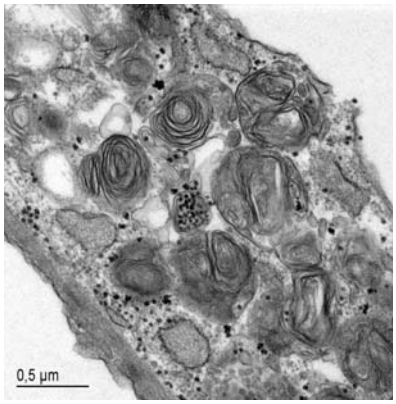


Figure 23
Ultrastructural appearance of a primary fibroblast derived from the fascia of an incisional hernia patient, displaying autophagic vacuoles, autophagolysome-like structures, multilayered lamellar and fingerprint profiles and mitochondrial swelling

models. Moreover, soft-tissue repair devices are being investigated by means of "in vitro" and "in vivo" experimental models.

Research Lines

Extracellular matrix, inflammation and abdominal wall

The reconstruction of abdominal wall defects is the problem with which surgeons are confronted most often. These defects may have an acute (trauma, cancer, infections) or chronic (hernia pathology) origin. Despite technical advances, both physiopathology and treatment of the disease remains controversial, and further knowledge is needed.

Basic Research

We are trying to unravel the cellular and molecular mechanisms triggering incisional hernia (IH) formation. IH often occurs following laparotomy and can be a source of serious problems. There is evidence that a biological cause may underlie its development, but the mechanistic link between the local tissue microenvironment and tissue rupture is lacking. We have found de-regulated proteolytic and molecular inflammatory signaling in the abdominal wall tissues (fascia and skeletal muscle) of IH patients. Also, we have identified an ongoing complex interplay of cell death induction, aberrant fibroblast function and tissue loss in IH tissues, which eventually may give rise to tissue rupture in vivo. Currently, we are investigating changes in subsets of genes from IH-derived primary fibroblasts. Overall, these studies may provide a molecular mechanistic framework for better understanding IH formation, and reveal new molecular biomarkers and potential therapeutic targets. Current surgical practice supports the use of permanent prosthetic meshes as the best method for hernia repair. Still, no material has gained a preference for universal use and numerous complications are still reported. The understanding of cell-substrate interactions is fundamental for the improvement of tissue repair and regenerative medicine. We analyze different soft-tissue repair devices. Our approach includes surface and biomechanical characterization, as well as the analyses of host-implant interactions, using both "in-vitro" (primary fibroblasts derived from control and IH patients) and "in-vivo" (rats) experimental models. Our ultimate goal is to impact on the development of new tailored implants based on fibroblasts and biomimetic materials, which are clinically useful to repair damaged organs.

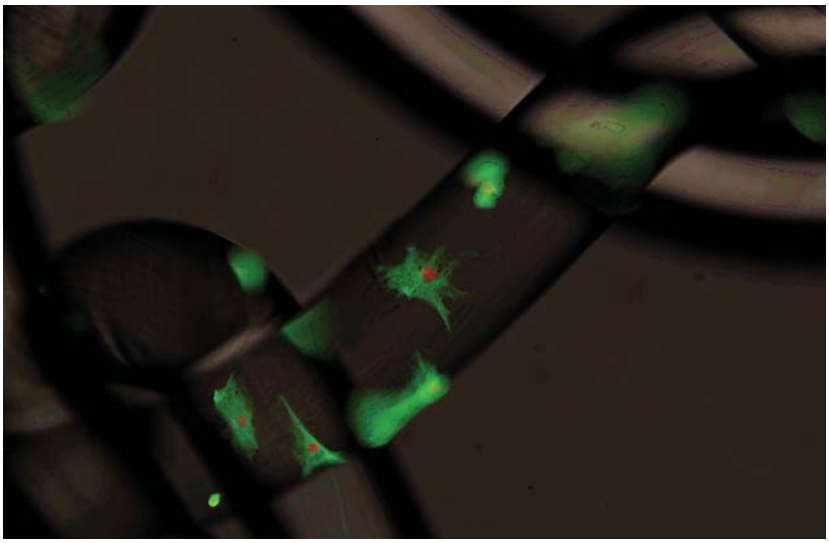


Figure 24
Representative vimentin-stained primary fibroblasts derived from the fascia of incisional hernia patients, grown on polypropylene meshes

Clinical Research

Simulation and virtual reality

In collaboration with Politechnic University of Catalonia and Rovira-Virgili University:

- *Virtual reality model of inguinal hernia:* Educational purposes: simulator of inguinal area; Clinical Research purposes: protective mechanisms against inguinal hernia formation.
- *Virtual reality model of the whole abdominal wall:* Educational purposes: simulator of abdominal wall; Clinical Research purposes: abdominal wall mechanical behavior.
- *Virtual reality model of synthetic mesh contraction:* Clinical/Translational research of physical contraction of synthetic mesh and its influence on hernia recurrence.

Hernia occurrence prevention

- Parastomal hernia prevention with synthetic mesh by laparoscopic approach: clinical study.
- Incisional hernia prevention with synthetic mesh: experimental study.

Surgical devices applied in abdominal wall surgery

In collaboration with Politechnic University of Catalonia and Rovira-Virgili University:

- 3D surgical vision.
- Surgical sutures – European Project.

F) Laboratory of Stem Cells and Cancer

Group Leader
Jordi Pétriz

Principal Investigator
Jordi Pétriz (PhD)

Research Team
Noelia Purroy (MD)
Verónica Pons (MD)
Jana Balbuena (Graduate Student)
Gisela Pachón (PhD)
Anna Esquerra (Technician)

Research Focus

The focus of the laboratory are the basic mechanisms that regulate Side Population stem cells. Stem cells reside in most tissues in a quiescent state, but rapidly become activated to both repair and regenerate the adjacent tissues. We are studying several genes involved in different aspects of stem cell activation, including some that encode for ABC transporters, and others that regulate self-renewal and differentiation. We are also interested in multidrug resistance and we use functional flow cytometry to examine the changes that occur in the accumulation of drugs into the cells over time.

Research Lines

Murine xenograft models for human ovary, testis, prostate, pancreas and colon cancers: Detection of bone marrow infiltration by Side Population cells

We are using xenograft models to examine the genes that regulate bone marrow infiltration in cancer. We isolate Side Population (SP) stem cells from normal tissue and from tumor cells, mainly for cell culture experiments as well as for transplantation in murine xenograft models and for the independent analysis and comparison of gene expression. We also develop non immortalized and non transformed cell models from stem cells with SP phenotype. We study the gene expression profiles to test the hypothesis that the expression of certain genes are associated with an immature cell phenotype as well as with a phenotype of tumor stem cell. We map the signaling pathways, self-renewal, and differentiation of cell SP, as well as stem cell miRNAs and ABC transporters and the mechanisms by which gene expression and resistance to chemotherapy are regulated. We study the presence of SP cells in human solid tumors, orthotopically implanted in athymic mice as well as their dissemination and infiltration in different tissues (i.e. bone marrow), with and without the expression of the green fluorescent protein as a marker gene.

Development of a new Cytomics Platform for the study of stem cell systems

Cancer is increasingly being viewed as a stem cell disease, both in its propagation by a minority of cells with stem cell-like properties and in its possible derivation from normal tissue stem cells. Recent findings suggest that stem cell biology may be more complex than originally anticipated and a subset of stem cells may alter their function in a manner that is more plastic and dynamic than previously thought. Considerable progress has been made by studying stem cell function based on the high efflux of fluorescent dyes. ABCG2, a half-transporter that belongs to the ATP binding cassette superfamily, is expressed in primitive stem cells, and is responsible for the formation of a Side Population (SP) with a Hoechst 33342 (Ho324) fluorescent profile blocked in the presence of multidrug reversal agents. SP cells are present in a wide variety of tissues and ABCG2 expression is believed to represent a common molecular mechanism for stem cells possessing multi-organ plasticity. The majority of SC enrichment protocols rely on fluorescence activated cell sorting (FACS), which allows cells to be selected based on the expression of a set of cell surface proteins. ABCG2 gene is an important determinant of the SP, and it might serve as a marker for stem cells from various sources. Cell sorting for the expression of ABC transporters provides a new strategy for stem-cell purification that could be used for cells from different organ sources. We also study single-cell gene expression profiling to relate the expression of specific genes to a particular cellular phenotype. FACS-based isolation of SP cells, in association with the mRNA expression analysis of gene expression in highly purified preparations of SC subsets on the basis of ABCG2 expression, provides important insights in stem cell biology. We apply the Cytomics Platform for the detection and isolation of SP cells from:

- Adipose tissue (in collaboration with Dr. Simó, MD, PhD, FIR-HUVH).
- Brain tumors (in collaboration with Dr. Sáez Castresana, MD, PhD, CIFA, University of Navarra).
- Xenograft models (in collaboration with Dr. Capellà, MD, PhD, IDIBELL).
- Peripheral blood and bone marrow from leukemic patients (in collaboration with Dr. Prósper, MD, PhD, CIMA and with Dr. Bosch, MD, PhD, HUVH).

Flow cytometry counting of CD34+ cells

Blood formation is sustained by a population of undifferentiated and metabolically quiescent hematopoietic stem cells (HSC) mainly found in the bone marrow. HSC

remain in the G0 compartment of the cell cycle, are able to self-renew, and differentiate into progenitors of all hematopoietic lineages. Their self-renewal and differentiation are regulated by a number of cytokines. A subset of hematopoietic cells presumably containing HSC express the cell surface antigen CD34; CD34+ purified fractions are enriched in colony-forming units and long-term culture initiating cells, whereas CD34- fractions are depleted. CD34+ cells obtained from either bone marrow or peripheral blood are commonly used in hemopoietic stem cell transplantation. They can be mobilized from bone marrow into peripheral blood by means of chemotherapy and/or cytokine stimulatory treatments, then collected for use in malignant disease therapy, HSC expansion studies, and gene therapy. The accurate enumeration of CD34+ cells has been shown to be important for predicting the success of engraftment after transplantation, as it can assure the presence of sufficient numbers of progenitor cells remaining in the graft. We have developed a new flow cytometry protocol for CD34+ progenitor counting in collaboration with the Quality Assessment of Haematopoietic Stem Cell Grafts Committee from The European Group for Blood and Marrow Transplantation (EBMT).

CURRENT RESEARCH PROJECTS

PI: Joan Morote Robles
Análisis del perfil transcripcional genómico en la Atrofia Proliferativa Inflamatoria (PIA) como lesión precursora del cáncer de próstata humano
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070536
Funding: 124,630 €
Duration: 2008 to 2010

PI: Soledad Gallego Melcón
Identificación de nuevas dianas terapéuticas en el rabdomiosarcoma: efectos de la silenciación de las vías de señalización celular de NOTCH, Hedgehog y RAS en esta neoplasia
Funding Agency: Asociación Española Contra el Cáncer
Reference: AECC_CAT_01_2007
Funding: 18,000 €
Duration: 2008 to 2010

PI: Joan Morote Robles
Identificación de marcadores proteómicos en orina para la detección precoz del cáncer de próstata: Convocatoria "Pedro Cifuentes Díaz" 2007
Funding Agency: Fundación Investigación Urologia
Reference: FIU_01_2007
Funding: 36,300 €
Duration: 2008 to 2010

PI: Jordi Petriz González
Desarrollo de una Plataforma de Citómica para el estudio funcional de células madre
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP07/00098
Funding: 42,000 €
Duration: 2008 to 2010

PI: Rosanna Paciucci Barzanti
Estudio de la modulación de la proliferación y progresión tumoral medida por PTOV1; interacción con las rutas de IGF-1, Notch y Wnt y expresión en tissue-arrays de tumores
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-03936
Funding: 181,500 €
Duration: 2009 to 2011

PI: Jaume Reventós Puigjaner
Caracterización molecular de los procesos de infiltración y diseminación tumorales y desarrollo de metástasis en cáncer de endometrio. Papel del RUNX1 en la promoción de las metástasis
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-03996
Funding: 96,800 €
Duration: 2009 to 2011

PI: Jordi Petriz González
Estudio de la contribución de las células de la Side Population en la infiltración de la médula ósea en modelos de xenotrasplante murino de tumores humanos de ovario, testículo, próstata, páncreas y colon
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI081132
Funding: 153,791 €
Duration: 2009 to 2011

PI: Rosanna Paciucci Barzanti
Estudio de la modulación de la proliferación y progresión tumoral medida por PTOV1; interacción con las vías de transducción de señal mediadas por IGF-1, Notch y Wnt y expresión en tissue arrays de tumores
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080547
Funding: 171,941 €
Duration: 2009 to 2011

PI: Andreas He Doll
Identificación de moléculas responsables de metástasis óseas en un modelo de ratones SCID humanizados
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00496
Funding: 96,800 €
Duration: 2010 to 2012

PI: Jaume Reventós Puigjaner
Identificación de marcadores proteómicos en orina para la detección precoz del cáncer de próstata
Funding Agency: Ministerio de Ciencia e Innovación
Reference: CIT-300000-2009-002
Funding: 386,420 €
Duration: 2010 to 2010

PI: Josep Roma Castanyer
Efectos de la silenciación de la vía de celular de Notch en el rabdomiosarcoma in vivo
Funding Agency: Asociación Española Contra el Cáncer
Reference: AECC-JB2009/02
Funding: 18,000€
Duration: 2010 to 2012

PI: Rosanna Paciucci Barzanti
Oncogénesis mediada por reprogramación traduccional en cáncer
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMM-2010-07
Funding: 24,000 €
Duration: 2010 to 2013

PI: Soledad Gallego Melcón
Name Notch patway inhibition as therapeutic target in rhabdomyosarcoma
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3/2010/101310
Funding: 179,720 €
Duration: 2010 to 2013

PI: Jaume Reventós Puigjaner
RTICC - Red Temática de Investigación Cooperativa de Cáncer
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0020/0058
Funding: 293,652.32 €
Duration: 2007 to 2011

PI: Jaume Reventós Puigjaner
Oncología Translacional
Funding Agency: AGAUR
Reference: 2009 SGR 487
Funding: 57,200 €
Duration: 2010 to 2013

PUBLICATIONS (Impact Factor: 121.380)

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Cebrecos I, Córdoba O, Deu J, Xercavins J, Rubio IT. «Can we predict local recurrence in breast conserving surgery after neoadjuvant chemotherapy?». *Eur J Surg Oncol* 2010 Jun; 36 (6): 528-34. ➲ IF: 2.564.

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Franco-Camps S, Cabrera S, Pérez-Benavente A, Diaz-Feijoo B, Bradbury M, Xercavins J, Gil-Moreno A. «Extraperitoneal laparoscopic approach for diagnosis and treatment of aortic lymph node recurrence in gynecologic malignancy». *J Minim Invasive Gynecol* 2010 Sep-Oct; 17 (5): 570-5. ➲ IF: 1.920.

Gallardo-Arrieta F, Doll A, Rigau M, Mogas T, Juanpere N, García F, Morote J, Nuñez F, Abal M, Lloreta J, Reventós J. «A transcriptional signature associated with the onset of benign prostate hyperplasia in a canine model». *Prostate* 2010 Sep 15; 70 (13): 1402-12. ➲ IF: 3.081.

Gallego S, Llort A, Gros L, Bueno J, Moreno A, Nieto J, Sánchez de Toledo J. «Post-transplant lymphoproliferative disorders in children: the role of chemotherapy in the era of rituximab». *Pediatr Transplant* 2010 Feb; 14 (1): 61-6. ➲ IF: 1.573.

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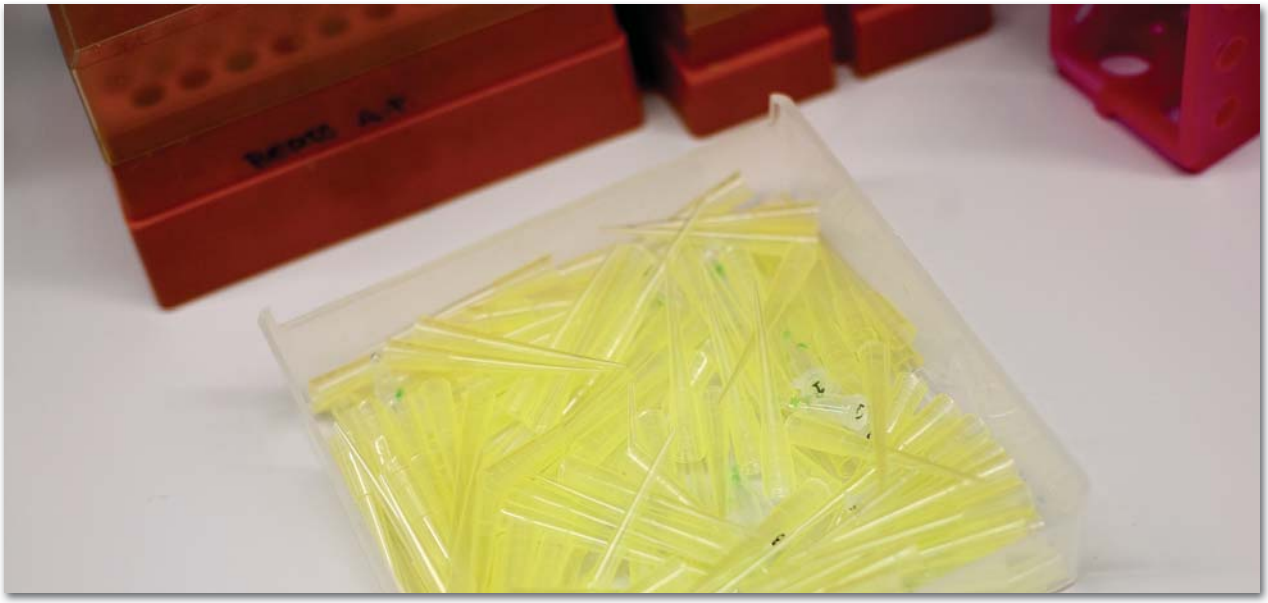

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AREA 1 ONCOLOGY AND GENETICS

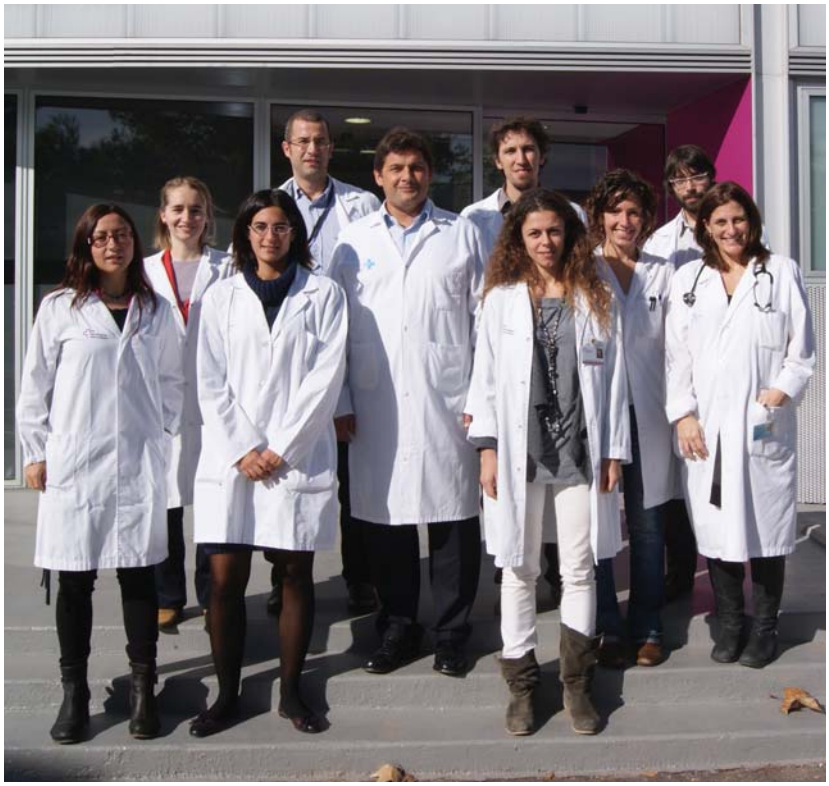
1.17 Experimental Hematology

Group Leader
Francesc Bosch Albareda
Tel. 93 27 46 00 (ext. 4946)
fbosch@vhebron.net

Researchers
Pablo Abrisqueta Costa
Pere Barba Suñol
David Beneitez Pastor
Javier Bueno Aribayos
Marta Crespo Maull
Mercedes Gironella Mesa
Andrés López Hernández
Isabel Massagué Ferrer
Margarita Ortega Blanco
Carlos Palacio García
Verónica Pons Escoll
David Valcárcel Ferreiras
Maria Teresa Vallespí Solé

Researchers in Training
Eva Calpe Berdiel
Anny Coro Jaramillo Rodríguez
Laura López Andreoni
Oriol Olivé Noguer
Noelia Purroy Zuriguel
Esther Sancho Ponce

Nursing, Technical and Administrative Staff
Elisenda Alonso Arias



OBJECTIVES

The main objectives of the Experimental Hematology group are the study of pathogenesis mechanisms and the progression of lymphoid neoplasies, as well as studying ex-vivo effects and ways of action of new experimental therapeutic regimens.

RESEARCH LINES

Pathogenesis mechanisms of Chronic Lymphocytic Leukemia (CLL)
Exploration of pathogenesis mechanisms in CLL with two objectives: identifying the cell of origin of the disease and the genetic or epigenetic mechanisms which cause the lack of growth regulation and cellullar proliferation.

progression factors and mechanisms in Chronic Lymphocytic Leukemia
Studying molecular and microenvironmental mechanisms related to clinical and biological progression of the disease.

2010 Impact Factor:
109.306

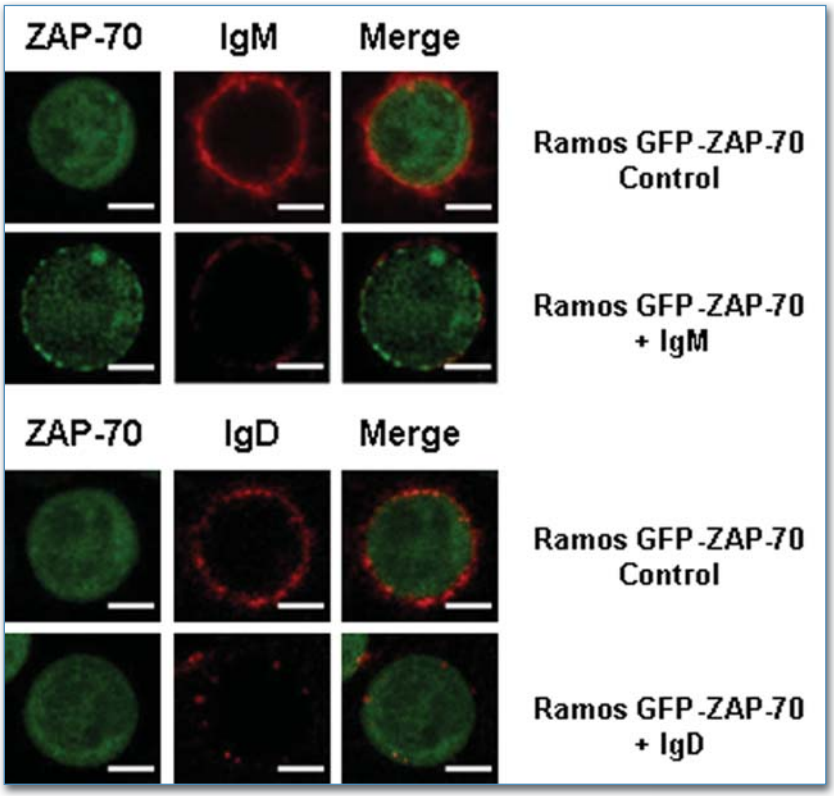


Figure 25
BCR signaling in B cells with ectopic ZAP-70 expression. After IgM stimulation ZAP-70 translocates from the cytoplasm to the membrane, whereas IgD stimulation does not affect ZAP-70 localization

CURRENT RESEARCH PROJECTS

Ex-vivo assessment of new therapeutic proposals in lymphoproliferative syndromes
Ex-vivo assessment of the response to new treatments taking into account the icroenvironmental protection that neoplastic cells find at lymphoidtissues. Investigation of action mechanism and affected signaling pathways.

Immunologic modulation and response to new treatments in myelodysplastic syndromes
Studying the 5q- syndrome and its response to treatment with immunomodulatory agents. Studying the effect in different lymphoid populations.

PI: Andrés López Hernández
Estudio fase II prospectivo, abierto, multicéntrico de Gemcitabina y Oxaliplatino + Rituximab en pacientes con linfomas agresivos (difuso de células grandes B y del manto) en recaída o resistencia no subsidiarios de ser sometidos a quimioterapia intensa
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00140
Funding: 751,410 €
Duration 2009 to 2011

PI: Francesc Bosch Albareda
Biología y valor pronóstico del comportamiento celular proliferante en la leucemia linfática crónica
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI08/0211
Funding: 116,638.88 €
Duration: 2009 to 2011

PUBLICATIONS
(Impact Factor: 109.306)

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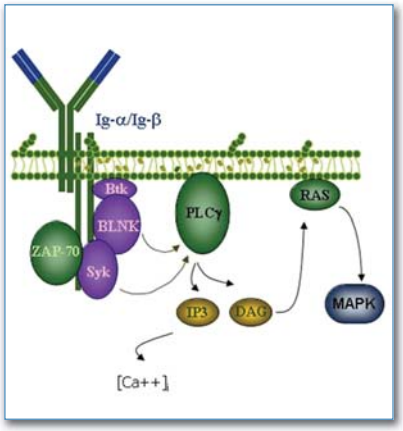

Figure 26
Signaling through the B Cell Receptor (BCR) in Chronic Lymphocytic Leukemia (CLL) cells with positive ZAP-70 expression

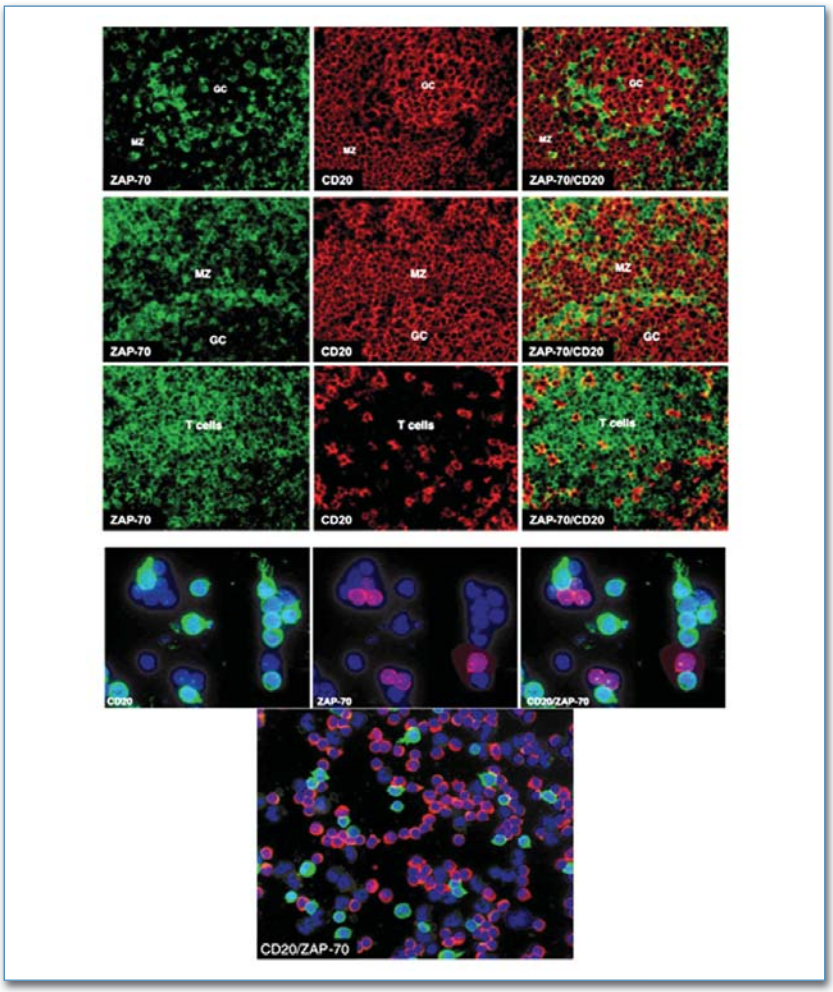

Figure 27
Lack of ZAP-70 expression in normal B lymphocytes (lymph node and peripheral blood)

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AREA 1 ONCOLOGY AND GENETICS

1.18 Molecular Pathology

Group Leader
Santiago Ramón y Cajal Agüeras
Tel. 93 274 68 09
santiago.ramonycajal@vhir.org

Researchers
Elena Allende Monclús
Josep Castellví Vives
Mª Carme Dinares Fernández
Ángel García Jiménez
Javier Hernández Losa
Carmela Iglesias i Felip
Stefania Landolfi
Elena Antima Martínez Saez
María Ángeles Montero Fernández
Arantxa Ortega Aznar
Carlos Parada Cobo
Santiago Ramón y Cajal Agüeras
Carmen Ruiz Marcellán
Natalia Tallada Serra
Inés de Torres Ramírez

Researchers in Training
Trond Aasen
Alba Martínez Díaz
Berta Pons López
Cristina Teixido Febrero
María A Vázquez Sánchez

Nursing, Technical and Administrative Staff
Berta Domínguez Pascuet
Isabel Espinosa Sanahuja
Laura Fernández Cabré
Roso Marès Pagès
Teresa Moliné Marimón
César Javier Sevillano Aguilera
María Rosa Somoza López de Haro

OBJECTIVES

Clinical Research

- Characterize potential tumor markers that have a role as prognostic factors in cancer.
- Study the cell signaling pathway and the role of the 4E-BP1 and eIFs factors in cancer.
- Study of senescence genes and their biochemical pathways in human tumors.

Basic research

- Study of the factors which control cap dependent and independent translation in tumors.
- Studying the mechanisms controlling senescence at the cellular level.
- Study the role of gap junctions in tumour biology and malignant progression.

2010 Impact Factor:
216.587

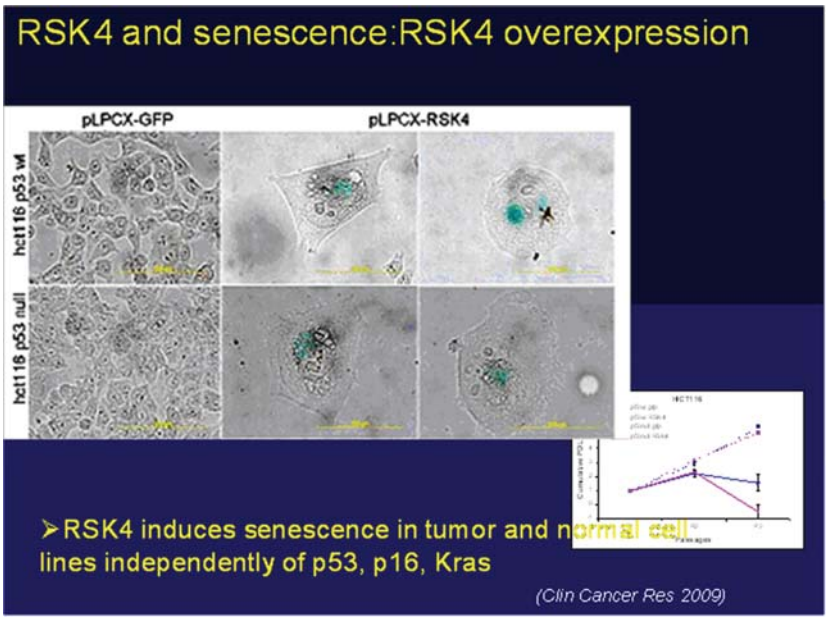


Figure 28
Overexpression of RSK4 induces mechanisms of cellular senescence including X-gal staining

RESEARCH LINES

Study of Cell Signalling pathway in human tumors. Identification of funnel factors

Santiago Ramón y Cajal Agüeras

We have characterized the levels of activation in Cell Signalling in a spectrum of solid tumors and correlated the levels of various factors, including mTOR and downstream proteins (p70S6K, S6, 4EBP1, eIF4E) with prognosis and grade of malignancy. Also, the factors involved in controlling the translation cap dependent and independent in malignant tumors are being characterized at the molecular level.

Study of gene expression of senescence in human tumors

Santiago Ramón y Cajal Agüeras

The expression of mARN genes identified by Dr.R. Bernards has been studied in normal and tumor tissue of cancer patients. This study identifies for the first time, RSK4 and KIAA0828 genes as genes whose role may be relevant in cancer. The expression of these genes is being studied in protein by Western blot and immunohistochemistry. We are also characterizing the biochemical pathways where these genes may be involved.

Identification of molecular targets associated with tumor progression and therapy resistance in colorectal carcinoma

Santiago Ramón y Cajal Agüeras

Studying colorectal cancer mechanisms of action of the central signal transduction pathways, identify potential molecular alterations that can be used as therapeutic targets and characterize the degree of genetic instability.

Study of new genes involved in proliferation

Matilde Lleonart Pajarín

Searching for new proliferative genes/tumor suppressor genes is being performed at our laboratory by carring out genetic screens. By the use of retroviral vectors as carriers of cDNA libraries (formed by mRNA from murine embryonic stem cells), primary cells are infected and screening for those clones able to bypass senescence are selected for further characterization. The marked morphological heterogeneity observed in several tumorigenic processes, support the hypothesis that several cancers have their origin in a stem cell. It is believed that genes expressed by embryonic stem cells, may play an important role in the tumorigenic mechanism. This project unravels the effect of immortal genes existing in embryonic stem cells, when they are forced to be expressed in primary and thereby mortal cells. These immortal genes are future candidate markers in tumors with potential prognosis value. The novel genes discovered are being analyzed in biopsies from patients with different kinds of tumors collected at the Pathology Department of the Vall d´Hebron Hospital.

Genomic transcriptional profile analysis in proliferative inflammatory atrophy (PIA) as a possible precursor of human prostate cancer

Inés de Torres Ramírez

To analyse transcriptional profiles of normal, PIA (proliferative inflammatory atrophy), PIN (prostatic intraepithelial neoplasia) and tu-

moral prostate using microarrays of selected tumoral tissue of prostatectomy specimens, in order to characterize gene expression modifications in prostate cancer versus PIN and PIA.
To analyse the biological response in tumoral / non-tumoral and co-culture them with monocytes in order to study transcriptional profile changes. From all the data obtained, overexpressed / under-expressed genes are being identified and validated. Stromal and inflammatory genes will also be explored for their potential use as early markers for prostatic cancer and their ability to identify PIA as a precursor lesion. (Prostate Research Traslational Unit.)

Long-term mast cell stabilization downregulates mucosal micro-inflammation in the jejunum of diarrhea-prone irritable bowel syndrome (IBS)

Inés de Torres Ramírez

Study of the effect of mast-cell stabilization on mucosal inflammation and clinical response. Immunohistochemistry analysis of microinflammation (mast cells, intraepithelial lymphocytes and eosinophils) in Irritable Bowel Syndrome (IBS). Biological inflammation was evaluated in pooled biopsies by quantitative real time PCR to analyze the expression of preselected genes implicated in innate immunity [Toll-like receptors (TLR) and defensins (DEF)], mast cell activation and growth and neuronal regulation. Mucosal eosinophils show restrained activation in the jejunum of diarrhea –prone irritable bowel syndrome patients. Pharmacological stabilization of mucosal mast cells effectively reduces pro-inflammatory gene expression profiles in the jejunal mucosa of D-IBS patients and concomitantly improves clinical manifestations. (Digestive Disease Research Unit.)

Study of PTOV1 modulation in tumor proliferation and progression: Interaction with IGF1 pathways. Notch and Wnt expression in TMAs of tumors

Inés de Torres Ramírez

To evaluate the expression (nuclear and cytoplasmatic) of PTOV1, Notch and Wnt on TMAs in c different histological types of carcinomas with low and high grades of malignancy. To correlate the immunoexpression with classical parameters of tumor behaviour: tumoral size, grade of malignancy, vascular permeation, lymph node metastasis in each histological subtype and demonstrated the role of PTOV1 as predictive molecular marker in carcinomas. (Research Biomedical Unit.)

Involvement of the human Hepatitis A Viral Receptor (hHAVcr-1) in renal cancer development and progression. Value as a diagnostic and prognostic biomarker in renal carcinomas

Inés de Torres Ramírez

We have postulated that hHAVcr-1 might constitute an important biomarker for early detection of ccRCC and could also be used as a target for therapy of kidney carcinomas, since immunotoxins directed against the monkey homologue of hHAVcr-1 could kill kidney cells.
Specific aims are focused to: i) determine the diagnostic and prognostic potential of hHAVcr-1 expression in renal cell carcinomas, by correlating hHAVcr-1 levels in archive, fresh surgical and TMA tissues with tumor anatomo-pathological characteristics and patient outcome and, ii) determine the function of hHAVcr-1, which remains elusive, in the development and progression of kidney carcinomas, using ccRCC derived cell lines with silenced or overexpressed hHAVcr-1. Tumors overexpressing or defective in hHAVcr-1 will be compared with controls, in relation to their behavior and anatomo-pathological characteristics. Differences are being correlated with proteomic and gene expression profiles obtained in each case. Differential expression pathways and target molecules correlating with absence/presence of hHAVcr-1 shall be identified. New strategies for diagnosis, prognosis and treatment of ccRCC must be further developed. (Programa de Recerca en Càncer Renal CIBBIM-IRHUVH.)

Study of genes involved in genotoxic response in carcinomas

Carlos Parada Cobo

The modulation of the response in chemotherapy agents that generate DNA alterations in human tumors allows surviving classic anticancer therapies. Knowledge of the key proteins that define this resistance can incorporate new prognostic markers in solid tumors. The characterisation of better diagnostic and prognostic markers is paramount to improve early diagnosis and treatment of

cancer. In that respect, we are studying two main protein networks in human carcinomas and their involvement in oncogenesis and sensitivity to chemotherapeutical agents.
The first one involves the network that regulates glycogen synthesis and depolymerisation, and thus, the regulatory elements in glucose storage. We have found some of these proteins to be good markers in early (low grade) tumors.
The second one studies the implications of ND10 associated proteins in response to classic anticancer treatments. ND10 is a nuclear multiprotein complex associated with functions such as DNA damage response, gene expression regulation and apoptosis.
We have found that at least three of the ND10 proteins are putative new prognostic markers in some types of human carcinoma.

Role of HER3 expression in carcinogenesis of endometrial and breast tumors. Search for new predictive markers to anti-HER treatments

Javier Hernández Losa

The cell signalling pathways downstream of epidermal growth factor receptor family members is tightly regulated in normal epithelial cells, and its alteration induce different cell processes (cell proliferation, cell growth, etc...) which trigger cellular transformation. Within this family of receptors, HER1/EGFR and HER2/neu are the best known, with other family members such as HER3 being subject to interest. The aim of the study is establish the role of HER3 protein expression by immunohistochemistry in endometrial and breast tumors, and establish any association with clinic-pathological parameters. Furthermore, we would like to know how HER3 is implicated in resistance mechanisms to anti-HER treatment agents.

Exercise capacity, peripheral muscle dysfunction and genotype in adults with cystic fibrosis

Arantxa Ortega Aznar

To study the degree and type of skeletal muscle involvement in CF patients who present exercise intolerance and their relationship with the genotype. To determine the relationship between the type and/or degree of skeletal muscle involvement by histologic and mitochondrial respiratory chain function study, and the CF genotype. Correlation study between exercise capacity, pulmonary function and genotype.

Mechanisms of cerebral aging: role of GSK3ß/cdk5 and sirtuins

Arantxa Ortega Aznar

Aging may be considered as an accumulation of changes in cells and tissues that increases the risk of disease and death. The senescence-accelerated prone mice SAMP8 is an aging model with brain histopathological signs and other aging-related disorders, such as ß-amyloid and tau protein aggregates and increased oxidative stress. If hyperphosphorylated, tau protein contributes to the development of a tauopathy, process linked to neurodegenerative diseases of the aging brain such as Alzheimer disease. Several kinases (PKC, ERK, CDK5 or GSK3ß) perform this tau protein post-transcriptional modification. We plan to determine the effect that inhibitors of these kinases such as lithium, in vivo and in vitro, could have in slowing down the brain neurodegenerative processes. Additionally, we will study the role of a newly described protein family, sirtuins. Sirtuins are ontogenically preserved proteins related to longevity. We will evaluate the gene and protein expression of Sirt 1, 2 and 3 in cultured neurons and in the brain of this mouse strain. We seek to elucidate the participation of sirtuins in cerebral ageing, using as a tools resveratrol, a flavonoid described as activator of these proteins, and caloric restriction, two paradigms that lead to an elongation of lifespan and neuroprotection in several animal models. In the in vitro studies, the role of GDNF in maintaining neuronal functionality and its correlation with sirtuins will be investigated because this trophic factor decreases with aging and shows a lesser expression in SAMP8 mice.

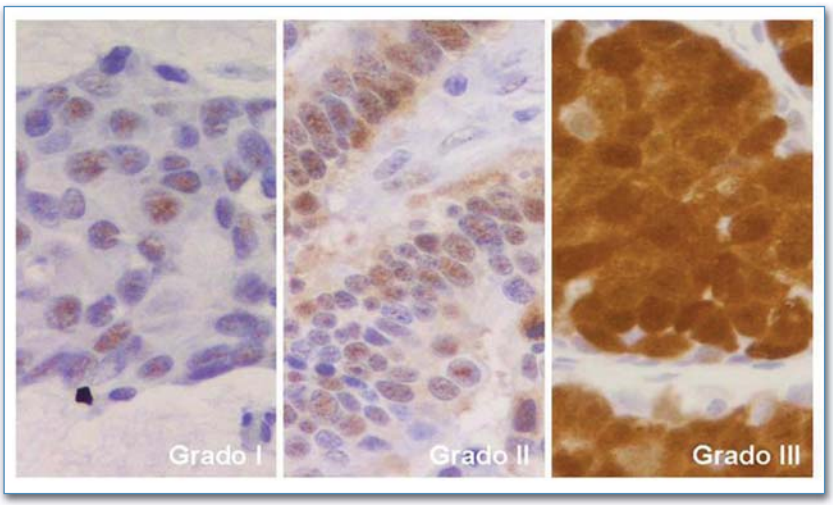


Figure 29
High p-4EBP1 expression correlate with tumoral grade. Immunohistochemistry in breast carcinomas

These studies will contribute to the development of new therapeutic strategies to prevent age-related neurodegenerative diseases.

Study of CAP-dependent and CAP-independent signalling pathways in breast carcinomas

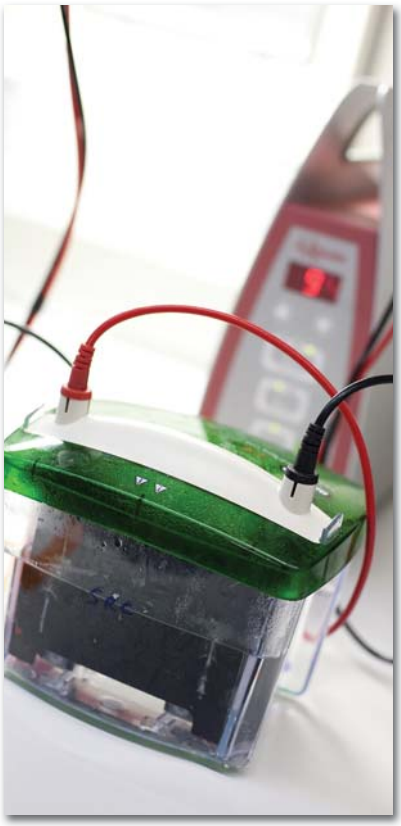
Josep Castellví Vives

In previous work we studied several factors involved in cell signalling pathways that control cell growth. We found that the phosphorylated form of 4E-BP1 was the only factor that correlated with prognosis, and histologic aggressive features in several types of cancers. 4E-BP1 is a key regulator of CAP-dependent traslation and its main function is the inactivation of eIF4E. However, not all aggressive tumors show activation of this factor. On the other hand, it has been shown that under hypoxia conditions in cells the translation of some key factors can be regulated by CAP-independent pathways, mediated by factors known as ITAFs. The aim of our study is to find the CAP-dependent/CAP-independent balance in tumors in relation to hypoxia, and evaluate its impact on prognosis.

Expression analysis and functional elucidation of connexins and pannexins in relation to human cancer progression and malignancy

Trond Aasen

Connexins and pannexins are structural units of gap junctions permitting direct intercellular communication. Deregulation of gap junctions is a frequent feature of carcinogenesis. We are characterizing the expression level of a variety of connexins and pannexins in primary and metastatic human tumors. In vitro we are studying how these proteins affect features related to the degree of malignancy such as migration, invasion and resistance to hypoxia. In connexin-deficient cell lines we are over-expressing specific wild-type



or truncated forms of connexins and pannexins using recently generated retroviral constructs. In cell lines expressing high levels of specific connexins, we knock-down the expression levels using established lentiviral shRNA strategies. We aim to correlate connexin expression and cell communication with malignancy using a variety of well characterized assays with particular focus on colony formation, migration, invasion, epithelial-to-mesenchymal transition, changes in tumor stem cell populations, and hypoxia and drug resistance. The aim of the study is to: 1) Identify any significant correlation between the expression of various gap junction proteins and malignancy, prognosis, chemo-resistance and overall survival in a variety of cancers 2) Gain mechanistic insight and identify direct functional roles of connexins and pannexins during tumor progression.

CURRENT RESEARCH PROJECTS

PI: Arantxa Ortega Aznar

Morfologia i genètica de la malaltia d'Alzheimer

Funding Agency: Fundació La Marató de TV3
Reference: MARATV3/97/3115
Funding: 36,060.72 €
Duration: 1997 to 2010

PI: Santiago Ramón y Cajal Agüeras

Correlación de la expresión de factores embudo 4EBP1, con la expresión de diferentes receptores epidérmicos: papel de HER3, HER2 y sus formas truncadas en diferentes tipos de tumor

Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/13/2008
Funding: 75,000 €
Duration: 2008 to 2011

PI: Santiago Ramón y Cajal Agüeras

Factores centrales o embudos en vías de señalización y senescencia: estudio molecular de las vías de activación e inhibición de receptores epidérmicos y de 4EBP1 y el F4E, así como de RSK4 en senescencia

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080143
Funding: 147,862 €
Duration: 2009 to 2011

PI: Cleofé Romagosa Pérez-Portabell

Papel de algunas moléculas clave de señalización celular y reparación del ADN en el pronóstico y patogénesis de los Sarcomas de Partes Blandas en Adultos

Funding Agency: Grupo Español Investigación Sarcomas (GEIS)
Reference: GEIS/2008
Funding: 18,000 €
Duration: 2008 to 2011

PI: Javier Hernández Losa
Papel de HER3 en la carcinogénesis de tumores de mama y endometrio. Búsqueda de nuevos factores predictivos de respuesta a tratamientos anti-HER
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMM2009/02
Funding: 49,200 €
Duration: 2009 to 2011

PI: Javier Hernández Losa
Papel de receptores epidermoides en cáncer. Papel de HER3 en tumores de mama y endometrio
Funding Agency: Fundación Caja Navarra
Reference: CAN2009-16662
Funding: 6,713.87 €
Duration: 2010 to 2010

PI: Carlos Parada Cobo
Mejoras diagnósticas y pronósticas del melanoma uveal (cáncer intraocular)
Funding Agency: Fundación Caja Navarra
Reference: CAN2009-16641
Funding: 1,116.75 €
Duration: 2010 to 2010

PI: Josep Castellví Vives
Implicación de la traducción cap-independiente, como vía alternativa a la cap-dependiente en condiciones de hipoxia en carcinomas de mama
Funding Agency: Fundació Santiago Dexeus Font
Reference: FSDF2009/03
Funding: 6,000 €
Duration: 2009 to 2011

PI: Santiago Ramón y Cajal Agüeras
Estudio de factores moleculares y vías de señalización asociados a resistencia/sensibilidad al tratamiento con Irvalec
Funding Agency: Centro para el Desarrollo Técnico Industrial (CDTI)
Reference: CENIT2009/01
Funding: 356,298.75 €
Duration: 2009 to 2012

PI: Santiago Ramón y Cajal Agüeras
RTICC - Red Temática de Investigación cooperativa de cáncer
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0020/0104
Funding: 566,495.18 €
Duration: 2007 to 2011

PI: Matilde Lleonart Pajarín
Oncología y patología molecular
Funding Agency: AGAUR
Reference: 2009 SGR 604
Funding: 39,520 €
Duration: 2010 to 2013

PI: Santiago Ramón y Cajal Agüeras
Patologia molecular
Funding Agency: AGAUR
Reference: 2009 SGR 756
Funding: 41,600 €
Duration: 2010 to 2013

PI: Santiago Ramón y Cajal Agüeras
RETICS de Biobancos
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD09/0076/00066
Funding: 299,000 €
Duration: 2010 to 2013

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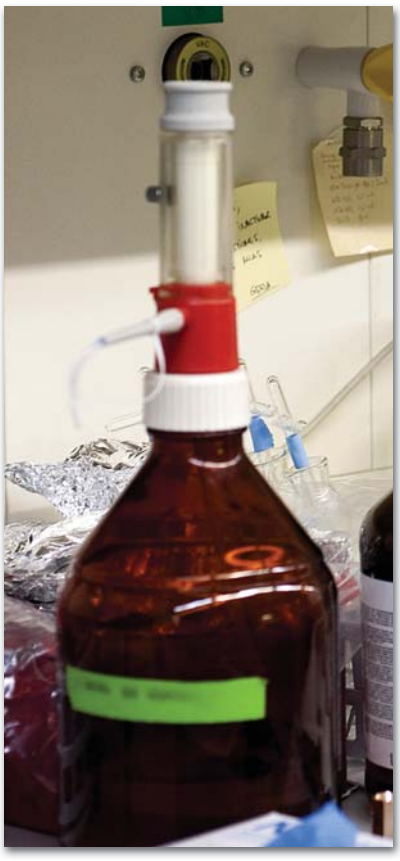

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AREA 1 ONCOLOGY AND GENETICS

1.19 Oncology and Molecular Pathology

Group Leader
Matilde Lleonart Pajarín
Tel. 93 489 41 69
matilde.lleonart@vhir.org

Researchers
Matilde Lleonart Pajarín

Researchers in Training
Ana Artero Castro
Mónica Bouzo Lorenzo
Andrea Francheska Feliciano Aguirre
Beatriz Sánchez Sendra

OBJECTIVES

The main objective of our group is the identification of novel prognosis and diagnosis factors which unveil novel strategies to design anti-cancer therapies. For such purposes, we have carried out massive genetic screens by using cDNA (sense and antisense) libraries to infect primary cells and target those cellular clones which have adquired immortalized properties. The complete characterization is carried out in vitro and in vivo. In vitro, it is performed at mRNA and protein level in infected cells with the putative oncogene or tumor suppressor gene versus the control cells. Proteins partners are identified and extensively characterized. Our final aim is to search for the importance of the identified genes in human tumors. We are therefore looking for identified genes/tumor suppressors in a broad range of human samples. We expect to find new strategies to target novel therapeutical pathways important in tumorigenesis.

2010 Impact Factor:
18.820

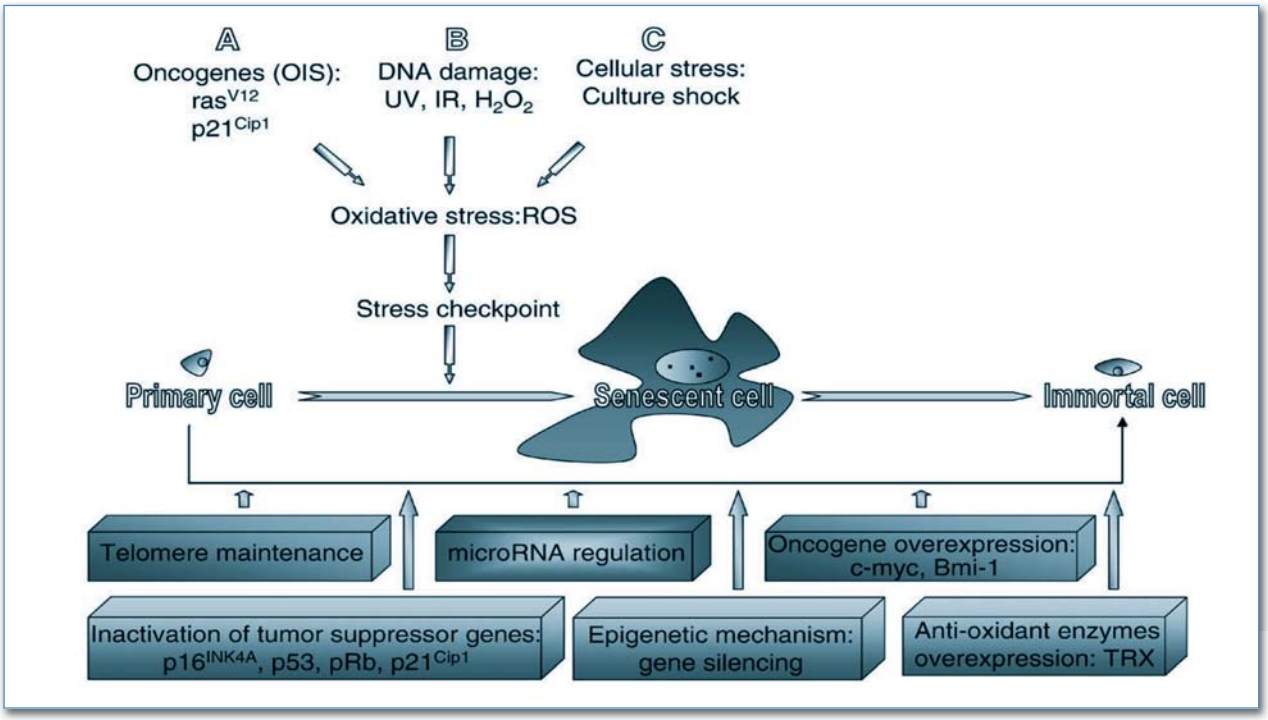

Figure 30
Overexpression of RSK4 induces mechanisms of cellular senescence including ?-gal staining

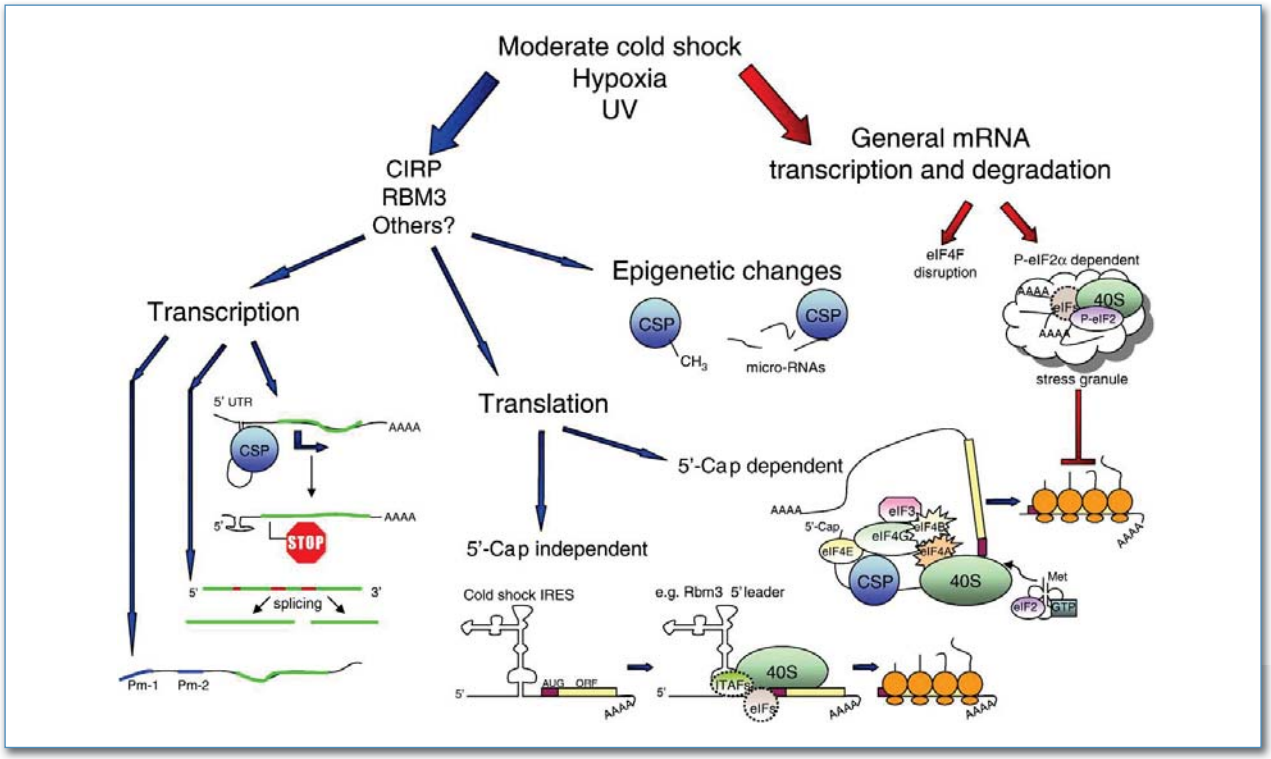

Figure 31
Immunohistochemistry in breast carcinomas. High p-4EBP1 expression correlates with tumoral grade

RESEARCH LINES

Detection of novel genes and tumor suppressor genes involved in senescence which have an important role in human tumors

Novel genes such as CIRP and RPLP1 have been discovered as well as tumor suppressor genes (SAHH). The proliferative genes have been found to be overexpressed in breast, colon and prostate tumors and the anti-proliferative genes have been found downregulated in nearly all main tumor types.

Detection of microRNAs as a novel tool for cancer therapy

We have performed a microRNA screen in primary cells to detect the microRNAs responsible for bypassing Ras-induced senescence. More than 30 different hits have been discovered that are being characterized in our laboratory.

Characterization of ribosomal proteins: Importance and function in tumorigenesis

We are studying the effect of a subgroup of ribosomal proteins in their role as proliferative genes in primary and cancer cell lines. The fact that ribosomal proteins are not only responsible for stabilizing the ribosome structure but they might have independent functions, place these proteins in an important scenario in tumorigenesis.

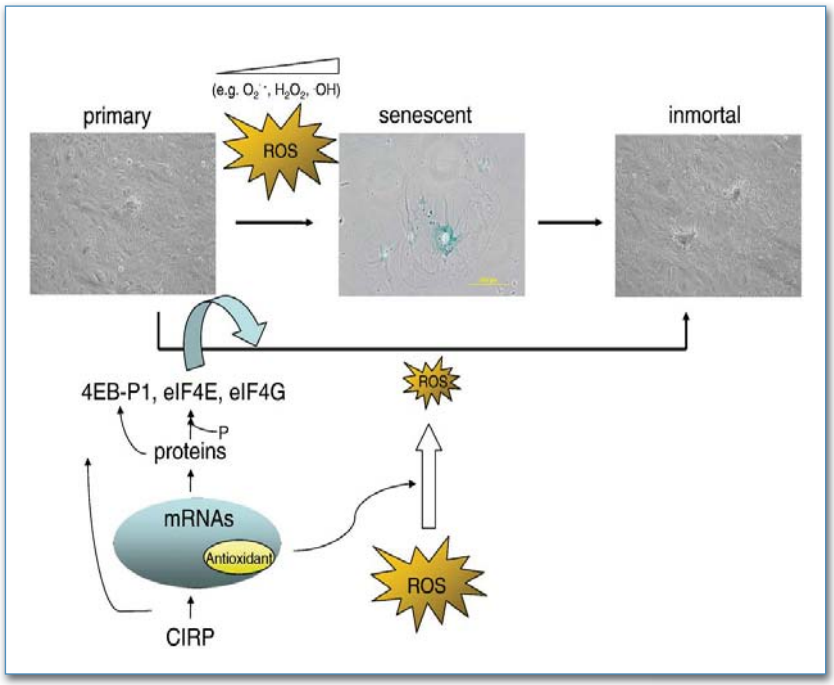

Figure 32
Proposed model for the dual role of CIRP in its contribution to bypassing senescence and providing immortalization in murine primary cells. To bypass senescence, CIRP might influence proliferation through two pathways: a) CIRP directly or indirectly induces mRNA/s and proteins involved in the initiation of translation to promote proliferation; b) CIRP binds and stabilizes specific mRNAs by direct interaction to provoke their activation. Certain mRNAs might be antioxidant mRNAs (e.g., TRX) that counteract the effects of ROS. High ROS accumulation provokes a stress response which forces wild-type cells to enter senescence. A considerable number of oncogenic proteins owe their proliferative potential to their ability to counteract the accumulation of ROS. Evidence that this might be the case for CIRP is discussed in the text. Note the presence of β-galactosidase positive cells (blue) in senescent cells

CURRENT RESEARCH PROJECTS

PI: Matilde Lleonart Pajarín

Identificación de nuevas dianas terapéuticas basadas en micro-RNA sobreexpresados en cáncer

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/02193
Funding: 147,015 €
Duration: 2010 to 2012

PUBLICATIONS (Impact Factor: 18.820)

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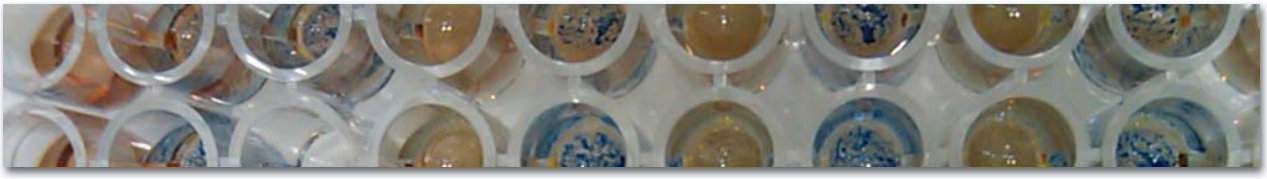


AREA 2 ENDOCRINOLOGY, GROWTH, METABOLISM AND DIABETES

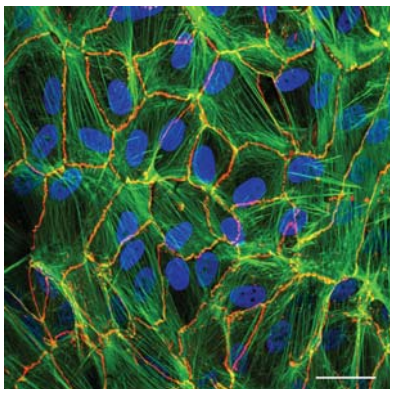
2.1 Diabetes and Metabolism

Group Leader
Rafael Simó Canonge
Tel. 93 489 41 72 / 73
rafael.simo@vhir.org

Researchers
Marta García Ramírez
Cristina Hernández Pascual
Albert Lecubé Torelló
David Martínez Selva
Jorge Mesa Manteca
Rafael Simó Canonge
Josep A. Villena Delgado

Researchers in Training
Anna Barbosa Desongles
Lidia Corraliza Márquez
Natàlia Enguix Elena
Jaime Lasheras Márquez
Marta Villarroel Fandos

Nursing, Technical and Administrative Staff
Olga Mestres Soler
Rosario Pardo Díaz
Lorena Ramos Pérez



STATE OF THE ART

The Diabetes and Metabolism Research Group has been recognized as a consolidated group by the Generalitat de Catalunya, as well as a group of excellence by the ANEP. Apart from belonging to CIBERDEM, our group is associated with the cardiovascular diseases network (RECAVA). Our research is mainly addressed to the pathophysiology of diabetic retinopathy and obesity with the final goal of discovering new therapeutic targets. Our combination of basic and clinical research is important not only in obtaining relevant results, but also in facilitating the rapid transference of these results to clinical practice.

OBJECTIVES

Our general aim in the field of diabetic retinopathy is to discover new therapeutic targets. In the next two years the main objectives will be:

- To identify the mechanisms that trigger neurodegeneration and its consequences in the early stages of diabetic retinopathy through the use of integrated systems biology.
- To determine the molecular mechanisms involved in blood-retinal barrier disruption and to evaluate potential new drugs for the treatment of diabetic macular edema.

2010 Impact Factor:
63.491

- To explore the proteomic and metabonomic profile of the vitreous fluid of diabetic patients vs. non diabetic patients.

In the field of obesity research we are investigating new candidates involved in its pathogenesis. The main objectives during the next years will be:

- To identify by proteomic analysis of cerebrospinal fluid new regulators of food intake.
- To determine the influence of SHBG/sex-steroids on fat properties and distribution and the incidence of diabetes.
- To investigate the role of the mitochondria in obesity, insulin resistance and type 2 diabetes.

Regarding endothelial dysfunction and cardiovascular disease in type 2 diabetic patients, we are testing new methods of evaluating endothelial damage and the prevalence of and the main factors accounting for true silent ischemia.

RESEARCH LINES

Physiopathology of diabetic retinopathy. A new approach using integrated biological systems. This is the main area of our research

Insulin resistance and obesity: new pathogenic candidates and the study of co-morbidities

Endothelial dysfunction, dyslipideamia and cardiovascular disease in type 2 diabetes

CURRENT RESEARCH PROJECTS

PI: Josep A. Villena Delgado
Papel del coactivador PGC-1 beta en tejido adiposo blanco y su contribución al desarrollo de la obesidad y la diabetes de tipo 2
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-03644
Funding: 168,190 €
Duration: 2009 to 2011

PI: Josep A. Villena Delgado
Implication of Estrogen-Related Receptors in the etiology of diabetic cardiomyopathy: identification of ERRs as potential pharmacological targets for treatment of diabetic cardiomyopathy
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3/2008/082610
Funding: 199,138 €
Duration: 2009 to 2012

PI: Josep A. Villena Delgado
Función del coactivador transcripcional PGC-1β en tejido adiposo: contribución al desarrollo de la obesidad y diabetes del tipo 2
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080681
Funding: 148,830 €
Duration: 2009 to 2011

PI: David Martínez Selva
Sex hormone-binding globulin (SHBG): Identification of the molecular mechanisms that regulate its expression and role in body fat distribution and in the development of type 2 diabetes
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP08/00058
Funding: 42,000 €
Duration: 2009 to 2011

PI: Rafael Simó Canonge
Neurodegeneración en la patogénesis de la retinopatía diabética incipiente. Estudio de los mecanismos implicados a través de un abordaje integrado de biología de sistemas
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2009-07408
Funding: 181,500 €
Duration: 2010 to 2012

PI: David Martínez Selva
Papel de la Sex Hormone-Binding Globulin (SHBG) y de los esteroides sexuales en la distribución de la grasa corporal en la aparición de la diabetes mellitus tipo 2
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00144
Funding: 81,070 €
Duration: 2010 to 2012

PI: Rafael Simó Canonge
Neurodegeneration as an early event in the pathogenesis of diabetic retinopathy. Study of involved mechanisms and new therapeutic strategies
Funding Agency: European Foundation for the Study of Diabetes
Reference: EFSD-2010-02
Funding: 100,000 €
Duration: 2010 to 2012

PI: Rafael Simó Canonge
RECAVA - Red Temática de Investigación en Enfermedades Cardiovasculares
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0014/1014
Funding: 27,840 €
Duration: 2008 to 2011

PI: Rafael Simó Canonge
Grup de Recerca en Diabetis i Metabolisme
Funding Agency: AGAUR
Reference: 2009 SGR 739
Funding: 43,680 €
Duration: 2010 to 2013

PI: Rafael Simó Canonge
Identification of neurodegenerative mechanisms that promote development of diabetic retinopathy: the role of insulin signalling and apoptosis
Funding Agency: CIBERDEM
Reference: NEURORET-DIAB
Funding: 32,000 €
Duration: 2009 to 2010

PI: Rafael Simó Canonge
Glycogen-Induced Dysfunctions in Pancreas and Retina and their involvement in the Ethiogenesis of Diabetes mellitus
Funding Agency: CIBERDEM
Reference: GIDIPRED
Funding: 30,000 €
Duration: 2009 to 2010

PI: Rafael Simó Canonge
Determinants of insulin resistance and of disorders of glucose tolerance, including diabetes, in severe obesity, and their changes after bariatric surgery-induced weight loss
Funding Agency: CIBERDEM
Reference: DIASOBS
Funding: 25,000 €
Duration: 2009 to 2010

PI: Rafael Simó Canonge
Adult Adipose Tissue-Derived Progenitor Cells: Influence of the clinical phenotype and adipose depot origen in their biological properties
Funding Agency: CIBERDEM
Reference: StemOb
Funding: 30,000 €
Duration: 2009 to 2010

PUBLICATIONS
(Impact Factor: 63.491)

Barba I, García-Ramírez M, Hernández C, Alonso MA, Masmiquel L, García-Dorado D, Simó R. Metabolic fingerprints of proliferative diabetic retinopathy. An 1H NMR-based metabonomic approach using vitreous humor. *Invest Ophthalmol Vis Sci* 2010 Sep; 51 (9): 4416-21. ➲ IF: 3.431.

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Lecubé A, Sampol G, Lloberes P, Romero O, Mesa J, Morell F, Simó R. Asymptomatic sleep-disordered breathing in premenopausal women awaiting bariatric surgery. *Obes Surg* 2010 Apr; 20 (4): 454-61. ➲ IF: 2.934.

Lecubé A, Sampol G, Muñoz X, Hernández C, Mesa J, Simó R. Type 2 diabetes impairs pulmonary function in morbidly obese women: a case-control study. *Diabetologia* 2010 Jun; 53 (6): 1210-6. ➲ IF: 6.551.

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Núñez-Cortés JM, Pedro-Botet Montoya J, Pintó Sala X, Montoya JP, Simó Canonge R, Santos PG, Soldevilla JG, Mijares AH, Sánchez LF. Residual vascular risk: recommendations of the Spanish Initiative for the Reduction of Residual Risk. *Med Clin (Barc)* 2010 Jul 3; 135 (4): 165-71. ➲ IF: 1,231.

Pardina E, Ferrer R, Baena-Fustegueras JA, Lecubé A, Fort JM, Vargas V, Catalán R, Peinado-Onsurbe J. The Relationships Between IGF-1 and CRP, NO, Leptin, and Adiponectin During Weight Loss in the Morbidly Obese. *Obes Surg* 2010 May; 20 (5): 623-32. ➲ IF: 2.934.

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AREA 2 ENDOCRINOLOGY, GROWTH, METABOLISM AND DIABETES

2.2 Nephrology

Group Leader
Daniel Serón Micas
Tel. 93 274 62 19
dseron@vhebron.net

Researchers
Irene Agraz Pamplona
Jorge-Juan Bartolomé Espinosa
M. Carme Cantarell Aixendri
María Eugenia Espinel Garuz
Joan Fort Ros
María Asunción Galicia Basart
Francesc Moreso Mateos
Mario Morlans Molina
Manel Perelló Carrascosa
Daniel Serón Micas
José Luis Tovar Méndez
Josepa Vila Presas

Nursing, Technical and Administrative Staff
Iván Gil Carballeira

OBJECTIVES

The Renal Unit is divided into three areas: clinical nephrology, dialysis and transplantation. There is a head of department, 15 staff nephrologists, 4 part time nephrologists and 8 training nephrologists. The hospitalization area has 26 beds, and its own peritoneal and haemodialysis units. In 2009 there were 1270 inpatients, 9000 outpatient visits and 75 renal transplants were performed. Three staff member are professors at the Autonomous University of Barcelona. The Renal Unit has undertaken a deep transformation in order to reinforce clinical and basic research that focuses on two main topics: progression of renal insufficiency and atheromatosis in chronic kidney disease. A clinical research facility to monitor observational studies and clinical trials has been built.

2010 Impact Factor:
39.003

RESEARCH LINES

Progression of renal insufficiency
This area is focused on native kidney diseases and renal transplantation. Multicentre clinical trials evaluating treatment of different glomerular diseases constitute the main area of interest in the study of glomerular disease as well as risk factors and mediators of renal damage in the progression of IgA nephropathy. In renal transplantation, main areas of interest are treatment of chronic humoral rejection, proteomic studies of cultured renal tubular cells to evaluate markers of injury and specific markers for nephrotoxicity due to immunosuppressive agents such as mTOR inhibitors and anticalcineurinic drugs and its possible clinical application. Recurrence of renal disease after transplantation, especially focal segmental glomerulosclerosis is another ongoing study.

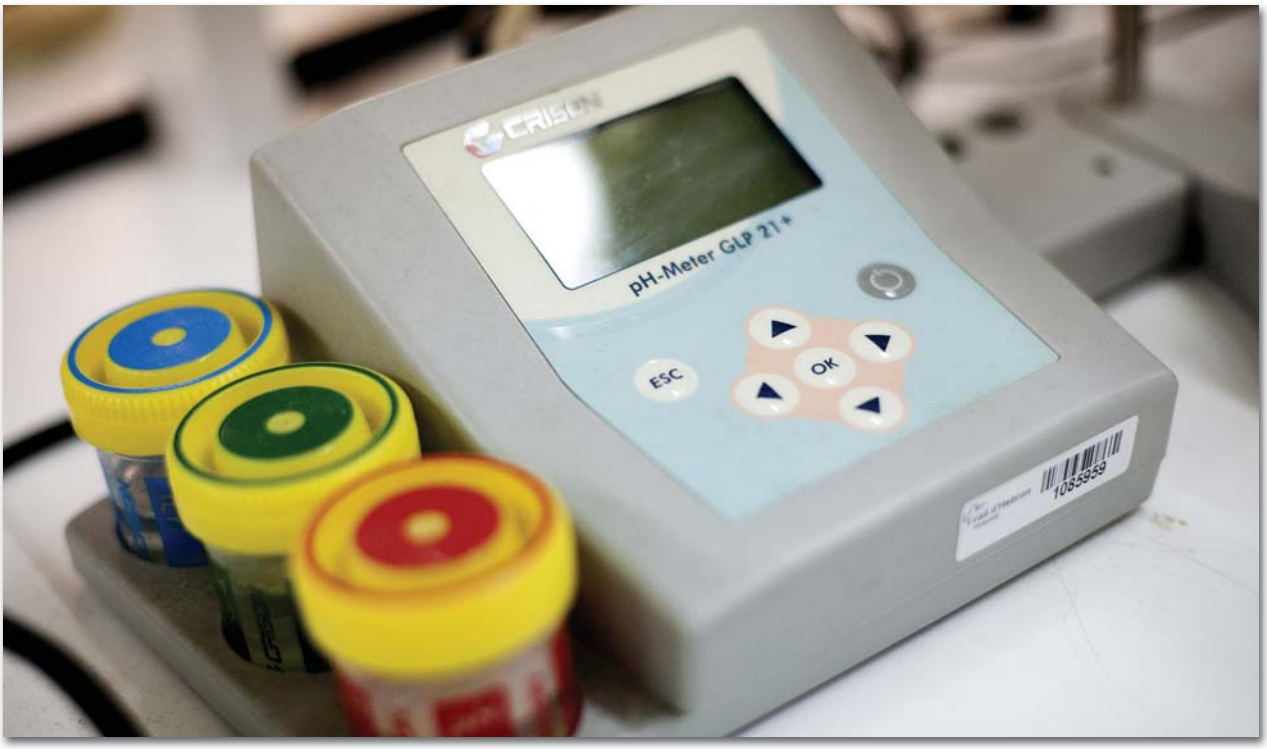
Atheromatosis in chronic kidney disease
Influence of innate immunity alterations in the progression of subclinical atheromatosis in patients with renal insufficiency of the native kidney and recipients of a kidney transplant. In this study classical and new risk factors such as low grade inflammation, oxidative stress, endothelial damage and regeneration are considered.

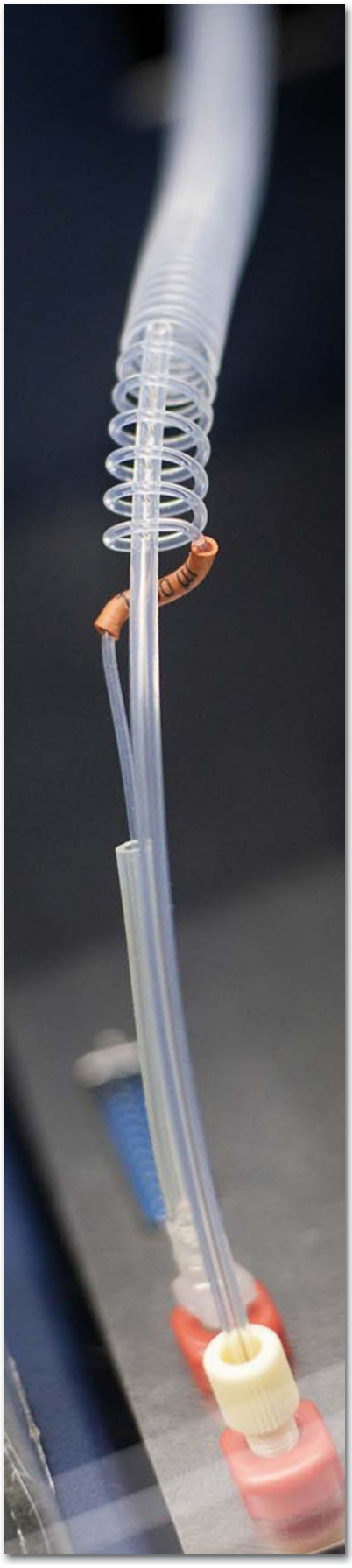
CURRENT RESEARCH PROJECTS

PI: M. Carme Cantarell Aixendri
Estudio piloto de selección del régimen inmunodepresor basado en anti-calcineurínico o libre de anti-calcineurínico dependiendo de la aloreactividad celular donante-específica mediante técnica de elipost en receptores de un injerto renal D
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90455
Funding: 6,897 €
Duration: 2007 to 2011

PI: María Eugenia Espinel Garuz
Efecto del ARA-II Olmesartan en el metabolismo del potasio en pacientes con insuficiencia renal crónica
Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-197
Funding: 43,482.09 €
Duration: 2010 to 2011

PI: Francesc Moreso Mateos
Inmunosupresión óptima en pacientes con alto riesgo de diabetes de novo tras el trasplante renal: un estudio prospectivo, multicéntrico, controlado y randomizado
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00158
Funding: 54,907.50 €
Duration: 2009 to 2011





PUBLICATIONS
(Impact Factor: 39.003)

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Otero A, Francisco A de, Gayoso P, Garcia F, Valveny N, Calbet D, Lara MA de, Vega F, Laviades C, Vives PJ, Pena Porta JM, Marco J, Solis A, González AL, Fresnedo GF, Navarro JF, Joga JA, Fort J, Castelao AM, Fonseré N, Tornero F, Quintana M, Villoria López K, Rubio E, Bernis C, Gironés M, Asin JL, Jaras JH, Rius A, Rico MG. Prevalence of chronic renal disease in Spain: results of the EPIRCE study. *Nefrologia.* 2010; 30 (1): 78-86. doi: 10.3265/Nefrologia.pre2009.Dic.5732. ➲ IF: 0.533.

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AREA 2 ENDOCRINOLOGY, GROWTH, METABOLISM AND DIABETES

2.3 Paediatric Endocrinology

Group Leader
Antonio Carrascosa Lezcano
Tel. 93 489 30 63
ancarrascosa@vhebron.net

Researchers
Marian Albisu Aparicio
Laura Audí Parera
Núria Camats Tarruella
María Clemente León
Mónica Fernández Cancio
Norma I García Reyna
Sandra Gussinyé Canabal
Miguel Gussinyé Cañadel
Diego Yeste Fernández

Researchers in Training
Agnès Moretones Barnès

Nursing, Technical and Administrative Staff
Ana Agudo Canales
Pilar Andaluz López

OBJECTIVES

Translational (clinical, biochemical and molecular) research into paediatric endocrine diseases.

2010 Impact Factor:
14.354

RESEARCH LINES

Normal growth and development patterns in children

Our group contributed to the establishment of normal charts for both sexes for height, weight and BMI from birth to adult height in Spain (Spanish Growth Studies 2008 and 2010: cross-sectional and longitudinal studies). The charts are for autochthonous and immigrant populations. The cross-sectional autochthonous charts comprise those for: newborns from 26 to 42 weeks GA and normal children from birth to 22 years. The longitudinal autochthonous study comprises charts according to age at onset of the pubertal growth spurt (very early, early, intermediate, late and very late). The charts for the immigrant population now available comprise those at birth for children of parents from the Magreb, SubSaharan Africa and Central and South America and those to adult height for children from the Magreb and SubSaharan Africa. These charts are necessary for the correct evaluation of children with skeletal growth and nutrition disorders.

Growth delay in children: phenotype-genotype (GH1, GHRHR, GHR genes) associations

Children with growth retardation are being molecularly analysed (GH1 and GHRHR depending on the clinical and biochemical phenotypes) and differences between gene sequences in the normal population and patients are being progressively described. Potentially pathogenic mutations detected are being functionally analysed in children with growth retardation (idiopathic growth retardation and SGA) and treated with GH. The association between growth responses at different periods up to the end of growth and the genotypes for the GHR gene exon 3 deletion have been analysed and are continuously monitored up to final height.

Genetic contribution to adult height (GH1 and GHRHR genes)

Our Group established the complete map of SNPs in GH1 (proximal promotor and complete coding and non-coding introns) and GHRHR (promoter and exons) genes and the frequency of the GHR gene exon 3-deletion polymorphism in our normal adult height control population of both sexes with height between -2 and +2 SDS. A significant association between several of the detected SNPs and height-SDS has been demonstrated.

Human epiphyseal growth cartilage chondrocyte proliferation and gene expression regulation

Postnatal regulation of skeletal growth by growth hormone (GH), insulin-like growth factor I (IGF-I), thyroid hormone, androgens and oestrogen, and the need for their adequate circulating concentrations which vary depending on developmental stages, is well known; however, the physiological role of glucocorticoid (GC) on skeletal growth is poorly understood, except for the deleterious effects of its excess. Vitamin D (VitD) has been well described as a calcium homeostasis regulator as has its deficiency as a deleterious effect; however, possible direct effects of VitD on growth plate biology have scarcely been studied. To analyze the mechanisms involved in androgen, thyroid hormone, oestrogen, glucocorticoid (GC), vitamin D (VitD), growth hormone (GH) and insulin-like growth factor I (IGF-I) regulation of epiphyseal growth cartilage biology during human foetal life, we used chondrocytes obtained in primary and first passage cultures as a cellular model.

Bone mass in children

Our Group established the charts for bone mineral density (BMD) in normal children from birth to adulthood. These charts are necessary for the correct evaluation of skeletal bone mass in children at risk of developing diminished mineral density before the maximum BMD peak is attained, which predisposes to osteopenia and osteoporosis in adulthood.

Predisposing environmental and genetic factors of rickets

Our Group contributed to an initial epidemiological study on the prevalence of rickets in Primary Care Areas of Catalonia involving autochthonous and immigrant infants. We further contributed to an international study conducted within the European Society for Paediatric Endocrinology (ESPE) on epidemiological and genetic factors in rickets in Middle Eastern countries. We are now contributing to further studies on the biochemical and genetic characteristics of autochthonous and immigrant children, in relation to vitamin D and calcium metabolism.

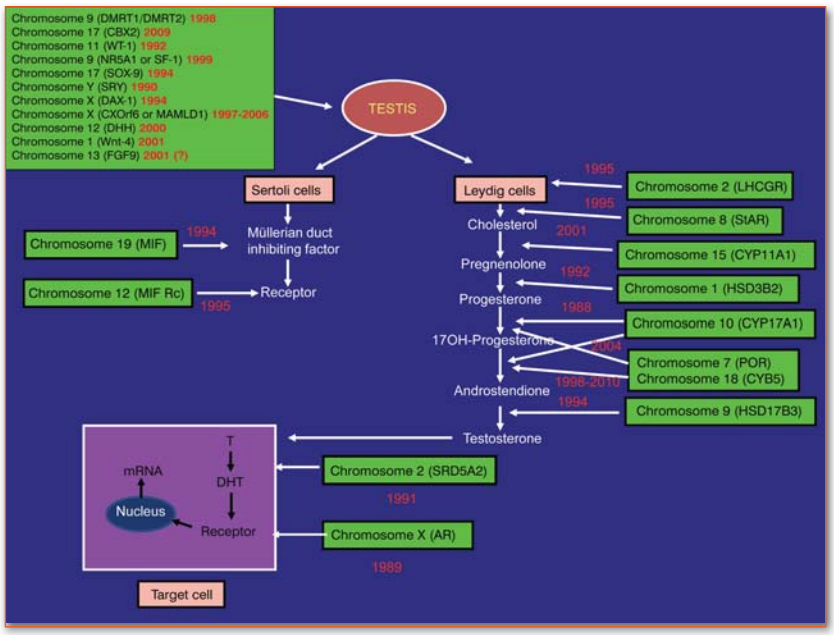


Figure 33
The main genes involved in 46,XY male sex development during foetal life with chromosomal location and cloning year

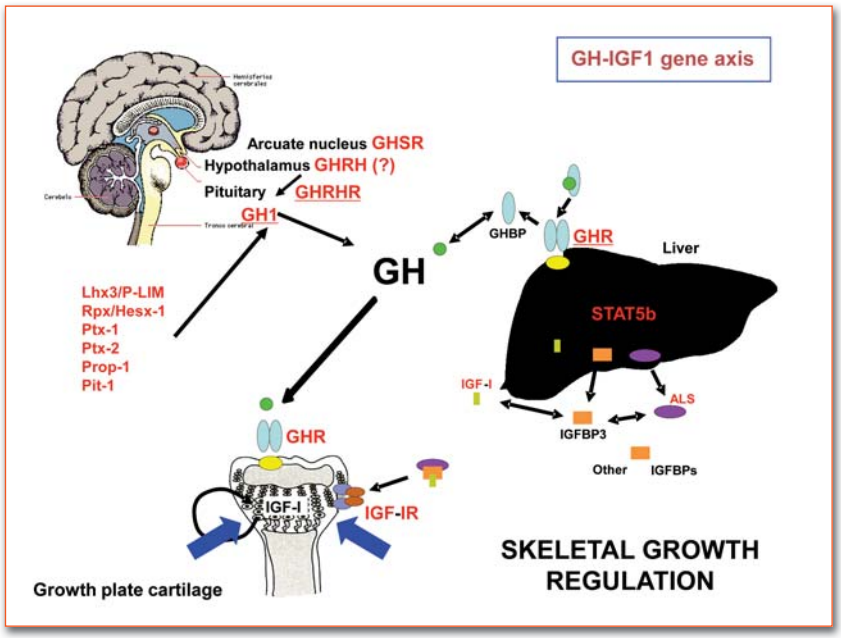


Figure 34
Analysis of postnatal skeletal growth regulating genes

Congenital hypothyroidism: Catalan referral center for diagnosis and therapy. Identification of mutations in thyroid hormone synthesis genes

Our Group forms a reference centre for the diagnosis and treatment of congenital hypothyroidism. The approach is multidisciplinary with the collaboration of paediatric endocrinologists, psychologists and the research laboratory. The latter, located in Hospital La Paz (Madrid) contributes to the molecular diagnosis of thyroid hormone synthesis genes.

Hypothyroxynaemia in extreme preterm infants

Our Group established the values of thyroid hormones (T4, T3, free-T4, free-T3 and TSH) from birth to 1 year of age in preterm infants 27-37 weeks of gestational age and contributes to the evaluation of hypothyroxinemia of preterm infants.

Disorders of sex development (DSD): clinical and molecular diagnosis (AR, SRD5A2, HSD17B3, CYP17A1, NR5A1, MAMLD1)

Our Group forms a reference centre for the diagnosis and treatment of DSD. The approach is multidisciplinary with the collaboration of paediatric endocrinologists, geneticists, pathologists, paediatric surgeons, psychologists and the research laboratory. The latter contributes to the molecular diagnosis of 46,XY DSD patients, with diagnoses being offered to all other hospital centres in Spain. Functional analysis of novel mutations in NR5A1 gene are being performed in collaboration with the Paediatric Endocrinology and Diabetology Unit of the Berne University Hospital for Children.

Familial isolated glucocorticoid deficiency (FGD) (MC2R, MRAP, StAR genes)

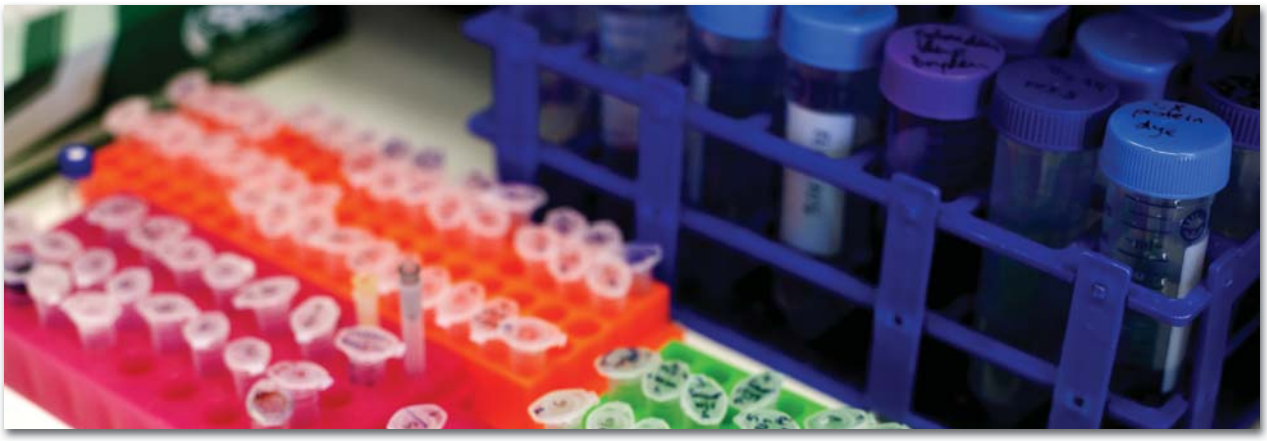
Novel mutations in MC2R and StAR genes are now being described in patients with FGD. Functional analysis of novel mutations will be established in collaboration with the Paediatric Endocrinology and Diabetology Unit of the Berne University Hospital for Children.

Hyperinsulinism and hypoglycaemia

Our Group forms a reference centre for the diagnosis and treatment of infants and children with hyperinsulinaemia and hypoglycaemia syndrome. The approach is multidisciplinary with the collaboration of paediatric endocrinologists, paediatric surgeons and the research laboratory. The latter contributes to the molecular diagnosis of genes involved in this syndrome.

Type 1 diabetes: new therapeutic immunomodulators (international clinical trial)

D/P3/07/4 "A phase III 3 arm randomized, double-blind, placebo-controlled multicentre study to investigate the impact of Diamyd on the progression of diabetes in patients newly diagnosed with type 1 Diabetes Mellitus". Promoted by Dyamid Therapeutics.



Childhood obesity: metabolic complications and therapeutic approaches

Our Group forms a reference centre for the diagnosis and treatment of infants and children with obesity. The approach is multidisciplinary with the collaboration of paediatric endocrinologists, nutritionists and psychologists. We have developed a new therapeutic program "niñ@s en movimiento" and have begun training medical professionals as educators in childhood obesity. More than 250 medical professionals have been trained and our program is applied now in 32 health centres in Spain and one in Mexico. The metabolic complications of childhood obesity are also evaluated.

CURRENT RESEARCH PROJECTS

PI: Laura Audí Parera

Marcadores moleculares de la acción de los andrógenos: aplicaciones básicas al conocimiento de la regulación de la diferenciación sexual y diagnósticas en el pseudohermafroditismo masculino

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060903
Funding: 125,840 €
Duration: 2007 to 2010

PI: Antonio Carrascosa Lezcano

Estudio funcional de nuevas mutaciones en el gen GH1 en una población de 728 pacientes con retraso crónico de crecimiento secundario a deficiencia de GH o a GH con actividad biológica disminuida y buena respuesta clínica al tratamiento con GH

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070145
Funding: 148,830 €
Duration: 2008 to 2011

PI: Antonio Carrascosa Lezcano

Fisiopatologia del creixement

Funding Agency: AGAUR
Reference: 2009 SGR 31
Funding: 47,840 €
Duration: 2010 to 2013

PUBLICATIONS (Impact Factor: 14.354)

Audí L, Fernández-Cancio M, Carrascosa A, Andaluz P, Torán N, Piro C, Vilaró E, Vicens-Calvet E, Gussinyé M, Albisu MA, Yeste D, Clemente M, Hernández de la Calle I, Campo M del, *et al.* Novel (60%) and Recurrent (40%) Androgen Receptor Gene Mutations in a Series of 59 Patients with a 46,XY Disorder of Sex Development. *J Clin Endocrinol Metab* 2010 Apr; 95 (4): 1876-88. ➲ IF: 6.202.

Camina-Tato M, Morcillo-Suárez C, Bustamante MF, Ortega I, Navarro A, Muntasell A, López-Botet M, Sánchez A, Carmona P, Julia E, Tórtola MT, Audí L, Oksenberg JR, Martín R, Montalban X, Comabella M. Gender-Associated Differences of Perforin Polymorphisms in the Susceptibility to Multiple Sclerosis. *J Immunol* 2010 Nov 1; 185 (9): 5392-404. ➲ IF: 5.646.

Clemente M, Gussinyeé M, Arranz JA, Riudor E, Yeste D, Albisu M, Carrascosa A. Glycogen storage disease type III with hypoketosis. *J Pediatr Endocrinol Metab* 2010 Aug; 23 (8): 833-6. ➲ IF: 0.738.

Padilla N, Perapoch J, Carrascosa A, Acosta-Rojas R, Botet F, Gratacós E. Twelve-month neurodevelopmental outcome in preterm infants with and without intrauterine growth restriction. *Acta Paediatr* 2010 Oct; 99 (10): 1498-503. doi: 10.1111/j.1651-2227.2010.01848.x. ➲ IF: 1.768.

AREA 3 CARDIOVASCULAR DISEASES, HEMOSTASIS AND HYPERTENSION

3.1 Cardiovascular Diseases, Hemostasis and Hypertension

Group Leader
David García-Dorado García
Tel. 93 489 40 38
dgdorado@vhebron.net

Researchers
Elena Abad Adán
Santiago Aguadé Bruix
Francesc Xavier Armengol Castells
Ignasi Barba Vert
José Antonio Barrabés Riu
Neus Bellera Gotarda
Pedro Betrián Blasco
Bart Bijnens
Albert Brotons
Dimpna Calila
Jaume Candell Riera
Jaume Casaldàliga Ferrer
Joan Castell Conesa
Josefa Cortadellas Àngel
Enric Domingo Ribas
Laura Dos Subirà
Arturo Evangelista Masip
Ignacio Ferreira González
Joan Àngel Ferrer
Queralt Ferrer Menduina
Jaume Figueras Bellot
Enrique Galve Basilio
Bruno García del Blanco
David García-Dorado García
Gemma Giralt García
Josep Girona Comas
Teresa González Alujas
Ferran Gran Ipiña
Laura Gutiérrez García-Moreno
Javier Inserte Igual
Rosa María Lidón Corbi
Begoña Manso García
Eli Miró Casas
Àngel Moya Mitjans
Imanol Otaegui Irurueta
Gaietà Permanyer Miralda
Núria Rivas Gándara
Ivo Roca Luque
Jordi Pérez Rodón
Antonia Pijuan Domènech
Josep Pinar Sopena
José Rodríguez Palomares
Antonio Rodríguez Sinovas

Principal investigators of research lines

Marisol Ruiz Meana
Jaume Sagristà Sauleda
Armando Salas Lobato
Antonia Sambola Ayala
Joan Sánchez de Toledo Sancho
Vicenç Serra García
Teresa Subirana
Pilar Tomos Mas
Asunción Torrents Fernández

Clinical Research
Mª Ángeles Carmona Ramírez
Úrsula Gimeno Mañas
Nadia Llavero Muñoz

Post MIR
Omar Abdul-Jawad Altisent
Gerard Martí Aguasca
Mireia Andrés Villarreal
Jordi Bañeras Rius
Eduard Bosch Peligero
Sergio Moral Torres
Gisela Teixidó Tura
Eduardo Villacorta Argüelles

Predoc
Verónica Aliaga
Amelia Carro Hevia
Gemma Cuberas Borros
Celia Fernández Sanz
Giuliana Garibaldi
Josep Ramón Marsal Mora

Axel Mercè Sarrias
Marcos Poncelas Nozal
María Nazarena Pizzi
Roger Quispe Marca
Laura Romero Grillo
Paula Andrea Rudenick
José A. Sánchez García
Nuria Norma Tejerina

Postdoc
Elena Abad Adán
Amanda Denuc Isern
Ana María Díaz Calvo
Víctor Hernando Martínez

Nursing, Technical and Administrative Staff
Rodrigo Berguenda Pinto
Maria Dolors Bofill Rovira
Anna Casanovas Hernández
Purificación Cascant Castelló
Mª Teresa Fernández Taranilla
Maria Angels Garcia Sánchez
Daniel Gómez García
Manuel Valero Gómez Guillén
Lourdes Muelas Godoy
Elsa Nieto Santa
Mª Teresa Pastor Amorós
Dorita Quiroga Brañas
Aida Ribera Solé
Giuliana Ríos Quiñones
Ángeles Rojas López

OBJECTIVES

The Mission of the Research Group on Cardiovascular Diseases (Consolidated Research Group of the Generalitat de Catalunya, DURSI 2009SGR0802) is to reduce the social and sanitary impact of cardiovascular diseases by improving their prevention, diagnosis and treatment. This mission is achieved through a highly multidisciplinary, translational research program including molecular and cellular investigation, clinical studies, and epidemiological and outcome research studies. The group is a member of the Spanish Network for Research of Cardiovascular Diseases and of the Center for Epidemiology and Public Health of the Instituto de Salud Carlos III (Ministry of Science).

RESEARCH LINES

Myocardial protection during ischemia and reperfusion

David García-Dorado García

This line investigates the molecular mechanisms of cell injury, in particular cell death, secondary to myocardial ischemia-reperfusion syndrome. The final aim is the development of new therapeutic strategies to limit infarct size in patients with acute coronary or other conditions causing myocardial ischemia.

Sub-lines:

1.1. Mitochondrial changes and mitochondria-sarcoplasmic reticulum interaction during myocardial ischemia-reperfusion.
1.2. Role of Connein43, in particular in its mitochondrial localization in cell death and cardioprotection signalling during ischemia-reperfusion.
1.3. Cytoskeletal fragility and calpain activation as a mechanism of reperfusion injury.
1.4. Microvascular injury in reperfused myocardium.
1.5. Prevention of LV remodelling by siRNA inhibition in reperfused myocardium.
1.6. Effect of ageing on myocardial tolerance to ischemia.
1.7. Coadjuvant cardioprotection in patients with STEMI undergoing primary percutaneous coronary intervention.
1.8. NMR-based metabolomics in ischemia-reperfusion.
1.9. Systems biology approaches to myocardial diseases.

Pathophysiology of acute coronary syndrome

Jaume Figueras Bellot

The aim of this line is to provide the basis for the pathophysiological stratification of patients with acute coronary syndrome that will allow optimization of evaluation and treatment.

Sub-lines:

2.1. Platelet functions in acute coronary syndromes.
2.2. Determinants of LV remodelling.
2.3. Tissue factor as a predictor of final infarct size in patients with STEMI receiving primary PCI.
2.4. Antithrombotic treatment in patients with high thromboembolic risk receiving coronary stents.

2010 Impact Factor:
364.079

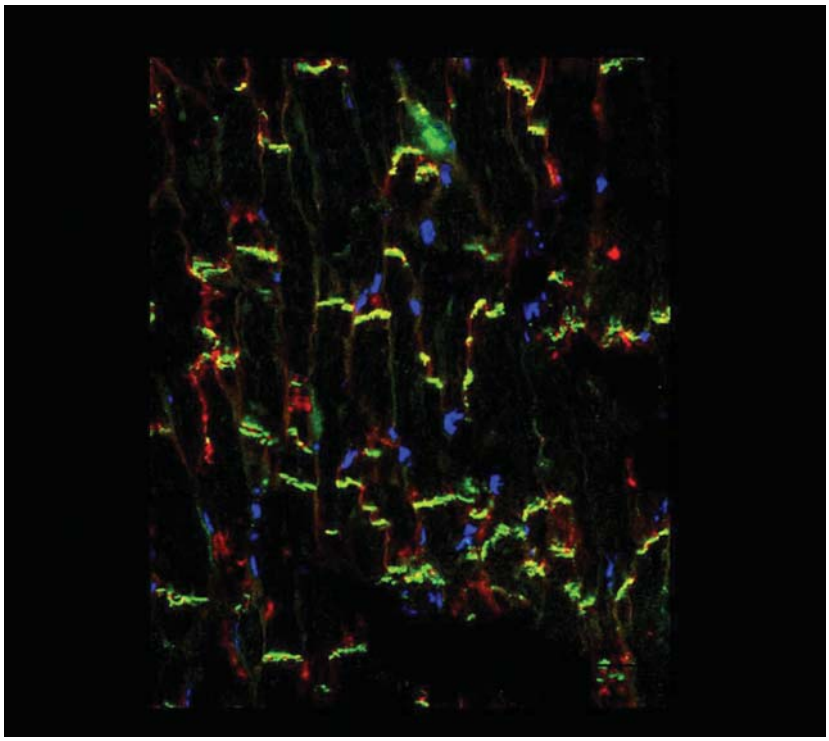


Figure 35
Molecular models: Confocal image showing (in red) expression of Cx43 in a cardiac slice obtained from an ischemic (30 min) heart from a wild-type mice. Intercalated disks were identified by staining with antibody raised against pan-Cadherin (Cad.) (green). Nuclei were marked with Hoeschst 33342 (blue)

Prognostic stratification of patients with ischemic heart disease by nuclear cardiology
Jaume Candell Riera
This line aims to develop new methodologies for the evaluation of the functional significance of coronary disease.
Sub-lines:

3.1. Evaluation of non-significant coronary stenos.
3.2. Assessment of myocardial viability.
3.3. Prognostic significance of silent ischemia.
3.4. Multimodal imaging and 3D image fusion.

Myocardial diseases and heart failure
Enrique Galve Basilio
Molecular mechanisms of cardiomyopathies and determinants of heart failure.
Sub-lines:

4.1. Genotype/phenotype relation in hyperthrophyc cardiomyopathy.
4.2. Analysis of myocardial fibrosis by NMR and new biomakers.
4.3. Mitochondrial function in heart failure.

Valvular heart disease
Pilar Tornos Mas
The aim of this line is the improvement in survival and quality of life of patients with heart valve disease through improving pathophysiologic understanding, diagnostic characterization and treatment.
Sub-lines:

5.1. Epidemiology, pathophysiology and treatment of aortic stenosis, with emphasis on trans-catheter aortic valve implantation.
5.2. Determinants of the results of surgical treatment of cardiac valve diseases.
5.3. Endocarditis: natural history and results of early surgical treatment.

Arrhythmias and syncope
Àngel Moya Mitjans
Diagnosis and treatment of syncope, arrhythmias and heart failure.
Sub-lines:

6.1. Diagnostic work-up in syncope.
6.2. Pharmacological treatment of syncope.
6.3. Predictors of adequate ICD discharge.
6.4. Early resynchronization therapy after AMI.
6.5. Application of robotics to ablation procedures in patients with atrial fibrillation.

Pericardial diseases
Jaume Sagristà Sauleda
Studies on the pathophysiology, natural history, prognostic stratification and treatment of patients with pericardial and diseases.
Sub-lines:

7.1. Pathophysiology of pericardial syndromes.
7.2. Prevention of recidives in patients with pericarditis.
7.3. Pericarditis in patients with cancer.

Diseases of the aorta

Arturo Evangelista Masip

The general purpose of this line is to improve our understanding of the pathophysiology and natural history of the differnt forms of acute and chronic diseases of the aorta, including aneurism, ulcer, intramural hematoma and dissection, with particular attention paid to genetic alterations of the connective tissue, with the final aim of improving their diagnosis and treatment.

Sub-lines:

8.1. Diagnostic evaluation of aortic dissection.
8.2. Prognostic determinants in aortic dissection.
8.3. Intramural hematoma as a new form of aortic disease.
8.4. Molecular pathophysiology, prognostic evaluation and treatment of Marphan syndrome.
8.5. Models of aortic diseases in silico, physical, biological.

Congenital heart disease

Jaume Casaldàliga Ferrer

Studies on the pathophysiology and clinical management of congenital heart diseases from intrautero life to adulthood.

Sub-lines:

9.1. Pathophysiology and evolution of systemic right ventricle.
9.2. Pharmacological treatment in patients with systemic right ventricle.
9.2. Chronic volume overload of the right ventricle.
9.3. Predictors of arrhythmic events after surgical treatment of TOF.
9.4. Remodelling of the right ventricle after surgery.
9.5. Consequences of LV outflow obstruction in TGV treated with atrial switch.
9.6. Percutanous transcatheter pulmonary valve implantation.

Outcome research and evaluation of health technologies

Ignacio Ferreira González

This line aims to generate knowledge on the impact patient care methodologies and biomedical research programs, including analysis of effectivity of therapeutic strategies in acute coronary syndromes and cardiovascular procedures, quality of life studies, theoretical studies on methodological aspects of clinical trials and registries, and methods to evaluate the social impact of biomedical research.

Sub-lines:

10.1. Variability in clinical practice and long term results of drug eluting stent implantation in Spain.
10.2. Evaluation of resources and strategies for myocardial reperfusion in patients with acute myocardial infarction in Spain.
10.3. Evaluation of risk stratification algorithms and results in cardiac surgerycoronary artery stenting with drug eluting stents.
10.4. Quality of life in very old patients with aortic valve stenosis receiving aortic valve prostheses.
10.5. Evaluation of Health-care delivery in relation to cerebrovascular disease in Catalonian hospitals.
10.6. Evaluation of the social impact of biomedical research in Catalonia.

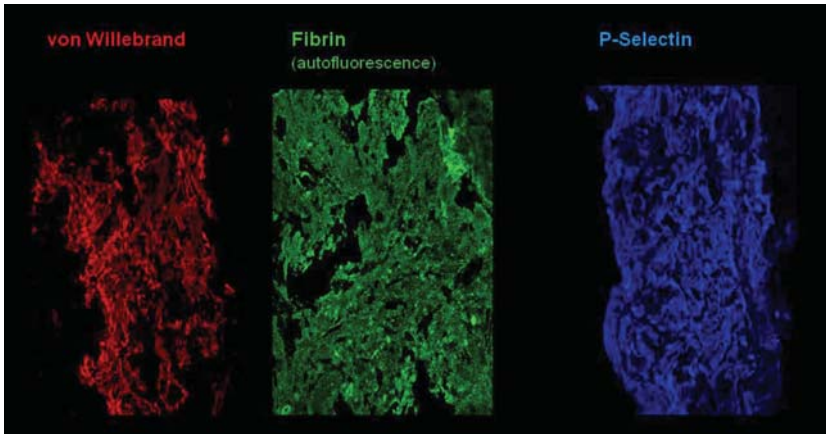


Figure 36
Human samples: Analysis of intracoronary thrombi obtained from patiens with acute myocardial infarction submitted to primary percutaneous coronary intervention

CURRENT RESEARCH PROJECTS

PI: Gaietà Permanyer Miralda

Assessment of stroke care in Catalonia after the implementation of an organised and integrated acute stroke care plan

Funding Agency: Fundació La Marató de TV3
Reference: TV3/062810
Funding: 191,813 €
Duration: 2007 to 2010

PI: Àngel Moya Mitjans

Safety, feasibility and efficacy of bone marrow mononuclear stem cells intracoronary transplantation and of cardiac resynchronization therapy in patients with acute myocardial infarction

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070932
Funding: 163,350 €
Duration: 2008 to 2011

PI: Arturo Evangelista Masip
Eficacia y seguridad de losartan vs atenolol en la prevención de la dilatación progresiva de la aorta en la población de pacientes con síndrome de Marfan
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90396
Funding: 249,865 €
Duration: 2007 to 2011

PI: David García-Dorado García
Protección miocárdica durante la reperfusión pacientes síndrome coronario agudo con elevación del segmento ST sometidos a angioplastia primaria: efecto de la adenosina intracoronaria sobre el tamaño del infarto y remodelado ventricular
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90511
Funding: 461,010 €
Duration: 2007 to 2012

PI: Jaume Figueras Bellot
Nitratos nocturnos en la prevención del edema agudo de pulmón
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90720
Funding: 52,030 €
Duration: 2007 to 2010

PI: Joan Castell Conesa
Neuroimatge amb SPECT en cefalea per abús de medicaments
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3_072210
Funding: 199,800 €
Duration: 2008 to 2011

PI: Ignacio Ferreira González
Interrupción de la doble antiagregación durante el primer año tras la implantación de stent liberador fármacos: factores determinantes e impacto sanitario
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/90031
Funding: 71,995 €
Duration: 2008 to 2010

PI: Pilar Tornos Mas
Degenerative-calcific aortic valve disease: from pathogenical to epidemiological characterization
Funding Agency: CNIC
Reference: CNIC-09
Funding: 415,955 €
Duration: 2008 to 2012

PI: Josep Pinar Sopena
Prevalence of degenerative aortic stenosis and aortic sclerosis in the Spanish population
Funding Agency: CNIC
Reference: CNIC_2_2007
Funding: 301,530 €
Duration: 2008 to 2010

PI: Santiago Aguadé Bruix
Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease. EVINCY-StudyGrant No 222915
Funding Agency: European Commission
Reference: EVINCY-222915
Funding: 56,266 €
Duration: 2009 to 2011

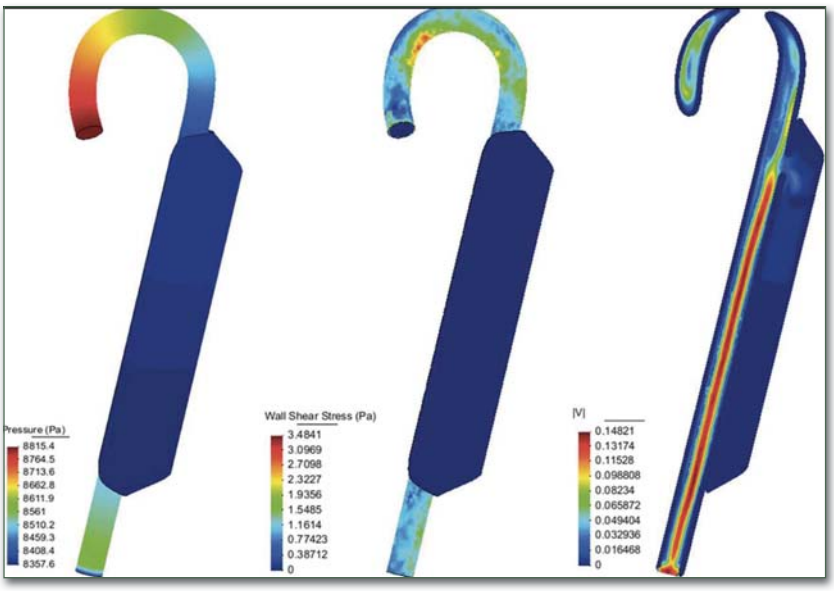
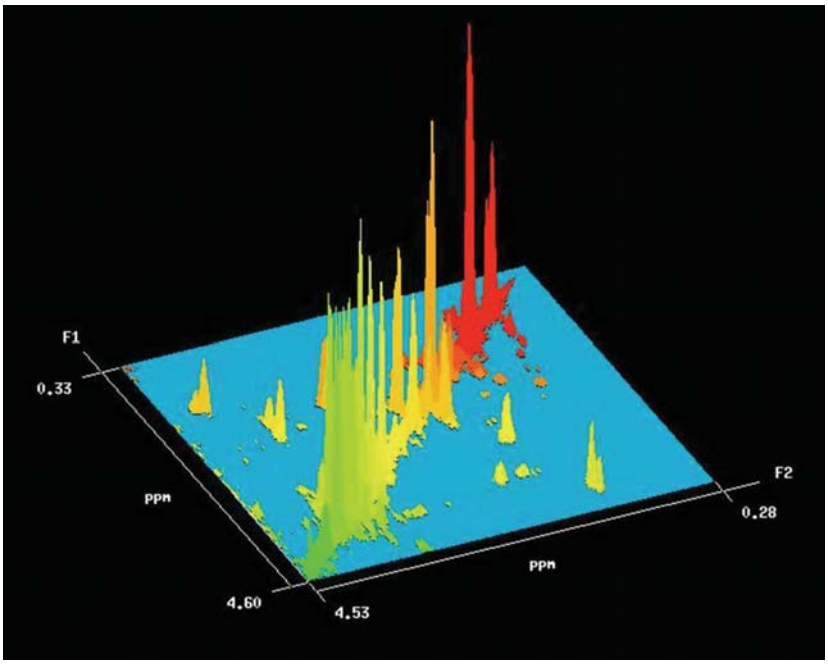


Figure 37
Bioinformatics and computer simulation: Maps of pressure, shear stress and velocity in an in silico model of aortic dissection

PI: Laura Dos Subirá
Antagonistas aldosterónicos en el tratamiento de pacientes con ventrículo derecho sistémico: ensayo clínico aleatorizado
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90112
Funding: 195,204.86 €
Duration: 2007 to 2011

PI: David García-Dorado García
Modulación de la función mitocondrial y señalización de la cardiopatía endógena por canales mitocondriales de Conexina 43
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-03067
Funding: 665,500 €
Duration: 2009 to 2013

Figure 38
High throughput methods and systems biology: NMR proton based two-dimensional spectra obtained in the NMR spectroscopy and metabolomics platform



PI: Jaume Casaldàliga Ferrer
Predictors of right ventricular positive remodelling after pulmonary valve replacement in adult patients with repaired tetralogy of fallot and long stading pulmonary regurgitation
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3/2008/082510
Funding: 80,750 €
Duration: 2009 to 2011

PI: Javier Inserte Igual
Caracterización de los mecanismos de regulación de la proteasa calpaína durante la isquemia/reperfusión miocárdica y su contribución a la muerte celular
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080238
Funding: 43,802 €
Duration: 2009 to 2011

PI: Arturo Evangelista Masip
Análisis de la biomecánica de la disección de aorta descendente. Base experimental y estudio mediante técnicas de imagen de los predictores de dilatación severa. Implicaciones terapéuticas
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080608
Funding: 50.578,00 €
Duration: 2009 to 2011

PI: Jaume Sagristà Sauleda
Eficacia de la colchicina administrada en el primer brote de pericarditis para evitar la aparición de recidivas
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00290
Funding: 26,015€
Duration: 2009 to 2011

PI: Antonia Sambola Ayala
Características inmunohistoquímicas y moleculares del trombo resistente a la fibrinólisis
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01014
Funding: 57,475 €
Duration: 2010 to 2012

PI: Marisol Ruiz Meana
Efecto de la edad sobre la función mitocondrial y el tipo de muerte celular durante la isquemia-reperfusión miocárdica
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/02034
Funding: 50,215 €
Duration: 2010 to 2012

PI: Antonio Rodríguez Sinovas
Papel de la conexina 43 en el daño miocárdico por isquemia-reperfusión en las arritmias de la isquemia y en la cardioprotección por precondicionamiento
Funding Agency: Sociedad Española de Cardiologia
Reference: SEC2009/01
Funding: 12,000 €
Duration: 2010 to 2010

Figure 39
Cardiologists at the bench: A Resident in cardiology during her stay in the lab as part of her training, a young cardiologist in his post-MIR research training, and a biochemist, funded by RECAVA RETICS, analyze mitochondrial respiration and genetics in a human myocardial sample

PI: Ignacio Ferreira González
Estudio ACDC (Adherencia al Tratamiento en Pacientes Coronarios después de un cateterismo con colocación de un stent liberador de fármacos). Seguimiento de dos años
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/90598
Funding: 31,884 €
Duration: 2010 to 2011

PI: Antonia Sambola Ayala
Eficacia y seguridad de la doble antiagregación comparada con anticoagulación oral+doble antiagregación en pacientes con fibrilación auricular de bajo-moderado riesgo sometidos a la implantación de un stent coronario
Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-200
Funding: 408,000 €
Duration: 2010 to 2011

PI: Ignacio Ferreira González
Implantación de prótesis aórtica transcatéter respecto a la cirugía convencional en pacientes con estenosis aórtica severa: daño neurológico y su repercusión funcional
Funding Agency: Sociedad Española de Cardiología
Reference: SEC-2010-01
Funding: 18,000 €
Duration: 2010 to 2012

PI: Arturo Evangelista Masip
Valoración del remodelado ventricular y de la reserva contráctil en el síndrome de Marfan
Funding Agency: Sociedad Española de Cardiología
Reference: SEC2009/02
Funding: 16,000 €
Duration: 2010 to 2011

PI: David García-Dorado García
RECAVA - Red Temática de Investigación en Enfermedades Cardiovasculares
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0014/0025
Funding: 1,297,449.59 €
Duration: 2007 to 2011

PI: David García-Dorado García
Patologia cardiocirculatòria
Funding Agency: AGAUR
Reference: 2009 SGR 802
Funding: 56,160 €
Duration: 2010 to 2013

PI: David García-Dorado García
Cardio Repair European Multidisciplinary Initiative (CARE-MI)
Funding Agency: European Comission
Funding: 557,746 €
Duration: 2010 to 2015

PUBLICATIONS (Impact Factor: 364.079)

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AREA 3 CARDIOVASCULAR DISEASES, HEMOSTASIS AND HYPERTENSION

3.2 Reparative and Therapy of the Heart

Group Leader
Manuel Galiñanes Hernández
Tel. 93 489 40 38
manuel.galinanes@vhir.org

Researchers
Kelly Casós Vásquez
Miguel Ángel Castro Alba
Juan Manuel Gracia Baena
María López Cavanillas

OBJECTIVES

The two main objectives of the group are:

- To reduce myocardial injury induced by ischemia and reperfusion through a better understanding of the underlining mechanisms and the design of new therapeutic approaches.
- To repair the damaged myocardium by elucidating the mechanisms of stem cell homing, proliferation and differentiation and exploitation of their therapeutic potential.

2010 Impact Factor:
9.514

RESEARCH LINES

Characterization of the susceptibility of the human myocardium to ischaemic/reperfusion-induced injury and its response to protective interventions as compared to other mammalian hearts.
This project will also determine the role of protein kinases in the induction of injury or protection in various animal species, including human beings.

Elucidation of the differential time-course responses of the various myocardial cell components to ischaemic/reperfusion-induced injury and their own recovery/repair following reperfusion and the administration of growth factors and stem cells

Utility of stem cell therapy and growth factors to repair the damaged heart

CURRENT RESEARCH PROJECTS

PI: Manuel Galiñanes Hernández
Cardio Repair European Multidisciplinary Initiative (CARE-MI)Project number: 242038
Funding Agency: European Commission
Reference: CARE-MI-242038
Funding: 557,746 €
Duration: 2010 to 2015

PUBLICATIONS (Impact factor: 9.514)

Ang KL, Raheel F, Bajaj A, Sosnowski A, Galiñanes M. Early impact of aortic wrapping on patients undergoing aortic valve replacement with mild to moderate ascending aorta dilatation. *J Cardiothorac Surg* 2010 Aug 6; 5:58. ➲ IF: 0.737.

Ang KL, Shenje LT, Reuter S, Soonpaa MH, Rubart M, Field LJ, Galiñanes M. Limitations of conventional approaches to identify myocyte nuclei in histologic sections of the heart. *Am J Physiol Cell Physiol* 2010 Jun; 298 (6): C1603-9. ➲ IF: 4.013.

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AREA 4 NEUROSCIENCES

4.1 Alzheimer

Group Leader
Mercè Boada Rovira
Tel. 93 274 61 41
mboada@vhebron.net

Researchers
Mercè Boada Rovira
Francesc Pujadas Navinés

Neurologists
Mikel Olabarrieta Paul
Antoni Palasí Franco

Neuropsychologist
Belén Gutiérrez

Psychologist
Diana Liébana Gutiérrez

OBJECTIVES

- To correlate the specific biomarkers in CSF (beta-amyloid 42 protein, total and phosphorilated Tau) in the extracerebral compartment (plasma).
- Determine, at a molecular level, a risk profile associated with other biomarkers to complete the basic range that gathers different Alzheimer's clinical phenotypes and therapeutic strategies on specific targets.
- To investigate the preventive value of nutritional factors related with oxidative stress, antinflammatory and neurovascular risk.
- Design and experimental development of new pharmacologic treatments in Alzheimer's disease.
- Research in genetics to identify new genes associated with Alzheimer's disease.

RESEARCH LINES

Signaling proteins
Mercè Boada Rovira
To determine which proteins, related to neurodegenerative diseases and congophilic angiopathy, can, en bloc, be a marker for disease prediction or evolution.

Research in genetics
Mercè Boada Rovira
GWAS Project (Study with CHARGE, GERAD1 and EASI1 groups).
Identification of genetic factors linked to the risk of developing late onset Alzheimer's disease (LOAD). We use Candidate Gene Approach Strategies or Genome Wide Association Studies (GWAS) to select genetic markers that are assessed in a wide series of cases and controls. (Sudha Seshadri, Annette L. Fitzpatrick, M. Arfan Ikram, Anita L. DeStefano, Vilmundur Gudnason, Mercè Boada et al. Genome-wide Association Studies of Alzheimer's Disease. *JAMA* 2010 May 12; 303 [18]: 1832-40.)
The design of this research process includes well defined validation strategies and a final meta-analysis from the obtained results. The identification of new genes for LOAD means a big step in the ethiopathogenic knowledge of the disease and will allow the development of new preventive and therapeutic medium term strategies. In this line, the project will be extended in order to obtain the identifi-

2010 Impact Factor:
51.246

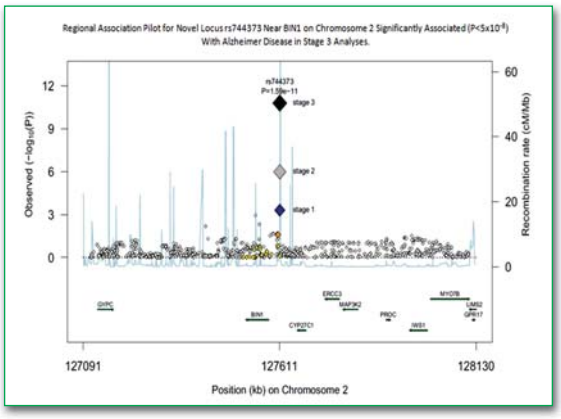


Figure 40
Location on chromosome 2 of a new gene for Alzheimer's disease

cation of genetic factors linked to tau positive and granulin positive mutations in fronto-temporal lobar degenerations, understood as an orphan treatment disease.

CURRENT RESEARCH PROJECTS

PI: Mercè Boada Rovira[a,b]
Collaborators: J. Montaner[c], F. Pujadas[a], L. Tárraga[b], O. López[d], J. T. Becker[d], S. Valero[e], J. Castells[f], G. Cuberas[f], A. Espinosa[b], G. Vinyes[b], M. Rosende-Roca[b], M. Ibarria[b], C. Lorenzo[f]

Study of prodromal Alzheimer's disease and memory complaints in biomarkers and neuroimaging, as well as in transversal study of the amnesic disorder as a key symptom of conversion to AD.
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI10/00945
Funding: 135,520 €
Duration: 2008 to 2013

PI: Mercé Boada Rovira[a,b] **and Joan Montaner Villalonga**[c]

Participación de sistemas proteolíticos en la progresión de la angiopatía amiloide cerebral
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070737
Funding: 161,535 €
Duration: 2008 to 2011

PI: Mercè Boada Rovira[a,b]
Collaborators: L. Tárraga[b], I. Hernández[b], M. Rosende-Roca[b], A. Lafuente[b], M. Alegret[b], A. Espinosa[b], G. Vinyes[b], J. Arbizu[g], M. Simó[h], J. Castell[f], I. Roca[d], C. Lorenzo[f], G. Cuberas[f], O. López[d]

Identification of prodromal Alzheimer's disease by amyloid and neuronal damage imaging markers in PIB-PET, FDG-PET and MR spectroscopy and diffusion-tensor imaging in subjects with probable amnnestic MCI.
Funding Agency: Agència d'Avaluació de Tecnologia i Recerca Mèdiques. Departament de Salut de la Generalitat de Catalunya.
Reference: 390
Funding: 108,812.70 €
Duration: 2009 to 2012

PUBLICATIONS
(Impact Factor: 51.246)

Aguera-Ortiz LF, Sánchez Ortiz C, Durán Alonso JC, García López MT, Garzón Maldonado F, Gómez Camello A, Boada M, *et al.* [Memantine in the pharmacologic treatment of moderately severe to severe Alzheimer's disease in Spain (MEMORY study)]. *Rev Neurol* 2010 Nov 1; 51 (9): 525-34. ➲ IF: 1.234.

Alegret M, Vinyes-Junque G, Boada M, Martínez-Lage P, Cuberas G, Espinosa A, Roca I, Hernández I, Valero S, Rosende-Roca M, Mauleon A, Becker And JT, Tárraga L. Brain Perfusion Correlates of Visuoperceptual Deficits in Mild Cognitive Impairment and Mild Alzheimer's Disease. *J Alzheimers Dis* 2010; 21 (2): 557-67. ➲ IF: 3.832.

Boada M, Antunez C, López-Arrieta J, Galán JJ, Morón FJ, Hernández I, Marín J, Martínez-Lage P, Alegret M, Carrasco JM, Moreno C, Real LM, González-Pérez A, Tarraga L, Ruiz A. CALHM1 P86L Polymorphism is Associated with Late-Onset Alzheimer's Disease in a Recessive Model. *J Alzheimers Dis* 2010; 20 (1): 247-51. ➲ IF: 3.832.

Francisco J de, Pujadas F, Toledo M, Santamarina E, Quintana M, Edo MC, Centeno M, Álvarez Sabín J. A study of right-left shunt in transient global amnesia. *Neurologia* 2010 Mar; 25 (2): 83-89. ➲ IF: 0.596.

Gustavsson A, Jonsson L, McShane R, Boada M, Wimo A, Zbrozek AS. Willingness-to-pay for reductions in care need: estimating the value of informal care in Alzheimer's disease. *Int J Geriatr Psychiatry* 2010 Jun; 25 (6): 622-32. ➲ IF: 1.981.

Gustavsson A, Jonsson L, Rapp T, Reynish E, Ousset PJ, Andrieu S, Cantet C, Winblad B, Vellas B, Wimo A, Boada M, *et al.* Differences in resource use and costs of dementia care between European countries: baseline data from the ICTUS study. *J Nutr Health Aging* 2010 Aug; 14 (8): 648-54. ➲ IF: 1.712.

Hernández-Guillamón , Mawhirt S, Fossati S, Blais S, Parés M, Peñalba A, Boada M, Couraud PO, Neubert TA, Montaner J, Ghiso J, Rostagno A. Matrix metalloproteinase 2 (MMP-2) degrades soluble vasculotropic amyloid-beta E22Q and L34V mutants delaying their toxicity for human brain microvascular endothelial cells. *J Biol Chem* 2010 Aug 27; 285 (35): 27144-58. ➲ IF: 5.328.

Lambert JC, Sleegers K, González-Pérez A, Ingelsson M, Beecham GW, Hiltunen M, Combarros O, Bullido MJ, Brouwers N, Bettens K, Berr C, Pasquier F, Richard F, Boada M, *et al.* The CALHM1 P86L Polymorphism is a Genetic Modifier of Age at Onset in Alzheimer's Disease: a Meta-Analysis Study. *J Alzheimers Dis* 2010; 22 (1): 247-55. ➲ IF: 3.832.

Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, Harold D, Schrijvers EM, Ramírez-Lorca R, *et al.* Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA* 2010 May 12; 303 (18): 1832-40. ➲ IF: 28.899.

[a] Neurology Department. Hospital Universitari Vall d'Hebron – VHIR-UAB. Barcelona. Spain.
[b] Fundació ACE. Institut Català de Neurociències Aplicades. Barcelona. Spain.
[c] Neurovascular Research Laboratory and Neurovascular Unit. Neurology and Medicine Departments-Hospital Universitari Vall d'Hebron – VHIR-UAB. Barcelona. Spain.
[d] Departments of Neurology, Psychiatry, and Psychology, University of Pittsburgh School of Medicine. Pittsburgh, Pennsylvania.
[e] Psychiatry Department. Hospital Universitari Vall d'Hebron. UAB. Barcelona. Spain.
[f] Nuclear Medicine Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
[g] Neurology Department, Clínica Universidad de Navarra, Pamplona, Navarra. Spain.
[h] Nuclear Medicine Service, CRC- Hospital Quiron. Department of Medicine, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.

AREA 4 NEUROSCIENCES

4.2 Cell Signaling and Apoptosis

Group Leader
Joan Xavier Comella Carnicé
Tel. 93 489 42 75
joan.comella@vhir.org

Researchers
Paulina Carriba Domínguez
Joan Xavier Comella Carnicé
Joaquín López Soriano
Rana Moubarak
Stéphanie Reix

Researchers in Training
Koen Galenkamp
Fernando Marqués Fernández
Laura Planells Ferrer
Jorge Urresti Ibáñez

OBJECTIVES

The main goal of the group is the study of programmed death cell events in the vertebrate nervous system. We are mainly interested in the characterization of proteins with capability for antagonizing death receptor-mediated cell death, mainly that promoted by TNFRs and Fas, and its relation with survival and signaling pathways. This approach may contribute to a better understanding of the physiopathology of neurodegenerative illnesses (such as Alzheimer or Parkinson), characterized by an excess of cell death, or neurooncologic processes (such as neuroblastoma or glioblastoma), which present a lack of cell death. In addition, our studies may improve our knowledge in a way that will open new therapeutic targets for these illnesses.

RESEARCH LINES

Characterization of the role of LFG (lifeguard) as an antiapoptotic protein, antagonist of Fas receptors and highly expressed in the nervous system.

We want to know its antiapoptotic mechanism of action, and to characterize the proteins functionally interacting with it, in particular SoxN.

2010 Impact Factor:
7.178

Investigate the relevance and function of the two isoforms of FAIM, the short form (S) and the long form (L), in the nervous system.
Faim-S promotes neural differentiation, while Faim-L is an antagonist of different death receptors. We want to know why there is a dual function, through identification and characterization of proteins selectively associated with each isoform.

TNF is classically considered as a promoter of cell death through its specific receptor.
However, in certain circumstances TNF promotes cell survival and differentiation. We want to study the antiapoptotic mechanisms of TNF, and to analyze its potential neuroprotector role in brain damage.

We aim to characterize death receptor antagonist function in the development of neuroblastoma.
We will generate in vivo and in vitro models that will allow us to study the apoptotic/antiapoptotic machinery expression status, and the role of certain death receptor antagonists in the resistance to apoptosis in these tumors. We are also interested in demonstrating the existence of cancer stem cells in this kind of tumor.

CURRENT RESEARCH PROJECTS

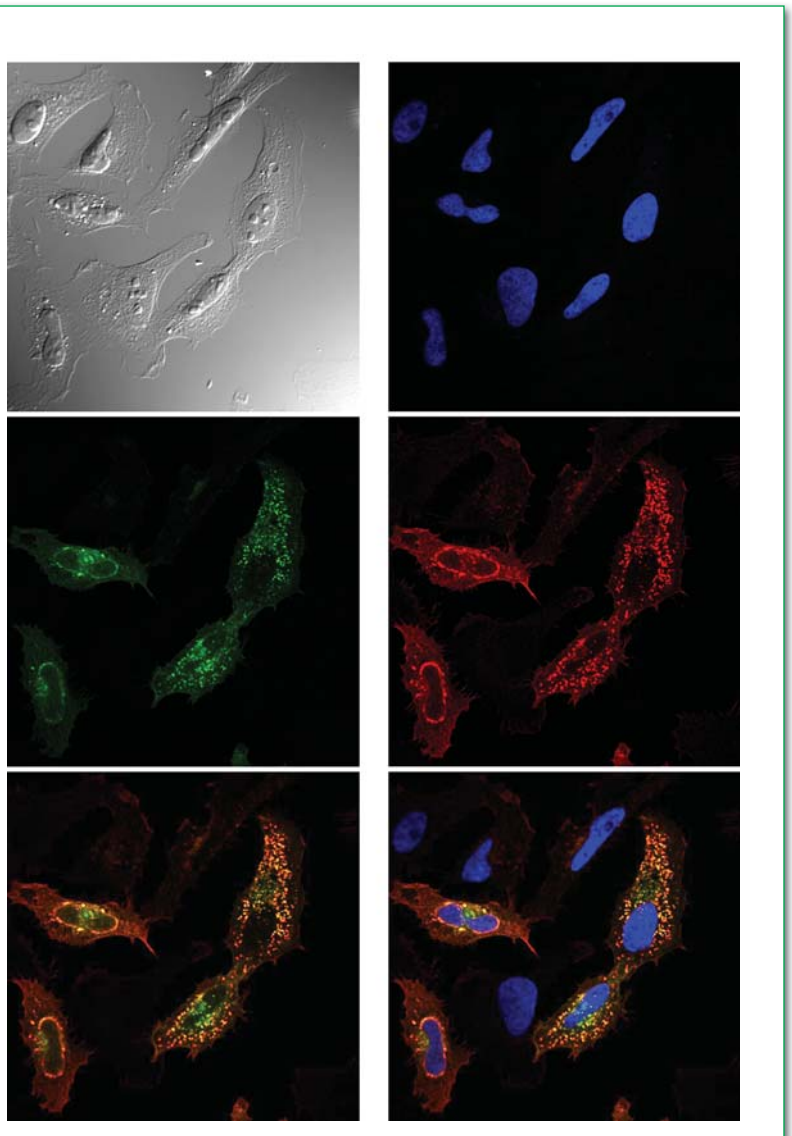
PI: Francisco Javier Vitorica Fernández (University of Seville)
Activación glial en el proceso neuroinflamatorio: una potencial diana terapéutica para la enfermedad de Alzheimer
Funding Agency: CIBERNED (Proyectos Cooperativos)
Reference: 2010/08
Funding: 250,000 € (40,000 € Joan Comella's subproject)
Duration: 2010 to 2012

PI: Joan X. Comella
Caracterización del proceso de muerte neuronal inducido por el factor de necrosis tumoral
Funding Agency: Dirección General de Investigación – Ministerio de Educación y Ciencia
Reference: SAF2007_60287
Funding: 143,000 €
Duration: 2007 to 2010

PUBLICATIONS
(Impact Factor: 7.178)

Moubarak RS, Solé C, Pascual M, Gutiérrez H, Llovera M, Pérez-García MJ, Gozzelino R, Segura MF, Iglesias-Guimarais V, Reix S, Soler RM, Davies AM, Soriano E, Yuste VJ, Comella JX. The death receptor antagonist FLIP-L interacts with Trk and is necessary for neurite outgrowth induced by neurotrophins. *J Neurosci* 2010 Apr 28; 30 (17): 6094-105. ➲ IF: 7.178.

Figure 41
HeLa transfected with GFP-Lifeguard-FLAG



AREA 4 NEUROSCIENCES

4.3 Clinical Neuroimmunology

Group Leader
Xavier Montalban Gairín
Tel. 93 274 62 02
esclerosimultiple@vhebron.net

Researchers
Luis Agulló Rueda
Manuel Comabella López
Carme Costa Riu
Herena Eixarch Ahufinger
Carmen Espejo Ruiz
Nicolás Fissolo
Ingrid Galán Cartañá
Carlos Nos Llopis
Ramil Nurtdinov
Jordi Río Izquierdo
Jaume Sastre Garriga
Mar Tintoré Subirana

Researchers in Training
Mª Jesús Arévalo Navines
Georgina Arrambide García
Ana Belén Caminero Rodríguez
Ester Cantó Puig
Joaquín Castillo Justribó
Mª del Carmen Edo Cobos
Marta Fernández Bustamante
Ana Gutiérrez Franco
Alejandro Horga Hernández
Sunny Malhotra
Mª José Mansilla López
Susana Otero Romero
Francisco Pérez Miralles
Carmen Tur Gómez

Nursing, Technical and Administrative Staff
Mireia Castillo Juárez
Zoraida Castro Ruiz
Joana Fitó Guillamón
Milagros Fraga Pereira
Carmen González Triguero
Josep Graells Salvador
Rosalía Horno Ocaña
Ilaria Laganà
Olga Montón Belenguer
Elisabeth Morilla Castillo
Dúnia Muñoz Valdivieso
Gemma Rodríguez Martín
Marta Sallent Borsot
Eva Simón Marcó
Silvia Soler García
Sergio Vergara Ruiz
Mª José Vicente Pecino
Núria Vilarrasa Díaz

OBJECTIVES

The main objectives of the Clinical Neuroimmunology group through research are to improve the quality of life of persons living with multiple sclerosis (MS) and attain a greater understanding of the pathogenic mechanisms, aiming to develop new and more effective therapeutic means. Other interests in research are: therapeutic tools in MS; disease susceptibility, diagnostic and prognostic markers in MS; study of the response to interferon-beta treatment in MS patients; clinical and radiological study of primary-progressive MS; research for therapeutic targets and/or therapeutic approaches; epidemiology of MS.

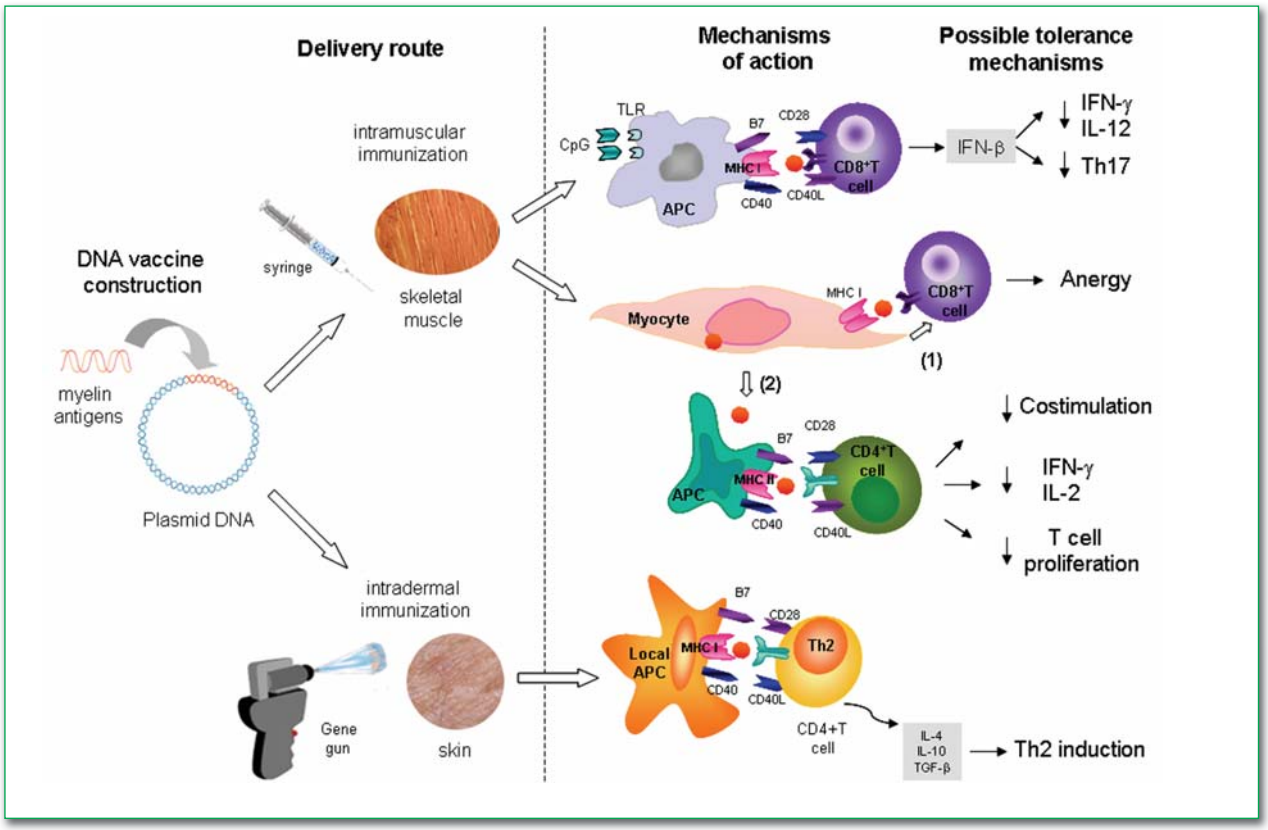


Figure 42
Possible mechanisms of immune tolerance induction by DNA vaccines. Vaccines that aim to induce immune tolerance in MS consist of bacterial plasmids into which gene sequences encoding for myelin antigens are incorporated. Plasmids are then delivered into cells either by intramuscular needle immunization (syringe) or by intradermal injection into the skin via gene gun. Afterwards, plasmids are taken up by different cell types, antigens processed and presented to the immune cells such that a specific immune response is generated or altered

RESEARCH LINES

Therapeutic Research in multiple sclerosis

Carlos Nos Llopis

During 2010, the Clinical Neuroimmunology Research Group participated in 21 international clinical trials, namely, 10 phase II, 10 phase III, and 1 phase IV trials as well as 11 extension studies of previous trials, i.e. 6 phase II and 5 phase III trials. Xavier Montalban is involved, as a member of the Steering Committee, in the conduct of seven of these trials and is the principal investigator of 3 international phase III clinical trials.

Susceptibility, diagnostic and prognostic markers in multiple sclerosis

Search for candidate genes in susceptibility regions for multiple sclerosis

Manuel Comabella

This line of research seeks to characterize the genetic component of multiple sclerosis by genotyping candidate genes involved in disease etiopathogenesis.

Search for clinical, radiological and biological prognostic markers in patients presenting with a clinically isolated syndrome (CIS) suggestive of MS

Mar Tintoré

Since 1995, patients presenting with a CIS or first attack suggestive of MS are included in a prospective cohort study. Clinical variables (age, gender topography of the syndrome), radiological variables (number of lesions, number

2010 Impact Factor:
194.695

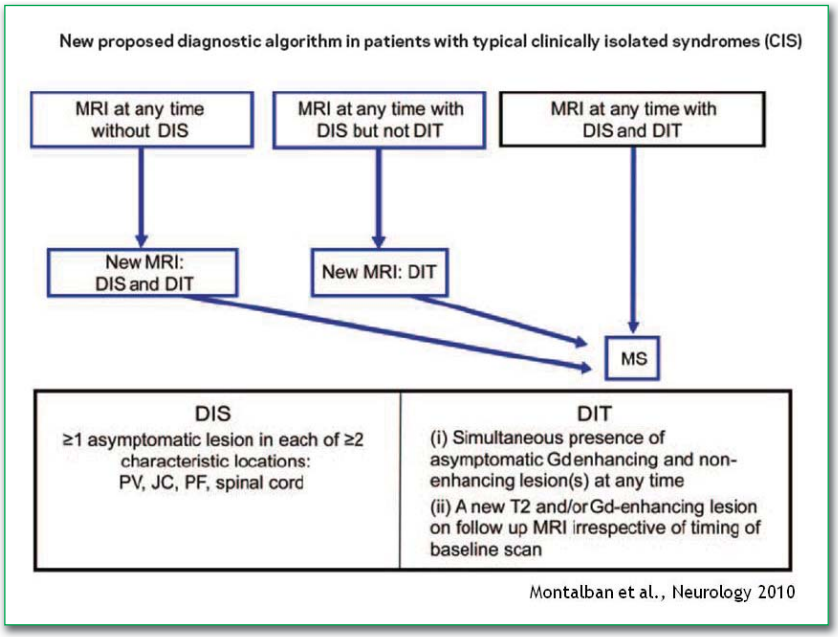


Figure 43
This algorithm only applies to patients with typical CIS, aged 14 to 50 years and after having performed a complete diagnostic workup.
Gd gadolinium-enhancing lesion; PV periventricular; JC juxtacortical; PF posterior fossa; BS brainstem; SC spinal cord; DIS dissemination in space; DIT dissemination in time

of Barkhof criteria, topography of the lesions, atrophy measures), neurophysiological variables (visual, brainstem and somestesic evoked potentials) as well as biological markers (IgG and IgM oligoclonal bands, neurofilaments light and heavy chains, fetuin A, GFAP, anti-neurofascin antibodies, anti-glycan panel) are studied as predictors of conversion to MS and as predictors of disability progression. Mathematical models with different combinations of the variables listed above are investigated.

Search for biomarkers associated with conversion to multiple sclerosis in patients with clinically isolated syndromes

Manuel Comabella

The main objective of this line of research is to validate diagnostic and prognostic biomarkers that may be playing given roles in the conversion to multiple sclerosis in patients with a first neurological event suggestive of demyelinating disease.

Value of NMO-IgG determination in patients with clinically isolated syndromes who develop a relapsing optic neuritis or myelitis phenotype

Carme Costa

The objective is to study the value of NMO-IgG determination in a cohort of clinically isolated syndrome (CIS) patients who develop an NMO phenotype consisting of sequential or relapsing optic neuritis and myelitis.

Study of the cognitive deficit in patients with clinically isolated syndromes suggestive of multiple sclerosis

Mª Jesús Arévalo

Since 2002, patients presenting with a CIS or first attack suggestive of MS are included in a prospective cohort study of cognition. Clinical, radiological (conventional and non-conventional MRI techniques) and neuropsychological variables are studied.

Study of the response to interferon-beta treatment in multiple sclerosis patients

Clinical and radiological prognostic factors of response to treatment with interferon-beta

Jordi Río

Cohort study to establish outcome measures for clinical trials with clinical validity and clinical and radiological indicators associated with poor response to treatment.

Search for biomarkers involved in the response to interferon-beta in patients with multiple sclerosis

Manuel Comabella

Study to identify gene signatures that may predict the good or bad response to interferon-beta in patients with multiple sclerosis before initiating treatment or in the first months of treatment.

Prediction studies of development of neutralizing antibodies in patients with multiple sclerosis treated with interferon-beta

Manuel Comabella

This project aims to identify gene expression signatures that may help to predict patients who will develop neutralizing antibodies against interferon-beta.

Clinico-radiological investigation of PPMS (Primary Progressive Multiple Sclerosis)

Jaume Sastre and Carmen Tur

Primary Progressive Multiple Sclerosis (PPMS) lacks effective treatment at the present time to slow disability progression. This is, at least, partly due to the scarcity of scientifically sound outcome measures, that are able to readily detect changes induced by experimental therapies. It is, therefore, fundamental to incorporate newly developed outcome measures, with higher sensitivity to change providing better correlations with clinical parameters. A prospective study is now in place to investigate such issues. Other projects related to this line of investigation in patients with PPMS are: clinical and radiological correlations, prognostic markers and diagnostic criteria.

Investigation of brain activation underpinnings of cognitive function using fMRI

Jaume Sastre and Mª Jesús Arévalo

Cognitive impairment is frequent in MS patients and has a major impact on activities and participation of people with MS. Cognitive performance is only partially related to MRI visible brain damage as the brain neuroplastic potential may compensate for loss of neurons and axons through use of alternative pathways. fMRI is potentially useful tool to monitor the affected brain neuroplastic potential as it enables us to visualize brain activation in such alternative pathways. Its use as a surrogate marker in clinical trials aiming at cognitive restoration also warrants further investigation. In our unit we are involved in several studies aiming at a further delineation of such potential.

Research for therapeutic targets and/or therapeutic approaches

Genomic signature-based small molecule screening of neural stem cells to identify novel compounds to enhance oligodendrogenesis

Carme Costa

Genomic signatures will be defined in the different stages of differentiation from neural stem cells to mature oligodendrocyte. The signatures will be used to identify new drugs that could induce oligodendrogenesis. In vitro validation will be performed to confirm that the addition of these compounds to cells under different stages of lineage commitment produces the desired gene expression signature. The selected compounds will be finally tested in vivo, in an experimental autoimmune encephalomyelitis mouse model.

DNA vaccination as a therapy of multiple sclerosis

Nicolás Fissolo

To evaluate the potential of DNA vaccines as a possible treatment of MS, plasmid vectors expressing auto-antigens involved in the disease will be created and tested in experimental autoimmune encephalomyelitis, the animal model of MS.

Tolerance induction in experimental autoimmune encephalomyelitis using gene therapy

Jordi Barquinero and Carmen Espejo

Previous collaborative works with the group of Gene and Cell Therapy of our institution resulted in the development of a therapeutic strategy in which bone marrow cells were genetically modified to express a self-antigen with the aim of inducing antigen-specific tolerance. We could see a therapeutic effect even in the absence of myeloablation, thus suggesting that a concrete population of cells generated in the cell culture, but not cells with a repopulating capacity, were responsible for the therapeutic effect seen in these mice. We have identified a candidate population, called myeloid derived suppressor cells that might be mediating the antigen-specific effect.

Role of the heat shock protein (HSP)-70 in the pathogenesis of multiple sclerosis

Carmen Espejo

By means of interfering RNA, we are studying whether silencing HSP-70 expression changes the level of protection of the cells from the central nervous system in front of stimulus like the inflammation typical of MS.

Role of semaphorins 3A and 7A in neuroregeneration and immune regulation in EAE model

Carmen Espejo

This project aims to study the role of semaphorin 3A (sema3A) and sema7A, two axonal guidance molecules also involved in the regulation of immune responses, in experimental autoimmune encephalomyelitis (EAE) pathogenesis as well as their therapeutic implications.

Inhibition of Delta-like ligand-4 as a therapy in a murine model of multiple sclerosis

Herena Eixarch

Delta-like ligand-4 (Dll4) is one of the ligands for Notch, which has been specifically implicated in the differentiation of Th1 T-cells and may have a role in the development of Th17 immune responses. Taking into account that Th17 responses are directly involved in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS), our hypothesis is that the inhibition of Dll4 could have a beneficial effect on a MOG-induced EAE model.

TNF signaling pathway in multiple sclerosis

Luís Agulló

This project has 3 main objectives: first, to find changes in the immune response resulting from TNFRSF1A polymorphisms, that could allow the development of specific treatments for these patients in the future, second, to evaluate in animal models the selective blockade of type 1 and 2 receptors of TNF by siRNA as a potential therapy in EM, and, finally, to propose pharmacophores that interact selectively with TNF receptors 1 or 2 and that could be the structural base for the development of new drugs.

Intrathecal IgM and IgG synthesis in experimental autoimmune encephalomyelitis

Carmen Espejo

Experimental autoimmune encephalomyelitis (EAE) is an inducible demyelinating disease serving as animal model for multiple sclerosis (MS). Both Cerebrospinal fluid (CSF)-restricted oligoclonal IgG and IgM bands are detectable in MS patients. In addition, IgG oligoclonal bands are used as a paraclinical tool to help in MS diagnosis. We aim to study intrathecal IgG and IgM synthesis over time in EAE model.

EpidEMcat

Susana Otero

The CEM-Cat and its Medical Advisory Committee (established in 2008 and composed of lead neurologists specialized in the management and research of MS in Catalonia) coordinates a project that aims to characterize the epidemiology of MS in Catalonia. A prevalence study in the Osona region has been finalized and sent for publication. At the present time the ongoing research line is an incidence study in Catalonia using an official MS Registry of new cases, with a wide representation of hospitals throughout Catalonia. The Registry as well as the results from previous studies will lead to collaborative studies on possible risk factors associated with the disease.

Clinical practice guidelines on multiple sclerosis

Susana Otero

A collaborative project to develop clinical practice guidelines on Multiple Sclerosis undertaken by the Catalan Agency for Health Information, Assessment and Quality (AIAQS) and the Multiple Sclerosis Center of Catalonia (CEM-Cat) was launched in 2010. The guideline is based on the methodology set by the National Guidelines Program of the Spanish National Health Service. This process seeks the participation of all opinion leading healthcare professionals involved in the management of MS with the aim to provide a useful tool for integrated care. As a distinct feature, the guideline will incorporate the subjective perceptions and preferences of people living with MS, their families and caregivers.

CURRENT RESEARCH PROJECTS

PI: Manuel Comabella López
Estudio de genes candidatos en regiones de susceptibilidad para la esclerosis múltiple
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061906
Funding: 131,890 €
Duration: 2007 to 2010

PI: Xavier Montalban Gairín
Estudio de la heterogeneidad de la esclerosis múltiple remitente-recurrente mediante resonancia magnética y perfiles de expresión génica
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061334
Funding: 150,040 €
Duration: 2007 to 2010

PI: Carmen Espejo Ruiz
Función de las proteínas de choque técnico (HSP, heat shock protein)-70 en la patogenia de la esclerosis múltiple
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP07/00146
Funding: 42,000 €
Duration: 2008 to 2010

PI: Manuel Comabella López
United Europeans for the development of Pharmacogenomics in Multiple Sclerosis (UEPHA-MS) Grant Agreement No 212877
Funding Agency: European Commission
Reference: UEPHA-MS-212877
Funding: 186,640.70 €
Duration: 2008 to 2012

PI: Manuel Comabella López
Búsqueda de nuevos tratamientos para la esclerosis múltiple mediante screening *masivo de librerías de fármacos basado en perfiles de expresión génica usando mapas de conectividad*
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/04/2008
Funding: 73,250 €
Duration: 2008 to 2011

PI: Mar Tintoré Subirana
Estudio de marcadores biológicos pronóstico en pacientes con síndromes clínicos aislados sugestivos de esclerosis múltiple
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080788
Funding: 59,229.50 €
Duration: 2009 to 2011

PI: Manuel Comabella López
Estudio con células madre para encontrar nuevos tratamientos en la esclerosis múltiple
Funding Agency: Fundación Caja Navarra
Reference: CAN-15271
Funding: 42,843.62 €
Duration: 2009 to 2010

PI: Carmen Espejo Ruiz
¿Podemos retrasar o evitar la neurodegeneración en la esclerosis múltiple?
Funding Agency: Fundación Caja Navarra
Reference: CAN2009-16365
Funding: 15,753.98 €
Duration: 2010 to 2010

PI: Manuel Comabella López
Validación de marcadores biológicos asociados con la conversión a esclerosis múltiple en pacientes que presentan síndromes clínicos aislados
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00788
Funding: 134,915 €
Duration: 2010 to 2012

PI: Carmen Espejo Ruiz
Función de las semaforinas 3A y 7A, moléculas de guía axonal, en la neurorregeneración y la regulación de la respuesta inmunitaria en la encefalomielitis autoinmune experimental
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01180
Funding: 173,030 €
Duration: 2010 to 2012

PI: Manuel Comabella López
Búsqueda de marcadores de bioactividad del interferón-beta alternativos a la proteína MXA
Funding Agency: Fundación Salud 2000
Reference: MERCK-2009-05
Funding: 20,000 €
Duration: 2010 to 2011

PI: Manuel Comabella López
Estudio de la heterogeneidad en la susceptibilidad a la muerte celular por apoptosis en pacientes con esclerosis múltiple: búsqueda de dianas terapéuticas
Funding Agency: Fundación Alicia Koplowitz
Reference: FAK-2010-03
Funding: 75,000 €
Duration: 2010 to 2012

PI: Xavier Montalban Gairín
REEM - Red Española de Esclerosis Múltiple
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD07/0060/0020
Funding: 277,004.53 €
Duration: 2008 to 2011

PI: Xavier Montalban Gairín
Unitat de Neuroimmunologia Clínica (UNiC)
Funding Agency: AGAUR
Reference: 2009 SGR 793
Funding: 43,680 €
Duration: 2010 to 2013

PI: Susana Otero Romero
EpidEMcat
Funding Agency: Departament de Salut, Generalitat de Catalunya
Funding: 200,000 €
Duration: 2008 to 2011

PUBLICATIONS (Impact Factor: 194.695)

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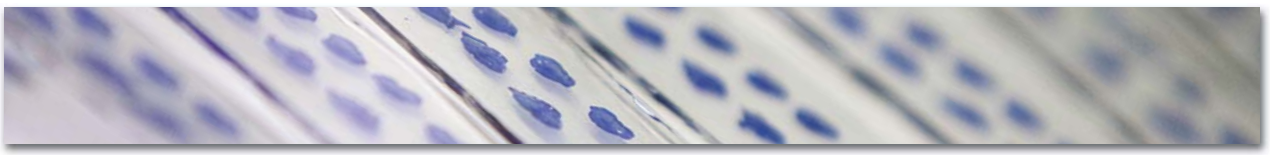

AREA 4 NEUROSCIENCES

4.4 Headache and Neurological Pain

Group Leader
Patricia Pozo Rosich
Tel. 93 274 66 06
patricia.pozo@vhir.org

Researchers in Training
Joan Durà Miralles
Jessica Fernández Morales

Nursing, Technical and Administrative Staff
Susana Gómez Baeza

OBJECTIVES

Primary headaches (migraine, cluster headache) are very prevalent and extremely disabling. The mission of the Headache & Pain Group is to study the pathophysiology of primary headaches (migraine and trigemino-autonomic cephalalgias) and other neurological pain disorders using preclinical, translational and clinical research. This is the first laboratory in Catalonia and Spain solely dedicated to the study of headache as a brain disorder.

2010 Impact Factor:
3.702

RESEARCH LINES

Genetics

- CHROMIG project: genotyping migraine (chronic & episodic)
- Pharmacogenomics

Translational studies

- Neuroimaging using SPECT in medication overuse headache and migraine patients
- Serum biomarkers in migraine (metaloproteases)
- Neurophysiology evaluation in migraine, ERPs (event related potentials - cortical mapping), study of the emotional and neurophysiological response towards an affective multimodal dictionary.
- Headache & Intracraneal Idiopathic Hypertension.
- Neuropsychological evaluation of migraine and medication-overuse headache patients.

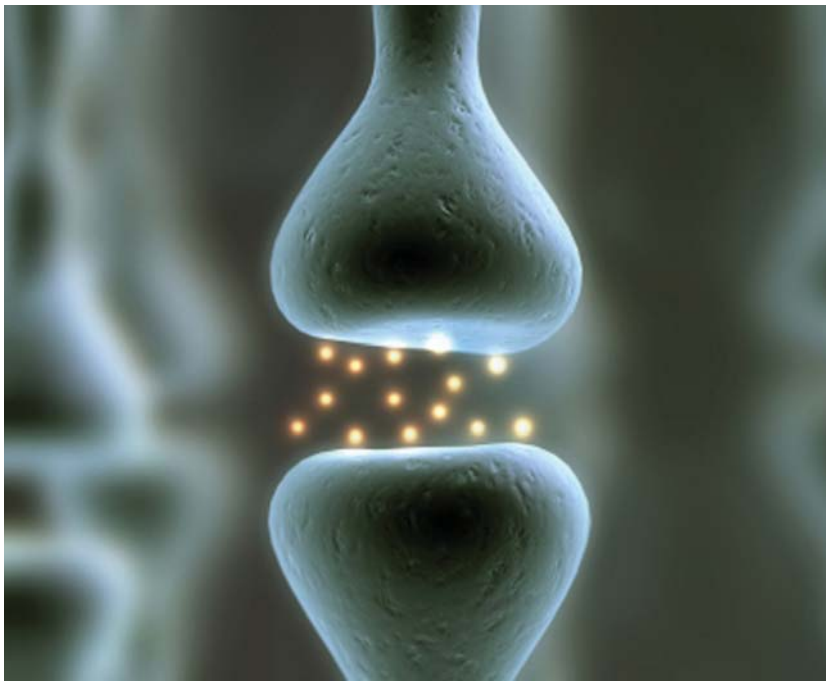

Figure 44
Synapsis which enables a nerve impulse

PUBLICATIONS
(Impact Factor: 3.702)

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Preclinical studies

Neurophysiological studies of the trigeminovascular and the thalamocortical systems

Clinical trials

During the last few years we have conducted 6 clinical trials in phase II for the treatment of acute migraine and 2 clinical trials for the prevention of migraine.

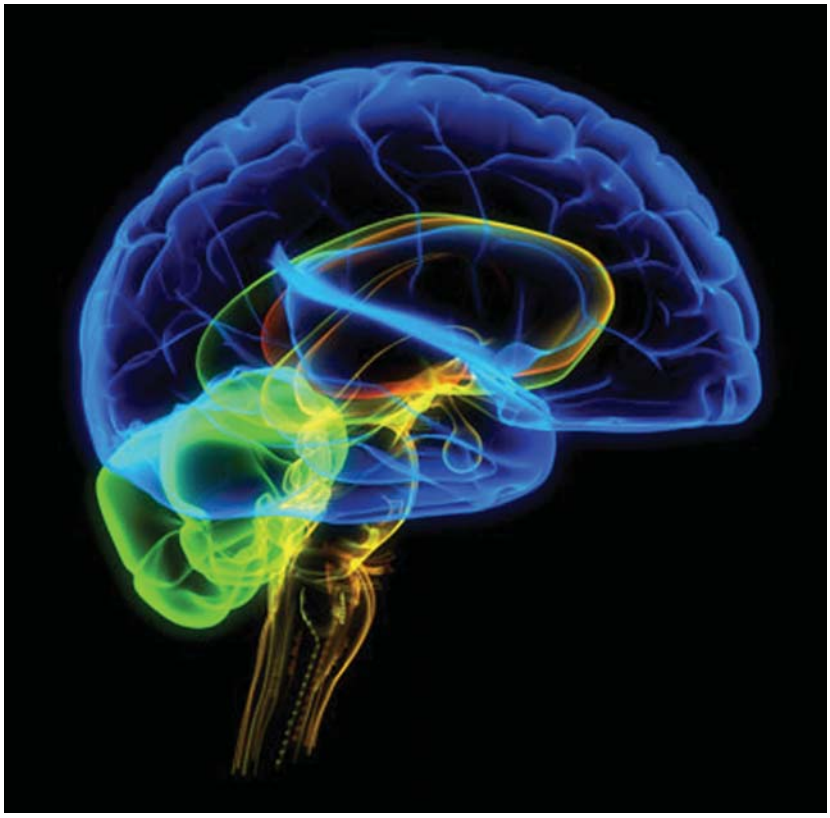

Figure 45
Brain circuitry

AREA 4 NEUROSCIENCES

4.5 Magnetic Resonance and Neuroradiology

Group Leader
Àlex Rovira Cañellas
Tel. 93 274 67 32
alex.rovira@idi-cat.org

Researchers
Juli Alonso Farré
Cristina Auger Acosta
Francisco Javier Aymerich Martínez
Laura Frascheri Verzelli
José Luis Munuera del Cerro
Deborah Pareto Onghena
Àlex Rovira Cañellas

Researchers in Training
Raquel Mitjana Penella
Silvana Isabel Sarria Estrada
Sahyly Siurana Montilva

Nursing, Technical and Administrative Staff
Juan Francisco Corral Gámez
Silvia Gelabert Udina
Elena Huerga Núñez
Ana Maria Nieto Montoya

Welcome to the Neuro Magnetic Resonance research group. We invite you to have a look at a viable and efficient way to use MR technology to carry out research projects. In the pages that ensue, you will find a broad description of who we are and how we work. The unit is directed by Dr. Àlex Rovira (neuroradiologist). Overall MR research coordination is under Dr. Juli Alonso (biochemist), while clinical coordination is under Dr. Cristina Auger (neuroradiologist).

OBJECTIVES

The multidisciplinary character of our group (neuroradiologists, physicists, biochemists, engineers, and MR technologists) allows us to divide objectives into two aspects.

The first focuses on the pathophysiologic mechanisms implicated in pathologies such as multiple sclerosis (MS), hepatic encephalopathy, and stroke through the application of MR techniques, carrying out qualitative and quantitative analyses.

Second, with the experience acquired along the years in performing MR studies, we can act as a platform for designing projects, processing images, and quantitative analysis of MR data. As a major imaging resource for the Hospital, the unit strives for excellence in its dual mission of research and service.

2010 Impact Factor:
82.348

RESEARCH LINES

Application of MR imaging and spectroscopy techniques to the study of multiple sclerosis

Àlex Rovira Cañellas

This research line is focussed on studying the predictive value of magnetic resonance imaging variables in MS and investigation in brain plasticity. Other current interests include obtaining information about pathophysiologic processes (neural damage and demyelination) and incorporating pattern recognition techniques into analysis of magnetic resonance spectra for differentiating between demyelinating lesions and glial tumors, or between clinical forms of multiple sclerosis.

Application of MR imaging and spectroscopy techniques to the study of hepatic encephalopathy

Juli Alonso Farré

The objective of this line is to obtain information about the pathophysiologic mechanisms involved in the development of hepatic encephalopathy. It is mainly focussed on cerebral edema: its characteristics, evolution, and relationship with clinical variables.

Functional MR imaging

Deborah Pareto Onghena

In this line we work on the implementation of protocols for investigating motor, visual, and cognitive tasks as well as to the analysis of functional MR imaging (fMRI). We believe that the capability of fMRI to detect cortical areas that activate when a specific task is being performed may be of great importance as a monitoring tool to determine the effect of disease and assess the efficacy of therapies.

Development of software for image analysis

Francisco Javier Aymerich Martínez

The application of computer vision techniques, image processing, pattern recognition and diffuse logic to the analysis of magnetic resonance images allows the development of software focused specifically on this type of images.

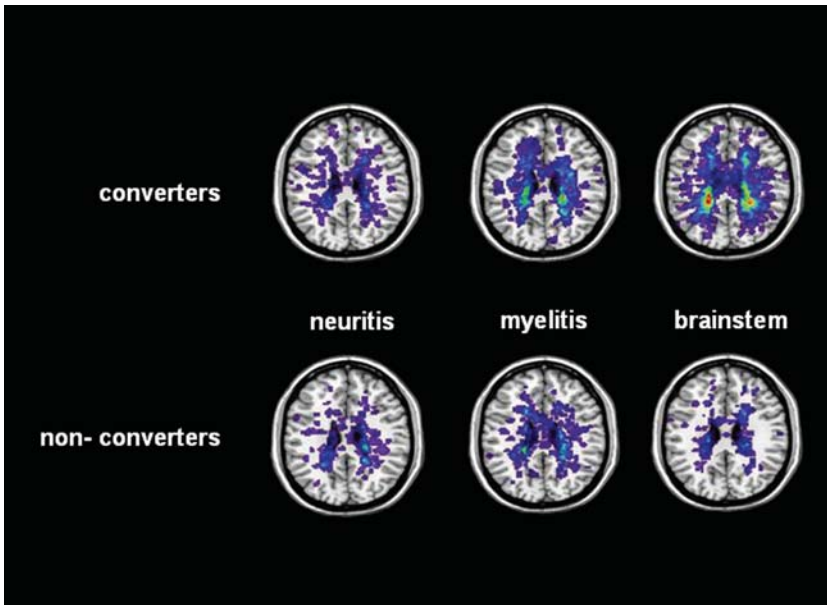

Figure 46
Lesion probability maps of clinically isolated syndrome patients whose first attack was optic neuritis, myelitis or brainstem syndrome and the conversion to multiple sclerosis

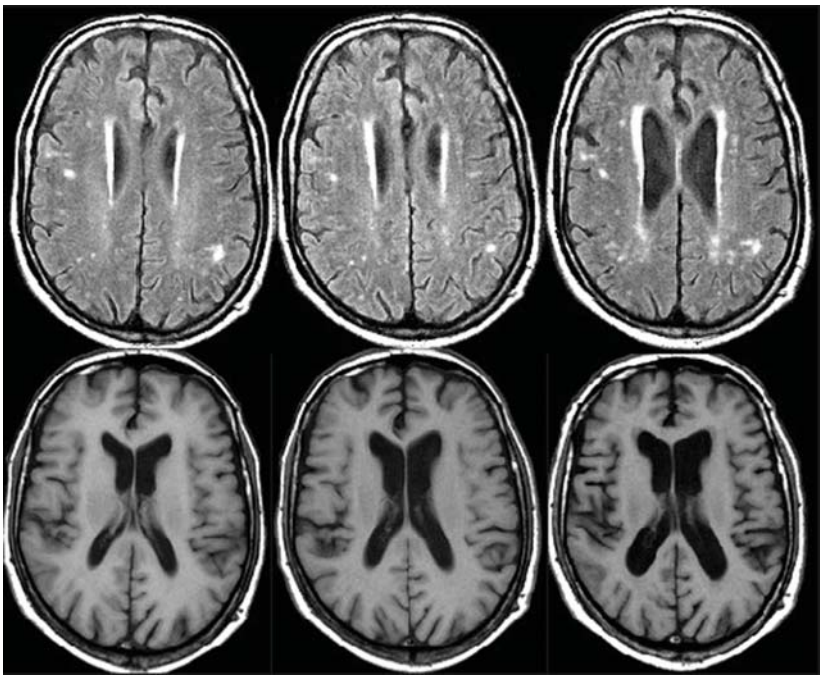

Figure 47
Brain fast fluid attenuated inversion recovery (top) and T1-weighted (bottom) axial images of a cirrhotic patient before liver transplantation (left), at short term (center), and at long term (right) after transplantation. Top images show a decrease in lesion volume in the short term followed by an increase in the long term after liver transplantation. Bottom images show an enlargement of ventricles in the consecutives assessments

Design of MR protocols and quantitative analysis of the images

Àlex Rovira Cañellas

With the development of research projects centred on the lines described above we have acquired an important experience that allows us to offer services involving protocol design and quantitative image analysis with existing or in-house-developed computer tools for projects carried out in other public or private institutions.

PUBLICATIONS
(Impact Factor: 82.348)

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AREA 4 NEUROSCIENCES

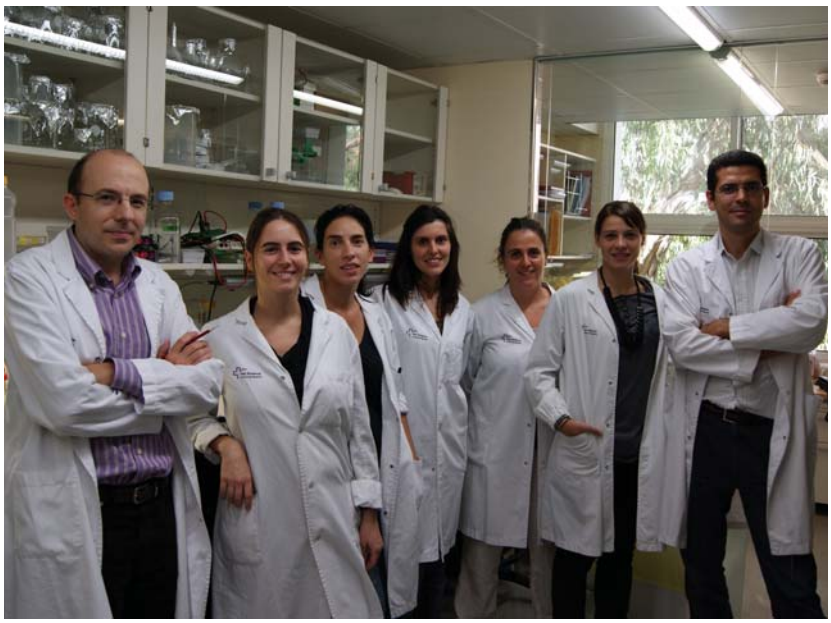
4.6 Neurodegenerative Diseases

Group Leader
Miquel Vila Bover
Tel. 93 489 45 43
miquel.vila@vhir.org

Researchers
Jordi Bové Badell
Iria Carballo Carbajal
Marta Martínez Vicente
Celine F Perier
Miquel Vila Bover

Researchers in Training
Ariadna Recasens Ibabe

Nursing, Technical and Administrative Staff
Mireia Humà Pérez
Annabelle Parent
Esther Pérez Gracia



OBJECTIVES

The research conducted in our group is geared toward elucidating the molecular mechanisms of neuron cell death occurring in neurodegenerative disorders, with the aim of finding a cure for this group of disabling, currently incurable, neurological diseases. To this end, our work has mostly focused so far on Parkinson's disease (PD), a particular neurodegenerative disorder mainly characterized by the degeneration of a specific set of neurons that are anatomically confined to a small region of the brain called *substantia nigra pars compacta* (SNpc) and that produce the neurotransmitter dopamine. Elucidating the molecular mechanisms underlying neurodegeneration in Parkinson's disease should allow the development of new therapeutic strategies aimed at blocking neuronal death in this disorder, as well as elicit important clues to identifying molecular pathways that might be common to other neurodegenerative conditions.

2010 Impact Factor:
78.772

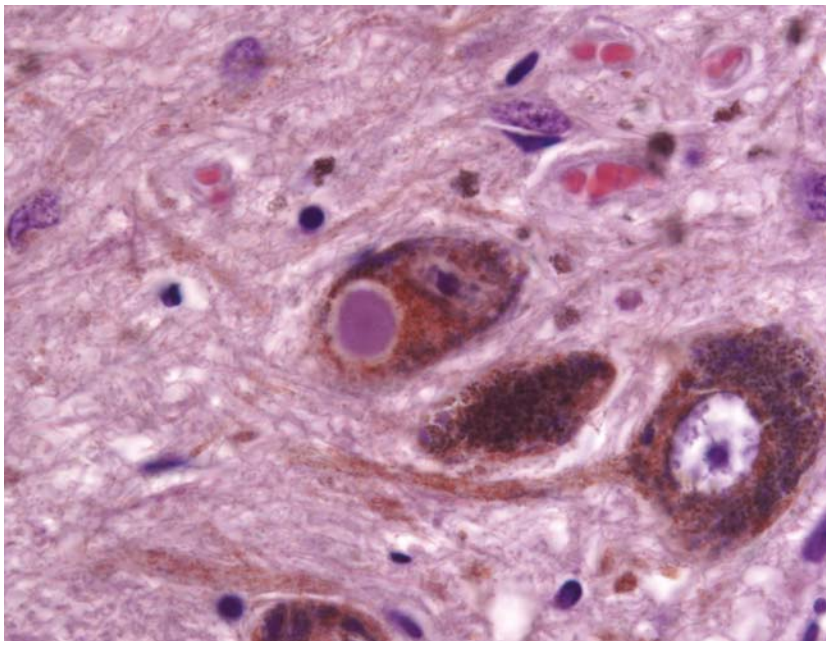


Figure 48
Post-mortem brain sample from a PD patient showing a Lewy body in a pigmented dopaminergic nigral, which classically appear with hematoxylin/eosin staining as one or more eosinophilic spherical body (pink colour) with a dense core surrounded by a halo

RESEARCH LINES

Mitochondrial dysfunction and Parkinson's disease

Miquel Vila Bover

Mitochondrial dysfunction, in particular at the level of complex I of the mitochondria respiratory chain, has long been implicated in the pathogenesis of PD. However, a primary direct pathogenic role of complex I deficiency in PD-related neurodegeneration remains to be elucidated. Some of our current research projects are aimed at determining the cause and role of mitochondrial alterations in PD.

Targeting programmed cell death in Parkinson's disease

Miquel Vila Bover

Programmed cell death (PCD), a physiological process that occurs naturally during development in which molecular programs intrinsic to the cell are activated to cause its own destruction, is inappropriately re-activated in PD, causing SNpc dopaminergic neurodegeneration. We are currently exploring the mechanisms that activate and regulate PCD pathways in PD in order to identify new molecular targets of potential therapeutic significance to attenuate or prevent dopaminergic neurodegeneration.

Role of intracytoplasmic neuronal inclusions in Parkinson's disease

Miquel Vila Bover

From a neuropathological point of view, PD is characterized not only by the loss of nigrostriatal dopaminergic neurons but also by the presence in affected brain regions of intraneuronal proteinacious cytoplasmic inclusions, called Lewy bodies (LB). However, the mechanisms of formation and significance of LB to the disease process remains to be elucidated. Our group is currently studying the potential involvement of lysosomal- and proteasomal-mediated cellular degradation pathways on the formation of LB, as well as the mechanisms of spread of LB pathology.

Role of mutated proteins associated to familial forms of Parkinson's disease

Miquel Vila Bover

In the past few years, mutations that cause familial forms of PD have been identified in several genes, including alpha-synuclein, parkin, DJ-1, PINK-1 and Dardarin/LRRK2. Exploring how these mutations lead to familial forms of PD should provide important clues to understanding the pathogenesis of the sporadic forms of the disease and allow the development of new genetic models of PD.

Autophagy alterations in Huntington's disease

Marta Martinez Vicente and Miquel Vila Bover

Autophagy is the degradation of intracellular components inside lysosomes, it is a highly conserved mechanism of quality control in the cells and is essential for the maintenance of cellular homeostasis and the control of an efficient cellular response to stress. Intracellular accumulation of altered and misfolded proteins is the basis of most neurodegenerative disorders; recent studies have shown that a primary failure in autophagy could be responsible for the accumulation of these altered proteins inside the affected neurons. Alterations in autophagy have been associated with Huntington's disease. Preliminary results show a failure in macroautophagy, the main lysosomal

pathway responsible for the degradation of cytosolic proteins and organelles. This failure can be compensated for by the activation of other alternative proteolytic pathways that can degrade cytosolic soluble proteins; however the insoluble aggregates (one of the main hallmarks of this disease) and organelles remain inside the cell. The long term accumulation of undigested organelles, especially mitochondria, can be a new source of intracellular oxidative stress. Indeed, dysfunctional mitochondria and oxidative stress have already been described as major contributors to neuronal loss in Huntington's disease and the deficient degradation of dysfunctional mitochondria by autophagy becomes an aggravating factor in the pathophysiology of this disease. The overall goal of the project is to study the failure of mitochondria turnover by autophagy (mitophagy) in Huntington's disease. Identifying the role of huntington protein in autophagy and the molecular mechanism of its failure in Huntington's disease would be essential for future efforts to restore proper autophagic activity and make sure that dysfunctional organelles will be properly eliminated.

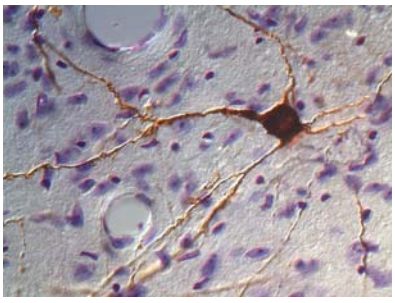


Figure 49
Dopaminergic neuron in the substantia nigra of a mouse ventral midbrain revealed by immunohistochemistry against tyrosine-hydroxilase (TH, brown colour), the rate-limiting enzyme of dopamine synthesis

CURRENT RESEARCH PROJECTS

PI: Miquel Vila Bover
Mecanismos y relevancia de la formación de cuerpos de Lewy en la enfermedad de Parkinson
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI071019
Funding: 217,679 €
Duration: 2008 to 2011

PI: Celine F Perier
Control de calidad de las mitocondrias: implicación en la enfermedad de Parkinson
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00255
Funding: 160,325 €
Duration: 2010 to 2012

PI: Miquel Vila Bover
Mecanismos de propagación y progresión de la enfermedad de Parkinson: rol de los cuerpos de Lewy
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2009-06575-E
Funding: 35,000 €
Duration: 2010 to 2011

PI: Marta Martínez Vicente
Altered autophagy in Huntington's disease
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP09/00184
Funding: 34,836.65 €
Duration: 2010 to 2012

PI: Marta Martínez Vicente
Alteración de la autofagia en la enfermedad de Huntington
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2009-08374
Funding: 110,395.65 €
Duration: 2010 to 2012

PI: Miquel Vila Bover
Grup de Recerca en Malalties Neurodegeneratives
Funding Agency: AGAUR
Reference: 2009 SGR 664
Funding: 41,600 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 78.772)

Cuervo AM, Wong ES, Martínez-Vicente M. Protein degradation, aggregation, and misfolding. *Mov Disord* 2010; 25 Suppl 1: S49-54. ➲ IF: 4.014.

Dehay B, Bové J, Rodríguez-Muela N, Perier C, Recasens A, Boya P, Vila M. Pathogenic lysosomal depletion in Parkinson's disease. *J Neurosci* 2010 Sep 15; 30 (37): 12535-44. ➲ IF: 7.178.

Lee JH, Yu WH, Kumar A, Lee S, Mohan PS, Peterhoff CM, Wolfe DM, Martínez-Vicente M, Massey AC, Sovak G, Uchiyama Y, Westaway D, Cuervo AM, Nixon RA. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell* 2010 Jun 25; 141 (7): 1146-58. ➲ IF: 31.152.

Martínez Vicente M, Talloczy Z, Wong E, Tang G, Koga H, Kaushik S, Vries R de, Arias E, Harris S, Sulzer D, Cuervo AM. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat Neurosci* 2010 May; 13 (5): 567-76. ➲ IF: 14.345.

Perier C, Bové J, Dehay B, Jackson-Lewis V, Rabinovitch PS, Przedborski S, Vila M. Apoptosis-inducing factor deficiency sensitizes dopaminergic neurons to parkinsonian neurotoxins. *Ann Neurol* 2010 Aug; 68 (2): 184-92. ➲ IF: 9.317.

Sotiriou E, Vassilatis DK, Vila M, Stefanis L. Selective noradrenergic vulnerability in alpha-synuclein transgenic mice. *Neurobiol Aging* 2010 Dec; 31 (12): 2103-14. ➲ IF: 5.937.

Wang Y, Martínez-Vicente M, Kruger U, Kaushik S, Wong E, Mandelkow EM, Cuervo AM, Mandelkow E. Synergy and antagonism of macroautophagy and chaperone-mediated autophagy in a cell model of pathological tau aggregation. *Autophagy* 2010 Jan; 6 (1): 182-3. ➲ IF: 6.829.

AREA 4 NEUROSCIENCES

4.7 Neuromuscular and Mitochondrial Pathology

Group Leader
Antonio Luis Andreu Périz
Tel. 93 489 49 80
toni.andreu@vhir.org

Researchers
Yolanda Cámara Navarro
Elena García Arumí
Emiliano González Vioque
Ramón Martí Seves
Gisela Nogales Gadea
Tomas Pinós Figueras

Researchers in Training
Marc Cuadros Arasa
Javier Torres Torronteras

Nursing, Technical and Administrative Staff
Ramiro Martínez Estéfano
Mª Jesús Melia Grimal

OBJECTIVES

The group focuses on the study of pathogenic mechanisms of mitochondrial DNA mutations (mtDNA) associated with diverse neuromuscular syndromes. It is especially interested in understanding the pathogenic mechanisms involved in mutations of structural genes of mtDNA, as well as the adaptative mechanisms of the cell in mtDNA depletion syndrome. In addition, it performs the genetic and molecular study of diverse neurological syndromes and glycogenosis type III and V.

RESEARCH LINES

Study of pathogenic mechanisms of mutations in mitochondrial DNA (mtDNA) structural genes

Antonio Luis Andreu Périz and Elena García Arumí

Characterization of phenotypic effects of mitochondrial DNA mutations using a model of transmitocondrial hybrids. We are currently working with mutations in; ribosomal RNA (12S rRNA), in tRNA (tRNA lys, tRNA Leu (UUR)), and subunits; complex I (ND6), complex IV (COI) and complex V (ATP6).

Characterization of genotype-phenotype association in McArdle's disease

Antonio Luis Andreu Périz

We are characterizing the elements that define genotype-phenotype association in McArdle's disease, produced by mutations in the gene of the muscular isoform of glycogen phosphorylase. In addition, we are generating the knock-in mouse for the common mutation in Caucasian population (R50X) studying its phenotypic effects.

2010 Impact Factor:
23.480

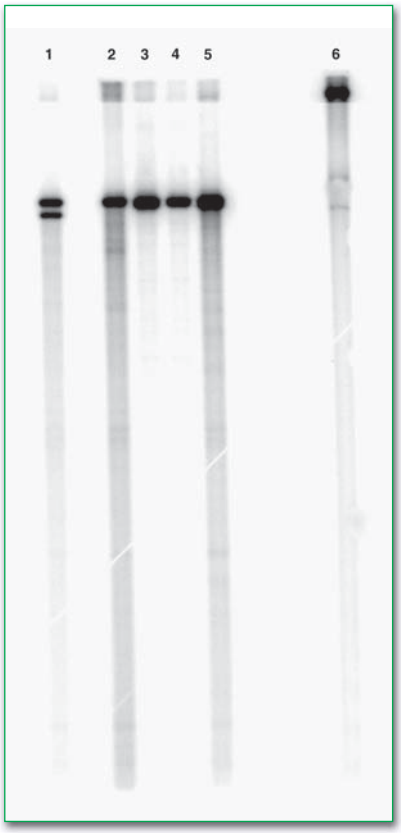


Figure 50
Southern blot analysis of mitochondiral DNA (mtDNA) from several muscle samples. DNA isolated from muscle biopsies was digested with the restriction enzyme *PvuII* (which cuts the circular human mtDNA in a single target), resolved in an agarose gel, transferred to a nylon membrane and hybridized with a radioactive probe, specific for mtDNA. Lane 1: patient with a mtDNA single deletion; lanes 2 and 5: patients with mtDNA multiple deletions; lanes 3 and 4: patients with no mtDNA deletions; lane 6: uncut DNA

Genetic and biochemical study of mitochondrial DNA depletion syndromes: MNGIE, depletion due to deficiency of TK2 and dGK. Implications on the control of nucleotide pool
Ramón Martí Seves
Experimental studies to determine the influence of imbalances in concentrations of nucleotides on the maintenance of mtDNA.

Study of possible therapeutic approaches for the Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) disease
Ramón Martí Seves
Study the effects of restoring tymidine phosphorylase activity on the biochemical phenotype and mitochondrial function in MNGIE, as a preliminary approach for a possible treatment by gene therapy.

CURRENT RESEARCH PROJECTS

PI: Antonio Luis Andreu Périz
Acción coordinada para el estudio de los mecanismos determinantes de la expresión fenotípica de las mutaciones en genes reguladores del sistema de fosforilación oxidativa (parte 1: Aproximación en modelos celulares)
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070347
Funding: 233,409 €
Duration: 2008 to 2010

PI: Antonio Luis Andreu Périz
Automatización de métodos de diagnóstico molecular de enfermedades mitocondriales. (Parte 2, Hospital Vall d'Hebron: Validación del Mitochip (V2.0) de Affymetrix para el Screening de mutaciones en el DNA mitocondrial)
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI08/90355
Funding: 82,885 €
Duration: 2009 to 2010

PI: Ramón Martí Seves
Estudio preclínico del tratamiento del MNGIE mediante terapia génica, usando un vector lentivírico en un modelo murino. Seguimiento a largo plazo y bajo sobrecarga de timidina
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01591
Funding: 126,445 €
Duration: 2010 to 2012

PI: Elena García Arumí
Caracterización del transcriptoma de las enfermedades producidas por mutaciones del DNA mitocondrial: aproximación en modelos celulares
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01602
Funding: 97,405 €
Duration: 2010 to 2012

PI: Antonio Luis Andreu Périz
Patologia Neuromuscular i Mitocondrial
Funding Agency: AGAUR
Reference: 2009 SGR 1520
Funding: 0,00 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 23.480)

Domingo P, Torres Torronteras J, Pomar V, Giralt M, Domingo JC, Gutiérrez MD, Gallego-Escuredo JM, Mateo MG, Cano-Soldado P, Fernández I, Pastor-Anglada M, Vidal F, Villarroya F, Andreu A, Martí R. Uridine Metabolism in HIV-1-Infected Patients: Effect of Infection, of Antiretroviral Therapy and of HIV-1/ART-Associated Lipodystrophy Syndrome. *PLoS One* 2010 Nov 15; 5 (11): e13896. ➲ IF: 4.351.

Martí R, Nascimento A, Colomer J, Lara MC, López-Gallardo E, Ruiz-Pesini E, Montoya J, Andreu AL, Briones P, Pineda M. Hearing loss in a patient with the myopathic form of mitochondrial DNA depletion syndrome and a novel mutation in the TK2 gene. *Pediatr Res* 2010 Aug; 68 (2): 151-4. ➲ IF: 2.607.

Nogales-Gadea G, Mormeneo E, García-Consuegra I, Rubio JC, Orozco A, Arenas J, Martín MA, Lucia A, Gómez-Foix AM, Martí R, Andreu AL. Expression of Glycogen Phosphorylase Isoforms in Cultured Muscle from Patients with McArdle's Disease Carrying the p.R771PfsX33 PYGM Mutation. *PLoS One* 2010 Oct 5; 5 (10). pii: e13164. ➲ IF: 4.351.

Rae DE, Noakes TD, San Juan AF, Pérez M, Nogales-Gadea G, Ruiz JR, Morán M, Martín MA, Andreu AL, Arenas J, Lucia A. Excessive skeletal muscle recruitment during strenuous exercise in McArdle patients. *Eur J Appl Physiol* 2010 Nov; 110(5): 1047-55. ➲ IF: 2.047.

Rivera H, Merinero B, Martínez-Pardo M, Arroyo I, Ruiz-Sala P, Bornstein B, Serra-Suhe C, Gallardo E, Martí R, Morán MJ, Ugalde C, Pérez-Jurado LA, Andreu AL, Garesse R, Ugarte M, Arenas J, Martín MA. Marked mitochondrial DNA depletion associated with a novel SUCLG1 gene mutation resulting in lethal neonatal acidosis, multi-organ failure, and interrupted aortic arch. *Mitochondrion* 2010 Jun; 10 (4): 362-8. ➲ IF: 4.145.

Vives-Bauza C, Magrané J, Andreu AL, Manfredi G. Novel role of ATPase subunit C targeting peptides beyond mitochondrial protein import. *Mol Biol* Cell 2010 Jan; 21 (1): 131-9. ➲ IF: 5.979.

AREA 4 NEUROSCIENCES

4.8 Neurotraumatology and Neurosurgery (UNINN)

Group Leader
Joan Sahuquillo Barris
Tel. 93 274 62 13 / 93 489 41 88
sahuquillo@neurotrauma.net

Researchers
Fuat Arikan Abelló
Marcelino Bàguena Martínez
María Dolores de la Calzada Álvarez
Jannet Paola Cano Granda
Alejandro Farré Mas
Ángel Garnacho Vega
Francisco Ramón Martínez Ricarte
Miriam de Nadal Clanchet
Ma. Antonia Poca Pastor
Marylín Riveiro Vilaboa
Ángel Robles González
Joan Sahuquillo Barris
María Sueiras Gil
Ramón Torné Torné
Jordi Vilalta Castan

Researchers in Training
Carmen Airado Cerrato
Beatriz García López
Tamara Martínez Valverde
M. Ángeles Merino Ojer
Alba Peña Paris
Irina Andreea Radoi
Ángela Sánchez Guerrero
Elisabeth Solana Díaz
Mª Ángeles Vidal Jorge

Nursing, Technical and Administrative Staff
Mercedes Arribas Serrano
Lourdes Expósito Mozas
Joana Segura Segura
Mónica Tarradas Ustrell

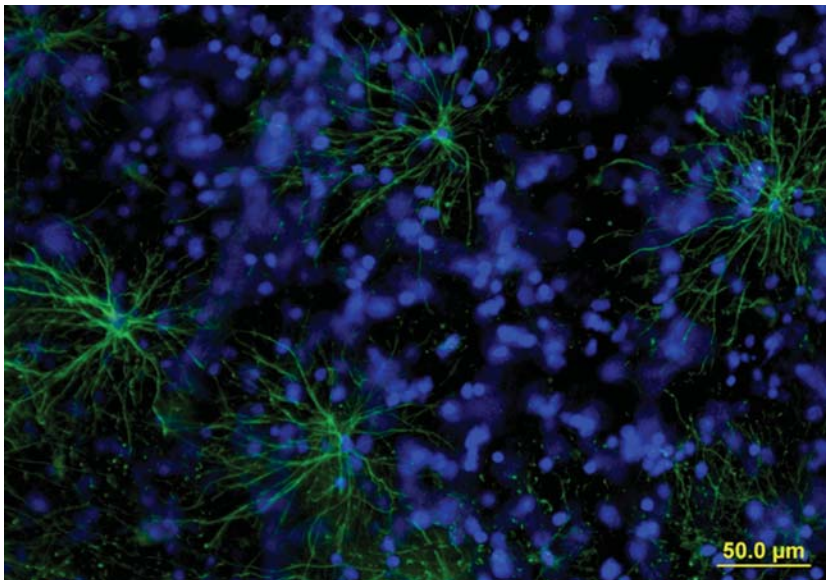
The Neurotraumatology and Neurosurgery Research Unit (UNINN) was established in late 1990 and since 2007 it has been part of the Universitat Autònoma de Barcelona (Spain) research groups. The UNINN has been audited and given the accreditation of "Consolidated Research Group" by the Catalan autonomous government (2005 SGR 0411, recently re-accreditated in 2009: SGR2009-00495).
Our research projects, traditionally clinically oriented, have incorporated basic research without losing a patient-centered orientation, and aim at increasing the amount of translational research that may improve prognosis and quality of life.
The UNINN is fully integrated into the European research community, acting as the coordinator of multicenter and international studies and routinely collaborating in the drafting of clinical practice guidelines. Our most recent contribution in this area is a Cochrane review on the indications and benefits of decompressive craniectomies in head-injured patients and refractory intracranial hypertension.

2010 Impact Factor:
34.519

OBJECTIVES

The main aim of the UNINN is to increase understanding of the neurobiological, physiopathological and functional mechanisms taking place in patients with different neurological disorders (neurotraumatic injuries, CSF dynamics abnormalities, craniocervical malformations, malignant middle cerebral artery infarction, and neuro-oncology), in order to acquire new knowledge that when transferred to the clinical setting, might improve functional outcome in these patients. To achieve our mission, our research unit will create more partnerships with multidisciplinary research groups at different national and international centers, conducting translational research in the above mentioned disorders.

Figure 51
Human brain tissue slices cultured in vitro for five days, stained with immunofluorescence against the glial marker GFAP *(glial fibrillary acidic protein)* [green] and counterstained with DAPI *(4',6-diamidino-2-phenylindole)* [blue]



RESEARCH LINES

Consolidated Lines

Neurotraumatology
Joan Sahuquillo Barris and Ángel Garnacho Vega
GENERAL AIMS: To study alterations in brain metabolism, neurochemical alterations, pathophysiology, and new monitoring techniques and treatments in traumatic brain injury (TBI) and in neurocritical patients.

SPECIFIC AIMS: 1) To increase knowledge of tissular metabolic and O_2 transport alterations in acute brain lesions. 2) To study cerebral and systemic neuro-inflammatory response through high resolution microdialysis techniques. 3) To analyze peri-infarct depolarization phenomena in patients with acute brain injury (COSBID European study). 4) To apply high-resolution microdialysis to define the molecular profile of post-traumatic brain edema and the contribution of non-selective cationic channels to its formation; and 5) To study mitochondrial dysfunction after traumatic brain injury (TBI) in patients and in histotoxic hypoxia can be modelled and reproduced in adult human brain slices obtained from surgically extracted specimens.

Hydrocephalus and alterations in the dynamics of cerebrospinal fluid (CSF)
Ma. Antonia Poca Pastor and Joan Sahuquillo Barris
GENERAL AIM: To study the pathophysiology of intracranial pressure (ICP) and alterations in CSF dynamics in patients with hydrocephalus and other intracranial pathologies.

SPECIFIC AIMS: 1) To gain greater insight into the physiopathology of normal pressure hydrocephalus and idiopathic intracranial hypertension *(pseudotumor cerebri)* and to study new diagnostic and therapeutic strategies. 2) To determine the biochemical alterations (neurotransmitters and neuropeptides) in these patients, as well as their role in cognitive function and sleep disturbances; and 3) To correlate cognitive deficit with morphological and functional alterations in different cerebral structures, such as the *corpus callosum* and subcortical white matter.

Malignant Middle Cerebral Artery Infarction (MMCAI)
Joan Sahuquillo Barris
GENERAL AIM: To expand on the physiopathology, metabolic alterations, and monitoring of patients with malignant MCA infarction.

SPECIFIC AIMS: 1) To gain greater insight into the physiopathology, metabolic alterations, and monitoring of patients with malignant middle cerebral artery infarction. 2) To optimize treatment through the use of novel techniques, such as moderate hypothermia and decompressive craniectomy. 3) To characterize the inflammatory response profile (cerebral and systemic) triggered by massive ischemic stroke. 4) To optimize the treatment of severe head injury and MMCAI using new therapeutic techniques such as the combination of moderate hypothermia and decompressive craniotomy;

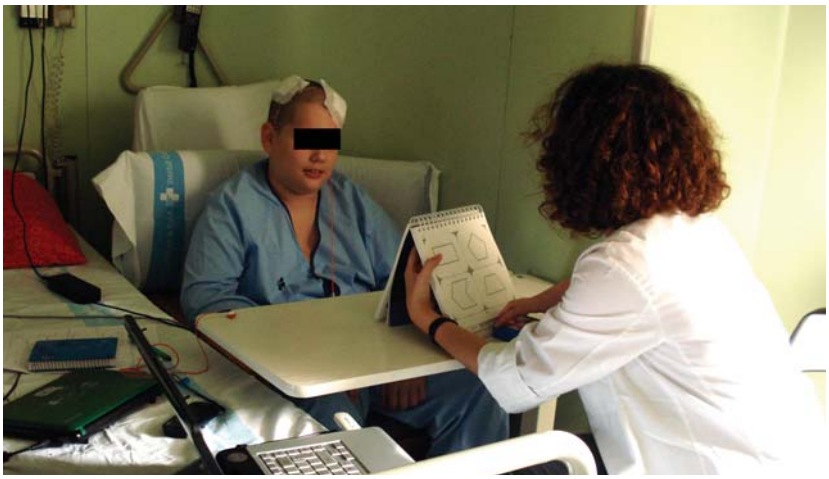


Figure 52
Cognitive assessment of a patient undergoing intracranial pressure monitoring

and 5) To study and evaluate the quality of life of patients who survive a malignant middle cerebral artery infarction (MMCAI).

Emerging lines

Congenital malformations of the cranio-vertebral junction

Ma. Antonia Poca Pastor and Joan Sahuquillo Barris

AIMS: 1) To improve knowledge of the physiopathology of craniocervical malformations, particularly Chiari Type I (MC-I), and quantify the clinical, social and occupational repercussions of this malformation. 2) To study the genetic bases of this malformation and its penetrance in family members. 3) To study sleep disturbances (particularly type and frequency of sleep apneas) associated with Chiari Type I malformations; and 4) To study the quality of life of patients with a craniocervical malformation without surgical treatment, as well as those with surgical treatment before and after surgery.

Neuro-oncology

Joan Sahuquillo Barris and Francisco Ramón Martínez Ricarte

In this new line of translational research, we collaborate actively with the Vall d'Hebron Institute of Oncology (VHIO) lead by Dr. J. Baselga and especially with the "Gene Expression and Cancer" laboratory led by Dr. J. Seoane. AIMS: 1) To develop a patient registry, centralized in external servers, to study the epidemiology, diagnosis and treatment results of primary and secondary brain tumors (Gliomas and metastases). 2) To develop a methodology for studying quality of life and cost-effectiveness of surgery and certain treatments in patients with malignant CNS tumors. 3) To study the cost-effectiveness of cortical mapping in low-grade tumors removed by awake craniotomy. 4) To develop cell lines of glioma primary cultures and glioma stem cells for improving knowledge of route regulation at all levels, especially pre- and-post-transcriptional; and 5) To study potential therapeutic targets derived from knowledge of the factors involved in the regulation of neuro-oncogenesis in glial cell tumors.

CURRENT RESEARCH PROJECTS

PI: Ma. Antonia Poca Pastor

Implicación de los neuropéptidos hipocretina-1, melatonina y cortistatina en las alteraciones de los ciclos sueño-vigilia de los pacientes con hidrocefalia normotensiva

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070681
Funding: 59,176.26 €
Duration: 2008 to 2011

PI: Joan Sahuquillo Barris

Advanced Arterial Hypotension Adverse Event Prediction Through a Novel Bayesian Neural Network (AVERT-IT) Grant No 217049

Funding Agency: European Commission
Reference: AVERT-IT-217049
Funding: 129,304 €
Duration: 2008 to 2011

PI: Joan Sahuquillo Barris

Respuesta metabólica e inflamatoria de los fenómenos de despolarización propagada (spreading depresión y SD -like) en pacientes con lesiones cerebrales traumáticas e isquémicas. Aproximación a una potencial nueva diana terapéutica

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080480
Funding: 85,789 €
Duration: 2009 to 2011

PI: Joan Sahuquillo Barris

Análisis del perfil temporal de los mediadores de respuesta neuroinflamatoria en el espacio extracelular cerebral mediante microdiálisis cerebral de alta resolución en pacientes con un traumatismo craneoencefálico grave

Funding Agency: Fundación Mapfre Medicina
Reference: MAPFRE/2009/01
Funding: 14,629 €
Duration: 2010 to 2011

PI: Joan Sahuquillo Barris
Análisis del perfil temporal de los mediadores de respuesta neuroinflamatoria en el espacio extracelular cerebral mediante microdiálisis cerebral de alta resolución en pacientes con un traumatismo craneoencefálico grave
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMM-2010-10
Funding: 44,736 €
Duration: 2010 to 2013

PI: Joan Sahuquillo Barris
Mecanismos moleculares implicados en la génesis del glioma y estudio de las células madre tumorales. Identificación de nuevas dianas terapéuticas y marcadores para la estratificación en pacientes y respuesta a fármacos
Funding Agency: Asociación Española Contra el Cáncer
Reference: AECC-GE2010-07
Funding: 175,000 €
Duration: 2010 to 2015

PI: Joan Sahuquillo Barris
Unitat d'Investigació de Neurotraumatologia i Neurocirurgia (UNINN)
Funding Agency: AGAUR
Reference: 2009 SGR 495
Funding: 0,00 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 34.519)

Anido J, Saez-Borderias A, González-Junca A, Rodón L, Folch G, Carmona MA, Prieto-Sánchez RM, Barba I, Martínez-Saez E, Prudkin L, Cuartas I, Raventós C, Martínez-Ricarte F, Poca MA, García-Dorado D, Lahn MM, Yingling JM, Rodón J, Sahuquillo J, Baselga J, Seoane J. TGF-beta Receptor Inhibitors Target the CD44(high)/Id1(high) Glioma-Initiating Cell Population in Human Glioblastoma. *Cancer Cell* 2010 Dec 14; 18 (6): 655-68. ➲ IF: 25.288.

Arikan F, Vilalta J, Romero FJ, Porta I, Martínez-Ricarte FR, Sahuquillo J. Primary decompressive craniectomy in patients with aneurysmatic subarachnoid hemorrhage. Results of a pilot study in 11 cases. *Neurocirugia (Astur)* 2010 Dec; 21 (6): 452-460. ➲ IF: 0.247.

Calzada MD de la, Poca MA, Sahuquillo J, Matarín M, Mataró M, Solana E. Cognitive event-related brain potentials (P300) in patients with normal pressure hydrocephalus. Results of a prospective study. *Neurologia* 2010 Jan-Feb; 25 (1): 32-9. ➲ IF: 0.596.

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Piper I, Chambers I, Citerio G, Enblad P, Gregson B, Howells T, Kiening K, Mattern J, Nilsson P, Ragauskas A, Sahuquillo J, Donald R, Sinnott R, Stell A, Sahuquillo J, Pickard JD, Mins R, Whittle I, Dunn L, Rydenhag B, Kiening K, Iencean S, Pavalkis D, Meixensberger J, Goffin J, Vajkoczy P, Stocchetti N, Citerio G, Chambers IR, Corte F della, Hell J, Enblad P, Mascia L, Jarzemaskas E, Stocker R. The brain monitoring with Information Technology (BrainIT) collaborative network: EC feasibility study results and future direction. *Acta Neurochir (Wien)* 2010 Nov; 152 (11): 1859-71. ➲ IF: 1.472.

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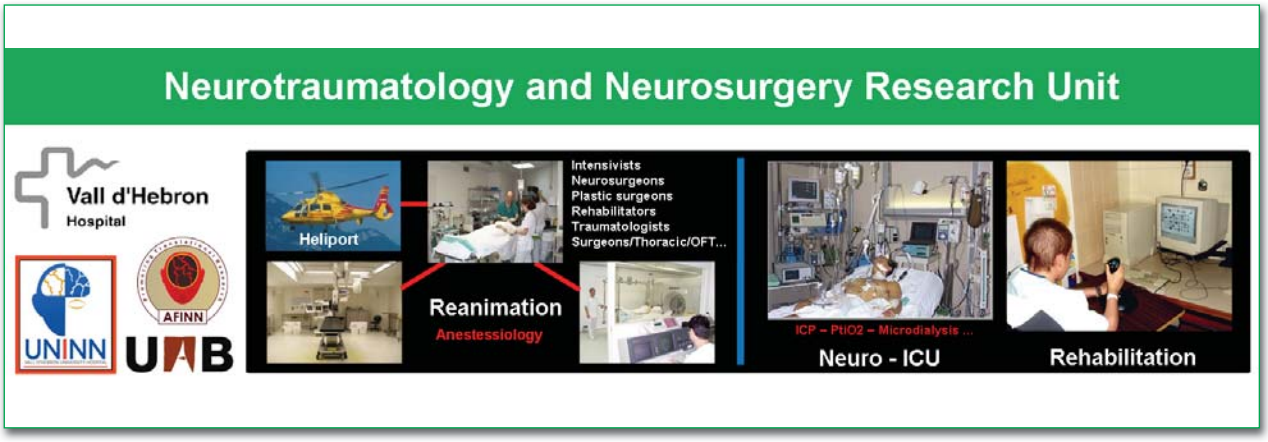

AREA 4 NEUROSCIENCES

4.9 Neurovascular Diseases

Group Leader
Joan Montaner Villalonga
Tel. 93 489 40 29 / 93 489 40 73
joan.montaner@vhir.org

Researchers
José Álvarez Sabín
Mª Pilar Delgado Martínez
Israel Fernández Cadenas
Lidia García Bonilla
Maria del Mar Hernández Guillamón
Carlos Molina Cateriano
Joan Montaner Villalonga
Marc Ribó Jacobi
Anna Rosell Novel
Marta Rubiera
Esteban Santamarina

Researchers in Training
Mireia Campos Martorell
Sophie Domingues
Teresa García Berrocoso
Andreu Massot
Maite Mendioroz
Anna Morancho Retana
Cristina Nafría Pérez
Miriam Navarro
Jorge Pagola Pérez Blanca
Mireia Parés Oliva
Yolanda Riba Llena
Alberto del Río Espinola
David Rodríguez Luna

Nursing, Technical and Administrative Staff
Veronica Barceló Romero
Cristina Boada Llamas
Natalia Corbeto López
Laura Deu Lozano
Borja Felix Rojas
Sandra García Menéndez
Dolors Giralt Casellas
Gonzalo Pablo Mazuela Águila
Mª Pilar Meler Amella
Gema Mª Ortega Linares
Laura Ortega Torres
Anna Penalba
Manuel Quintana Luque

OBJECTIVES

One in six persons in the world will suffer a stroke during their lifetime; in fact neurovascular disease is the number one killer among Spanish women. To change these dramatic figures, the Neurovascular research group is focused on the discovery of new diagnostic and therapeutic targets to improve the prevention, diagnosis and treatment of neurovascular diseases. For that purpose six consolidated lines of research work in concert to try to achieve these goals, looking for stroke biomarkers that would be useful as diagnostic and prognostic tools; the genetic risk factors that allow us to identify people at risk of suffering a stroke or new prevention strategies, especially in cases of silent neurovascular disease. Moreover, our studies and characterization of some molecular processes following cerebral ischemia, might improve stroke treatment, especially those pharmacological therapies to improve the thrombolytic approaches in the acute phase and cell therapy strategies used to trigger neurorepair after the ischemic insult. We are also experts in the research of some specific stroke subtypes such as Cerebral Amyloid Angiopathy in the border of neurovascular and Alzheimer disease.

2010 Impact Factor:
192.267

RESEARCH LINES

Biomarkers

Joan Montaner Villalonga, Teresa García Berrocoso, Anna Penalba Morenilla and Cristina Boada Llamas

The use of plasma biomarkers is becoming increasingly popular in several fields of medicine. In fact, decision-making processes using biomarkers are widely accepted in medical situations such as initiating lipid lowering therapies (LDL), diagnosing acute myocardial infarction (troponins), and ruling out pulmonary embolism suspicions (D-dimer), among others.

Therefore we believe that biochemical markers of strokes, will really open "a window to the brain...". In fact, in this research line we aim to answer relevant clinical questions through the use of biomarkers. Our main objectives using mainly plasma proteins are:

- To predict stroke risk.
- To make stroke diagnoses.
- To differentiate stroke subtypes.
- To establish evolution and prognosis.
- To use Biomarkers as treatment end-points.

Some of our findings might have therapeutic implications since biological markers described by the group such as MMP-9 are well associated with Blood Brain Barrier disruption. In this direction, we have described MMP-9 predicting haemorrhagic complications among stroke patients receiving thrombolytic treatment. These approaches might contribute to increase safety of reperfusion treatments. The impact of this research line is clear, since this article (*Circulation* 2003) has been cited more than 180 times since its publication. The study of these molecules will also have diagnostic implications because we have proposed the biochemical diagnosis of strokes by means of the identification of a biomarkers panel that distinguishes between a stroke and other stroke-mimicking conditions. This might contribute to ensurin that only genuine stroke patients are referred to stroke centers, saving the system huge resources.

These two examples, identification of biomarkers to predict tPA related bleedings and a diagnostic stroke test are examples of translational research in which the Neurovascular Research Lab is filing patents to be licensed to Biotech companies able to develop diagnostic kits in which our biomarkers might be placed and used in clinical practice. This might close the circle of applied research.

Reviews of our group in which you may find detailed info about these biomarkers:

- Foerch C, Montaner J, Furie KL, Ning MM, Lo EH. Searching for oracles? Blood biomarkers in acute stroke. *Neurology* 2009; 73 (5): 393-9.
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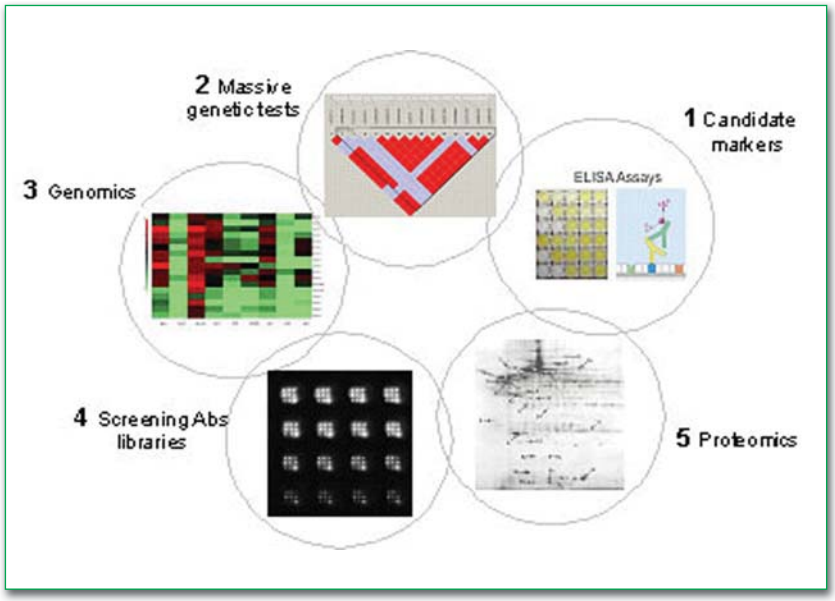

Figure 53
We are using a combination of discovery techniques and biological human and animal samples to identify new stroke-related biomarkers

PROJECTS: We are involved in several projects with public or private funding supporting our research on stroke biomarkers. One such exciting project is FIS PI 08/361 "Identificación y uso de biomarcadores pronósticos en el ictus isquémico", aiming to identify biomarkers that predict the main causes of stroke worsening (Infarct growth, cardiac complications, hemorrhagic transformation, infections, recurrence or new vascular events) to guide Stroke Unit allocation and in-patient stays for our patients.

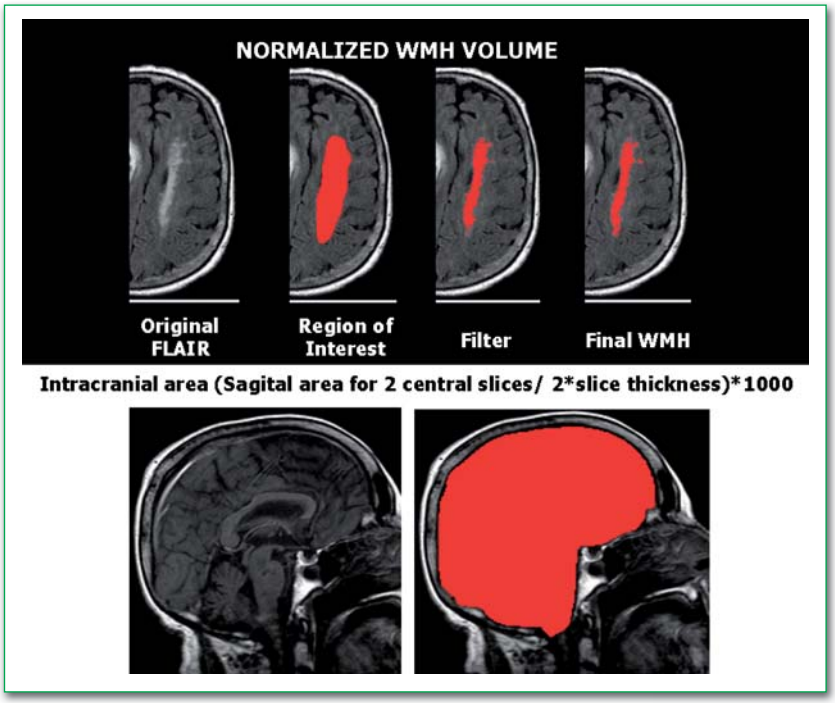

Figure 54
Example of the WMH volume calculation using currently available MRI imaging software

INTERNATIONAL COLLABORATIONS: The discovery and validation of good candidate biomarkers requires multidisciplinary approaches and replication in well designed multicentric and international studies. For that purpose we are actively collaborating with well known leading stroke research groups:

- Eng Lo, Xiaoing Wang, Ming Ming Ning (Boston, USA).
- Jean Charles Sanchez, Natacha Turck (Geneva, Switzerland).
- Denis Vivien, Carine Ali, Eduardo Anglés-Cano (Caen, France).

RESEARCH TOOLS AND TECHNIQUES: We are using a combination of discovery techniques and biological human and animal samples to identify new stroke-related biomarkers: One example is "protein arrays". In our laboratory, we have been using these new technologies and we currently use the Search-Light Assays (Aushon Biosystems) which allows us to study more than 170 human proteins and also many candidates from different animal species. We offer access to our technology to other groups. For more information, please refer to http://www.lin-bcn.com/ Also these biomarkers may be specifically tested not only as circulating markers in plasma or serum but in the components of interest of the Neurovascular Unit, that we dissect by using the LCM Leica LMD6000 microscope, for Laser Capture microdissection. An example which combines both techniques may be found at: Cuadrado E, Rosell A, Penalba A, Slevin M, Álvarez-Sabín J, Ortega-Aznar A, Montaner J. Vascular MMP-9/TIMP-2 and neuronal MMP-10 up-regulation in the human brain after stroke: a combined Laser Microdissection and Protein Array Study. *Journal of Proteome Research* 2009; 8 (6): 3191-7.

BIOBANKS: All these results have been made possible due to the development of a "blood library" including more than 2000 stroke samples and a "brain library" that allowed us to describe for the first time the "human stroke proteome" with the outstanding collaboration of so many patients, relatives and clinicians of the Stroke Unit.

Stroke prevention

Mª Pilar Delgado Martínez and Iolanda Riba Llena

Since cerebrovascular diseases and dementia are responsible for a huge economic burden, the early detection of patients at high risk of them, and the implementation of preventive measures as soon as possible, is of great interest and may result in health care savings. The purposes of our research are:

- To promote awareness and knowledge of strokes in the general population and enhance collaboration between primary care services and hospital departments.
- To accurately predict those patients at high-risk of first stroke by the determination of novel risk factors or markers (neuroimaging or biological markers), and therefore to improve stroke risk stratification.
- To incorporate a standardized assessment of cognition in stroke research.
- To determine why interventions may be widely applied or not by means of cost-efficiency studies.
- To study quantitative predictors of preventive treatment compliance.

FUTURE PROJECT: "Silent cerebral infarction detection and biomarkers associated with the risk of stroke in the hypertensive Spanish population".
Silent cerebral infarctions (SCI) detected with neuroimaging techniques, particularly with brain MRI, are common in the healthy aged population and even more frequent in selected patients at risk, such as hypertensive patients. SCI constitute a preclinical stage of cerebrovascular disease and might precede both stroke and cognitive decline; therefore we think that their identification in hypertensive patients would be an appropriate and cost-efficient tool, to prevent further strokes and dementia.
Our current project will include a estimated sample size of 1000 hypertensive patients, with no known history of cerebrovascular disease or dementia. Silent Cerebral Infarctions (SCI) will be detected by MRI and the determination of several clinical and biological factors (plasma and genetic biomarkers) will be performed on baseline. The patients will be followed-up for at least 3 years, to assess the presence of incident strokes and/or cognitive impairment. This study will allow us to determine the largely unknown prevalence of silent cerebral infarctions in our setting. Also, the identification of SCI will help us to better define the risk stratification in hypertensive patients. Patients at higher risk will be our target population for the development of new preventive strategies based on the results of randomized clinical trials.
Finally, this project will be carried out thanks to the collaboration between Neurovascular Research Laboratory, Primary Care Physicians Services and Nephrology Department of Vall d'Hebron, among others, and will result in the improvement of the link between Primary Care Systems and the remaining hospitalary services, will favor the future of the preventive treatment and care of patients.

Cerebral Amyloid Angiopathy
Maria del Mar Hernández Guillamón, Mª Pilar Delgado Martínez and Mireia Parés Oliva
CURRENT PROJECT: Involment of proteolytic systems in the progression of Cerebral amyloid angiopathy (CAA) is produced by the accumulation of β-amyloid protein within the meningeal and brain vessels. It is the second leading cause of cerebral hemorrhages. However, nowadays, factors related to brain bleedings following amyloid deposition are largely unknown. The understanding of the molecular mechanisms that lead to cerebral hemorrhage may be the basis for future treatments. Previous evidences of our group have shown that Matrix Metalloproteinases (MMPs) are related to brain bleeding. Now, we aim to investigate the relationship between these proteolytic systems and the appearance of intracraneal hemorrages in CAA.
Our study includes:

- The identification of both tissue and plasma biomarkers for the diagnosis and prognosis of CAA-related hemorrhages.

- The search for the genetic markers related to proteolytic systems that could determine the risk of suffering a recurrence in CAA. We are studying a cohort of probable CAA patients that have been recruited in Hospital Vall d'Hebron in collaboration with the Stroke Project of the Cerebrovascular Diseases Study Group (Spanish Society of Neurology).

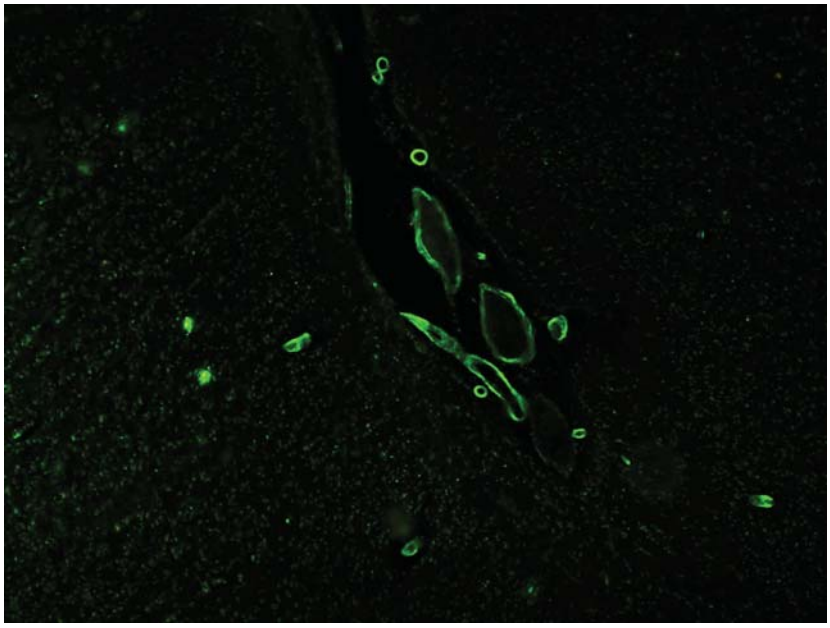

Figure 55
Thioflavin-S staining of fibillar β-amyloid within brain vessels of CAA patient's sections

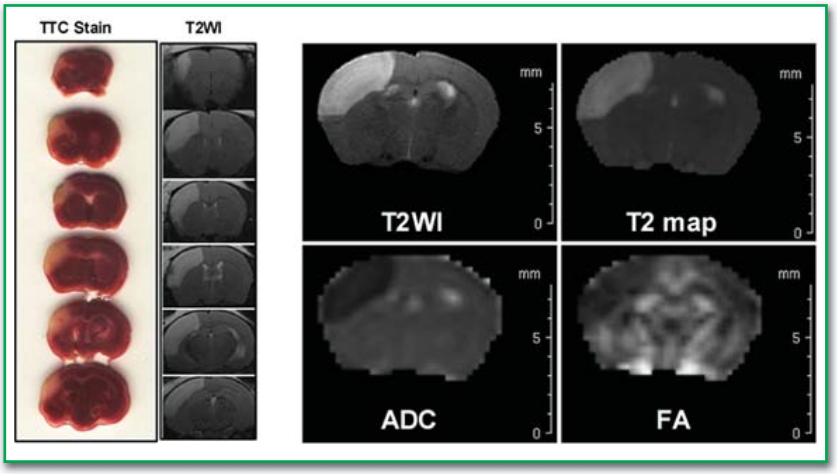

Figure 56
Global changes in brain gene expression (microarrays) after human intracerebral haemorrhage (ICH)

- The study of the role of MMPs in β-amyloid stimulated vascular cells in vitro. Cultured cells of the neurovascular unit are challenged with different β-amyloid peptides and the implication of MMPs in β-amyloid cleavage and cell toxicity are studied using cellular and molecular biology methodology. For this purpose, we use the human cerebral endothelial cell line hCMEC/D3, primary cultures of human leptomeningeal smooth muscle cells and rat/mouse glial and neuronal cultures. Thioflavin-S staining of fibillar β-amyloid within brain vessels of CAA patient's sections.

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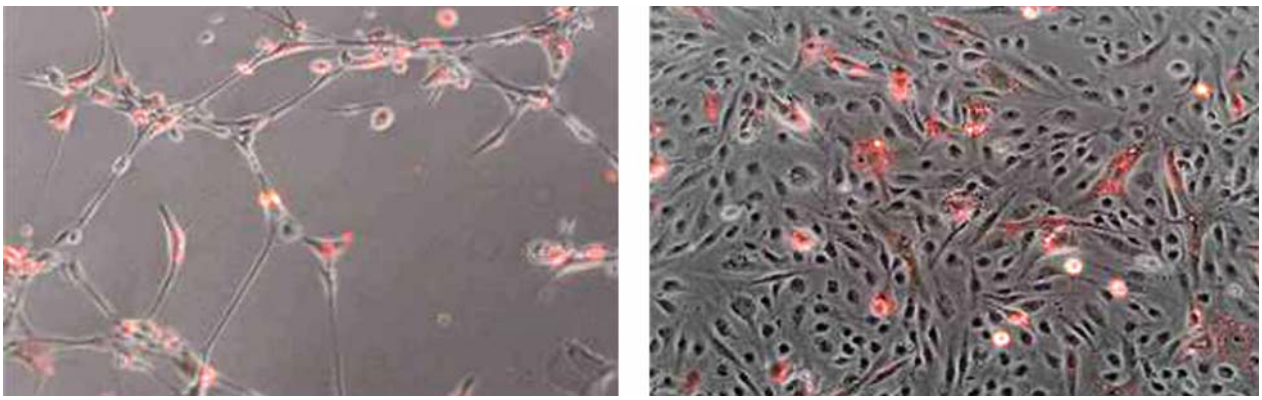


Figure 57
Left: In vitro angiogenesis of human EPCs (red) and mature endothelial cells (hCMEC/D3). Right: In vitro cell adhesion of human EPCs (red) on a mature endothelial cell layer

Collaborations:

- Mercè Boada, Fundació ACE, Barcelona, Spain (www.fundacioace.com).
- Jorge Ghiso and Agueda Rostagno, Pathology Dept. Langone Medical Center. New York University, New York, USA.
- Ignacio Romero, Life Science Dept. Open University. Milton Keynes, UK.

Neurorepair

Anna Rosell Novel, Miriam Navarro Sobrino, Anna Morancho Retana and Verònica Barceló Romero

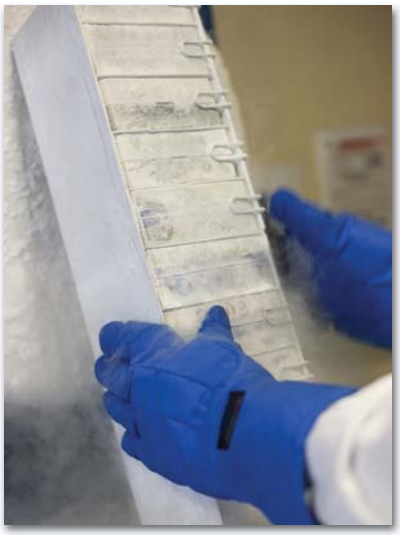
New therapies beyond the hyperacute phase of stroke are needed to be able to treat many more patients in delayed phases of this devastating disease. The idea that neurovascular plasticity contributes to stroke recovery is a powerful concept for stroke therapy. Obviously, the therapeutic time window for interventions based on promoting recovery would be much larger than those for targeting acute stroke. In this context, long-term neuroreparative therapies will have to target two essential phenomena to achieve brain neurorecovery after stroke: to restore the cerebral blood flow and to promote neuroregeneration. To achieve these major goals, both angiogenesis and neurogenesis need to be enhanced in the ischemic brain. Classically, the formation of new blood vessels was thought to be mediated exclusively by embryogenic vasculogenesis followed by the sprouting of endothelial cells from preexisting vessels during angiogenesis. In the last decade, this standard dogma was overturned with the identification of the existence of circulating bone marrow-derived endothelial progenitor cells (EPCs). These cells are capable of differentiating, ex vivo, into endothelial-phenotyped cells, and now comprise a new model for endothelial generation and vessel repair (Asahara *et al.*, 1997). These cells comprise a potential cell-based and growth-factor source of an alternate approach to enhance angio-neurogenic responses. In fact, newborn neurons (neurogenesis) and new vascular components (angiogenesis) form a microenvironment that has been termed the neurovascular niche [Ohab *et al.*, 2006] were angiogenesis and neurogenesis are linked thorough specific growth factors.

Angiogenesis and neurogenesis occur endogenously after stroke. Our goal is to study these two complex phenomena both in experimental and human studies to finally potentiate them correctly to improve brain function and neurorecovery after stroke.

Experimental Models and Techniques

In vivo stroke models: Cerebral ischemia affecting the cortical territory of the Middle Cerebral Artery (MCA) is occluded at the level of the M1 portion (distal occlusion). This model has been chosen because it presents very low mortality rates allowing long-term studies. Besides, the infarct is restricted to the cortex with clear boundary areas with normal cerebral blood flow and never affects neuroblast-rich areas such as the subventricular zone (then, both angiogenesis and neurogenesis can occur). Functional outcome is assessed by the cylinder and corner tests which have been reported to be appropriate tests for this type of cortical infarct. Additionally, histology and immunohistochemistry studies are conducted to evaluate brain repair and angio-neurogenic processes.

Endothelial Progenitor Cell Cultures: EPCs are obtained from the Mononuclear cell fraction of human blood and from mouse



spleen. MNCs are cultured in fibronectin-coated plates with complete cell culture medium EGM-2MV. Both human and murine cell cultures yield an early EPC population (also called *Circulating Angiogenic Cells*) obtained at day 4-7 after plating and late outgrowth. EPC colonies (also called *Endothelial Colony Forming Cells*) appear from day 10 as colonies with high proliferation capacity and tubulogenic capacity.

In vitro Oxygen-Glucose Deprivation: Endothelial cells and endothelial progenitor cells are challenged to a transitory oxygen and glucose deprivation to study their angio-vasculogenic responses to ischemia and to test how potential treatments that could modify these responses.

Angiogenesis-related techniques: Angio-vasculogenic mechanisms are studied in a variety of in vitro assays including Matrigel® tubulogenesis, cell migration using trans-well assays or cell adhesion to a mature monolayer of endothelial cells. Our studies focus on the angio-vasculogenic responses of both endothelial progenitor cells and mature endothelial cells such as the human cell line of microvascular endothelial cells (hCMEC/D3).

NMR Imaging: Bruker-BIOSPEC 70/30 USR, 7 T Preclinical MRI System is used for the neuroimaging studies. Neuroimaging studies are conducted in vivo to follow-up the ischemic lesion. Specific sequences are performed to assess axonal degeneration/regeneration and changes in cerebral blood flow and angiogenesis.

Neuroprotection

Lidia García Bonilla and Mireia Campos Martorell

BACKGROUND: The only approved stroke treatment so far is acute thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) when administered within 3-4.5 hours after onset of symptoms. However, a limited number of patients (5-8%) profit from this treatment, primarily because of the narrow therapeutic time-window and the risk of brain bleedings beyond thrombolytic therapy to achieve the recanalization of the occluded artery. Moreover, the inflammatory response that accompanies necrotic brain injury contributes to acutely aggravate the progression of ischemic pathology. Inflammatory and brain damaged cells release a variety of cytotoxic agents including cytokines, MMPs and ROS which induce more cell damage as well as disruption of BBB and brain edema. Therefore, it would be desirable to improve the efficacy and safety of thrombolytic therapy for stroke using combined anti-inflammatory strategies that may ameliorate the ischemic injury and means the best therapy translated at the clinical level. Our research, conducted on experimental models of cerebral ischemia, is focused on the development of neuroprotective strategies aimed to salvage ischemic brain tissue by means complementary to reperfusion. Our goal is to find a multimodal treatment that combines the administration of tPA together with other co-agents (as simvastatin and/or anti-aggregants with anti-inflammatory and neuro-protective properties) in an attempt to obtain the most therapeutic benefit in the acute phase of ischemic stroke.

EXPERIMENTAL MODELS AND TECHNIQUES: Ischemic stroke has a complex pathophysiology involving the interplay of many different cells and tissues. Animal models of ischemic stroke are procedures inducing cerebral ischemia, which satisfactorily mimic this cerebrovascular disease. Therefore, stroke research conducted on animal models has been shown to be essential for the treatment approach of ischemic stroke.

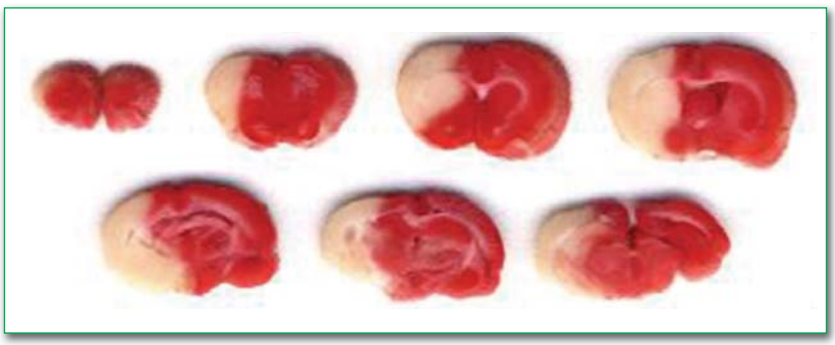


Figure 58
Image of TTC staining on rat brain slices that show infarction in MCA-supplied lateral cortex and striatum territories after induction of focal cerebral ischemia

Intra-arterial Suture Occlusion Model of Focal Cerebral Ischemia. Infarction in the territory of the middle cerebral artery (MCA) is induced by extracranial vascular occlusion in rats. A heat-blunted 4/0 nylon-monofilament is used to block the origin of MCA during 90 or 120 min and then, the monofilament is removed and reperfusion is allowed during the followed 24, 48 or 72 h. This model mimics a clinical situation where recanalization of the occluded artery takes place, allowing test neuroprotectants that could potentially be co-administered with reperfusion agents like tPA.

Embolic Model of Focal Cerebral Ischemia. There is great clinical scientific interest in the animal stroke model by clot embolism due to the high incidence of human thrombotic stroke and the use of reperfusion therapy with tPA, which can be assayed on this model. Thromboembolic occlusion at the proximal level of MCA is achieved by injection of a rich fibrin clot through the internal carotid artery in the rat. Clots were previously performed using arterial blood from a donor rat. Thrombolytic therapy with tPA (9 mg/kg) is administered by tail vein infusion (2 mg/mL; 75 ?L/min) at different times points (2, 3, 4 hours) after occlusion. Relative Cerebral Blood Flow (rCBF) is measured in the cortex supplied by the MCA by continuous Laser Doppler flowmetry (LDF) to ensure the success of the artery occlusion or reperfusion in these models. To examine the grade of infarction on rats, analysis of the infarct volume is evaluated using 2,3,5-triphenyltetrazolium chloride (TTC) staining and the neurological score is assayed with a 9-point neurological at baseline (1-2 h) and each 24 h after occlusion. NMR ImagingBruker-BIOSPEC 70/30 USR, 7 T Preclinical MRI System is used for neuroimaging studies. Neuroimaging studies are conducted in vivo to evaluate the

cytotoxic edema and ischemic lesion (DWI, ADC map and T2WI) in the acute phase. Specific sequences are performed to assess Brain-Blood Barrier disruption (DCE) and occurrences of intracranial hemorrhages (T2*WI). Angiography is performed to document MCA occlusion or recanalization.

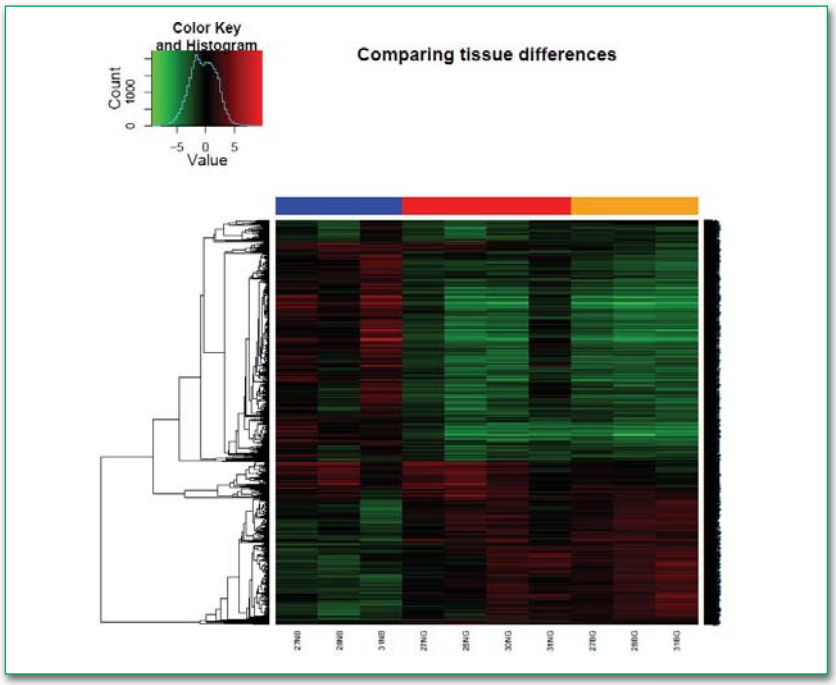


Figure 59
Experimental model of distal Middle Cerebral Artery occlusion in mice showing histological (TTC) and neuroimaging (MRI) correspondence of the obtained cortical brain infarction

Genetics

Israel Fernández Cadenas, Maite Mendioroz Iriarte, Sophie Domingues and Alberto del Río Espinola

Neurovascular Genetics is an important part of the research of our Laboratory.

FIRSTLY, we are participating in the first pharmacogenomic study in patients treated with tPA, the Geno-tPA project. In this project, we work on polymorphisms in genes related to biological processes such as inflammation, proteolysis and hemostasis, which are capable of modifying the response to thrombolysis treatment. The goal is to analyze about 200 polymorphisms in 540 patients. More than 13 mutations have already been studied and more than 6 articles have been published in international journals, showing, for example, for the first time the risk of suffering hemorrhagic complications. Recanalization rates after treatment are determined genetically through genes such as the factor XIII (PMID: 16857944), the Angiotensin Converting Enzyme (PMID: 16442232) and the Thrombin-activatable fibrinolysis inhibitor (PMID: 17723126).

SECONDLY, the *GRECOS project* (Genotyping RECurrence Of Stroke) is a genetic ongoing multi-center prospective longitudinal cohort study whose primary objective is to identify the genetic markers that determine the risk of suffering a stroke recurrence. The recruiting process started in February 2007, and the final cohort is composed of about 1800 patients who suffered a first episode of ischemic or hemorrhagic stroke, with a follow up of three years. In this group of patients, we have analyzed about 200 polymorphisms in candidate genes related to inflammation, hemostasis, apoptosis, angiogenesis, proteolisis, and other processes. The genotyping was performed through the SNPlex platform of the National Centre of Genotyping (http://www.cegen.org) and at present we are replicating the results in a new cohort.

THIRDLY, the *CONIC project* is a case-control study which attempts to determine the genetic risk factors associated with stroke. Two different groups of persons will be recruited and various biological samples will be extracted, such as DNA, RNA, plasma and serum, as well as routine information. The first group, the "cases" will be composed of patients from the Geno-tPA study and have suffered an ischemic stroke. The second group, the "controls" will be formed by 540 healthy persons free of vascular disease. 200 polymorphisms have been analyzed and differences between the case and control groups have been studied. This will lead to the identification of genes and genetic variants (polymorphisms but also haplotypes or copy number variants) implicated in stroke disease. Moreover, functional studies will be performed to determine the exact contribution of each variant described at the biological level.

FOURTHLY, we are performing the first Genome Wide Analysis in Spanish stroke samples, identifying up to 1 million SNPs in 240 patients. The project, called *project GRECAS,* is in the genotyping process and we will have the results next year. In addition a new GWAs has been funded by the Spanish government called *GWAs Geno*

tPA. Apart from these studies, our group offers a service of Neurovacular Genetic Consultation by a neurologist. This consultation aims to specifically diagnose patients (and their families) with cerebrovascular diseases of genetic origin. Special attention will be dedicated to diseases such as Fabry's disease, CADASIL, CARASIL, Rendu-Osler, but we also regularly attend patients with any suspicion of genetic and hereditary cerebrovascular disease. From this consultation, we recently published the first case of CARASIL syndrome in a Caucasian population demonstrating that this disease is common and not restricted to the Asian population.

SERVICES OFFERED BY OUR GENETIC DEPARTMENT. We offer consultation by a specialized neurologist and genetic diagnosis of CADASIL: Exons 3 y 4: 365 Euros - Time necessary: about 3 weeks.
Complete gene: 1,177 Euros - Time necessary: about 2 months (Prices obtained from the Diario Oficial de Galícia Nº141 21 julio 2006, Anexo V).
The Neurovascular Research Laboratory actively collaborates with two consortia: The IGSC (International Genetic Stroke Consortium), a consortium that joins the most remarkable international groups working in the genetic component of stroke. The other one is the GeneStroke consortium (www.genestroke.com), a national consortium in which we are the coordinators. The aim of this consortium is collaboration among different centers, and to perform genome-Wide Analysis in the Spanish population.

CURRENT RESEARCH PROJECTS

PI: Joan Montaner Villalonga
GRECOS Project: Genotyping Recurrence risk of Stroke
Funding Agency: Fundació La Marató de TV3
Reference: TV3/062610
Funding: 198,662 €
Duration: 2007 to 2010

PI: José Álvarez Sabín
Influencia de las células endoteliales progenitoras sobre la modulación espacio-temporal de la angiogénesis y la vasculogénesis tras el ictus isquémico humano
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060471
Funding: 240,185 €
Duration: 2007 to 2010

PI: Marc Ribó Jacobi
Búsqueda de patrones genéticos predictivos de la evolución del paciente con ictus isquémico después del tratamiento con tPA
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060586
Funding: 211,145 €
Duration: 2007 to 2010

PI: Joan Montaner Villalonga
Geno-tPA: búsqueda de patrones genéticos predictivos de la evolución del paciente con ictus isquémico después del tratamiento con tPA
Funding Agency: Fundación Ramón Areces
Reference: ARECES/1/2006
Funding: 110,000 €
Duration: 2007 to 2010

PI: Joan Montaner Villalonga
Estrategias para mejorar la eficacia y seguridad del tratamiento con simvastatina en la fase aguda del ictus isquémico: STARS trial
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90195
Funding: 175,450 €
Duration: 2007 to 2011

PI: Joan Montaner Villalonga
European Stroke Research Network (EUSTROKE) Grant Agreement No 202213Health-F2-2008-202213
Funding Agency: European Commission
Reference: EUSTROKE-202213
Funding: 463,200 €
Duration: 2008 to 2013

PI: Joan Montaner Villalonga
Identificación y uso de biomarcadores pronósticos en el ictus isquémico
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080361
Funding: 228,690 €
Duration: 2009 to 2011

PI: Maria Mar Hernández Guillamón
Beneficio de la simvastatina en el tratamiento trombólico combinado del ictus en modelos de isquemia cerebral en rata
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080481
Funding: 126,687 €
Duration: 2009 to 2011

PI: Joan Montaner Villalonga
GRECAS: genotipando el riesgo y eficacia de clopidogrel o aspirina tras el ictus; hacia una prevención secundaria personalizada
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00137
Funding: 289,190 €
Duration: 2009 to 2011

PI: Joan Montaner Villalonga
European Stroke Research Network
Funding Agency: Ministerio de Ciencia e Innovación
Reference: EUS2008-03610
Funding: 97,000 €
Duration:2009 to 2013

PI: Marc Ribó Jacobi
Neuroprotección mediante sistema de "perfusión artificial" de la penumbra isquémica con sangre arterial oxigenada
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01660
Funding: 77,440 €
Duration: 2010 to 2012

PI: Joan Montaner Villalonga
Fomento de la equidad de género en la atención al ictus
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/90401
Funding: 24,200 €
Duration: 2010 to 2011

PI: María Pilar Delgado Martínez
Silent clinical infarction detection and biomarkers associated with the risk of stroke in the hypertensive Spanish population
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP09/00136
Funding: 44,400 €
Duration: 2010 to 2012

PI: Anna Rosell Novel
Neurorepair Treatments for Cerebral Ischemia using Endothelial Progenitor Cells (EPCs)
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP09/00265
Funding: 45,000 €
Duration: 2010 to 2012

PI: Joan Montaner Villalonga
RENEVAS - Red de Investigación Cooperativa Neurovascular
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0026/0010
Funding: 719,909.78 €
Duration: 2007 to 2011

PI: Joan Montaner Villalonga
Grup de Recerca en Malalties Neurovasculars
Funding Agency: AGAUR
Reference: 2009 SGR 432
Funding: 46,800 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 192.676)

Alexandrov AV, Tsivgoulis G, Rubiera M, Vadikolias K, Stamboulis E, Molina CA, Alexandrov AW. End-Diastolic Velocity Increase Predicts Recanalization and Neurological Improvement in Patients With Ischemic Stroke With Proximal Arterial Occlusions Receiving Reperfusion Therapies. *Stroke* 2010 May; 41 (5): 948-52. ➲ IF: 7.041.

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Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt H, Jiménez-Conde J, Hansen BM, Fernández-Cadenas I, Cortellini L, Ayres A, Schwab K, Juchniewicz K, Montaner J, *et al.* Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. *Ann Neurol* 2010 Dec; 68 (6): 934-43. ➲ IF: 9.317.

Blanco M, Sobrino T, Montaner J, Medrano V, Jiménez C, Masjuan J, Gómez-Escalonilla C, Luis P de, Arboix A, Castillo J, Blanco M, Castillo J, Álvarez-Sabín J, *et al.* Stroke with polyvascular atherothrombotic disease. *Atherosclerosis* 2010 Feb; 208 (2): 587-92. ➲ IF: 4.522.

Cuadrado E, Rosell A, Colomé N, Hernández-Guillamón M , García-Berrocoso T, Ribó M, Alcázar A, Ortega-Aznar A, Salinas M, Canals F, Montaner J. The Proteome of Human Brain After Ischemic Stroke. *J Neuropathol Exp Neurol* 2010 Nov; 69 (11): 1105-15. ➲ IF: 4.564.

Domingues-Montanari, Fernández-Cadenas I, Río-Espinola A del, Corbeto N, Krug T, Manso H, Gouveia L, Sobral J, Mendioroz M, Fernández-Morales J, Álvarez-Sabín J, Ribó M, Rubiera M, Obach V, Martí-Fábregas J, Freijo M, Serena J, Ferro JM, Vicente AM, Oliveira SA, Montaner J. Association of a Genetic Variant in the ALOX5AP with Higher Risk of Ischemic Stroke: A Case-Control, Meta-Analysis and Functional Study. *Cerebrovasc Dis* 2010 Mar 30; 29 (6): 528-537. ➲ IF: 3.535.

Domingues-Montanari, Fernández-Cadenas I, Río-Espinola A del, Mendioroz M, Fernández-Morales J, Corbeto N, Delgado P, Ribó M, Rubiera M, Obach V, Martí-Fábregas J, Freijo M, Serena J, Montaner J. KCNK17 genetic variants in ischemic stroke. *Atherosclerosis* 2010 Jan; 208 (1): 203-9. ➲ IF: 4.522.

Domingues-Montanari, Fernández-Cadenas I, Río-Espinola A del, Mendioroz M, Ribó M, Obach V, Martí-Fábregas J, Freijo M, Serena J, Corbeto N, Chacón P, Álvarez-Sabín J, Montaner J. The I/D polymorphism of the ACE1 gene is not associated with ischaemic stroke in Spanish individuals. *Eur J Neurol* 2010 Nov; 17 (11): 1390-2. ➲ IF: 2.510.

Domínguez C, Delgado P, Vilches A, Martín-Gallán P, Ribó M, Santamarina E, Molina C, Corbeto N, Rodríguez-Sureda V, Rosell A, Álvarez-Sabín J, Montaner J. Oxidative Stress After Thrombolysis-Induced Reperfusion in Human Stroke. *Stroke* 2010 Apr; 41 (4): 653-60. ➲ IF: 7.041.

Fernández-Cadenas I, Río-Espinola A del, Rubiera M, Mendioroz M, Domingues-Montanari, Cuadrado E, Hernández-Guillamón M, Rosell A, Ribó M, Álvarez-Sabín J, Molina CA, Montaner J. PAI-1 4G/5G polymorphism is associated with brain vessel reocclusion after successful fibrinolytic therapy in ischemic stroke patients. *Int J Neurosci* 2010 Apr; 120 (4): 245-51. ➲ IF: 0.855.

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Hernández-Guillamón M, García-Bonilla L, Solé M, Sosti V, Parés M, Campos M, Ortega-Aznar A, Domínguez C, Rubiera M, Ribó M, Quintana M, Molina CA, Álvarez-Sabín J, Rosell A, Unzeta M, Montaner J. Plasma VAP-1/SSAO Activity Predicts Intracranial Hemorrhages and Adverse Neurological Outcome After Tissue Plasminogen Activator Treatment in Stroke. *Stroke* 2010 Jul; 41 (7): 1528-35. ➲ IF: 7.041.

Hernández-Guillamón M, Mawhirt S, Fossati S, Blais S, Parés M, Penalba A, Boada M, Couraud PO, Neubert TA, Montaner J, Ghiso J, Rostagno A. Matrix metalloproteinase 2 (MMP-2) degrades soluble vasculotropic amyloid-beta E22Q and L34V mutants delaying their toxicity for human brain microvascular endothelial cells. *J Biol Chem* 2010 Aug 27; 285 (35): 27144-58. ➲ IF: 5.328.

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Lees KR, Bluhmki E, Kummer R von, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, Allen K, Álvarez-Sabín J, Molina C, *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010 May 15; 375 (9727): 1695-703. ➲ IF: 30.758.

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Mikulik R, Dusek L, Hill MD, Fulep E, Grotta JC, Ribó M, Molina C, Alexandrov AV. Pattern of Response of National Institutes of Health Stroke Scale Components to Early Recanalization in the CLOTBUST Trial. *Stroke* 2010 Mar; 41 (3): 466-70. ➲ IF: 7.041.

Molina CA. Futile Recanalization in Mechanical Embolectomy Trials. A Call to Improve Selection of Patients for Revascularization. *Stroke* 2010 May; 41 (5): 842-3. ➲ IF: 7.041.

Molina CA, Selim MH. General or Local Anesthesia During Endovascular Procedures. Sailing Quiet in the Darkness or Fast Under a Daylight Storm. *Stroke* 2010 Nov; 41 (11): 2720-1. ➲ IF: 7.041.

Morancho A, Rosell A, García-Bonilla L, Montaner J. Metalloproteinase and stroke infarct size: role for anti-inflammatory treatment? *Ann N Y Acad Sci* 2010 Oct; 1207: 123-33. doi: 10.1111/j.1749-6632.2010.05734.x. ➲ IF: 2.670.

Navarro-Sobrino M, Rosell A, Hernández-Guillamón M, Penalba A, Ribó M, Álvarez-Sabín J, Montaner J. Mobilization, endothelial differentiation and functional capacity of endothelial progenitor cells after ischemic stroke. *Microvasc Res* 2010 Dec; 80 (3): 317-23. ➲ IF: 3.075.

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Ribó M, Rubiera M, Pagola J, Rodríguez Luna D, Meler P, Flores A, Álvarez Sabín J, Molina CA. Bringing Forward Reperfusion with Oxygenated Blood Perfusion beyond Arterial Occlusion during Endovascular Procedures in Patients with Acute Ischemic Stroke. *AJNR Am J Neuroradiol* 2010 Nov; 31 (10): 1899-902. ➲ IF: 3.296.

Río Espinola A del, Fernández Cadenas I, Mendioroz M, Gutiérrez Agullo M, Fernández MT, Fernández Morales J, Maisterra O, Domingues Montanari S, García Patos V, Solé E, Montaner J. Novel human pathological mutations. Gene symbol: NOTCH3. Disease: CADASIL. *Hum Genet* 2010 Apr; 127 (4): 474. ➲ IF: 4.523.

Río Espinola A del, Solé E, Montaner J. Pathophysiology of CADASIL disease. *Med Clin (Barc)* 2010 Jul 10; 135 (5): 222-30. ➲ IF: 1.231.

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AREA 4 NEUROSCIENCES

4.10 Pediatric Neurology

Group Leader
Alfons Macaya Ruiz
Tel. 93 489 43 34
alfons.macaya@vhir.org

Researchers
Susana Boronat Guerrero
Daniel Carranza Rojo
Alfons Macaya Ruiz
Solange Miguel Queralt
Francina Munell Casadesús
Miquel Raspall Chaure
Manuel Roig Quilis
Mireia del Toro Riera

Researchers in Training
Alba Berlanga Bustos
Ingrid Figueras León
Marina Flotats Bastardas
Iris García Martínez
Laura Monlleó Neila
Aintzane Urbizu Serrano
Maria Àngels Vidal Jorge
Marta Vila Pueyo

Technician
Marta Rebull Santamaria

OBJECTIVES

The Pediatric Neurology Research group is mainly involved in the study of genetic diseases of the developing nervous system. The main emphasis is on paroxysmal neurological disorders and neuromuscular disorders. A common theme across the different projects, besides the identification of the molecular basis of several of these rare disorders, is the investigation of molecules involved in their pathophysiological mechanisms and the effective translation of these findings into the fields of molecular diagnosis, genetic counselling and newly developed gene or drug therapies.

2010 Impact Factor:
24.345

RESEARCH LINES

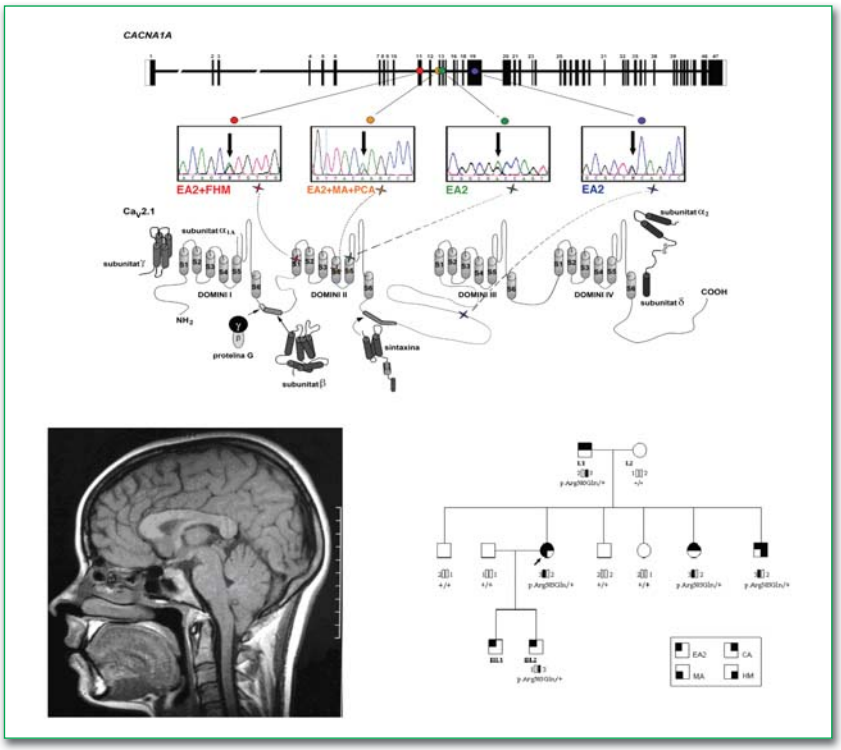
Pediatric neurogenetics

Alfons Macaya Ruiz

Neurogenetics of paroxysmal neurological disorders (neuronal channelopathies). Genetic and epigenetic basis of neural tube defects and Chiari type I malformation. Clinical researchers have collected samples from more than 2000 patients with paroxysmal neurological disorders (migraine, epilepsy, paroxysmal movement disorders and episodic ataxias) and over 300 patients with Chiari I malformation. Current strategies include whole-genome linkage analysis, exome sequencing, customized array re-sequencing, SNP-based genetic association studies and expression analysis in fetal tissues. The goals in this area are:

- To identify novel genetic variants responsible for these diseases.
- To establish a correlation between the genetic variants and the clinical forms of the disease.
- To perform functional studies of the mutant proteins.
- To design an animal model of cortical spreading depression, with emphasis on epigenetic modification of susceptibility genes.

Figure 60
Top: identified mutations in the CACNA1A gene, encoding the alpha subunit of the CaV2.1 neuronal channel, associated with various pediatric paroxysmal neurological phenotypes. Bottom, left: MRI scan of a patient with Chiari I malformation. Bottom, right: a pedigree segregating the CACNA1A p.Arg583Gln mutation with variable clinical expressivity: EA2= Episodic ataxia type 2; CA= cerebellar atrophy, MA= migraine with aura; HM= hemiplegic migraine.
Solid symbols denote D19S1150 allele co-seggregating with the disease phenotypes



Neuromuscular disorders
Francina Munell Casadesús
The main goal is the development of novel approaches and models for the study of genetic neuromuscular disorders. Our main objectives are:

- To identify the molecular pathways involved in skeletal muscle regeneration.
- To identify potential therapeutic targets to improve skeletal muscle regeneration in muscular dystrophies.
- To study the role of steroid hormones and their receptors in myogenesis.
- To identify the molecular pathways involved in the pathogenesis of spinal muscular atrophy (in spinal cord and skeletal muscle).
- To design an exon-array to identify mutations in patients with neuromuscular disorders of unknown etiology by massive sequencing.

CURRENT RESEARCH PROJECTS

PI: Alfons Macaya Ruiz
Genetic basis of Chiari type I malformation
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3_062710
Funding: 194,125 €
Duration: 2007 to 2011

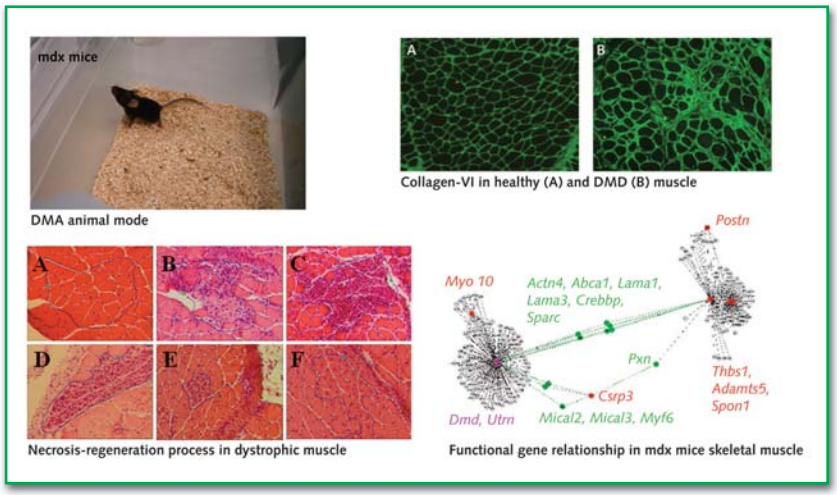
PI: Manuel Roig Quilis
Papel del TGFβ en la progresión de la distrofia muscular de Duchenne
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061164
Funding: 98,010 €
Duration: 2007 to 2010

PI: Alfons Macaya Ruiz
Bases genéticas de la malformación de Chiari tipo I
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061606
Funding: 84,216 €
Duration: 2007 to 2010

PI: Manuel Roig Quilis
Defining targets for therapeutics in Spinal Muscular Atrophy. GENAME Project
Funding Agency: Fundación Genoma España
Reference: GENAME
Funding: 168,800 €
Duration: 2007 to 2010

PI: Mireia del Toro Riera
Estudio del metabolismo de la glucosa y el glucógeno en células musculares en cultivo y fibroblastos de paciente afecto de la forma infantil de la enfermedad de Pome y controles sanos
Funding Agency: Fundación Genzyme
Reference: FEEL2008/01
Funding: 10,000 €
Duration: 2009 to 2011

Figure 61
- Anticlockwise: The mdx mouse, a commonly used model for the study of dystrophin deficiency.
- H&E staining depicting muscle necrosis-regeneration.
- Immunohistochemical analysis of extracellular proteins in human myoblasts from a DMD patient.
- Functional interaction of genes differentially expressed in dystrophic muscle along the disease course



PI: Alfons Macaya Ruiz
Genes y migraña: clonaje posicional en migraña familiar y expresión en la depresión cortical propagada experimental
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2009-13182-C03-03
Funding: 90,750.02 €
Duration: 2010 to 2012

PI: Francina Munell Casadesús
Acciones de los receptores de andrógenos y estrógenos en la diferenciación miogénica y su modulación como estrategia terapéutica para revertir la diferenciación anómala del músculo deficiente en distrofia
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00097
Funding: 154,275 €
Duration: 2010 to 2012

PI: Alfons Macaya Ruiz
Grup de Recerca en Neurologia Infantil HUVH
Funding Agency: AGAUR
Reference: 2009 SGR 78
Funding: 41,600 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 24.345)

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Burton BK, Guffon N, Roberts J, Ploeg AT van der, Jones SA, Toro M del, *et al.* Home treatment with intravenous enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II - data from the Hunter Outcome Survey. *Mol Genet Metab* 2010 Oct-Nov; 101 (2-3): 123-9. ➲ IF: 2.897.

Corominas R, Sobrido MJ, Ribases M, Cuenca-León E, Blanco-Arias P, Narberhaus B, Roig M, Leira R, López-González J, Macaya A, Cormand B. Association study of the serotoninergic system in migraine in the Spanish population. *Am J Med Genet B Neuropsychiatr Genet* 2010 Jan 5; 153B (1): 177-84. ➲ IF: 3.481.

Couce ML, Aldamiz-Echevarría L, Baldellou A, Blasco J, Bueno MA, Dalmau J, Vega A de la, Toro M del, Díaz C, Lama R, Leao E, Marrero M, Navas VM, Pintos G. Recommendations and management of Type I hereditary or hepatorenal Tyrosinemia. *An Pediatr (Barc)* 2010 Nov; 73 (5): 279.e1-4. ➲ IF: 0.363.

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Urbizu A, Cuenca-León E, Raspall-Chaure M, Gratacòs M, Conill J, Redecillas S, Roig-Quilis M, Macaya A. Paroxysmal exercise-induced dyskinesia, writer's cramp, migraine with aura and absence epilepsy in twin brothers with a novel SLC2A1 missense mutation. *J Neurol Sci* 2010 Aug 15; 295 (1-2): 110-3. ➲ IF: 2.324.

AREA 4 NEUROSCIENCES

4.11 Peripheral Nervous System

Group Leader
José Gámez Carbonell
Tel. 93 274 65 96
jgamez@vhebron.net

Researcher
José Gámez Carbonell

Nursing, Technical and Administrative Staff
Ma. Mercè Badía Canto

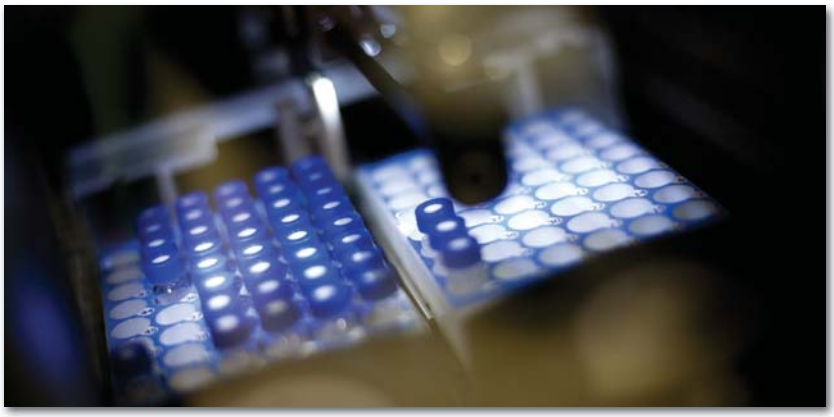
OBJECTIVES

Our laboratory, in the Neuromuscular Disorders Unit of the Neurology Department, has a twenty-year history of providing clinical care and research in amyotrophic lateral sclerosis (ALS) and other motor neuron diseases (hereditary spastic paraplegias, postpolio syndrome, Hirayama's disease, spinal muscular atrophies), myasthenia gravis, genetically determined myopathies, and peripheral neuropathies.

We believe that some ALS cases may be due to missing or surplus genetic information in the chromosomes, which are the structures in each cell that package an individual's genetic information. Our research aims to ascertain the specific genes involved in ALS, and the contribution of DNA rearrangements in causing the disease. As a result, our main research lines are Molecular Mechanisms of ALS, and Genetic Mutations in Familial ALS, including predisposing or modifying gene factors. Despite the fact that several major genes are known to cause ALS, the precise connection between mutant proteins and their pathological pathways is uncertain. We are currently investigating the role of signalling genes in the pathogenesis of familial and sporadic forms of ALS. Our work also involves searching for effective biomarkers in blood and CSF which enable assessment of new candidate drugs for treatment of this devastating disease. The success of translational medicine depends on the results in animal models, and biomarkers of the disease's progression are therefore important tools for new therapies in humans.

Our research is also currently focused on myasthenia gravis, myopathies and peripheral neuropathies in order to achieve a better understanding of the clinical, genetic and pathological correlations of these diseases.

2010 Impact Factor:
13.476



RESEARCH LINES

Molecular Mechanisms of ALS

Genetic Mutations in Familial ALS

PUBLICATIONS
(Impact Factor: 13.476)

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Gámez J, Carmona F, Raguer N, Ferrer-Sancho J, Martín-Henao GA, Martí-Beltrán S, Badía M, Gratacós M, Rodríguez-González E, Seoane JL, Pallero-Castillo M, Burgos R, Puiggros C, Pasarín A, Bori-Fortuny I. Cellular transplants in amyotrophic lateral sclerosis patients: an observational study. *Cytotherapy* 2010 Sep; 12 (5): 669-77. ➲ IF: 2.204.

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AREA 4 NEUROSCIENCES

4.12 Psychiatry and Mental Health

Group Leader
Miquel Casas Brugué
Tel. 93 489 42 94
mcasas@vhebron.net

Researchers
Marisol Ampudia Rodríguez
Óscar Andión Pérez
José María Argüello Alonso
M Carmen Barral Picado
Nuria Bassas Bolivar
Miquel Jordi Bel Aguado
Ana Bielsa Carrafa
Rosa Maria Bosch Munsó
Mª Dolores Braquehais Conesa
Eugeni Bruguera Cortada
Natalia Calvo Piñero
Miquel Casas Brugué
Francisco Collazos Sánchez
Marina Comín Zafón
Margarita Corominas Roso
Montserrat Corrales de la Cruz
Joan Creixell Sureda
Constanza Daigre Blanco
Francisco Javier Eiroa Orosa
Sara Guila Fidel Kinori
Gideoni Fusté Coetzee
Beatriz Gancedo Villegas
Javier Agustín Gastaminza Pérez
Andrea di Genova
Begoña P Gonzalvo Cirac
Lara Grau López
Carlos Jacas Escarcellé
Pilar Lusilla Palacios
Nieves Gu Martinez Luna
Laia Miquel de Montagut
José Eduardo Montejo Celis
Mariana I Morais Nogueira
José Antonio Navarro Sanchís
Gemma Nieva Rifa
Gemma Parramón Puig
Marta Quesada Franco
Adil Qureshi
José Antonio Ramos Quiroga
Marta Ribases Haro
Vanesa Richarte Fernández
Amanda Rodríguez Urrutia
Carlos Roncero Alonso
Xavier Salas Puig
Sergi Valero Ventura

Researchers in Training
Xavier Castells Cervelló
Albert de Bonis Freixes
Hilda Wara Revollo Escudero
María Victoria Trasovares Navarrete

Nursing, Technical and Administrative Staff
Olga Corcoles Verdejo
Maria Emilia Dip Pérez
Gemma Escuder Romeva
Esther García Giménez
Anna Giannoni Pastor
Victoria López Craver
María Cecilia Navarro Marfisis
María Begoña Olivares Mariscal
Cristina P Sánchez Mora
Yolanda Santaella Andres
Ruth Tasqué Cebrián
Yemima Villegas Urbina

OBJECTIVES

Consolidating Clinical Research Programs already started, emphasizing the interaction of various diseases and research of genetic-based common etiopathogenic mechanisms.

RESEARCH LINES

Trimorbility: TDAH, TLP and Addictions
Miquel Casas Brugué

Obsessive - compulsive disorders
Miquel Casas Brugué

Disorder and Attention Deficit Hyperactivity Disorder in adults (ADHD)
José Antonio Ramos Quiroga

Borderline Personality Disorders (BPD)
Marc Ferrer Vinardel

Tabagism
Eugeni Bruguera Cortada

Dual Pathology
Carlos Roncero Alonso

Transcultural Psychiatry
Francisco Collazos Sánchez

Interconsultation Psychiatry in general Hospitals and Liaison Psychiatry
Gemma Parramón Puig

Interconsultation Psychiatry in children's Hospitals and Liaison Psychiatry
Javier Agustín Gastaminza Pérez

Sexual Dysfunctions
José Antonio Navarro Sanchís

Chronic Fatigue
Naia Saez Francàs

Suicide
Marta Quesada Franco

Post-Traumatic Stress Disorder
José María Argüello Alonso

Gender Abuse
Joan Creixell Sureda

Psychiatric Genetics
Marta Ribases Haro

Developmental Disorders
Ana Bielsa Carrafa

Obsessive - compulsive disorder in Children and Young People
Nuria Bassas Bolivar

2010 Impact Factor:
106.222

CURRENT RESEARCH PROJECTS

PI: Miquel Casas Brugué
Estudio de la eficacia de la cafeína en el tratamiento de mantenimiento de pacientes con dependencia de cocaína
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90713
Funding: 119,548 €
Duration: 2007 to 2012

PI: Marta Ribases Haro
Genetic susceptibility factors in attention-deficit/hyperactivity disorder (ADHD): a two stage genome-wide association study
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3/2009/01
Funding: 149,712.50 €
Duration: 2010 to 2012

PI: Marta Ribases Haro
Genetic susceptibility factors in Attention-Deficit/Hiperactivity Disorder (ADHD)
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP09/00119
Funding: 44,700 €
Duration: 2010 to 2012

PI: José Antonio Ramos Quiroga
Estudio farmacogenético con metilfenidato en niños con trastorno por déficit de atención con hiperactividad
Funding Agency: Fundación Alicia Koplowitz
Reference: FAK-2010-04
Funding: 75,000 €
Duration: 2010 to 2012

PI: Sara Guila Fidel Kinori

Protección de la confidencialidad en las historias clínicas informatizadas: los pacientes en la consulta de Salud Mental hospitalaria

Funding Agency: Fundació Víctor Grífols i Lucas
Reference: VGL-2010-01
Funding: 5,000 €
Duration: 2010 to 2011

PUBLICATIONS (Impact Factor: 106.222)

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Braquehais MD, Sher L. Posttraumatic stress disorder in war veterans: a discussion of the Neuroevolutionary Time-depth Principle. *J Affect Disord* 2010 Sep; 125 (1-3): 1-9. ➲ IF: 3.763.

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AREA 5 DIGESTIVE PHYSIOPATHOLOGY AND HEPATOLOGY

5.1 Digestive Transplants

Group Leader
Ramon Charco Torra
Tel. 93 274 61 13
rcharco@vhebron.net

Researchers
Joaquín Balsells Valls
Itxarone Izaskun Bilbao Aguirre
Laia Blanco Cuso
Francisco Javier Bueno Recio
Mieria Caralt Barba
Ramon Charco Torra
Cristina Dopazo Taboada
Francisco José Espín Álvarez
José Luis Lázaro Fernández
Javier Naval Álvaro
Roberto Rodríguez Revuelto
Gonzalo Sapisochin Cantis

OBJECTIVES

- Clinical studies on immunosuppression in human liver transplantation.
- Experimental research in minimally invasive surgery through naturals orifices or NOTES together with Dr. J.R. Armengol Miró from Endoscopy Service.
- Experimental research in hepatic surgery.
- Clinical research in hepatic and bile-pancreatic surgery.
- Clinical research in intestinal transplantation.
- Clinical research in partial hepatic transplantation (Vivo donations and/or split).

RESEARCH LINES

Morbidity and quality of life after liver transplantation
Itxarone Izaskun Bilbao Aguirre, Javier Bueno Recio and Cristina Dopazo Taboada
Risk factors of early and late morbimortality after liver transplantation in adults and children.

Treatment of hepatocellular carcinoma
Ramon Charco Torra, Gonzalo Sapisochin Cantis, Joaquin Balsells Valls and Lluís Castells Fusté
Management of different treatments for hepatocarcinoma using resection, transplantation, percutaneous methods, chemoembolization and chemotherapy.

2010 Impact Factor:
18.298

Treatment of liver metastases of colorectal cancer
Ramon Charco Torra, José Luis Lázaro Fernández, Cristina Dopazo Taboada, Gonzalo Sapisochin Cantis and Josep Tabernero Caturla
New surgical techniques and chemotherapy treatments.

Technical advances in hepatobiliopancreatic surgery and transplantation
Joaquín Balsells Valls, José Luis Lázaro Fernández and Ramon Charco Torra
Evaluating new technologies: laparoscopy, robotics and image processing.

Pancreatic function after pancreatectomy
Joaquin Balsells Valls and Javier Naval Álvaro
Evaluating antibiotic elimination by pancreatic liquid.

Advances in staging of pancreatic cancer
Joaquin Balsells Valls and Javier Naval Álvaro
Studying sentinel ganglion.

Treatment of plaquetopenia after liver transplantation
Gonzalo Sapisochin Cantis, Itxarone Izaskun Bilbao Aguirre, José Luis Lázaro Fernández, Lluís Castells Fusté and Ramon Charco Torra
Evaluating splenic flow occlusion.

Post-transplant monitoring in paediatric liver transplantation
Javier Bueno Recio and Ramon Charco Torra
Advances in vascular thrombosis prevention.

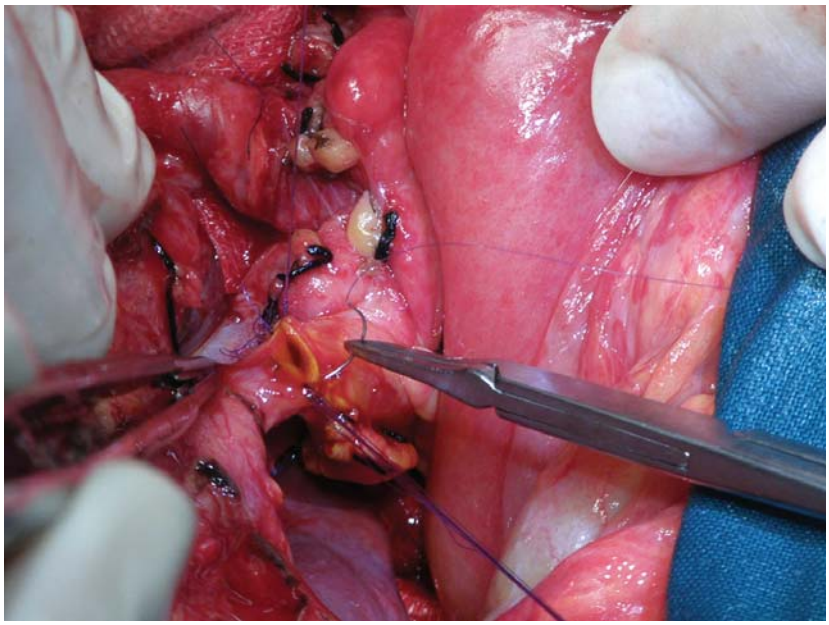


Figure 62
Liver transplantation. Biliary anastomosis

PUBLICATIONS
(Impact Factor: 18.298)

Bueno J, Pérez-Lafuente M, Venturi C, Segarra A, Barber I, Molino JA, Romero A, Ortega J, Bilbao I, Martínez-Ibáñez V, Charco R. No-touch hepatic hilum technique to treat early portal vein thrombosis after pediatric liver transplantation. *Am J Transplant* 2010 Sep; 10 (9): 2148-53. ➲ IF: 6.433.

Sapisochin G, Bilbao I, Balsells J, Dopazo C, Caralt M, Lázaro JL, Castells L, Allende H, Charco R. Optimization of Liver Transplantation as a Treatment of Intrahepatic Hepatocellular Carcinoma Recurrence After Partial Liver Resection: Experience of a Single European Series. *World J Surg* 2010 Sep; 34 (9): 2146-54. ➲ IF: 2.696.

Schnitzbauer AA, Zuelke C, Graeb C, Rochon J, Bilbao I, *et al.* A prospective randomised, open-labelled, trial comparing sirolimus-containing versus mTOR-inhibitor-free immunosuppression in patients undergoing liver transplantation for hepatocellular carcinoma. *BMC Cancer* 2010 May 11; 10(1): 190. ➲ IF: 2.736.

Trunecka P, Boillot O, Seehofer D, Pinna AD, Fischer L, Ericzon BG, Troisi RI, Baccarani U, Ortiz de Urbina J, Wall W, McCaughan G, Jones R, Troisi RI, Roover A de, Mies S, Moreira L, Lima A, Cantisani G, Wall W, Kneteman N, Grant D, Roy A, Scudamore C, Tchervenkov J, Trunecka P, Clavien P, Candinas D, Seehofer D, Fischer L, Schmidt J, Schlitt J, Ortiz de Urbina J, Bilbao I, Charco R, *et al.* Once-daily prolonged-release tacrolimus (ADVAGRAF) versus twice-daily tacrolimus (PROGRAF) in liver transplantation. *Am J Transplant* 2010 Oct; 10 (10): 2313-23. doi: 10.1111/j.1600-6143.2010.03255.x. ➲ IF: 6.433.

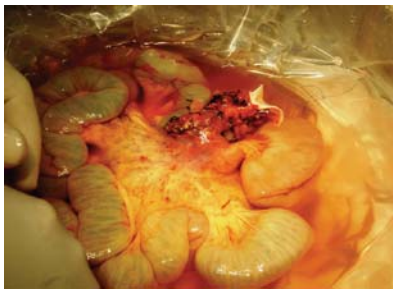


Figure 63
Intestinal graft

AREA 5 DIGESTIVE PHYSIOPATHOLOGY AND HEPATOLOGY

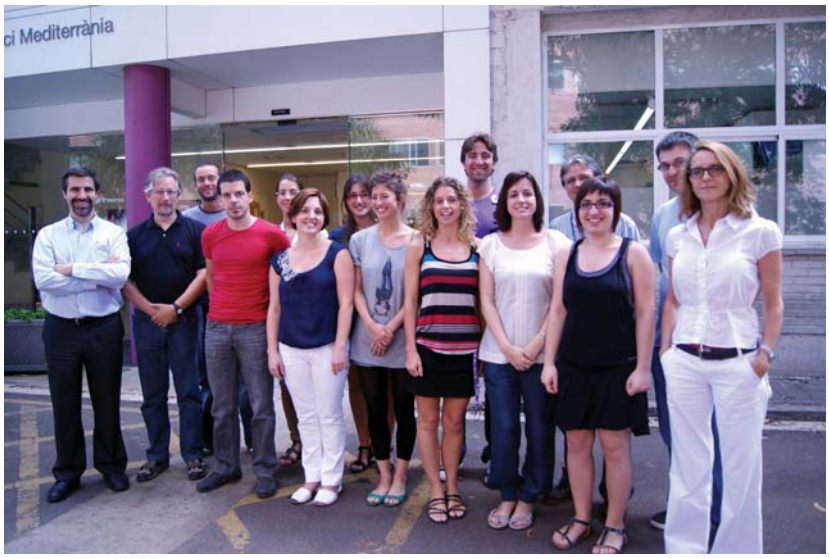
5.2 Liver Diseases

Group Leader
Jaume Guardia Massó
Tel. 93 274 61 10
jguardia@vhebron.net

Researchers
Maria Buti Ferret
Lluis Castells Fusté
Rafael Esteban Mur
Juan Ignacio Esteban Mur
Joan Genescà Ferrer
Antonio González Fernández
Jaume Guardia Massó
Rosendo Jardí Margalef
Maria Martell Pérez-Alcalde
Beatriz Mínguez Rosique
Lluís Palenzuela Díaz
Josep Quer Sivila
Francisco Rodríguez Frias
Silvia Sauleda Oliveras
Victor Manuel Vargas Blasco
Lluís Viladomíu Catà

Researchers in Training
José Trinidad Altamirano Gómez
Salvador Augustin Recio
Nerea Beguiristain Celayeta
Laia Chavarria Vilarasau
Maria del Mar Coll Loperena
María Dolores Cubero León
Nahia Ezcurdia Garmendia
Rita García Martínez
Maria Homs Riba
Marc Oria Alonso
David Tabernero Caellas

Nursing, Technical and Administrative Staff
Judit Carbonell Segura
Silvia Maritza Cuenca Barrero
Damir García Cehic
Mª del Tránsito González García
Laura Millán Segovia
Immaculada Raurell Saborit
Jordi Romero Giménez
Maria Margarita Torrens Buscató



OBJECTIVES

Our group is interested in the clinical and basic aspects of liver diseases. We have two main research areas: viral hepatitis (etiology, virology, epidemiology, pathogenesis and therapy) and liver cirrhosis and its complications (portal hypertension, encephalopathy, hepatocellular carcinoma, liver failure), including liver transplantation.

RESEARCH LINES

Hepatitis B, Molecular biology and therapy

Maria Buti Ferret and Rosendo Jardí Margalef

Genomic variability of hepatitis B virus, epidemiology. Mutations related to antiviral resistance. New therapies. Natural history.

Hepatitis C, molecular biology, immune response and therapy

Rafael Esteban Mur, Juan Ignacio Esteban Mur and Josep Quer Sivila

Genomic variability of hepatitis C virus, quaiespecies. Immune response in chronic disease. Natural history. New therapies. Molecular markers of antiviral response.

Portal hypertension

Joan Genescà Ferrer and Maria Martell Pérez-Alcalde

Physiopatholy of splanhnic arterial vasodilation. Treatment of variceal bleeding.

Liver failure and metabolic encephalopaties

Juan Córdoba Cardona

Physiopathology and treatment of cerebral edema and liver failure. Mechanisms implicated in metabolic encephalopaties.

Liver transplantation and hepatocarcinoma

Víctor Manuel Vargas Blasco, Lluis Castells Fusté and Beatriz Mínguez Rosique

Hepatitis C postransplantation. New inmmunosuppressors. Prognostic factors and new therapies for hepatocarcinoma.

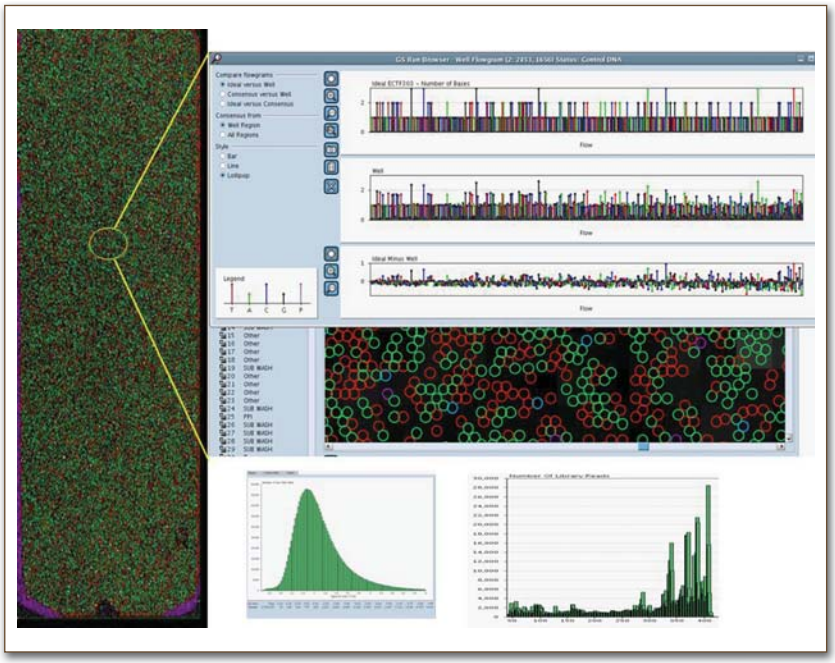


Figure 64
Hepatitis C virus (HCV) pyrosequencing results. Raw data from a Genome Sequencer FLX Titanium picotiter plate using the Ultra-deep Pyrosequencing 454/Roche platform. Left image shows one of the two lanes in which the picotiter plate was divided. Upper right image is a magnification of a small region (yellow circle) and the Flowgram obtained from one of the 3.2million wells that compose the plate. From each flowgram, GS-FLX software generates a text file with the sequence for a total of around 1 million correct reads (one read = one sequence). Bottom-left graphic indicates the number of wells that have passed the internal 454 filter. Bottom-right image shows the length of the sequences obtained and the number of reads per length

CURRENT RESEARCH PROJECTS

PI: Lluís Castells Fusté

TOH/VIH-05: Trasplante hepático en pacientes infectados por el VIH en España (2005-2007)TOH/VIH-09: Trasplante hepático en pacientes infectados por el VIH en España (2009-2011)

Funding Agency: Fundación invest. y prevención SIDA - FIPSE
Reference: FIPSE/TOH/VIH
Funding: 28,800 €
Duration: 2006 to 2012

PI: Víctor Manuel Vargas Blasco

Efectos de la infusión de albúmina en el episodio de encefalopatía hepática. Estudio aleatorizado y multicéntrico en pacientes con cirrosis hepática

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070641
Funding: 71,390 €
Duration: 2008 to 2011

PI: Silvia Sauleda Oliveras

Caracterización serológica, inmunológica y molecular de donantes de sangre con infección oculta por virus de la hepatitis B

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070754
Funding: 45,980 €
Duration: 2008 to 2010

2010 Impact Factor:
155.762

PI: Víctor Manuel Vargas Blasco
Estudio doble ciego, aleatorizado y controlado sobre la eficacia de la administración combinada de albúmina y midodrina en la prevención de las complicaciones de pacientes con cirrosis en lista de espera de trasplante hepático
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90744
Funding: 30,250 €
Duration: 2007 to 2011

PI: Juan Córdoba Cardona
Alteración de la barrera hematoencefálica y edema cerebral en la insuficiencia hepática experimental
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080698
Funding: 258,335 €
Duration: 2009 to 2011

PI: Joan Genescà Ferrer
Estudio multicéntrico, aleatorizado, doble-ciego, controlado con placebo, sobre la eficacia del tratamiento con beta-bloqueantes para prevenir la descompensación de la cirrosis con hipertensión portal
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00070
Funding: 122,815 €
Duration: 2009 to 2011

PI: Joan Genescà Ferrer
Papel del sistema nervioso simpático en la génesis y mantenimiento de las alteraciones hemodinámicas (vasodilatación mesentérica) de la hipertensión portal (SIMPATHAL)
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2009-08354
Funding: 84,700 €
Duration: 2010 to 2012

PI: Josep Quer Sivila
Estudio dinámico de quasiespecies de VHC por pirosecuenciación en fase aguda y crónica durante tratamiento antiviral (PIROVIRUSC)
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2009-10403
Funding: 121,000 €
Duration: 2010 to 2012

PI: Francisco Rodríguez Frías
Análisis de la cuasiespecie viral en la infección por virus de la hepatitis B: evolución natural y asociada al tratamiento antiviral
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00899
Funding: 90,750 €
Duration: 2010 to 2012

PI: Juan Córdoba Cardona
Efectos de la administración de fenilacetato y ornitina en pacientes con cirrosis hepática que presentan una hemorragia digestiva
Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-190
Funding: 43,962 €
Duration: 2010 to 2011

PI: Juan Ignacio Esteban Mur
Estudio de quasiespecies de los virus de la hepatits B y C (VHB y VHC) y de polimorfismos genómicos asociados a respuesta al tratamiento antiviral por pirosecuenciación
Funding Agency: Centro para el Desarrollo Técnico Industrial (CDTI)
Reference: CDTI-2010-01
Funding: 875,000 €
Duration: 2010 to 2013

PI: Joan Genescà Ferrer
Unitat de Recerca en Malalties Hepatobiliars
Funding Agency: AGAUR
Reference: 2009 SGR 383
Funding: 54,080 €
Duration: 2010 to 2013

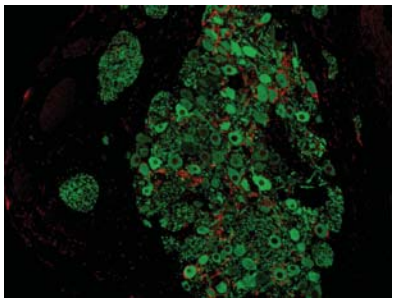


Figure 65
Immunofluorescence of superior mesenteric ganglion of a rat: adrenergic neuronal bodies stained with tyrosine hydroxilase (in green) surrounded by nitrergic axons stained by neuronal nitric oxide synthase (in red)

PUBLICATIONS
(Impact Factor: 155.762)

Boixadera H, Tomasello A, Quiroga S, Córdoba J, Pérez M, Segarra A. Successful Embolization of a Spontaneous Mesocaval Shunt Using the Amplatzer Vascular Plug II. *Cardiovasc Intervent Radiol* 2010 Oct; 33 (5): 1044-8. ➲ IF: 1.949.

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Buti M, Lurie Y, Zakharova NG, Blokhina NP, Horban A, Teuber G, Sarrazin C, Balciuniene L, Feinman SV, Faruqi R, Pedicone LD, Esteban R, Berr F, *et al.* Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. *Hepatology* 2010 Oct; 52 (4): 1201-7. ➲ IF: 10.840.

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García-Martínez R, Rovira A, Alonso J, Aymerich FX, Huerga E, Jacas C, Simón-Talero M, Vargas V, Córdoba J. A Long-Term Study of Changes in the Volume of Brain Ventricles and White Matter Lesions After Successful Liver Transplantation. *Transplantation* 2010 Mar 15; 89 (5): 589-94. ➲ IF: 3.498.

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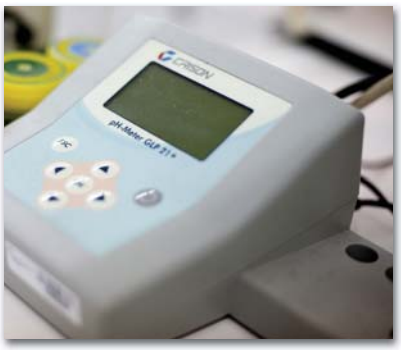

AREA 5 DIGESTIVE PHYSIOPATHOLOGY AND HEPATOLOGY

5.3 Physiology and Pathophysiology of the Digestive Tract

Group Leader
Fernando Azpiroz Vidaur
Tel. 93 274 62 59
fazpiroz@vhebron.net

Researchers
Ana María Accarino Garaventa
Carmen Alonso Cotoner
María Antolín Mate
Fernando Azpiroz Vidaur
Natalia Borruel Sainz
Francesc Casellas Jordà
Francisco Guarner Aguilar
Luisa Guarner Aguilar
Mar Guilarte Clavero
Carlos Hernández Ballesteros
Joan Ramon Malagelada Benaprés
Carolina Malagelada Prats
Chaysavanh Manichanh
Francesc Xavier Molero Richard
Francisco Javier Santos Vicente
María Vicario Pérez
Jaume Vilaseca Momplet

Researchers in Training
Monder Abu-Suboh Abadia
Sílvia Cardona Morito
Ana María González Castro
Meritxell Guila Matarín
Carlos Hernández Ballesteros
Beatriz Lobo Álvarez
Cristina Martínez Martínez
Virginia Robles Alonso
Antonio Torrejón Herrera
Encarna Varela Castro
Marc Pigrau Pastor

Nursing, Technical and Administrative Staff
Raimunda Carmen Alastrue Borbón
Montserrat Casellas Bartomeus
Milagros Gallart Mora
Sandra Estrella Cano
Josefa Mª Heredia Montiel
Sara Mendez Soriano
Gloria Santaliestra Vivaracho

OBJECTIVES

To investigate the integrated function of the intestinal tract including secretion, motility and absorption in health and disease, prioritising the transmission of knowledge to clinical practice. The research on digestive motility interacts with the disorders of visceral sensitivity, brain-gut axis and intestinal allergy. The research line on intestinal inflammation also interaction with some aspects of enteric flora in inflammatory bowel disease.

RESEARCH LINES

Hypersensitivity and dysmotility of the gastrointestinal tract
Fernando Azpiroz Vidaur
Research has been focused on the origin and mechanisms of the disorders of digestive function. Major advancements have been achieved in relation to the diagnostic methods to detect neuromyopathic disorders of the digestive tract. Noninvasive evaluation of intestinal motility has been approached using an original program of endoluminal image analysis applying computer learning techniques and automatic learning methods to videos obtained by means of capsule endoscopy. Furthermore, the possible mechanisms involved in

symptoms without apparent cause have been investigated; specifically, the mechanism of abdominal distension has been identified by means of morpho-volumetric analysis of the abdominal cavity and electromyography of the abdominal walls.

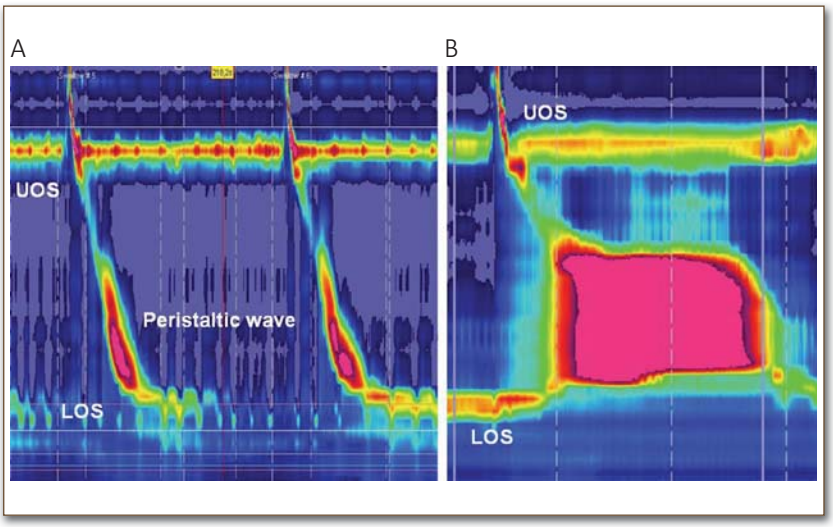

Figure 66
Esophageal high resolution manometry. A) *Normal manometry:* note the synchronous relaxation of the upper oesophageal sphincter (UOS) and lower oesophageal sphincter (LOS) and the increasing pressure and duration of the peristaltic wave. B) *Type III or Vigorous Achalasia:* note the characteristic impaired deglutive lower oesophageal sphincter relaxation and spastic contraction of the oesophageal body

Inflammatory pathways in the gut and therapeutic targets

Francisco Guarner Aguilar

This research programme includes five projects (supported by Spanish and European public research agencies) aimed at the investigation of the cross-talk and effects of live bacteria of the gut microbiota on the intestinal mucosa. In addition, the program includes four clinical/physiological studies that address the potential application of new knowledge gained in basic research on inflammatory bowel diseases.

Pathophysiology and treatment of pancreatic disorders

Francesc Xavier Molero Richard

The focus of our research is to study the series of pathophysiologic events leading to acute and chronic pancreatitis and, eventually, pancreatic cancer. We aim to take advantage of knowledge gained at our basic research program to design therapeutic strategies intended to prevent or ameliorate human pancreatic disorders. In rodent models of acute and chronic pancreatitis we examine pancreatic regeneration, fibrogenesis, acino-ductal trandifferentiation, stellate cell activation, epithelial-to-mesenchymal transition and cancer development. In human pancreatitis we investigate environmental and genetic determinants (with special focus on CFTR dysfunction) and new treatment modalities for acute and chronic pancreatitis.

Neuro-Immuno-Gastroenterology

Francisco Javier Santos Vicente

Irritable bowel syndrome (IBS), the group of microscopical enteritides, food allergy, gastrointestinal eosinophilopaties, and other functional disorders of the gastrointestinal tract represent more than 50% of digestive consultations. Their clinical course is chronic and recurrent. However, sensitive and specific diagnostic biological markers are lacking and clinical management is suboptimal. Interestingly, a common finding in the intestine of these patients is the presence of barrier dysfunction, mucosal inflammation and immune activation. Moreover, this finding may be related to the onset and severity of some major clinical symptoms, particularly in IBS. Therefore, our group pursues the detailed comprehension (genetic/gender, immunological, metabolic, cellular and molecular basis) of the mechanisms connecting environmental determinants (stress and infections) to the development of intestinal mucosal microscopical inflammation, with special focus in IBS. Our approach includes experimental studies in animal models and humans as well, yet remains inherently translational in the search for better targets helpful in the diagnosis, prevention and treatment of IBS and related disorders. In addition, preclinical and clinical assays are also being carried out.

2010 Impact Factor:
107.242

Figure 67
The intestinal microvilli from the enterocytes are microscopic cellular membrane protrusions that increase the area of nutrient absorption in the gastrointestinal tract, and are involved in biological functions such as secretion, cellular adhesion, mechanotransduction and defense against nocive substances present in the intestinal lumen (Bar=0.2μm)

CURRENT RESEARCH PROJECTS

PI: Francisco Guarner Aguilar
Señales antiinflamatorias del ecosistema microbiano intestinal
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2007-64411
Funding: 169,400 €
Duration: 2007 to 2010

PI: Francisco Javier Santos Vicente
Efecto de la estabilización prolongada del mastocito intestinal con cromoglicato disódico en la evolución clínica y la microinflamación de la mucosa intestinal en los pacientes con síndrome de intestino irritable tipo diarrea
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90148
Funding: 168,190 €
Duration: 2007 to 2011

PI: Fernando Azpiroz Vidaur
Dolor abdominal idiopàtic crònic: mecanismes fisiopatològics
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3_072010
Funding: 177,425 €
Duration: 2008 to 2011

PI: Francesc Xavier Molero Richard
Evaluation of the antifibrogenic-anti-inflammatory properties of the cox-2 inhibitor celecoxib in chronic pancreatitis
Funding Agency: Fundación Pfizer
Reference: PFIZER_01_2007
Funding: 63,952 €
Duration: 2007 to 2010

PI: Francisco Guarner Aguilar
Metagenomics of the Human Intestinal Tract (MetaHIT). Grant Agreement No 201052
Funding Agency: European Commission
Reference: METAHIT-201052
Funding: 652,590 €
Duration: 2008 to 2011

PI: Francesc Xavier Molero Richard
Transición epitelio-mesénquima y reclutamiento de fibrocitos en la reparación pancreática y en el desarrollo de pancreatitis crónica
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080342
Funding: 105,149 €
Duration: 2009 to 2011

PI: Francisco Javier Santos Vicente
Mecanismos moleculares subyacentes a la respuesta diferencial (género dependiente) de la barrera epitelial al estrés en el yeyuno humano. Papel del mastocito e implicaciones en el intestino irritable
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080940
Funding: 246,840 €
Duration: 2009 to 2011

PI: Fernando Azpiroz Vidaur
Neurofisiología y neuropatología digestiva
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2009-07416
Funding: 217,800 €
Duration: 2010 to 2012

PI: María Antolín Mate
La célula dendrítica como eje central en la respuesta a bacterias en la mucosa de pacientes con enfermedad inflamatoria intestinal
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00471
Funding: 85,910 €
Duration: 2010 to 2012

PI: Francisco Javier Santos Vicente
Role of mucosal eosinophols in the physiopathology of irritable bowel syndrome
Funding Agency: Rome Foundation
Reference: ROMEF-2010
Funding: 38,959.02 €
Duration: 2010 to 2011

PI: Fernando Azpiroz Vidaur
Desarrollo de nuevas metodologías y tecnologías emergentes de evidenciación de la eficacia de alimentos con propiedades de salud, para la reducción de riesgos de patologías crónicas en la edad media de vida (HENUFOOD)
Funding Agency: Centro para el Desarrollo Técnico Industrial (CDTI)
Reference: CENIT-2010-03
Funding: 450,000 €
Duration: 2010 to 2013

PI: Francisco Guarner Aguilar
Desarrollo de nuevas metodologías y tecnologías emergentes de evidenciación de la eficacia de alimentos con propiedades de salud, para la reducción de riesgos de patologías crónicas en la edad media de vida (HENUFOOD)
Funding Agency: Centro para el Desarrollo Técnico Industrial (CDTI)
Reference: CENIT-2010-04
Funding: 163,000 €
Duration: 2010 to 2013

PI: Francisco Javier Santos Vicente
Sistema de comunicació, col·laboració i compartició del coneixement a l'àmbit de la salut (Co4Salut)
Funding Agency: Generalitat de Catalunya - CIDEM
Reference: RD10-1-0041
Funding: 64,643.14 €
Duration: 2010 to 2012

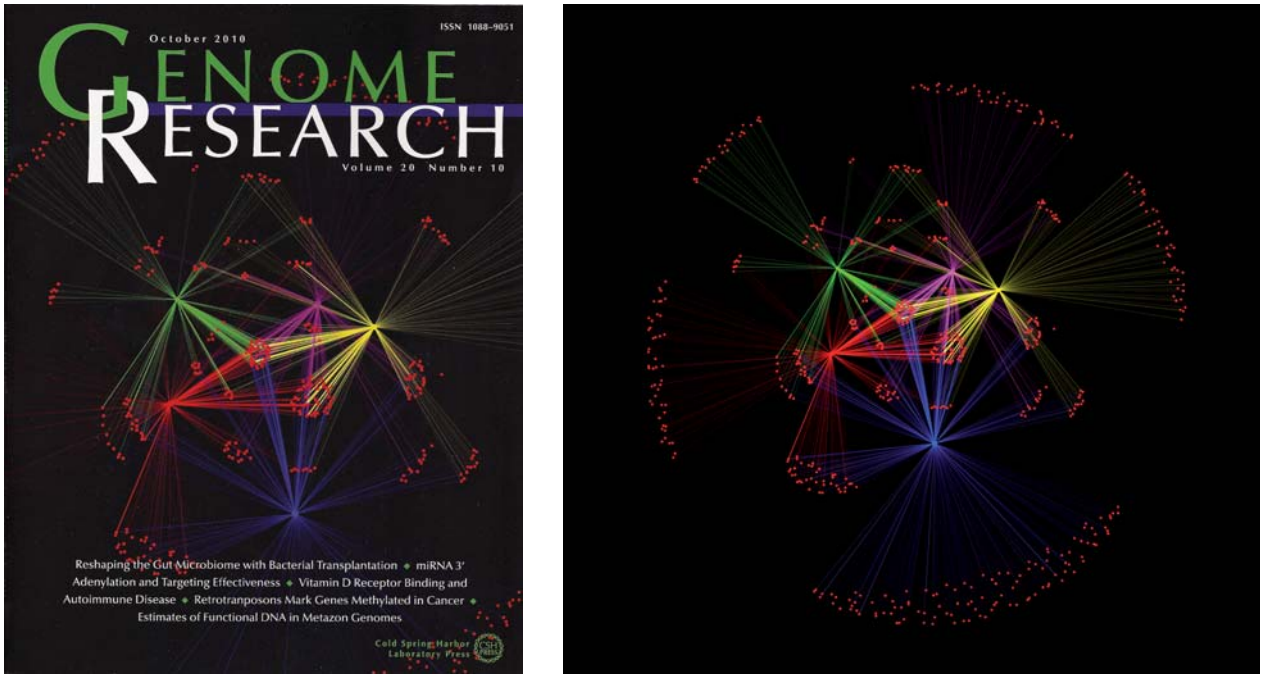

Figure 68
Network plots of shared microbial diversity. The relationships between phylotypes and samples are represented as a bipartite graph in which nodes are either phylotypes (small) or samples (large), and connecting lines between small and large nodes mean that the phylotype was found in the given sample. The gut microbiome includes more than one thousand different bacterial species, and only a subpopulation of them is found to be shared between individuals, as illustrated by the network plot created using Cytoscape (http://www.cytoscape.org/). Alteration of the gut microbiome has been associated with several intestinal disorders. As a potencial therapy, transplantation of the gut microbiome is revealed as a promising alternative to the use of prebiotics, probiotics, or antibiotics for reshaping this microbial ecosystem. [For details, see Manichanh *et al.,* 2011. PMID:20736229, Genome Research.])

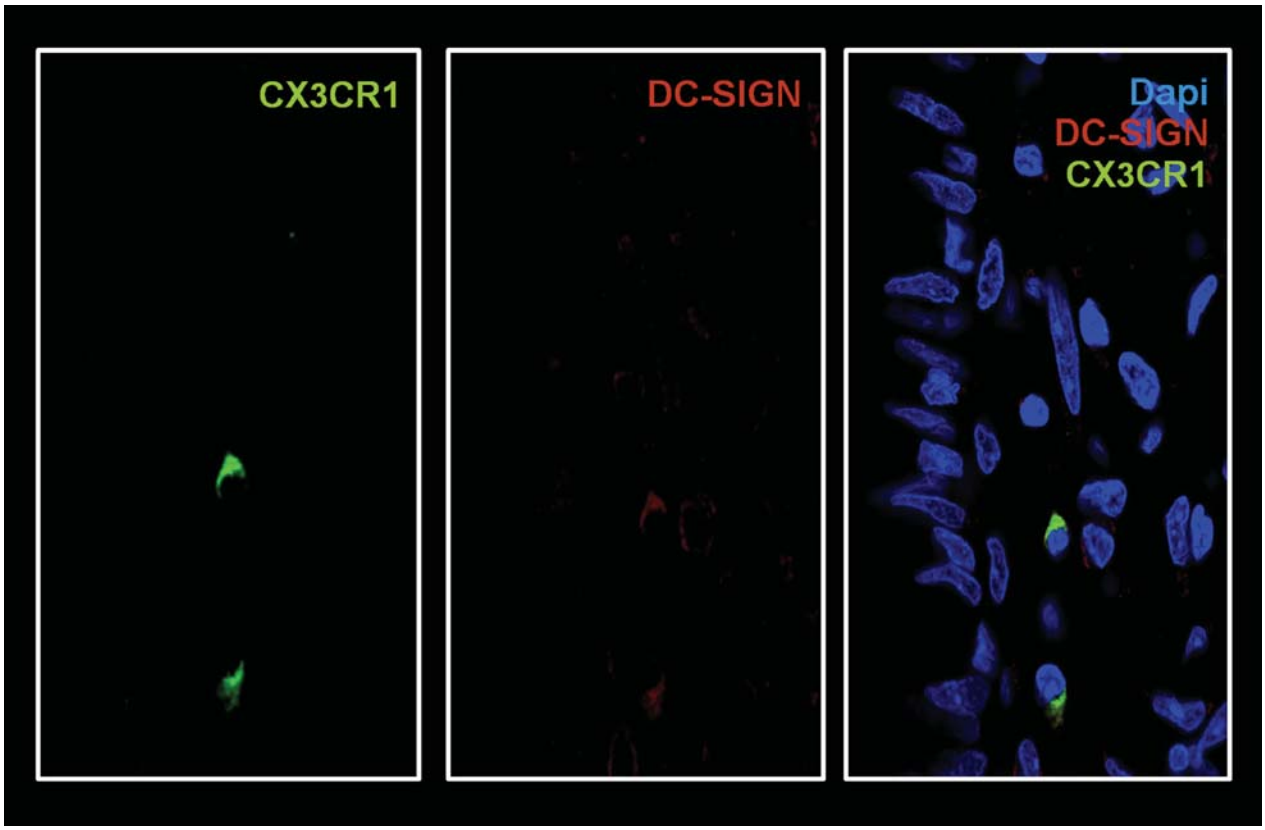

Figure 69
Representative microscopy images of two Dendritic Cells in the Lamina Propria co-expressing DC-SIGN and CX3CR1 from a Chron's Disease patient. "Dapi": cell nuclei staining (in blue); "DC-SIGN": DC-SIGN+DCs (in red) and "CX3CR1": CX3CR1+DCs (in green). Magnification x400

PI: Francesc Xavier Molero Richard
Grup de Recerca en Patologia Pancreàtica Exocrina
Funding Agency: AGAUR
Reference: 2009 SGR 256
Funding: 0.00 €
Duration: 2010 to 2013

PI: Fernando Azpiroz Vidaur
Unitat de Recerca del Sistema Digestiu
Funding Agency: AGAUR
Reference: 2009 SGR 219
Funding: 50,960 €
Duration: 2010 to 2013

PUBLICATIONS (Impact Factor: 107.242)

Amselem C, Puigdollers A, Azpiroz F, Sala C, Videla S, Fernández-Fraga X, Whorwell P, Malagelada JR. Constipation: a potential cause of pelvic floor damage? *Neurogastroenterol Motil* 2010 Feb; 22 (2): 150-3, e48. ➲ IF: 3.568.

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AREA 6 INFECTIOUS DISEASES

6.1 Clinical Research and Innovation in Pneumonia & Sepsis

Group Leader
Jordi Rello Condomines
Tel. 93 274 62 09
jrello@crips.es

Researchers
Rosa Alcaraz Peñarrocha
Roser Anglès Coll
Elena Arnau Faidella
Laura Campos García
Mercè Farré Viladrich
Elisabet Gallart Vive
Rosa Maria Gracia Gozalo
César Laborda Soriano
Lluís Llopart Corsà
Sandra Marquina Escoz
Joan Ramon Masclans Enviz
Núria Masnou Burralló
Mercedes Palomar Martínez
Marcos Pérez Carrasco
Águeda Pérez García
Isabel Porta Pampalona
Jordi Rello Condomines
Maria Alba Riera Badia
Judith Sacanell Lacasa
Lluís Tenorio López

Researchers in Training
Bárbara Borgatta
Berta Caralt Ramisa
Nuria Duran Mateo
Marina García García de Acilu
Alejandra García Roche
Sandra Leal Murillo
Carlos Andres López Rojas
Karla Malpica Basurto
Ana Parra Castillo
Purificación Pérez Terán
Jordi Riera del Brío
Marta Ulldemolins Gómez

Nursing, Technical and Administrative Staff
Paquita Cornet Ciurana
Rosa María Luque de la Roza

OBJECTIVES

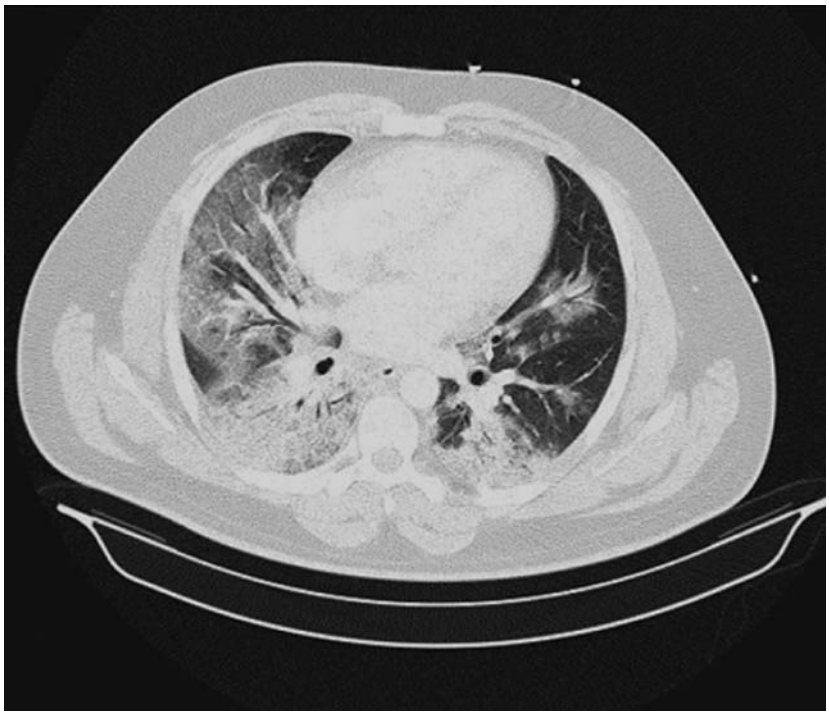
The aim of this group is to develop translational and clinical research in critical care. This group focuses on the most prevalent aspects of infections in the ICU (Ventilator-associated pneumonia, Severe Community-acquired pneumonia -and HCAP-, and opportunistic respiratory infections in severe immunocompromised patients), which represent the Research Lines of CIBERES, where Jordi Rello is head of cooperative research on Hospital-acquired pneumonia.

These activities focus on severe bacterial, fungal and viral (including influenza) infections. Diagnostic, Preventive and Management Issues are strategic. Infection control and surveillance in ICU are the main safety concerns in support of a WHO project on safety endorsed by the Spanish Ministry of Health. Several projects involving development, implementation and assessment of European care packages are ongoing. Team work is essential and we have the tranversal support of nursing staff and allied professional in multiple lines of research, as well as in specific lines of critical care nursing research.

Relevant operational objectives involve pk-pd modeling to achieve optimal dosage of chemotherapy agents to improve antibiotic policy reducing the emergence of resistance and optimizing outcomes. These objectives are achieved by the multidisciplinary team, including different medical specialities, Nurses, Engineers, Biotechnologists Pharmacists and other Health Care Workers.

Special objectives in Innovation areas in collaboration with pharmaceutical companies (therapies and vaccinations), other biotechnology companies (diagnosis, prevention and management), participating in technology transference projects with other research groups from CIBERES, and involvement in projects and networks endorsed by European Scientific Societies.

Figure 70
Computed tomography scan of the lung in a patient with Influenza A (H1N1)



RESEARCH LINES

Ventilator-associated pneumonia (VAP)
Jordi Rello Condomines
Translational research on respiratory infections in intubated patients. Prevention, Risk Factors, Management including dose optimization are priorities. Development and visualization of the VH-ICU paradigm, as a tool for management.

Severe Community-acquired Pneumonia (sCAP) & HCAP
Jordi Rello Condomines
Severe CAP is considered a Systemic Disease. Analysis of outcomes based on the contribution of genetic bacterial load, immunologic response and defenses. Research issues concern severe *pneumococcal pneumonia*, influenza viral pneumonia and other pathogens. Also the implementation of research projects on health-care associated pneumonia.

Respiratory Infections in Immunocompromised ICU patients
Jordi Rello Condomines
Research priorities include viral respiratory infections, yeasts and invasive fungal infections in immunocompromised ICU patients. Leading an international project on invasive pulmonary aspergillosis and a large multicentre study on infections in neutropenic patients.

Epidemiology and Infection Control in ICU Safety
Mercedes Palomar Martínez
Infection control and surveillance, as part of Safety projects in the ICU. In collaboration with ECDC and WHO endorsed projects. Includes collaboration with the meta-analysis unit of the ESICM.

Clinical Research in Critical Care Nursing
Maria Alba Riera Badia and Elisabet Gallart Vive
Multidisciplinary research projects, where nurse participation is crucial. Focusing on prevention of infections in patients with invasive devices, implementation of care packages, safety issues and outcome research.

Sepsis and Biomarkers (Emergent line)
Jordi Rello Condomines

Lung Transplant in ICU
Judith Sacanell Lacasa
Research in one of the core clinical Hospital projects, studying epidemiological variables as well as early morbidity and mortality of lung transplant patients and developing pharmacokinetic studies of immunosuppressive medications.

2010 Impact Factor:
117.627

Acute Respiratory Failure and Mechanical Ventilation

Joan Ramon Masclans Enviz

Translational research on ALI/ARDS patients in the ICU (pathophysiology and treatment) and the long term alterations observed in survivors. The group also includes an Experimental Research Line, focused on the effects of pharmacological treatments or treatment with modified mesenchymal stem cells in LPS-induced lung injury in mice.

CURRENT RESEARCH PROJECTS

PI: Jordi Rello Condomines

Grup de recerca en sèpsia i infecció respiratòria greu

Funding Agency: AGAUR
Reference: 2009 SGR 1226
Funding: 0,01 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 117.627)

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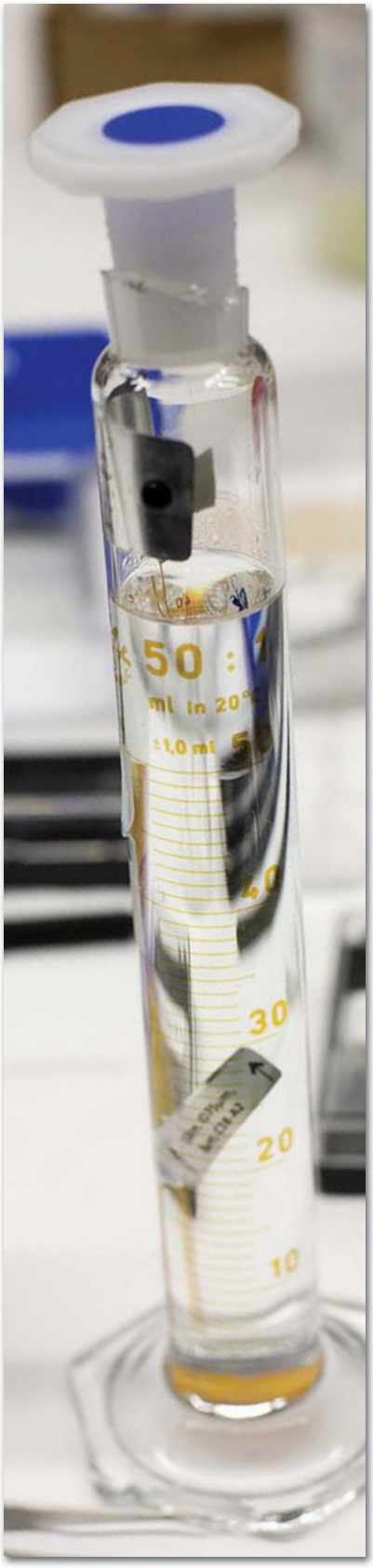

AREA 6 INFECTIOUS DISEASES

6.2 Infectious Diseases Department

Group Leader
Albert Pahissa Berga
Tel. 93 274 60 57 / 90
apahissa@vhebron.net

Researchers
Benito Almirante Gragera
Manuel Crespo Casal
Adrian Curran Fábregas
Vicente Falcó Ferrer
Nuria Fernández Hidalgo
Joan Gavaldà Santapau
Óscar Len Abad
Israel Molina Romero
Inmaculada Ocaña Rivera
Albert Pahissa Berga
Carles Pigrau Serrallach
Esteve Ribera Pascuet
Mª Dolores Rodríguez Pardo
Isabel Ruíz Camps
Sara Villar del Saz Cano

Researchers in Training
Joaquín Burgos Cibrian
Evelyn Lorena Cabral Galeano
Mireia Puig Asensio
Fernando Salvador Vélez
Roger Sordé Masip
Eva van de Eynde Otero

Nursing, Technical and Administrative Staff
Carmen Ferrer Barberà
Javier Gomis Rodríguez
Claudia Orbegozo Rubio
Mercè Pérez Bernal
Inmaculada Verdeguer Almaraz

OBJECTIVES

Since its origin the Infectious Diseases Service, founded in 1996, has had a vocation for teaching and research related to the health care field. The majority of the research developed by the service is clinical, carried out with the intention of deepening our knowledge of and attempting to provide answers to the problems that we see every day as doctors working in the complex environment of a hospital for patients with infectious diseases.
Each line of research has a lead physician who is a permanent member of the service staff and works directly on individual problems.

The service develops most of its research in the setting of two research networks; "Instituto de Salud Carlos III", REIPI (Spanish Network for Research in Infectious Pathology) and RIS (Spanish Network for Research on AIDS). Since 1999 our group has been considered to be a Consolidated Research Group in Catalonia.

RESEARCH LINES

Coinfection HIV / HCV

Manuel Crespo Casal

Use of the dynamics of viral response as a tool to individually tailor the duration of HCV treatment in HIV-coinfected patients. Study of the interaction between ribavirin and nucleoside-analogues inhibitors of HIV reverse transcriptase in a subgenomic HCV replicon.

2010 Impact Factor:
93.304

Opportunistic infections in HIV+ patients

Esteve Ribera Pascuet and Vicente Falcó Ferrer

The aim of this research is to analyze the incidence and the changes in clinical presentation of opportunistic infections in the era of highly active antiretroviral therapy. The improvements in the immunological status of HIV infected patients have led to new clinical problems, such as immune reconstitution inflammatory syndrome, that justify this clinical research.

Pharmacokinetics and toxicity of antiretroviral medication

Esteve Ribera Pascuet

Patients with HIV infection are treated with different drugs, including antiretrovirals and drugs for other purposes, which can have pharmacokinetic interactions with clinical significance or resulting in increased toxicity. This research is divided into pharmacokinetics and toxicity lines. The main objective of the pharmacokinetic research line is studying drug plasma levels of those drugs susceptible to presenting interactions, knowing whether drug levels are within the therapeutic range, evaluating potential interactions and evaluating the impact of some co-infections in plasma concentrations (chronic HCV infection, tuberculosis,...) and whether it is necessary to modify doses in these cases. The main objective of the toxicity line of research is to evaluate the side effects that can occur with antiretroviral therapy, especially mitochondrial toxicity, lypodistrophy and metabolic complications, looking for factors that contribute to their appearance and looking for potential solutions.

Orthopaedic bone and joint infection

Carles Pigrau Serrallach and Mª Dolores Rodríguez Pardo

The aim of the research is to evaluate epidemiological, etiological, diagnostic or therapeutical aspects of osteoarticular infections associated or not with the presence of metallic implants (prosthesis).

Community-acquired pneumonia. Streptococcus pneumoniae infections

Vicente Falcó Ferrer

In 2000 a 7 valent conjugate pneumococcal vaccine was approved for children. The implementation of this vaccine has led to clinical changes in the incidence and clinical presentation of pneumococcal invasive disease not only in children but also in adults. We are studying changes in incidence, clinical presentation of pneumococcal infection in adults, serotype distribution and antimicrobial resistance of Streptococcus pneumoniae. In the near future novel antipneumococcal vaccines will be implemented and a continuous monitoring of these infections is needed.

Infection in oncohematologic patients

Isabel Ruiz Camps

To establish the risk and type of infection in different populations receiving chemotherapy according to induced immunitary alteration. Prevention measures of infection, before and after chemotherapy. To create new protocols of diagnosis and prevention of infections with the use of new biological therapies in different oncological settings. To study the incidence, prevention and characteristics of the infections presented by the immigrant population undergoing chemotherapy.

Invasive fungal infections (IFI)

Joan Gavaldà Santapau and Isabel Ruiz Camps

Surveillance studies of invasive candidiasis in Spain. PK/PD antifungal studies in animal model. To study voriconazole and posaconazole plasma levels and their applications in the clinical management of IFI. To establish the risks, incidence, types and natural history of IFI in different settings to apply more rational and successful preventative strategies.

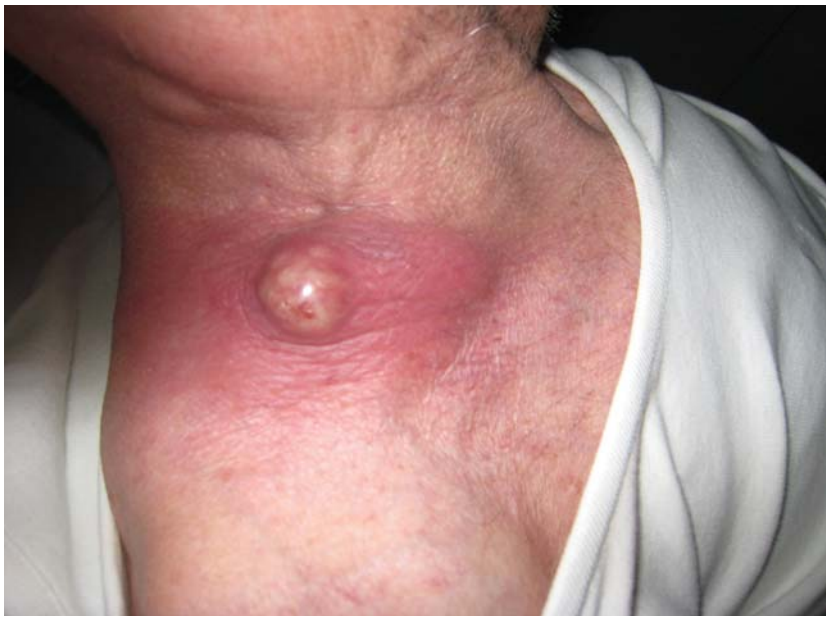

Figure 71
Tuberculoses disseminated with ganglionic affectation

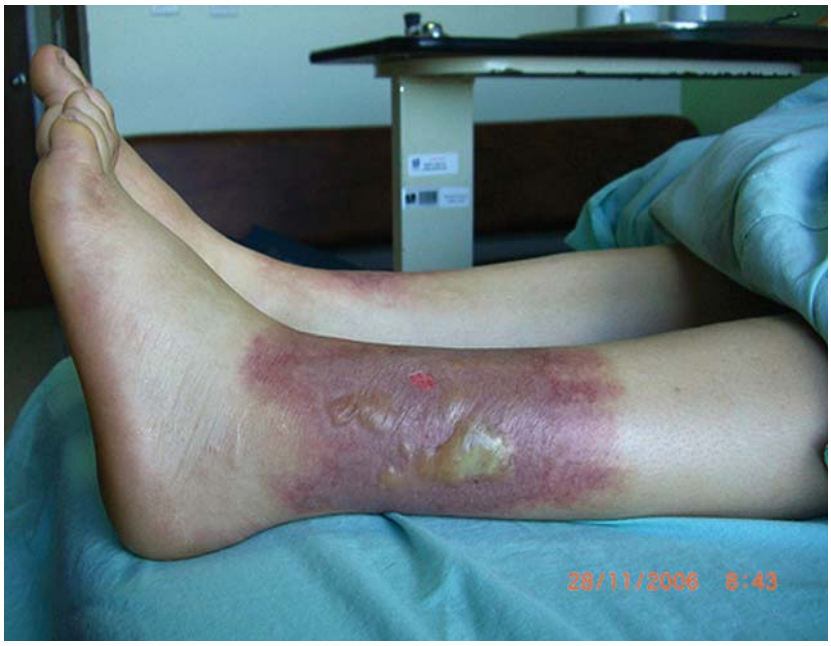

Figure 72
These kinds of infections are studied in this group

Infections in solid organ transplant
Joan Gavaldà Santapau and Oscar Len Abad
The research into infection in solid organ transplantation is based on knowledge of the epidemiology and risk factors for acquiring infections resulting from surgery, donation and immunosuppression as well as the development of intervention studies to prevent and treat these diseases.

Clostridium difficile *infection*
Dolores Rodríguez Cumplido and Benito Almirante Gragera
Due to the increasing number of cases of *Clostidium difficile* associated diarrhoea (CDAD) reported worldwide, our research line attempts to investigate the epidemiology of CDAD in the Barcelona area. Our aims are to determine the average annual incidence and the pooled-mean rate of CDAD for hospitalized patients, to describe the clinical characteristics and to obtain an overview of the antimicrobial susceptibility pattern, toxigenicity and genotypic features of CD isolates.

Imported infection
Benito Almirante Gragera and Israel Molina Romero
The main lines of research are focused on those cosmopolitan and tropical diseases often associated with poverty (Chagas disease, tuberculosis, leishmaniasis, malaria). We are developing new techniques for diagnosing and monitoring patients and new therapeutic schemes that offer a better option to those affected by these diseases. We are also devoting efforts to strengthen health systems in developing countries by supporting vertical programs, promoting research at local level, and creating new tools for non-attendance training of local health staff.

Infection caused by multiresistant microorganisms
Benito Almirante Gragera
We are studying the most relevant epidemiological, clinical, and therapeutic features of infections caused by multidrug-resistant pathogens, specially methicillin-resistant *S. aureus* and multidrug-resistant gram-negative bacilli.

Central catheter infection
Benito Almirante Gragera and Nuria Fernández Hidalgo
An in vivo experimental model of Staphylococci and Candida central-venous catheter-related infections has been developed. We are evaluating several courses of antimicrobials alone or in combination with anticoagulants.

Infective endocarditis
Benito Almirante Gragera and Nuria Fernández Hidalgo
We are studying the likely epidemiological changes to infective endocarditis at the beginning of the XXI century, focusing on their consequences for clinical outcome. Research is focused on modifiable risk factors for mortality.

Infections secondary to cytomegalovirus and Epstein Barr virus
Joan Gavaldà Santapau
Infections by virus of the family Herpesviridae and specifically cytomegalovirus (CMV) and Epstein Barr virus (EBV) are common in recipients of solid allografts. Besides the direct effects related to disease caused by the infection itself, indirect effects caused by its appearance are significant. CMV induces both immunosuppression of the host by producing superinfection due to opportunistic fungi and immunomodulation which can induce acute or chronic rejection of the graft. EBV is an oncogen virus which is related to Posttrasplant Lymphoproliferative Disease. In this research line includes several projects that are trying to find answers to the questions previously asked.

Animal models of infection

Joan Gavaldà Santapau

The aim of the Research Line using Animal Models of Infection carried out in the Research Lab on Infectious Diseases is to try to find answers to questions asked in the Clinical trial which cannot be answered by various methodological problems, and that once answered in the animal model allows us to consider different controlled clinical studies. Then, we have worked with the endocarditis models due to *viridans* streptococci, *S. aureus*, *E. faecalis*, pneumonia due to *S. pneumoniae*, peritonitis, invasive aspergilosis and catheter-related septicemia due to *Candida* spp. and *Staphylococcus* spp. trying to solve some problems we found in the clinics.

CURRENT RESEARCH PROJECTS

PI: Joan Gavaldà Santapau

Estudio in vitro e in vivo de la eficacia de antimicrobianos para la erradicación de biopelículas de S. aureus *(SA) y* Candida *spp. (CAN) formadas sobre materiales sintéticos, particularmente catéteres venosos centrales*

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070394
Funding: 100,717.98 €
Duration: 2008 to 2010

PI: Manuel Crespo Casal

Estudio de la efectividad a largo plazo del tratamiento de la hepatitis crónica C en pacientes coinfectados por VIH y VHC

Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90735
Funding: 13,310 €
Duration: 2007 to 2011

PI: Esteve Ribera Pascuet

Tratamiento antirretroviral una vez al día en pacientes con infección por el VIH-1 no tratados previamente y con cifras de linfocitos CD4+ inferiores a 100 cels/mm³. Estudio prospectivo aleatorizado, multicéntrico y abierto. Estudio ADVANZ-3

Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90942
Funding: 7,865 €
Duration: 2007 to 2011

PI: Manuel Crespo Casal

Cohorte de GESIDA de pacientes coinfectados por VIH y virus de hepatitis C que reciben tratamiento para la hepatitis C (2008-2010)

Funding Agency: Fundación invest. y prevención SIDA - FIPSE
Reference: FIPSE_36702_07
Funding: 3,300 €
Duration: 2008 to 2011

PI: Carles Pigrau Serrallach

Estudio comparativo de la eficacia de pautas «cortas» y «largas» de la combinación Rifampicina-Levofloxacino en la infección estafilocócica posquirúrgica precoz y hematógena de prótesis articular

Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00223
Funding: 9,680 €
Duration: 2009 to 2011

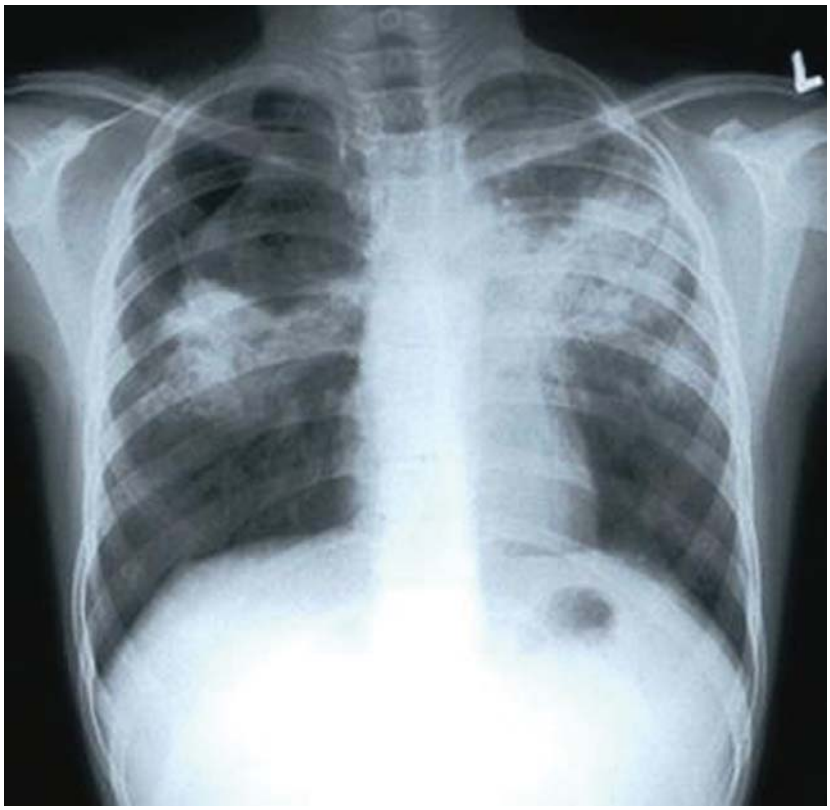

Figure 73
Pneumonia infection

PI: Albert Pahissa Berga
Incidencia de la infección por virus respiratorios en el trasplante de pulmón. Repercusión de la infección por virus respiratorios en la historia natural del rechazo crónico
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080554
Funding: 200,860 €
Duration: 2009 to 2011

PI: Israel Molina Romero
iNTER Support Action (International Network of Teleconsultation Excellence & Referral)Acronym: iSAGrant number: 223610
Funding Agency: European Commission
Reference: ISA-223610
Funding: 33,590 €
Duration: 2009 to 2012

PI: Esteve Ribera Pascuet
Concentraciones plasmáticas de fármacos antirretrovirales en pacientes con infección por VIH y VHC y cirrosis hepática
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/02123
Funding: 82,280 €
Duration: 2010 to 2012

PI: Isabel Ruiz Camps
Estudio de la relevancia clínica de la resistencia a zoles en un modelo animal de aspergilosis invasora: caracterización de parámetros PD/PK
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00433
Funding: 62,920 €
Duration: 2010 to 2012

PI: Albert Pahissa Berga
Protocolo de ensayo clínico de fase II, aleatorizado y abierto para el tratamiento etiológico de la enfermedad de chagas crónica con posaconazol y benznidazol
Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-201
Funding: 360,687.30 €
Duration: 2010 to 2011

PI: Albert Pahissa Berga
Malalties infeccioses
Funding Agency: AGAUR
Reference: 2005SGR 01039
Funding: 50,600 €
Duration: 2006 to 2010

PI: Albert Pahissa Berga
REIPI - Red Española de Investigación en Patología Infecciosa
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0008/0026
Funding: 717,528.16 €
Duration: 2007 to 2011

PI: Esteve Ribera Pascuet
RIS - Red de Investigación en Sida
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0006/0039
Funding: 259,958.31 €
Duration: 2007 to 2011

PI: Albert Pahissa Berga
Malalties infeccioses
Funding Agency: AGAUR
Reference: 2009 SGR 86
Funding: 0,00 €
Duration: 2010 to 2013

PUBLICATIONS (Impact Factor: 93.304)

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Almirante B, Pigrau C. Acute cholangitis. *Enferm Infecc Microbiol Clin* 2010 Sep; 28S2: 18-24. ➲ IF: 1.393.

Almirante B, Pigrau C. [Acute cholangitis.] *Enferm Infecc Microbiol Clin* 2010 Sep; 28S2: 18-24. ➲ IF: 1.393.

Antón A, López-Iglesias AA, Tórtola T, Ruiz-Camps I, Abrisqueta P, Llopart L, Marcos MA, Martínez MJ, Tudó G, Bosch F, Pahissa A, Anta MT de, Pumarola T. Selection and viral load kinetics of an oseltamivir-resistant pandemic influenza A (H1N1) virus in an immunocompromised patient during treatment with neuraminidase inhibitors. *Diagn Microbiol Infect Dis* 2010 Nov; 68 (3): 214-9. ➲ IF: 2.451.

Cabrero E, Griffa L, Burgos A, Merino D, Sánchez V, Muñoz Medina L, Hidalgo C, Curra A, Falcó V, *et al.* Prevalence and impact of body physical changes in HIV patients treated with highly active antiretroviral therapy: results from a study on patient and physician perceptions. *AIDS Patient Care STDS* 2010 Jan; 24 (1): 5-13. ➲ IF: 2.683.

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Fernández-Hidalgo N, Gavaldá J, Almirante B, Martín MT, López Onrubia P, Gomis X, Pahissa A. Evaluation of linezolid, vancomycin, gentamicin and ciprofloxacin in a rabbit model of antibiotic-lock technique for *Staphylococcus aureus* catheter-related infection. *J Antimicrob Chemother* 2010 Mar; 65 (3): 525-30. ➲ IF: 4.352.

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Marshall V, Martro E, Labo N, Ray A, Wang D, Mbisa G, Bagni RK, Volfovsky N, Casabona J, Whitby D, Ocaña I, *et al.* Kaposi sarcoma (KS)-associated herpesvirus microRNA sequence analysis and KS risk in a European AIDS-KS case control study. *J Infect Dis* 2010 Oct 1; 202 (7): 1126-35. ➲ IF: 5.865.

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Rodríguez-Bano J, Picón E, Gijón P, Hernández JR, Cisneros JM, Pena C, Almela M, Almirante B, Grill F, Colomina J, Molinos S, Oliver A, Fernández-Mazarrasa C, Navarro G, Coloma A, López-Cerero L, Pascual A. Risk Factors and Prognosis of Nosocomial Bloodstream Infections Caused by Extended-Spectrum beta-Lactamase-Producing *Escherichia coli*. *J Clin Microbiol* 2010 May; 48 (5): 1726-31. ➲ IF: 4.162.

Rodríguez-Bano J, Picón E, Gijón P, Hernández JR, Ruiz M, Pena C, Almela M, Almirante B, Grill F, Colomina J, Giménez M, Oliver A, Horcajada JP, Navarro G, Coloma A, Pascual A. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli:* risk factors and prognosis. *Clin Infect Dis* 2010 Jan 1; 50 (1): 40-8. ➲ IF: 8.195.

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AREA 6 INFECTIOUS DISEASES

6.3 Microbiology

Group Leader
Guillem Prats Pastor
Tel. 93 274 68 67
gprats@vhebron.net

Researchers
Antònia Andreu Domingo
Rosa María Bartolomé Comas
Estrella Caballero Requero
Gema Codina Grau
Alicia Coelho
Juan José González López
Núria Martín Casabona
Anna Maria Planes Reig
Guillem Prats Pastor
Teresa Tórtola Fernández

Researchers in Training
María Nieves Larrosa Escartín
Nuria Piedra Carrasco
Julieth Natalia Quintero Zárate
Eva Maria Roselló Mayans
Elena Sulleiro Igual

Nursing, Technical and Administrative Staff
Eva Borras López
Thais Cornejo Sánchez

OBJECTIVES

Microbiology group objectives are:

- Working on its main basic lines of activity: mechanisms of resistance to antimicrobials, pathogenicity, taxonomy and epidemiology, and infectious disease diagnostics.
- Promoting clinical research resulting from welfare work.
- Actively taking part in the RETIC network of the "Instituto de Salud Carlos III: Red Española de Investigación en Patologia Infecciosa (REIPI)".
- Continuing working in the "Laboratori de Suport a la Direcció General de Salut Pública de la Generalitat de Catalunya".

2010 Impact Factor:
57.332

RESEARCH LINES

Mechanism of antimicrobial resistance

Klebsiella pneumoniae *and* Escherichia coli *which carry β-lactamases blaCTX-M-15*
Alicia Coelho
Epidemiological and molecular study of *K. pneumoniae* clones and multiresistant *E. coli* which produce this enzyme. Our main goal is to define the epidemic expansion of these strains and to compare the vectors that carry these genes.

Plasmid mediated blaoxy
Juan José González López
Description of the first plasmid carrying blaoxy beta-lactamase; and study of its diffusion capacity.

Study of antimicrobial activity of new antimicrobials
Rosa M. Bartolomé
The progressive increase of resistance has promoted new research in new antimicrobials. This work evaluates the activity of new molecules on multiresistant bacterium with different mechanisms of molecular resistance.

Mycobacterium resistance to tuberculostatics
Núria Martín Casabona
Standardization techniques to study the sensitivity of M. tuberculosis and *M. avium*. Participating in the international WHO and IUATLD networks. Acting as Supranational Reference Laboratory for WHO in the control of the quality of the susceptibility tests of M. tuberculosis. Standardization susceptibility tests of *M. tuberculosis* to second-line drugs.

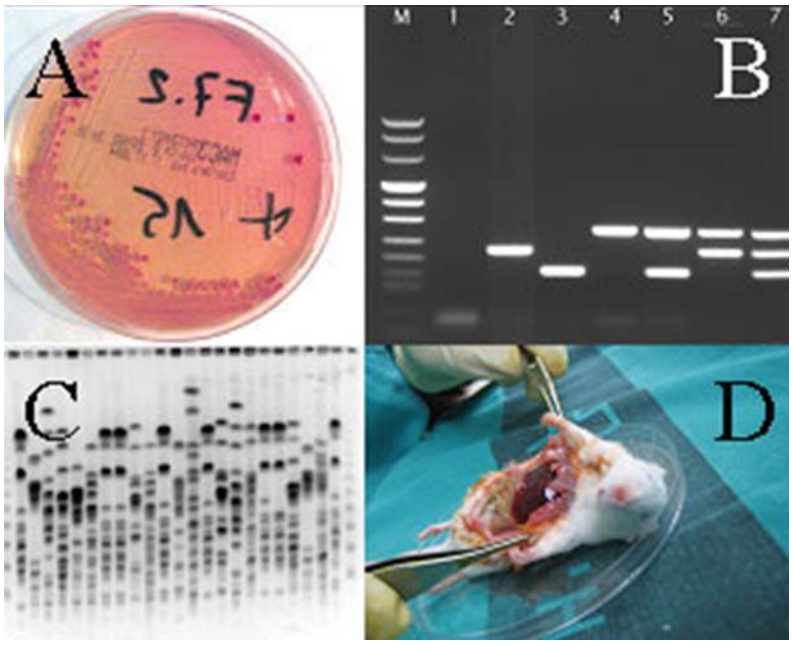
Pathogenicity

Escherichia coli: *Extraintestinal infection, population drifts and virulence factors*
Antònia Andreu
Study of virulence factors, philogenic groups and pathogenicity islands of E.coli which cause extraintestinal infections through molecular techniques. Evaluating the pathogenic capacity of strains of various philogenic groups with a variable number of virulence factors through and animal-experimentation model. Evaluating the resistance to phagocytosis by polynuclears and macrophages and the induction capacity of interleukines production.

Clostridium difficile *phatogenicity*
Rosa M. Bartolomé
Multicentric study, where different hospitals in the Barcelona metropolitan area take part, that studies the epidemiology of infections caused by *C. difficile*, the susceptibility to antimicrobials and the virulence molecular factors (toxins and genetic regulation) of the isolated strains.

Epidemiology and pathogenicity of Meticillin-resistant Staphylococcus aureus *(MRSA) in the outpatient environment*
Nieves Larrosa Escartín
Multicentric work between our group and other state centers that study the relationship between epidemiology of colonization and the pathological processes that cause MRSA and their relationship with strains of virulence factors.

Figure 74
A. Selecting the microorganisms to be studied
B. Establishing the phylogenic group
C. Clonality relationship between related microorganisms
D. Studying the correlation, in animal testing, between the potential pathogen of the microorganism and its phylogenic drift



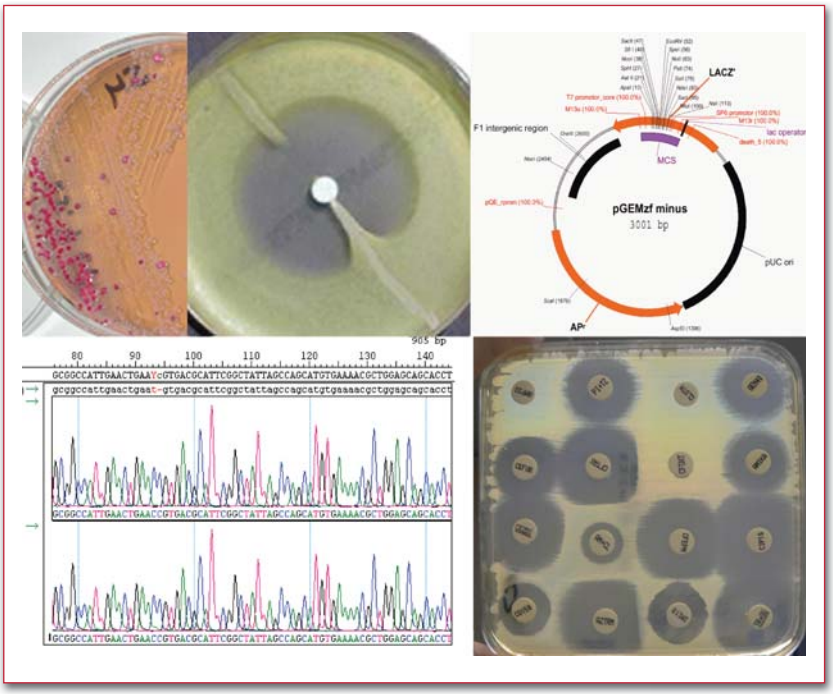


Figure 75
β-lactamase characterization
A. Bacterial isolation
B. Got's test
C. Cloning
D. Sequencing
E. Antibiogram

Taxonomy

Comparing the capacity of phenotypic and genotypic methods to classify enterobacteria
Juan José González López
Evaluating and studying new molecular targets to be used for the identification of bacteria when identifying bacterial species of clinical interest that are difficult to identify by means of traditional methods through sequencing and mass spectrometry.

Epidemiology and infectious disease diagnostic

Evaluating the effectiveness of the antipneumococcal vaccine conjugated 7-valente in the prevention of invasive pneumococcal disease in children under 5 years
Anna M. Planes Reig
Multicentric work that studies the effectiveness of the antipneumococcal vaccine conjugated 7-valent against the invasive disease caused by vaccine serotypes and also by those that have cross-reactivity, in children under 5 years; and the serotypes, clones and resistance profile distribution of *Streptococcus pneumoniae* in different clinical shapes of the invasive disease in children under 5 years, and also in carriers in order to evaluate the consequent drift after vaccination.

Incidence of infection by respiratory viruses in lung transplantation. Impact of infection by respiratory viruses in the natural history of chronic rejection
Gema Codina Grau
Diagnosis and dynamic tracking of the infection by respiratory viruses to investigate their incidence in lung transplantation in our country and evaluate the role played by respiratory viruses in the evolution of chronic rejection in patients subject to lung transplantation.

Quick identification of infections by Candida *yeasts*
Eva Roselló Mayans
Evaluation of the fungemia detection by PCR in hemoculture and in direct blood samples with *Candida* yeasts.

CURRENT RESEARCH PROJECTS

PI: Antònia Andreu Domingo
Patogenicidad de E. coli *uropatógeno y comensal en un modelo de infección urinaria ascendente en ratón*
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070971
Funding: 78,650 €
Duration: 2008 to 2011

PI: Guillem Prats Pastor
Utilización de la secuencia del gen de la beta-lactamasa cromosómica y de la espectrometría de masas MALDI-TOF para la identificación de las especies del género Enterobacter y géneros relacionados
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01702
Funding: 44,165 €
Duration: 2010 to 2012

PI: Guillem Prats Pastor
Grup d'Investigació en Microbiologia de l'Hospital Vall d'Hebron
Funding Agency: AGAUR
Reference: 2009 SGR 296
Funding: 42,640 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact factor: 57.332)

Alijotas-Reig J, Miró-Mur F, Planells-Romeu I, García-Aranda N, García-Giménez V, Vilardell-Tarrés M. Are Bacterial Growth and/or Chemotaxis Increased by Filler Injections? Implications for the Pathogenesis and Treatment of Filler-Related Granulomas. *Dermatology* 2010; 221 (4): 356-64. ➲ IF: 2.741.

Andreu A, Matas L. [Laboratory unification: advantages and disadvantages for clinical microbiology.] *Enferm Infecc Microbiol Clin* 2010 Oct; 28S3: 63-68. ➲ IF: 1.393.

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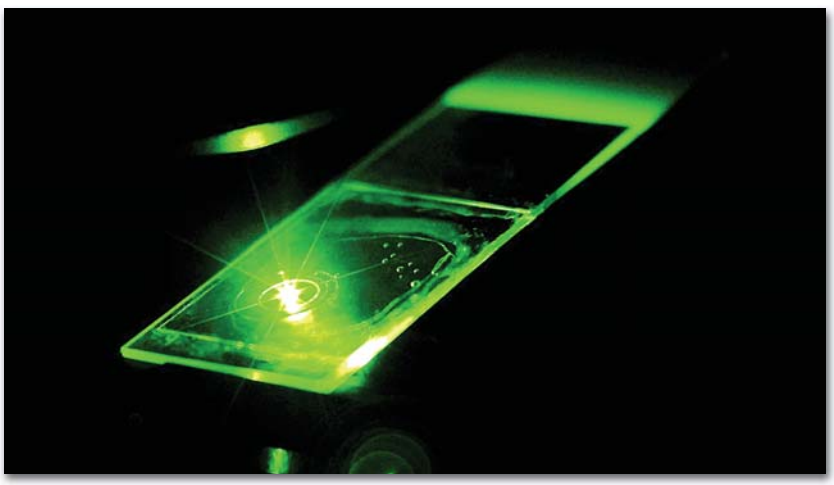

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AREA 6 INFECTIOUS DISEASES

6.4 Shock, Organ Dysfunction and Resuscitation (SODIR)

Group Leader
Joaquín Serra Vich
Tel. 93 274 60 73
joserra@vhebron.net

Researchers
José Luis Bóveda Treviño
Jesús Caballero López
Xavier Nuvials Casals
María Lourdes Pérez Rodríguez
Juan Carlos Ruiz Rodríguez

Researchers in Training
Alejandra García Roche
Simone Gattarello
Helena Puigderrajols Vehils
Jordi Riera del Brío
Adolf Ruiz Sanmartín

Nursing, Technical and Administrative Staff
Tatiana Acero Bailén
José Carlos Martín Santos

OBJECTIVES

The aim of the SODIR research group is integrated research on shock, sepsis and cardiopulmonary resuscitation (CPR). We have special interest in severe sepsis pathophysiology and its relationship with clinical outcome, analysis of prognostic factors, development of prognostic scores and analysis of biomarkers in severe sepsis. The group is also developing echocardiography studies to identify haemodynamic alterations in critically ill patients and searching for precipitant factors of in-hospital cardiac arrest. Another areas of interest to our group is the study of therapeutic hypothermia as a neuroprotection after cardiopulmonary arrest. The study of haemostasis in critically ill patients is another target. In the area of technology transfer our group is developing, in collaboration with the biomedical technology industry, a platform for data integration of critically ill patients with severe sepsis (SepsisNet Project) and a new system for continuous and non-invasive haemodynamic and respiratory monitoring.

RESEARCH LINES

Sepsis, severe sepsis and septic shock

Joaquín Serra Vich

The objectives of this research are investigation into the pathophysiology of systemic inflammatory response induced by infection and the study of biomarkers, analysis of factors related to the development of multiple organ dysfunction and outcome of severe sepsis and the development of early mortality prediction scales in severe sepsis. The group works in collaboration with the "Universitat Politècnica de Catalunya" in the application of artificial intelligence in the management of severe sepsis and is involved in a research consortium that is developing a project funded by the "Subprograma Avanza R + D + I" (Ministerio de

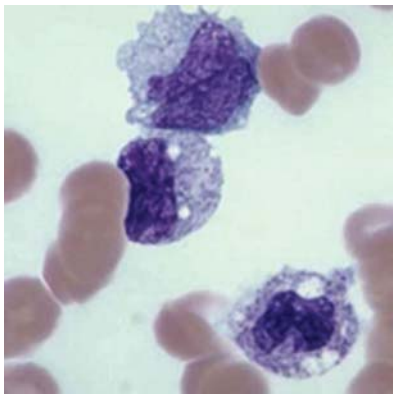
Industria, Turismo y Comercio. FEDER) which aims to generate intelligent alarms in critically ill patients, especially in severe sepsis, septic shock and multiple organ dysfunction. With the applied medical technology and applied research of PCB (Sabirmedical), the group is developing a system of intelligent data management of patients with severe sepsis [sub-project funded by the "Subprograma Avanza R + D + I" (Ministerio de Industria, Turismo y Comercio. FEDER)]. Currently, the group is participating in a decisive way in a new phase of the Surviving Sepsis Campaign and in several trials in septic shock and distributive shock.

Cardiopulmonary resuscitation
Joaquín Serra Vich
Evaluation of the implementation of a new methodology that enables audio improving data collection in medical care to inpatients experiencing cardiac arrest. Identification of precipitating factors of in-hospital cardiac arrest and peri-cardiac arrest situations.

Therapeutic hypothermia
Joaquín Serra Vich
Study of factors influencing the response to therapeutic hypothermia as neuroprotection in comatose survivors after in or out-of-hospital cardiac arrest and study of biomarkers of acute neurological injury in this patients.

Acute kidney injury
Joaquín Serra Vich
Identification of biomarkers and mechanisms of inflammation. Dialysis registration techniques. Study of coagulation, inflammation and endothelial injury in acute renal failure. Study of nephrotoxicity, alteration of renal tubule and pathophysiology of acute kidney injury. Drug dosage in renal dysfunction.

Figure 76
Toxic monocytes and neutrophils in severe sepsis



Monitoring the critically ill
Joaquín Serra Vich
Application of echocardiography and other non-invasive monitoring or minimally invasive systems in the study of pathophysiologic mechanisms of cardiac and hemodynamic dysfunction of critically ill patients. Collaboration in the development of a continuous and non-invasive new monitoring system of the hemodynamic and respiratory function. This project works in collaboration with the applied medical technological research of the "Parc Científic of Barcelona". Another objective is to deep in the knowledge of perfusion and tissue oxygenation through the study of the microcirculation and its involvement in the pathophysiology of severe sepsis with multiorgan dysfunction.

CURRENT RESEARCH PROJECTS

PI: Juan Carlos Ruiz Rodríguez
Sistema para la gestión de los datos clínicos de pacientes con Sepsis (SEPSISNET)
Funding Agency: Ministerio de Industria, Turismo y Comercio
Reference: TSI-020100-2009-204
Funding: 146,817 €
Duration: 2010 to 2011

PI: Juan Carlos Ruiz Rodríguez
Plataforma de Investigación para pacientes críticos (INTEGRA-UCI)
Funding Agency: Ministerio de Industria, Turismo y Comercio
Reference: TSI-020100-2010-625
Funding: 109,362.24 €
Duration: 2010 to 2011

AREA 7 RESPIRATORY AND SYSTEMICS DISEASES

7.1 Chronic Fatigue

Group Leader
José Alegre Martín
Tel. 93 489 47 02
18502jam@comb.es

Researcher
José Alegre Martín

OBJECTIVES

- Creation of a DNA bank for research in fibromialgia and chronic fatigue syndrome.
- Genetic susceptibility factors in chronic fatigue syndrome.
- Psychopathology of chronic fatigue syndrome.
- Cognitive impairment in chronic fatigue syndrome.
- Sexual dysfunction in CFS.
- XRMV retrovirus infection and differential cellular response in patients with chronic fatigue syndrome (CFS) and healthy blood donors.
- Establishment of a population database for patients diagnosed with CFS.
- Development of protocols to evaluate the functional reserve and capacity for physiological adaptation of patients with CFS.
- Nitric oxide metabolite production during exercise in chronic fatigue syndrome.
- Functional repercussions of neurovegetative alterations in patients with chronic fatigue syndrome.

2010 Impact Factor:
2.354

RESEARCH LINES

Population-based registry of chronic fatigue syndrome patient diagnoses in Spain

Genetic susceptibility factors in chronic fatigue syndrome

DNA bank for the study of patient diagnosed with fibromialgia and chronic fatigue syndrome

Prevalence of XRMV retrovirus infection in patients with chronic fatigue syndrome (CFS) and healthy blood donors, in Catalonia, Spain

XRMV retrovirus infection and differential cellular response in patients with chronic fatigue syndrome (CFS) and healthy blood donors

Neurovegetative dysfunction in patients with chronic fatigue syndrome

Physiological responses to leg exercise in patients with chronic fatigue syndrome

Nitric oxide metabolite production during exercise in chronic fatigue syndrome: A case-control study

Brain SPET quantification in chronic fatigue syndrome

Emergent pattern of cognitive alteration in chronic fatigue syndrome

Psychopathology of chronic fatigue syndrome

Study of ergometer parameters, cognitive function and biological markers in patients with chronic fatigue syndrome

Chronic fatigue syndrome and female sexual functioning

Partner relationship influence on the functional capacity in women with chronic fatigue syndrome

Randomized clinical trial of the effectiveness of nurse intervention in patients with chronic fatigue syndrome

Randomized clinical trial of the effectiveness of nurse intervention in patients with chronic fatigue after cancer treatment

Nicotinamide adenine dinucleotide (NADH) in patients with chronic fatigue syndrome

Alpha-1-antitrypsin in patients with chronic fatigue syndrome

Physical exercise programme in the treatment of chronic fatigue syndrome

Group Cognitive Therapy in the treatment of chronic fatigue syndrome

Proinflammatory and antiinflammatory cytokines in pleural effusion

Study of tuberculous pleural effusions

Randomized clinical trial of the effectiveness of alteplase in patients with paraneumonic pleural effusions

CURRENT RESEARCH PROJECTS

PI: José Alegre Martin
Registro de base poblacional de los pacientes afectos del síndrome de fatiga crónica
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/14/2006
Funding: 38,000 €
Duration: 2007 to 2010

PI: José Alegre Martín
Ensayo clínico para evaluar la eficacia de la intervención de enfermería en la mejora del impacto y la calidad de vida en el paciente diagnosticado del síndrome de fatiga crónica
Funding Agency: Becas de Investigación Colegio de Enfermeria de Barcelona
Duration: 2008 to 2010

IP: José Alegre Martín
Estudio del retrovirus XMRV en los pacientes diagnosticados del síndrome de fatiga crónica y un grupo de donantes aparentemente sanos en Cataluña
Funding Agency: Banco de Sangre y Tejidos de Cataluña
Duration: 2010

PI: José Alegre Martín
Estudio del retrovirus XMRV en los pacientes infectados por el VIH
Funding Agency: FIPSE
Duration: 2010

PUBLICATIONS
(Impact Factor: 2.354)

Alegre J, Roses JM, Javierre C, Ruíz-Baques A, Segundo MJ, Sevilla TF de. [Nicotinamide adenine dinucleotide (NADH) in patients with chronic fatigue syndrome.] *Rev Clin Esp* 2010 Jun; 210 (6): 284-8. ➲ IF: 0.584.

Suárez A, Guillamo E, Roig T, Blazquez A, Alegre J, Bermudez J, Ventura JL, García-Quintana AM, Comella A, Segura R, Javierre C. Nitric Oxide Metabolite Production During Exercise in Chronic Fatigue Syndrome: A Case-Control Study. *J Womens Health (Larchmt)* 2010 Jun; 19 (6): 1073-7. ➲ IF: 1.770.

AREA 7 RESPIRATORY AND SYSTEMICS DISEASES

7.2 Ear, Nose and Throat Disorders

Group Leader
Juan Lorente Guerrero
Tel. 93 274 64 15/63 80
20289jlg@comb.es

Researchers
Ana María García Arumí
Juan Lorente Guerrero
Enrique Perelló Scherdel
Joan Piñas Massó
Juan Luis Quesada Martínez
Pedro Quesada Marín

Researcher in Training
Jennifer Knäpper Martín

OBJECTIVES

- Defining similarities and differences between human patients and animals regarding this disease in order to use, if suitable, brachiocephalic dogs as an animal model in treatment options for human disease.
- Validating diagnostic accuracy of sentinel ganglion in pharyngeal-laryngeal carcinoma T1-2 N0 as stadiage tool, through a lympho-gammagraphy with SPECT-TC the day before the operation and the surgical localization of sentinel ganglion through a probe during the surgery.
- Determining the prevalence of gastroesophageal reflux in patients diagnosed with conventional sleep obstructive apnea syndrome, and evaluating the effectiveness of symptom quest in gastroesophageal reflux diagnosis in these patients.

RESEARCH LINES

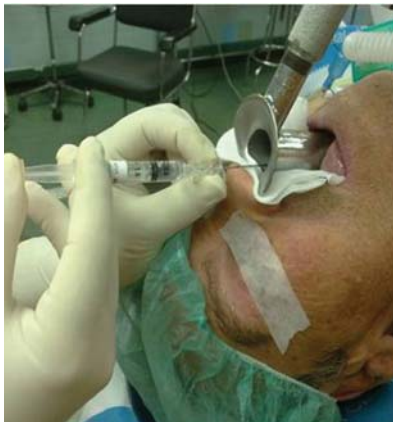
Research group in obstructive sleep apnea syndrome (OSAS)

Juan Lorente Guerrero

The research group in obstructive sleep apnea syndrome (OSAS), using the brachiocephalic breed, Boxer (English and French) as animal model constitutes Drs. Juan Lorente Guerrero (UAB Lecturer, "Hospital de la Vall d'Hebron"), Santiago Lavin González (Professor), Rafaela Cuenca Valera (Lecturer), Josep Pastor Milán (Lecturer), Roser Velarde Nieto (Specialized Technician in Research Support) and Marta Planellas Bachs (Associate Professor at the "Hospital Clínico Veterinario de la UAB"). The main objective of this investigation is to define similarities and differences between human patients and animals regarding this particular disease in order to, if suitable, use brachiocephalic breed as animal models in treatment options for the human disease.

OBJECTIVES: The specific objectives of this research line are the following:

1. Defining the histopathological and immunohistochemical changes with regard to myosin fiber distribution of type I and II, that produce soft palate in brachiocephalic dogs affected by upper airway obstruction syndrome, in dogs without this pathology which have been euthanized for different reasons.



2. Establishing existing similarities and differences between soft palates in brachiocephalic dogs affected by upper airway obstruction syndrome and the uvula of human patients with OSAS.

3. Determining the correlation between degree of injuries observed at histopathological and immunohistochemical level and the clinical presentation of each patient, firstly for the individual species and then a comparison between species.

4. Determining levels of canine acute-phase proteins (C-reactive protein, haptoglobin), as inflation indicators, and levels of cardiac troponin I, as myocardial damage indicator, in animals affected by upper airway obstruction syndrome to compare them afterwards with those that present in dogs that are not affected by this pathology.

5. Evaluating surgical treatment efficacy as a therapeutic alternative, in dogs affected by upper airway obstruction syndromes, through clinical monitoring, supported by complementary diagnostic tests.

Sentinel ganglion in pharynx and larynx carcinoma

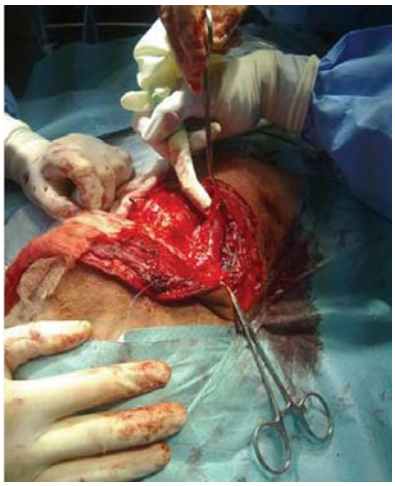
In this project, we are working on the patient collection phase. Currently we have 5 patients.

OBJECTIVES:

1. Validating sentinel ganglion diagnostic accuracy in carcinoma pharyngolaryngeal T1-2 N0 as staging tool, through a SPECT-CT lymphoscintigraphy the day before surgery and surgical location of sentinel ganglion using a probe during surgery.

2. Studying and identifying lymphatic drainage of these tumors.

3. Comparing its usefulness versus conventional staging in clinics and CT.



4. Avoiding overtreatment of patients, eliminating VCG in N0 when Sentinel Ganglion is negative (once this technique is validated).

Gastroesophageal reflux prevalence in patients with obstructive sleep apnea syndrome

Juan Lorente Guerrero, Juan Luis Quesada Martínez, Mª José Jurado Luque, Ana María Accarino Garaventa and Enrique Perelló Scherdel

Different studies suggest the association between gastroesophageal reflux disease (GERD) and OSAS, but GERD prevalence in OSAS and the severity of the influence of OSAS upon GERD is not yet known.

OBJECTIVE: The main objective of this study is to determine the prevalence of GERD in patients with obstructive sleep apnea syndrome using conventional polygraphic sleep. With this study we also want to assess the efficacy of a symptom questionnaire in the diagnosis of gastroesophageal reflux in these patients.

PURPOSE: Identifying patients with gastroesophageal reflux among patients affected by obstructive sleep apnea, in order to establish therapeutic measures to prevent GERD complications.

AREA 7 RESPIRATORY AND SYSTEMICS DISEASES

7.3 Immunology

Group Leader
Ricardo Pujol Borrell
Tel. 93 274 60 00 (ext. 6968)
rpujol@vhebron.net

Researchers
Isabel Caragol Urgelles
Roger Colobran
Teresa Español Borén
Manuel Hernández González
Mónica Martínez Gallo

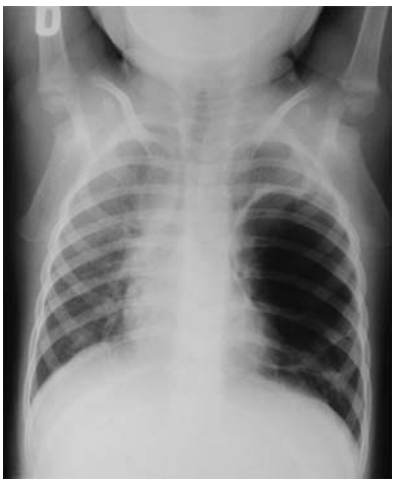


Figure 77
Lung cyst in a patient with Hyper IgE syndrome and a mutation in STAT3

OBJECTIVES

- We are interested in the physiopathogenic mechanisms (immunologic factors, infections, etc.) involved in the evolution and prognosis of patients with Primary Immunodeficiencies (PID).
- Also in the familial incidence of PID, mainly in Antibody production defects (Common variable and IgA deficiency) with the immunological studies and molecular defects already described.

RESEARCH LINES

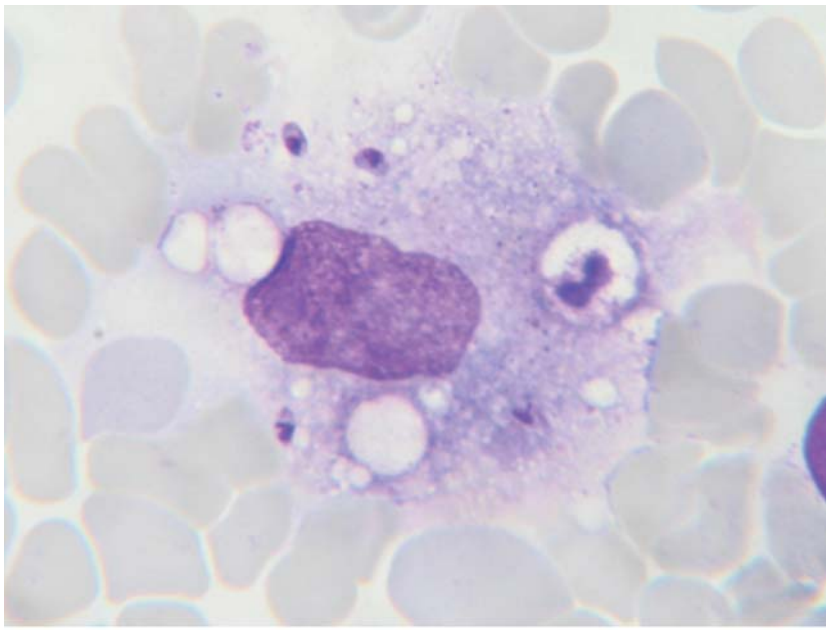
Studies on the physiopathogenic mechanisms (immunologic factors such as regulatory cells, memory B-cells, role of different infections, etc) involved in the evolution and prognosis of patients with Primary Immunodeficiencies (PID)
Teresa Español Borén and Drahomira Detkova Jancigova

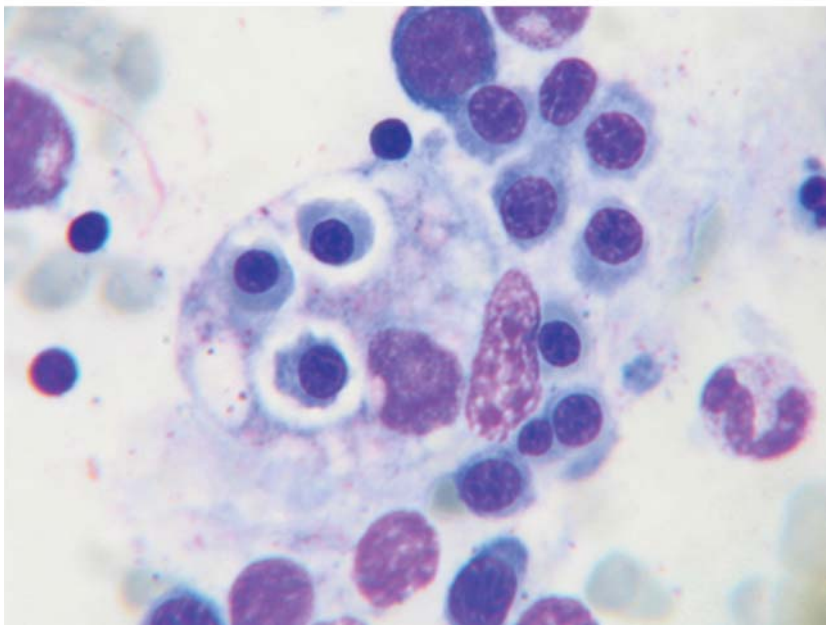
2010 Impact Factor:
28.146

Immunological studies of relatives of patients with Common variable immunodeficiency and IgA deficiency to discover the real incidence of these defects in family clusters, in order to will facilitate further genetic studies

Teresa Español Borén, Isabel Caragol Urgelles and Drahomira Detkova Jancigova

At the end of 2010, one new research line has been added. It deals with autoimmunity and tolerance and is based on previous experience of the group plus the newly incorporated Dr Pujol and the known association between immunodeficiency and autoimmunity.





PUBLICATIONS
(Impact Factor: 28.146)

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Beaucoudrey L de, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, Al-Muhsen S, Janniere L, Rose Y, Suremain M de, Kong XF, Filipe-Santos O, Caragol I, *et al.* Revisiting Human IL-12Rbeta1 Deficiency: A Survey of 141 Patients From 30 Countries. *Medicine (Baltimore)* 2010 Nov; 89 (6): 381-402. ➲ IF: 5.054.

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Martín A, Soler-Palacín P, Español T, Dapena JL, Urrutia E, Navarro M, Alvez F, Figueras C. [Spanish paediatric infectious diseases society consensus document on the treatment of fungal infections based on the immune response]. *An Pediatr (Barc)* 2010 Dec; 73 (6): 362.e1-8. ➲ IF: 0.363.

Woellner C, Gertz EM, Schaffer AA, Lagos M, Perro M, Glocker EO, Pietrogrande MC, Cossu F, Franco JL, Matamoros N, Pietrucha B, Heropolitanska-Plisz, Yeganeh M, Español T, *et al.* Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. *J Allergy Clin Immunol* 2010 Feb; 125 (2): 424-432.e8. ➲ IF: 9.165.

Figure 78
Visceral leishmaniasis in a patient with XL-CGD who developed a macrophage activation syndrome

Area 7 Respiratory and Systemics Diseases

7.4 Pneumology

Group Leader
Ferran Morell Brotad
Tel. 93 274 61 57
fmorell@vhebron.net

Researchers
Carles Bravo Masgoret
María Jesús Cruz Carmona
Jaume Ferrer Sancho
Susana Gómez Ollés
Javier de Gracia Roldán
Mª José Jurado Luque
Patricia Lloberes Canadell
Sergi Martí Beltrán
Víctor Monforte Torres
Ferran Morell Brotad
Antonio Moreno Galdó
Francisco Javier Muñoz Gall
Ramón Orriols Martínez
Oriol Roca Gas
Antonio Román Broto
Odile Romero Santo-Tomás
Gabriel Sampol Rubio
Rafael Vidal Pla

Researchers in Training
Antonio Álvarez Fernández
Daniel Álvarez Simón
Cristina Berastegui García
Mario Culebras Amigo
Marta Ollé Monge
Mercedes Pallero Castillo
Esther Rodríguez González
Laura Ruano Burgos
Mónica Sánchez Ortiz
Sara Sánchez Vidaurre
Ramón Antonio Toribio Abreu
Maria Isabel Velasco García
Ana Villar Gómez

Nursing, Technical and Administrative Staff
Edelia Catalán Hernández
Tatiana Lasheras Muñoz
Rosa Lloria Vergés
Sonia López Rodríguez
Montserrat Murillo Andres
Nuria Pelaz García de Ríos
Mª Antonia Ramón Belmonte
Mª Dolores Untoria Corral

OBJECTIVES

The *Grupo de Investigación en Neumología del Hospital Vall d'Hebron* (Pulmonology Research Group of Hospital Vall d'Hebron) is comprised of investigators with accredited experience in several areas, including clinical research, respiratory pathophysiology and basic/applied research. The Group encompasses professionals from various specialities (e.g., pulmonologists, biologists, anatomical pathologists, nursing staff, laboratory technicians, and physiotherapists) and has an organised structure of personnel dedicated to research, including pre-doctorate and post-doctorate interns, laboratory technicians, nurses, etc. This multidisciplinary team brings added value to the Group and guarantees the critical mass required to develop scientific projects. Moreover, the Group is integrated in Ciber de Enfermedades Respiratorias (CibeRes), a network established by the Instituto Carlos III, and is considered a Grup Consolidat (Consolidated Group) by the Departament d'Universitats, Recerca i Societat de la Informació (Department of Universities, Research and the Information Society) of the Generalitat de Catalunya (Autonomous Government of Catalonia). With respect to teaching activity, the Pulmonology Service is accredited to train three medical residents per year, with one titled professor and four associates. In addition, the Service carries out educational activity in the field of pulmonology in the Teaching Unit of the UAB (Autonomous University of Barcelona), and organises two doctorate courses per year in the setting of continuing education.

Figure 79
Whole body plethysmograph to measure the ventilatory function in mice

RESEARCH LINES

The clinical and basic research activity of the Pulmonary Research Group is mainly centred on inflammation and repair, respiratory failure, and tissue hypoxia. Moreover, there is an interrelationship between these efforts and the study of pathologies such as asthma, chronic obstructive pulmonary disease (COPD), lung fibrosis, infections, lung transplantation, pulmonary hypertension, and respiratory sleep disorders.

Work-related diseases, asthma and fibrosis

Ferran Morell Brotad

The Group is considered a referral team for the diagnosis and treatment of work-related lung diseases in Catalonia, focusing mainly on occupational asthma, hypersensitivity pneumonitis, and occupational disease caused by asbestos exposure. It is responsible for the creation and monitoring of the Spanish Registry of Occupational Diseases (EROL), an important task that had not been covered previously. The Group forms a part of the Grup Col.laboratiu per la Investigació de l'Asma per Soja a Barcelona (Collaborative Research Group for Soy Asthma in Barcelona). Moreover, it is an officially accredited center to carry out daily determinations of environmental levels of soy aeroallergens in Barcelona. For this purpose, the Group has an agreement with the Servicio de Medio Ambiente del Puerto de Barcelona (Environmental Service of the Port of Barcelona), which uses the re-

2010 Impact Factor:
122.241

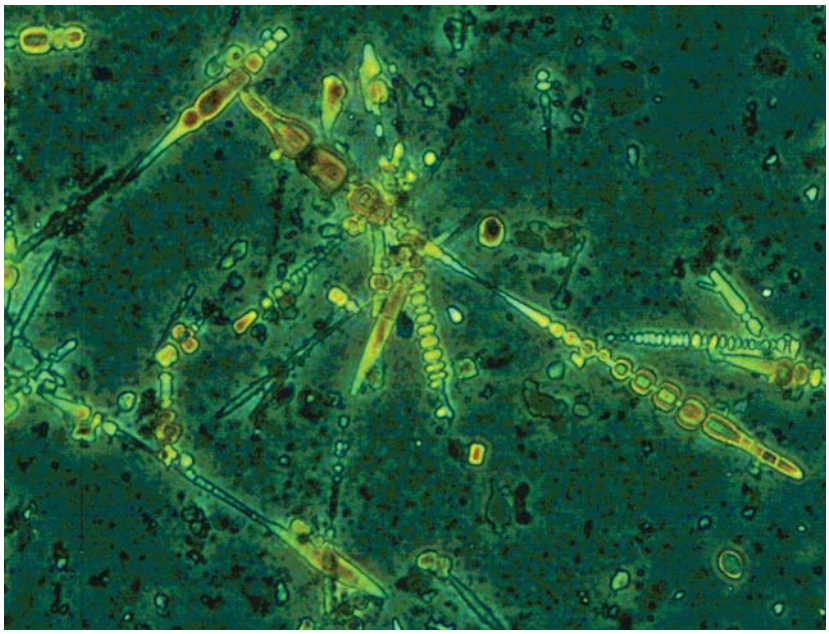

Figure 80
Asbestos bodies in lung

sults of these analyses to monitor the unloading of soy products in the city's port. This daily monitoring of soy aeroallergen in the city has helped the authorities begin to eliminate further asthma epidemics The Group has been given several awards for its work in the area of soy asthma, such as the Fundació Cor Vilacasas award (1993), the Science Award of the City of Barcelona (1995), and the Josep Trueta Award from the "Acadèmia de Ciències Mèdiques" (1995).

The team also has broad experience in the study of hypersensitivity pneumonitis, with a series of 150 patients that is one of the largest in the country, given the low prevalence of this condition. In addition, our center is considered a national referral hospital for the diagnosis and treatment of this pathology. Within the research into occupational disease due to asbestos exposure, our research laboratory is the only one in Spain that carries out determinations of asbestos bodies in the lung.

Cystic fibrosis and primary immunodeficiencies

Javier de Gracia Roldán

The Group has a dedicated outpatient care center for primary immunodeficiency and is the referral center for this disease. There is also a Catalonian Referral Unit for Cystic Fibrosis, which maintains the Spanish registry of bronchiectasis and patients with alpha1-antitrypsin deficit. Moreover, the team is considered to be expert in the control of tuberculous disease.

COPD and pleural diseases

Jaume Ferrer Sancho

In the field of COPD, the main research lines have centred on genetic aspects of the disease, with special emphasis on patents with emphysema due to alpha-1 antitrypsin deficit and exacerbation of COPD. Moreover, a research line has been initiated based on the study of inflammation in lung tissue by molecular biology techniques.

Lung transplantation and pulmonary hypertension

Antonio Román Broto

The Group performed the first successful lung transplantation in Spain. Currently, it is one of the hospitals where the largest number of lung transplants are carried out annually, which places it among the leading centers in Europe and the world for this activity.

Sleep disorders

Gabriel Sampol Rubio

The research effort also focuses on the various diagnostic and therapeutic options for respiratory sleep disorders, and, recently, on the vascular repercussions of these disorders. Currently the Group is participating in several multicenter endeavours in non-invasive mechanical ventilation and in a project financed by the FIS to assess the efficacy of treatment with continuous positive air pressure (CPAP) through a nasal route to reduce arterial pressure values in patients with sleep apnoea and arterial hypertension.

Paediatric respiratory diseases

Antonio Moreno Galdó

The Paediatric Pulmonology and Cystic Fibrosis Unit is a Spanish referral center for paediatric lung transplantation and pulmonary hypertension and a Catalonia referral center for children with cystic fibrosis, including the neonatal screening program. The main lines of research include the study of inflammation and bronchial hyperresponsiveness in asthma in infants and older children, the determination of reference values for spirometry in children and the study of lung function in children with sequelae of neonatal respiratory disease (bronchopulmonary dysplasia). The Unit has established a new line of study of ciliary motility and ultrastructure in primary ciliary dyskinesia to allow further study of this rare disease.

CURRENT RESEARCH PROJECTS

PI: María Jesús Cruz Carmona
Asociación de los alelos HLA clase II y riesgo de susceptibilidad en el asma ocupacional inducida por sustancias de bajo peso molecular en una población española: Implicaciones diagnósticas y terapéuticas
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI06/0256
Funding: 26,837.80 €
Duration: 2007 to 2010

PI: Javier de Gracia Roldán
Capacidad de esfuerzo, disfunción muscular periférica y genotipo en adultos con fibrosis quística
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061298
Funding: 72,600 €
Duration: 2007 to 2010

PI: Francisco Javier Muñoz Gall
Desarrollo de un modelo animal para el estudio del asma ocupacional ocasionada por la exposición a sales de persulfato
Funding Agency: Societat Catalana de Pneumologia
Reference: SOCAP/01/2007
Funding: 18,000 €
Duration: 2007 to 2010

PI: Francisco Javier Muñoz Gall
Desarrollo de un modelo animal para el estudio del asma ocupacional ocasionada por la exposición a sales de persulfato
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080204
Funding: 34,848 €
Duration: 2009 to 2011

PI: Patricia Lloberes Canadell
Efecto del tratamiento con presión continua positiva en la vía aérea (CPAP) sobre las cifras tensionales en pacientes con hipertensión arterial resistente. Estudio multicéntrico y aleatorizado. Estudio HIPARCO
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01574
Funding: 7,865 €
Duration: 2010 to 2012

PI: Ferran Morell Brotad
Unitat de Recerca de Pneumologia
Funding Agency: AGAUR
Reference: 2009 SGR 257
Funding: 54,080 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 122.241)

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Area 7 Respiratory and Systemics Diseases

7.5 Systemic Diseases

Group Leader
Miguel Vilardell Tarrés
Tel. 93 274 63 30
mvilardell@vhebron.net

Researchers
Juan José de Agustín de Oro
Cayetano Alegre de Miguel
Cristina Arnal Guimerà
Eva Balada Prades
Pere Barceló Garcia
José Àngel Bosch Gil
Victòria Cardona Dahl
Jesús Castro Marrero
Josefina Cortés Hernández
Vicenç Fonollosa Pla
Antonio Julià Cano
Moisés Labrador Horrillo
Joan Lima Ruiz
Olga Luengo Sánchez
Sara Marsal Barril
Fernando Martínez Valle
Consuelo Modesto Caballero
José Ordi Ros
Mari Carmen Pérez Bocanegra
Antonio San José Laporte
Agustí Sellas Fernández
Albert Selva O'Callaghan
Carmen Pilar Simeón i Aznar
Roser Solans Laque
Raül Tortosa Méndez
Miguel Vilardell Tarrés
Mª del Mar Villar Casares

Researchers in Training
Arnald Alonso Pastor
Anna Sala Cunill
Mª Teresa Torres Salido

Nursing, Technical and Administrative Staff
Cristina Canaleta
Mireia Castilla Rodríguez
Elena Granell Pallarés
Maria Lidon Felip Pascual
David Muro Fernández
Silvia Serrano Acedo

2010 Impact Factor:
158.067

Figure 81
The Rheumatology Research Group works on the development of personalized medicine in chronic inflammatory arthritis using genomic approaches, and is specialized in biobanking and the development of new bioinformatic tools

OBJECTIVES

Systemic autoimmune diseases are illnesses of unknown aetiology which present an autoantibody-mediated pathogenicity with heterogeneous clinical behaviour characterized by different clinical manifestations.
Our research is aimed at studying: *i)* their aetiology (both at the genetic and immunologic regulation levels); *ii)* their biological and clinical expression (detection of new markers that can help us to characterize each systemic autoimmune disease); *iii)* their morbimortality (by performing epidemiologic studies), *iv)* their response to the drugs given to the patients. With these objectives in mind, we seek to improve the diagnosis, clinical follow-up and prognosis of our patients.

RESEARCH LINES

Study of IFN-gamma/STAT and TGF-beta/SMAD pathways in lupus patients with skin involvement. Role in the evolution to fibrosis

José Ordi Ros

With this project we aim to study the status of the IFN-gamma/STAT and the TGF-beta/SMAD intracellular signal pathways in cutaneous biopsies of patients with lupus. We are now analyzing the expression of several molecules involved in these pathways to be able both to discern the main differences among the different types of cutaneous lupus and to interpret the residual fibrotic lesions observed in discoid lupus.

Lupus and apoptosis: Mechanisms of action of thalidomide and its analogues in refractory cutaneous lupus. Clinical and therapeutic implications

Jesús Castro Marrero

The main goal of this research line consists of studying the effect that thalidomide may have on skin viability and cellular proliferation processes. These mechanisms contribute to wound reepithelization in patients with cutaneous lupus. We are currently analyzing the expression level of several molecules involved in the apoptotic phenomena (Fas/FasL, Bcl-2, Bax, ...) and cell matrix regeneration in keratinocyte and fibroblast primary cell cultures treated with different doses of thalidomide.

DNA methylation study in Systemic Lupus Erythematosus (SLE) patients

Eva Balada Prades

DNA is hypomethylated in T cells from SLE patients. This may lead to an increase in the expression of some genes that are usually silenced and, consequently, autoimmune phenomena may develop. On the other hand, this "unprotected" DNA could be responsible for triggering anti-DNA antibodies. To find out why this DNA hypomethylation is taking place, we have evaluated the expression levels of different DNA methylases and demethylases. We have observed that two demethylases (MBD2 and MBD4) are overexpressed in T CD4+ lymphocytes of patients with SLE. We are now studying the effect the overex-

pression of these proteins may have in the expression regulation of different molecules involved in the immunologic response.

Infection and Autoimmunity: relevance of Human Endogenous Retrovirus (HERV) in Systemic Lupus Erythematosus (SLE)

Eva Balada Prades

Antibodies against HERVs have been detected in patients suffering from some autoimmune diseases such as SLE, rheumatoid arthritis, Sjögren's syndrome, and multiple sclerosis. We mainly focus our research on trying to detect these antibodies in our patients affected with SLE. We have recently cloned some recombinant proteins specific to HERVs. We are simultaneously evaluating the transcription levels of several HERV proteins in T CD4+ lymphocytes from SLE patients.

Detection of retrovirus XMRV in peripheral blood mononuclear cells of patients with Systemic Lupus Erythematosus

Eva Balada Prades

The presence of the recently discovered retrovirus XMRV ("xenotropic murine leukaemia virus-related virus") is currently being studied in our lab in patients with SLE. This virus has been detected in the blood samples of patients suffering from chronic fatigue syndrome (CFS). Interestingly, many patients with lupus also suffer from CFS. Based on these facts, in this project we establish as a hypothesis the possibility of finding XMRV DNA and RNA sequences in peripheral blood mononuclear cells from SLE patients, especially in those with CFS. We are currently setting up the previously described XMRV-specific PCR and RT-PCR assays. We will also study the immunologic response of these patients to particular XMRV proteins.

Urinary biomarker detection in lupus nephritis

José Ordi Ros

Our main goal in this project is to try to avoid the repeated renal biopsies needed for establishing both the diagnosis and the following up of patients who suffer with lupus nephritis. By using just urine from the patients, we want to find out whether there is one/several biomarker/s (MCP-1, TWEAK, NGAL, APRIL, RANTES, ...) that would allow us to establish particular diagnosis and prognostic criteria that are equally effective or even more accurate than those obtained with renal biopsy.

Immunologic lesional mechanisms in late adverse reactions to bioimplants

Jaume Alijotas Reig

The late clinical manifestations that arise when bioimplants are applied seem to have an immunologic basis. We are studying both the histological characteristics and the lesional mechanisms of the most frequently used implants. We try to analyze the role that bacteria may have in the induction and/or maintenance of these reactions and the possible correlation between particular HLA haplotypes and adverse effects.

Predictive kit to detect the possible establishment of late adverse effects related to bioimplants used in clinical practice

Jaume Alijotas Reig

There seems to be a high variability in the prevalence of adverse effects with an immunologic basis in relation to any implant used in clinical practice. We have managed to find a particular association of HLA haplotypes that increase the risk of developing these effects up to 600 times. We are currently working on setting up a safe and reliable biochip or kit which predicts this risk easily in a routine test.

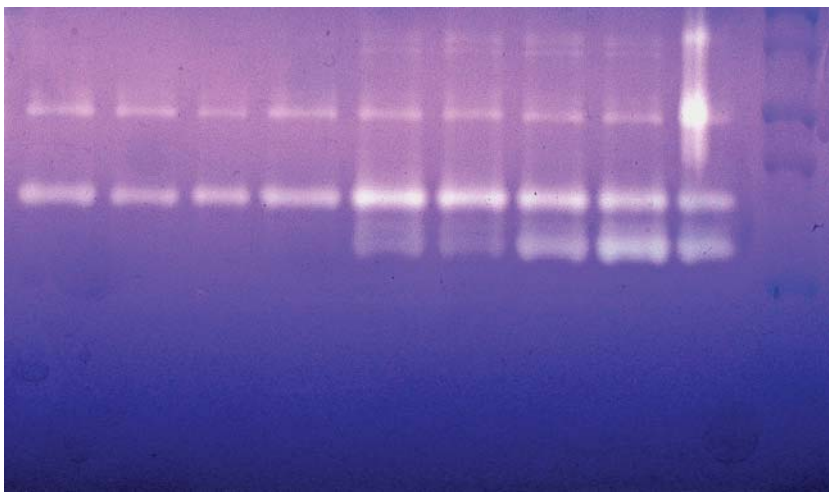


Figure 82
Pharmacologic mechanisms in cutaneous lupus. Induction of metalloproteinases (MMP2 i MMP9) in human skin fibroblasts after being treated with thalidomide

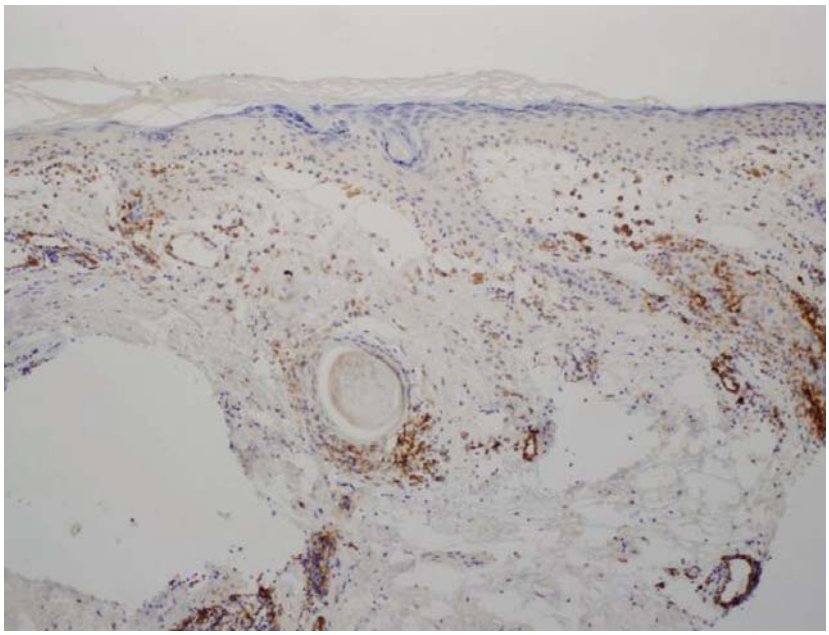


Figure 83
Dendritic cell infiltration (CD123+) in the skin of a patient with discoid lupus

Characterization of mastocyte mediators released at intestinal level in patients with food allergy and irritable bowel syndrome. Relationship with stress and intestinal permeability

Francisco Javier Santos Vicente and Mar Guilarte Clavero

This study establishes the importance of intestinal mastocytes in the regulation of intestinal permeability in two inflammatory diseases such as food allergy and irritable bowel syndrome. It includes both experimental animal models and human studies.

Serological marker study in anaphylaxis

Moisés Labrador Horrillo

We are performing a follow up study of different serological markers in patients who have suffered some anaphylactic episodes. The main goal consists of detecting anaphylaxis patients in the intensive care unit and to determine different serological and plasma markers, mainly tryptase and carboxypeptidase levels by means of a sandwich ELISA.

RECORD study (RECOmbinant allergens in diagnosis resolution)

Victòria Cardona Dahl

This study aims to detect the prevalence of specific IgE in patients polisensitized to pollen in Barcelona by means of the "component resolved diagnosis" technique from ISAC® (IgE specific microarray).

Cancer and myositis. Relevance of anti-p155 antibodies and importance of screening for cancer by Positron Emission Tomography and Computed Tomography (PET/CT)

Albert Selva O'Callaghan

Anti-p155 antibodies seem to be useful for the diagnosis of paraneoplastic myopathies. We have studied their prevalence and their diagnostic value in a cohort of 137 patients with inflammatory myopathies and we have observed that they have a high negative predictive value. On the other hand, screening by PET/TC does not contribute much to the conventional screening of cancer in these patients.

MYOGEN study. Genome Wide Association study in myositis

Albert Selva O'Callaghan

We are currently enrolled in this worldwide study to detect global genetic alterations in patients with myositis. Twenty centres in Europe and the United States are participating in this study. We are contributing by adding the genetic information of the patients from our population. Professor Frederick W. Miller (Bethesda, USA) and Dr. Ingrid Lundberg (Stockholm, Sweden) lead the project.

International Classification Criteria Project

Albert Selva O'Callaghan

This is a multicentric study aimed at defining new diagnostic criteria for muscular inflammatory diseases. Although criteria established by Bohan and Peter are still used in clinical practice, some inflammatory diseases such as inclusion body myositis are not included. The hytopathological classification compiled by Dalakas includes the latter entity but it does not take into account either paraneoplastic myositis nor those associated with systemic diseases.

Lung involvement in inflammatory myopathies

Albert Selva O'Callaghan

In this study we are investigating the natural history of this syndrome as mediated by anti-synthetase antibodies and the characterization of new antibodies that may be used as markers of lung involvement. It is also our aim to better understand the etiopathogenicity and the treatment of this organic illness in patients with myositis.

Canine-myositis study

Albert Selva O'Callaghan

We are collaborating with the Veterinary Faculty of the Barcelona Autonomous University (Dr. Santiago Lavin) along with the Department of Pathology of the University of California (Prof G. Diane Shelton). The only spontaneous animal myositis model is found in dogs, especially Collies, and when accompanied by cancer, in Boxers. Several antibodies have been described in dogs but it is not known if they are also found in humans. In dogs, myositis specific antibodies may be positive or negative. If human beings and dogs share a common autoimmune response, a new door might be opened to deepen our understanding of the etiopathogenia and the species-specificity of these illnesses.

Immunobiology and immunopathology of recurrent pregnancy loss and spontaneous loss

Jaume Alijotas Reig

Around 2-3% of reproductive-age couples suffer recurrent pregnancy losses. Almost 18% of couples that wish to have children suffer infertility problems. Simultaneously, 2-3% of all pregnant women are diagnosed with spontaneous loses. The expression of HLA molecules, specially type G, the degree of trophoblastic apoptosis, the outsourcing of new neoantigens such as phospholipids, the balance between Th1/Th2/Th3 cytokines, the type and quantity of CD4+CD25+Foxp3+ lymphocytes, the kind and the activity of uterine NK cells (uNK) cells, the presence or absence of blocking antibodies, and other mechanisms play different roles in the achievement of the so-called "tolerant microenvironment" needed to develop a normal pregnancy. Therefore, both autoimmune and alloimmune mechanisms are important. We aim to study which isolated, and specifically associated, anomalies can be identified as risk markers to be able to evaluate possible treatments.

Cellular microparticle study in women with and without antiphospholipid antibodies with recurrent pregnancy losses and preeclampsia

Jaume Alijotas Reig

Cellular microparticles (CMP) are released depending on the activation and/or the presence of cell apoptosis. They are capable of activating both inflammatory and coagulation pathways. It seems that levels of CMP are higher in healthy pregnant women. A working hypothesis establishes that an increase of CMP levels may be found in recurrent pregnancy losses and preeclampsia. It is thought that their thrombophilic capacity may be higher in those patients with anti-phospholipid antibodies, especially among those with lupus anticoagulant. We want to determine MPC levels in non-pregnant healthy women, pregnant women without previous abnormal obstetric events, women with recurrent pregnancy losses, and women with severe preeclampsia. We are also evaluating whether there are differences related to the presence or absence of antiphospholipid antibodies. Finally, we will also characterize the exact type of CMP (endothelial, platelet-like, leuco-monocyte, and trophoblastic).

Pathogenic role of cellular microparticles and anti-phospholipid/anti-cofactor antibodies in recurrent implantation failures related to In Vitro Fertilization (IVF)

Jaume Alijotas Reig

The prevalence of failed IVF is high or very high. Besides problems intrinsic to the technique, we know almost nothing about the possible underlying causes. Anti-phospholipid/anti-cofactor (aPL/aCF) antibodies have been associated with several obstetric complications. Nevertheless, the role that these aPL/aCF antibodies may have in failed IVF is not well defined. With this randomized study we want to understand better the use that these antibodies may have on a clinical daily basis. Along with microparticle analysis, we could find several elements that might act as risk markers, which in turn might even help us to fine-tune currently used therapeutic approaches.

Development of the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS/EUROMAP)

Jaume Alijotas Reig
and Inmaculada Farrán Codina

So-called obstetric antiphospholipid syndrome seems to have pathogenic, biological, therapeutic, and evolution features somehow different from those observed in patients who suffer from "classic" antiphospholipid syndrome. Although experience and scientific evidence seem to support this idea, there is a lack of information that would permit us to suggest changes in the classification and/or therapeutic criteria. The European Forum on Antiphospholipid Antibody Syndrome has decided to continue this project and it has chosen the Vall d'Hebron Hospital as the European Coordinating Centre. Many leading Spanish and European hospitals will participate in this multicentric study.

Proinflammatory cytokines TNF and IL-6 in cellular senescence. A HUVEC aging model

Jaume Alijotas Reig

Cells that are chronically exposed to inflammatory signals are more prone to aging than those which are not exposed to such signals. Human vascular endothelial cell (HUVEC) primary cultures activated with TNF-alpha probably increase the expression of ICAM and VCAM, synthesize ROS, and express senescence markers. It is not known what the principal intracellular pathway is (although it is thought that STAT may play a role) and it is unknown if one or more proinflammatory cytokines are needed to activate NF-KB. We are trying to find out the role that IFN-alpha and/or IL-6 and IL-1B may have on the aging inflammatory phenomena and we aim to detect the intracellular signal pathways (STAT). We are also working on the characterization of the genes involved in these abnormal biological responses.

Specific Antinuclear antibodies of scleroderma as markers for different clinical patterns

Carmen Pilar Simeón i Aznar and Vicenç Fonollosa Pla

We want to establish the relationship between the presence of specific autoantibodies for scleroderma (anti-centromere, anti-topoisomerase 1, anti-polymerase III, anti-U3 RNP, Anti-Th/To, Anti-Pm/Scl, anti-Ku) and the different demographic and clinical features as well as with the disease prognosis.

Genetic basis of scleroderma

Carmen Pilar Simeón i Aznar and Vicenç Fonollosa Pla

With this study we aim to study the genetic background of the disease to deepen knowledge of its pathogenesis, to be able to establish links between genetic variations and different clinical-biological patterns. This research is based on a multicentric study and it is led by Prof. Javier Martín of the "Instituto López-Neyra" of Parasitology, CSIC (Granada). We contribute to it by sending samples from our cohort of patients along with the clinical data.

Spanish Registry of Scleroderma patients (Systemic Autoimmune Diseases Group, Spanish Internal Medicine Association)

Carmen Pilar Simeón i Aznar and Vicenç Fonollosa Pla

This multicentric study includes 14 hospitals with a cohort of 916 scleroderma patients. Its main goal consists of determining both the prognostic factors and the survival of these patients.

Significance of Capillaroscopy in Raynaud's phenomenon and scleroderma

Carmen Pilar Simeón i Aznar and Vicenç Fonollosa Pla

We want to describe the capillaroscopy alterations observed in patients with Raynaud's phenomenon and scleroderma. Our main objective is to establish the different patterns that may be related to visceral involvement and to the prognosis in the early stages of the disease.

Protein expression of small collagenase 3 and leucine-rich proteoglycans in cutaneous tissue of patients with diffuse scleroderma

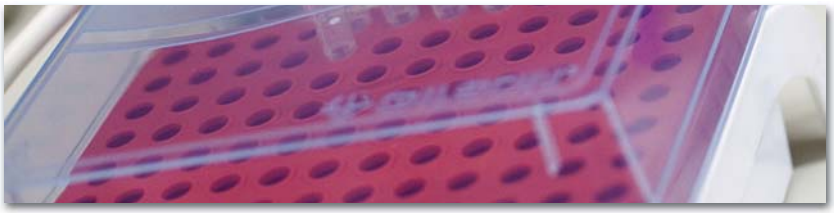
Carmen Pilar Simeón i Aznar and Vicenç Fonollosa Pla

This study, carried out along with researchers from the "Hospital del Mar" and from the "Institut Municipal d'Investigació Mèdica", aims to correlat the expression of SLRPs and MMP-13 with the severity of cutaneous involvement, hand dysfunctional capacity, capillaroscopy patterns, and cutaneous ultrasonography of patients affected with diffuse scleroderma in different evolutive stages of the disease.

Molecular basis of Rheumatoid Arthritis

Sara Marsal Barril

Genomewide Association Studies (GWAS) and whole genome gene expression analyses are being carried out to study the genetic basis of RA as well as to identify new biological markers of the response to biological therapies in this disease. The systematic analysis of RA and other directly related Immunomediated Inflammatory Diseases (i.e. IMIDs), will allow us to identify disease-specific molecular mechanisms but also more general processes associated to autoimmunity. One important objective is the identification of biomarkers that are specific for disease subtypes that are more relevant clinically. In parallel to this research, one of our main goals it the development of bioinformatic tools that allow us to improve the analysis of different types of genomic data.



Fybromialgia. Clinical and epidemiological aspects
Cayetano Alegre de Miguel
A systematic revision of the efficacy and security of pharmacological interventions in fybromialgia has been performed. A research line for the identification of biological markers for this disease has been recently initiated.

Juvenile Idiopathic Arthritis. Epidemiological, genetic and clinical aspects
Consuelo Modesto Caballero
An epidemiological study characterizing for the first time the incidence and prevalence of JIA in Catalonia has been coordinated. In this study, pediatric doctors from multiple primary health care centres have been collaborating. In low prevalence cases, genes recently characterized for the susceptibility to other inflammatory entitites like RA are being analyzed to identify potential causal mutations. The inclusion of Doppler Ecography technique in the systematic analysis of the musculoskeletical system of JIA will enable the identification of those cases having minimal residual forms of the disease.

CURRENT RESEARCH PROJECTS

PI: Sara Marsal Barril
Efectivitat, seguretat i adecuació dels medicaments biotecnològics en el tractament dels pacients amb artritis reumatoide
Funding Agency: Agència d'Informació Avaluació i Qualitat en Salut
Reference: AATRM053/02/2006
Funding: 46,560 €
Duration: 2007 to 2010

PI: Albert Selva O'Callaghan
Aticuerpos antitransglutaminasa en biopsias musculares de pacientes con miopía inflamatoria
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080450
Funding: 33,880 €
Duration: 2009 to 2011

PI: Miguel Vilardell Tarrés
Lupus y apoptosis: Mecanismo de acción de la talidomida y sus análogos en el lupus cutáneo refractario. Implicaciones clínicas y terapéuticas
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080112
Funding: 13,189 €
Duration: 2009 to 2011

PI: Sara Marsal Barril
Diagnóstico precoz de artritis reumatoide, psoriasis y enfermedad inflamatoria intestinal
Funding Agency: Fundación Caja Navarra
Reference: CAN-15450
Funding: 6,002.41 €
Duration: 2009 to 2010

PI: Victòria Cardona Dahl
Estudi RECORD (al·lergen RECOmbinants en Resolució Diagnòstica)
Funding Agency: Stat. Catalana d'Al·lèrgia i Immunologia Clínica
Reference: SCAIC2009/01
Funding: 9,000 €
Duration: 2009 to 2011

PI: Josefina Cortés Hernández
Ensayo clínico aleatorizado y controlado para evaluar la eficacia de la azatioprina vs. micofenolato sódico para el tratamiento de la fase de inducción y mantenimiento de la remisión de los brotes extra renales del lupus eritematoso sistémico (EUDRA 2008-008934-35)
Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-188
Funding: 213,508.13 €
Duration: 2010 to 2011

PI: José Ordi Ros
Estudio para evaluar la eficacia y seguridad de la lenalidomida en el tratamiento del lupus eritematoso cutáneo
Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-194
Funding: 204,000 €
Duration: 2010 to 2010

PI: Sara Marsal Barril
Proyecto IMID-Inc, "Biobanco IMIDs permite identificar biomarcadores y nuevas terapias". FEDER
Funding Agency: Ministerio de Ciencia e Innovación
Reference: IPT-010000-2010-36
Funding: 2,058,748.99 €
Duration: 2010 to 2013

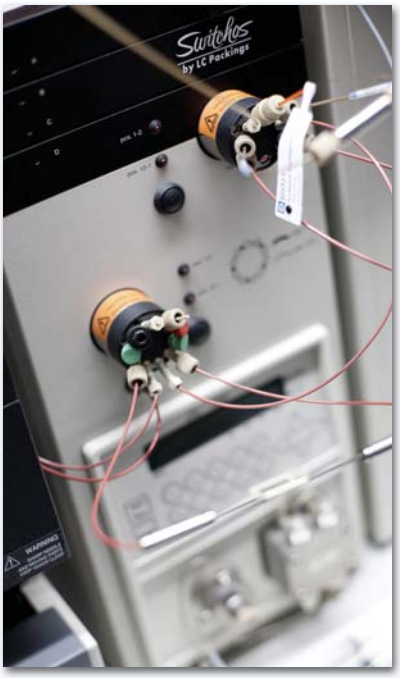
PI: Miguel Vilardell Tarrés
Autoimmunitat i malaltia trombòtica
Funding Agency: AGAUR
Reference: 2009 SGR 661
Funding: 49,920 €
Duration: 2010 to 2013

PI: Consuelo Modesto Caballero
Artritis inflamatòries de la infància: estudi prospectiu de la seva incidència i prevalència a Catalunya
Funding Agency: Fundació La Marató de TV3
Reference: TV3/032010
Funding: 111,384 €
Duration: from 2004 to 2011

PI: Sara Marsal Barril
Estudio de asociación de genoma completo en las enfermedades inflamatorias mediadas por mecanismos inmunes "WGAS-IMID"
Funding Agency: Ministerio de Ciencia e Innovación
Reference: PSS-010000-2008-36
Funding: 3,269,849 €
Duration: from 2008 to 2010

PI: Sara Marsal Barril
Estudio de asociación de genoma completo en nuevas enfermedades inflamatorias mediadas por mecanismos inmunes "WGAS-newIMID"
Funding Agency: Ministerio de Ciencia e Innovación
Reference: PSS-010000-2008-39
Funding: 732,973 €
Duration: from 2008 to 2010

PI: Sara Marsal Barril
Construcción de un predictor diagnóstico para las enfermedades inflamatorias mediadas por mecanismos inmunes "Predictor-IMID"
Funding Agency: Ministerio de Ciencia e Innovación
Reference: PSS-010000-2009-1
Funding: 1,448,244 €
Duration: from 2009 to 2010



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Alijotas-Reig J, Ferrer-Oliveras R, Rodrigo-Anoro MJ, Farrán-Codina I, Cabero-Roura L, Vilardell-Tarrés M. Anti-beta(2)-glycoprotein-I and anti-phosphatidylserine antibodies in women with spontaneous pregnancy loss. *Fertil Steril* 2010 May 1; 93 (7): 2330-6. ➲ IF: 3.970.

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Alijotas-Reig J, Miró-Mur F, Planells-Romeu I, García-Aranda N, García-Giménez V, Vilardell-Tarrés M. Are Bacterial Growth and/or Chemotaxis Increased by Filler Injections? Implications for the Pathogenesis and Treatment of Filler-Related Granulomas. *Dermatology* 2010; 221 (4):356-64. ➲ IF: 2.741.

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Pardos-Gea J, Pérez-López J, San José Laporte A, Vilardell Tarrés M. [Home intravenous antibiotic therapy of hepatic abscess: Safety, efficacy and predictive factor of hospital readmission.] *Med Clin (Barc)* 2010 Apr 17; 134 (11): 473-6. ➲ IF: 1.231.

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AREA 8 PATHOLOGY, CELLULAR AND GENE THERAPY

8.1 Bioengineering, Orthopedics and Surgery in Pediatrics

Group Leader
César Galo García Fontecha
Tel. 93 489 43 55/31 54/30 75
cgarcia@ir.vhebron.net

AREA PAEDIATRIC ORTHOPAEDICS

Coordinators
César Galo García Fontecha
Mario Aguirre Canyadell
Francisco Soldado Carrera
Roberto Vélez Villa

AREA PAEDIATRIC SURGERY

Coordinators
José Luis Peiró Ibáñez
Carlos Giné Prades
Gabriela Guillén Burrieza
Vicenç Martínez Ibáñez
José Fernando Vuletín Solís

AREA BIOENGINEERING

Margarita Codinach Creus
Mario Marotta Baleriola
Luciano Rodríguez Gómez

CURRENT RESEARCH PROJECTS

PI: Francisco Soldado Carrera
Determinación de marcadores de riesgo ecográficos de amputación en bridas amnióticas de extremidades en el feto ovino
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/0503
Funding: 41,745 €
Duration: 2008 to 2011

PI: Mario Aguirre Canyadell
Efectos del plasma rico en factores de crecimiento en la consolidación del callo óseo de elongación
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070874
Funding: 28,314 €
Duration: 2008 to 2010

2010 Impact Factor:
10.275

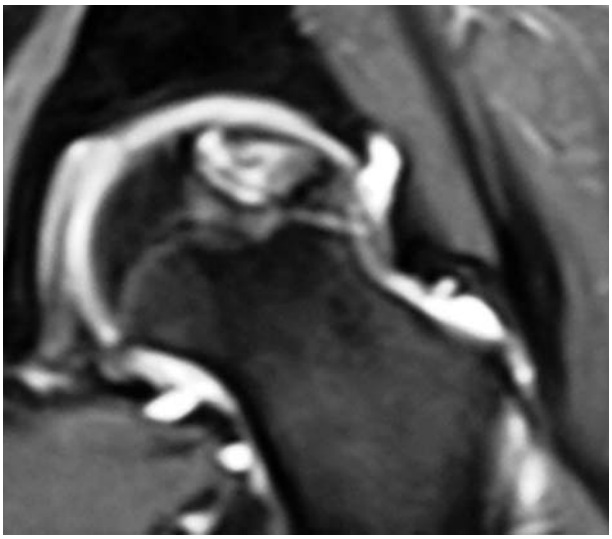

Figure 84
Femoral head necrosis

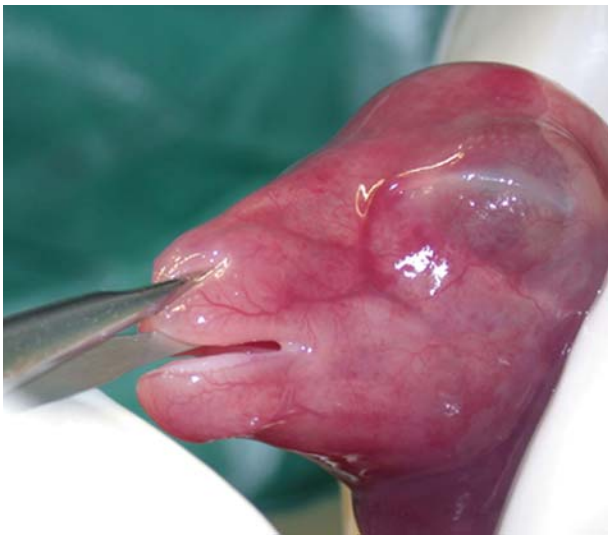

Figure 85
Induction of cleft in fetal sheep

PUBLICATIONS
(Impact Factor: 10.275)

Bueno J, Pérez-Lafuente M, Venturi C, Segarra A, Barber I, Molino JA, Romero A, Ortega J, Bilbao I, Martínez-Ibáñez V, Charco R. No-touch hepatic hilum technique to treat early portal vein thrombosis after pediatric liver transplantation. *Am J Transplant* 2010 Sep; 10 (9): 2148-53. ➲ IF: 6.433.

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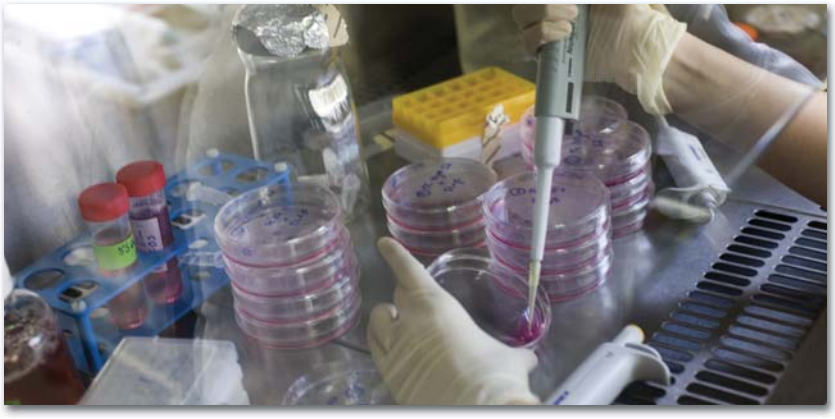
Valdivielso-Ortiz A, Barber I, Soldado F, Aguirre Canyadell M, Enriquez G. Solitary osteochondroma: spontaneous regression. *Pediatr Radiol* 2010 Oct; 40 (10): 1699-701. IF: 1.186.

PI: César Galo García Fontecha
Aplicación de células madre obtenidas de líquido amniótico para la regeneración neural y ósea en la reparación fetal del MMC en feto ovino
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/15/2008
Funding: 35,000 €
Duration: 2008 to 2011



AREA 8 PATHOLOGY, CELLULAR AND GENE THERAPY

8.2 Genetics

Group Leader
Alberto Plaja Rustein
Tel. 93 489 30 00
aplaja@vhebron.net

Researchers
Miguel del Campo Casanelles
Anna María Cueto González
Carmen Mediano Vizuete
Alberto Plaja Rustein
Teresa Vendrell Bayona

Nursing, Technical and Administrative Staff
Asunción Fernández Rodríguez

OBJECTIVES

The study of the genetic basis of human diseases, with special emphasis on those of chromosomal and genomic origin.

RESEARCH LINES

Study of complex and cryptic chromosomal reorganization and its phenotypic consequences

Study of aneuploidy and chromosomal instability

Study of segmental duplications, genomic reorganization and phenotypic consequences

Study of the genetic basis of autism spectrum disorders (ASD)

Study of fetal alcohol syndrome

Clinical and molecular studies of Williams syndrome

Elaboration of computer tools for welfare development of clinical genetics and attention to rare diseases

Genetics of cardiopathies

2010 Impact Factor:
45. 848

CURRENT RESEARCH PROJECTS

PI: Miguel del Campo Casanelles
Rare Disease Portal RD-PORTAL-Grant No 2006119Funding agency: Public Health Executive Agency (PHEA)
Funding Agency: European Commission
Reference: ORPHANET-2006119
Funding: 72,072 €
Duration: 2007 to 2010

PI: Miguel del Campo Casanelles
Evaluación de la eficacia y seguridad de Losartán en la reducción del estrés oxidativo y la disminución de la Tensión Arterial (TA) en pacientes con síndrome de Williams (SW) y dos o más copias del gen NCF1
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90123
Funding: 161,305.10 €
Duration: 2007 to 2010

PI: Alberto Plaja Rustein
Investigación del papel de las reorganizaciones genómicas en los defectos congénitos del corazón (DGC) y desarrollo de nuevas herramientas de diagnóstico genético prenatal y postnatal
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00632
Funding: 109.505,00 €
From: 2010 to 2012

PUBLICATIONS
(Impact Factor: 45.848)

Antonell A, Campo M del, Magano LF, Kaufmann L, Iglesia JM de la, Gallastegui F, Flores R, Schweigmann U, Fauth C, Kotzot D, Pérez-Jurado LA. Partial 7q11.23 deletions further implicate GTF2I and GTF2IRD1 as the main genes responsible for the Williams-Beuren syndrome neurocognitive profile. *J Med Genet* 2010 May; 47 (5): 312-20. ➲ IF: 5.751.

Audí L, Fernández-Cancio M, Carrascosa A, Andaluz P, Torán N, Piro C, Vilaró E, Vicens Calvet E, Gussinyé M, Albisu MA, Yeste D, Clemente M, Hernández de la Calle I, Campo M del, et al. Novel (60%) and Recurrent (40%) Androgen Receptor Gene Mutations in a Series of 59 Patients with a 46,XY Disorder of Sex Development. *J Clin Endocrinol Metab* 2010 Apr; 95 (4): 1876-88. ➲ IF: 6.202.

Badenas C, Rodríguez-Revenga L, Morales C, Mediano C, Plaja A, Pérez-Iribarne MM, Soler A, Clusellas N, Borrell A, Sánchez MA, Miró E, Sánchez A, Milà M, Jiménez W. Assessment of QF-PCR as the first approach in prenatal diagnosis. *J Mol Diagn* 2010 Nov; 12 (6): 828-34. ➲ IF: 3.413.

Díez O, Gutiérrez Enríquez S, Mediano C, Masas M, Saura C, Gadea N, Balmaña J. A novel de novo BRCA2 mutation of paternal origin identified in a Spanish woman with early onset bilateral breast cancer. *Breast Cancer Res Treat* 2010 May; 121 (1): 221-5. ➲ IF: 4.696.

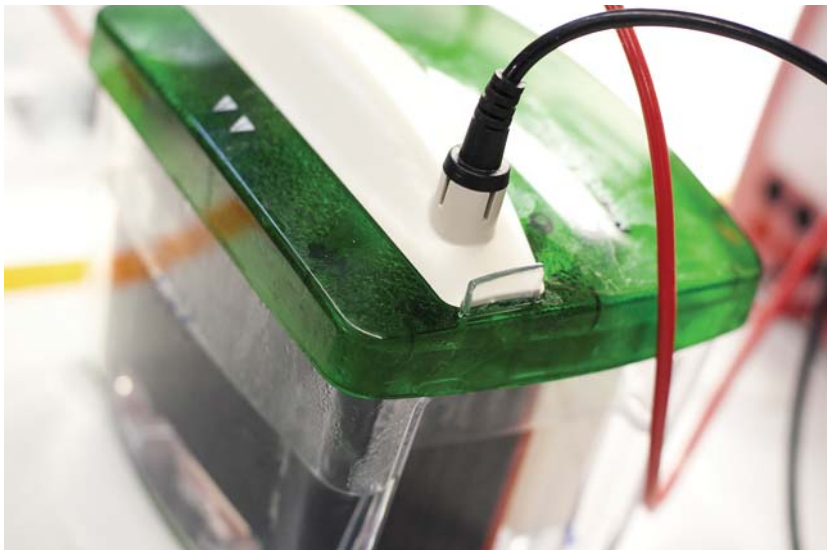
Jones KL, Hoyme HE, Robinson LK, Campo M del, Manning MA, Prewitt LM, Chambers CD. Fetal alcohol spectrum disorders: Extending the range of structural defects. *Am J Med Genet A* 2010 Nov; 152A (11): 2731-5. ➲ IF: 2.404.

Micale L, Turturo MG, Fusco C, Augello B, Jurado LA, Izzi C, Digilio MC, Milani D, Lapi E, Zelante L, Merla G. Identification and characterization of seven novel mutations of elastin gene in a cohort of patients affected by supravalvular aortic stenosis. *Eur J Hum Genet* 2010 Mar; 18 (3): 317-23. ➲ IF: 3.564.

Prat E, Rey JD, Ponsa I, Nadal M, Camps J, Plaja A, Campillo M, Algaba F, Gelabert A, Miró R. Comparative Genomic Hybridization Analysis Reveals New Different Subgroups in Early-Stage Bladder Tumors. *Urology* 2010 Feb; 75 (2): 347-55. ➲ IF: 2.365.

Rodríguez-Santiago B, Brunet A, Sobrino B, Serra-Juhe C, Flores R, Armengol L, Vilella E, Gabau E, Guitart M, Guillamat R, Martorell L, Valero J, Gutiérrez-Zotes A, Labad A, Carracedo A, Estivill X, Pérez-Jurado LA. Association of common copy number variants at the glutathione S-transferase genes and rare novel genomic changes with schizophrenia. *Mol Psychiatry* 2010 Oct; 15 (10): 1023-33. ➲ IF: 15.049.

Romanelli V, Belinchon A, Benito-Sanz S, Martínez-Glez V, Gracia-Bouthelier R, Heath KE, Campos-Barros A, García-Minaur S, Fernández L, Meneses H, López-Siguero JP, Guillén-Navarro E, Gómez-Puertas P, Wesselink JJ, Mercado G, Esteban-Marfil V, Palomo R, Mena R, Sánchez A, Campo M del, Lapunzina P. CDKN1C (p57(Kip2)) analysis in Beckwith-Wiedemann syndrome (BWS) patients: Genotype-phenotype correlations, novel mutations, and polymorphisms. *Am J Med Genet A* 2010 Jun; 152ª (6): 1390-7. ➲ IF: 2.404.



AREA 8 PATHOLOGY, CELLULAR AND GENE THERAPY

8.3 Maternal Fetal Medicine

Group Leader
Lluís Cabero Roura
Tel. 93 489 30 85
lcabero@vhebron.net

Researchers
Lluís Cabero Roura
Elena Carreras Moratonas
María del Mar Goya Canino
Teresa Higueras
Elisa Llurba
Anna Suy

Researcher in Training
María Carme Merced Vázquez

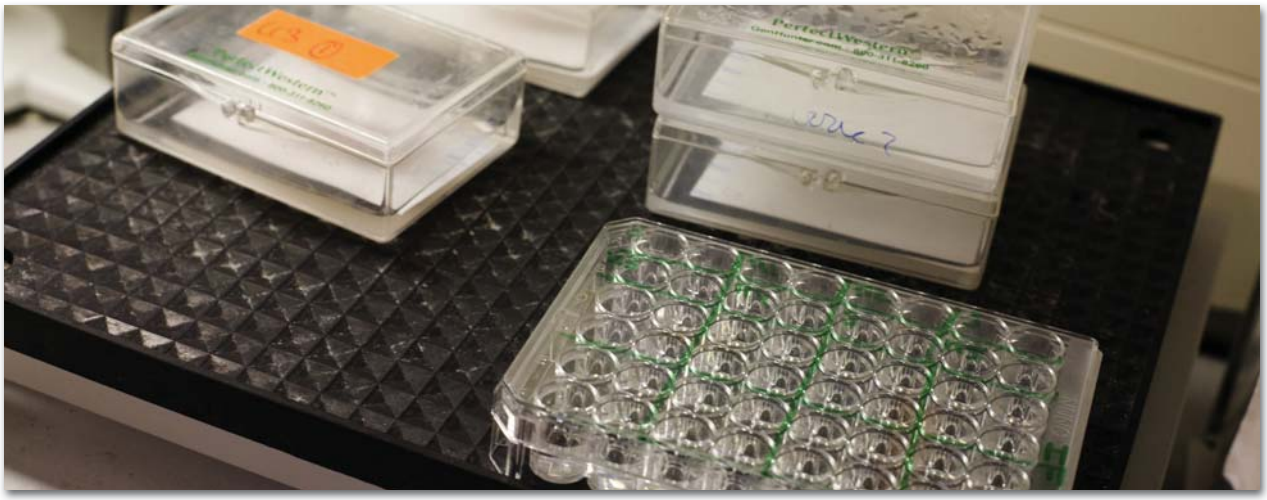
OBJECTIVES

The Maternal Fetal Medicine Research Group within the Department of Obstetrics of Vall d`Hebron University Hospital is one of the largest maternity units in Spain with more than 5,000 deliveries per year it constitutes a tertiary reference centre, fully accredited as a training centre, with 28 residents by the European Board and College of Obstetrics and Gynaecology (EBCOG) and the European Association of Perinatal Medicine (EAPM). The Maternal Fetal Medicine Research group work together with the Research Institute Vall d'Hebron (VHIR) wich promotes basic and applied research and hosts the laboratories of HUVH. The Maternal Fetal Medicine Research Group is formed by a network of interdisciplinary researches from clinical and basic science with the same focus of interest:

- Maternal and fetal specialist.
- Fetal and pediatric cardiologists specialist.
- Neonatal pediatrics specialist.
- Pediatric surgeons.
- The Investigation Center of Biochemistry and Molecular Biology (CIBBIM) group.
- The Immunology and Ageing Research group.
- Geneticians.
- Fetal and pediatric Radiologist.
- Anesthesiologist.
- Anatomopathologist specialized in congenital diseases.

There is a powerful and established synergy within the Maternal and Fetal Health Research Centre (www.medfetal.org) and the Research Institute of Vall d'Hebron Hospital (www.vhir.org), that provides the resources to develop eight different lines of research:

1) Lipid metabolism and oxidative stress in PE;
2) Angiogenic factors and uterine artery Doppler in the prediction of PE and IUGR;
3) Maternal and fetal cardiac function in PE and IUGR: cardiovascular risk;
4) Preterm birth: prediction and prevention;
5) Obesity in pregnancy;
6) Use of 3D-4D in fetal abnormalities;
7) Twin-to-twin transfusion syndrome, and
8) Experimental and clinical fetal therapy.



In the last 6 years this group has obtained 10 national grants and is currently coordinating two clinical trials on preterm birth (PECEP) and screening of PE and IUGR (UTOPIA) (clinicaltrials.gov). It is also involved in 3 other international clinical trials. This group has generated more than 72 original papers published in high impact factor international medical journals.

RESEARCH LINES

Prevention of preterm birth

María del Mar Goya Canino, Laia Pratcorona Alicart and María Carme Merced Vázquez

- Efficacy of the combined use of ultrasonographic cervical length and cervical fibronectin in the optimization of the clinical management of premature labour and labour induction.
- Prevention of preterm birth using cervical pessary in pregnant women with short cervix" (PECEP trial): randomized control trial to demonstrate the efficacy of pessary in the prevention of preterm birth.
- Cervical Occlusion Trial in women with cervical incompetence (European Multicentric Study).

Fetal Medicine

Elena Carreras Moratonas, José Luis Peiró Ibáñez, Silvia Arévalo Martínez, María Ángeles Sánchez Durán and Mª Teresa Higueras Sanz

This group has considerable experience in fetal surgery, being considered one of the pioneers in the field in Spain and Europe. Our present focuses of investigation are:

- Laser therapy for monochorionic pregnancy complications: twin-to-twin transfusion syndrome and selective intrauterine growth restriction (IUGR).
- Fetal surgery: in utero treatment for congenital diaphragmatic hernia intrauterine blood transfusion, Thoracic Shunting, amniotic band release, percutaneous dilatation of aortic valve estenosis.

Metabolic diseases: diabetes and obesity

María del Mar Goya Canino, Mari Carmen Domínguez Luengo, Juan Carlos Bello Muñoz and María Carme Merced Vázquez

- Fetal programming: evaluation in fetal life of the patological mechanisms that lead to cardiovascular risk factors later in life.
- Oxidative stress and lipid metabolism in women with Diabetes.
- Perinatal Outcomes in Twins with Pregestational Diabetes (National Multicenter study).
- Effect of TRA techniques on perinatal outcomes of twins with pregestational and gestational diabetes- GLOBE Study: Effect of racial differences on Obesity during pregnancy (International Study).

2010 Impact Factor:
22.134

Preeclampsia and intrauterine growth restriction
Elisa Llurba Olivé, Mari Carmen Domínguez Luengo, Maria Queralt Ferrer Menduiña, Olga Sánchez García and Maria Gemma Soro González

- UTOPIA study: randomized multi-centre trial to evaluate if uterine artery Doppler screening in mid-pregnancy is able to identify women at risk for PE and/or IUGR in whom an exhaustive control of pregnancy might decrease maternal and fetal complications.
- Pregnancy as a stress test for cardiovascular disease: evaluation of cardiac and biochemical markers of atherosclerosis in mothers and children with preeclampsia (PE) and/or intrauterine growth restriction (IUGR).
- Fetal programming: evaluation in the fetal life of the pathological mechanisms that lead to cardiovascular risk factors later in life.
- Role of angiogenic and anti-angiogenic factors in preeclampsia and intrauterine growth restriction.
- Prediction of PE and IUGR by uterine artery Doppler and biochemical markers of placental underperfusion in the first trimester of pregnancy.
- Oxidative stress and lipid metabolism in women with PE.

CURRENT RESEARCH PROJECTS

PI: Lluís Cabero Roura
Eficacia de la medición Doppler del flujo de las arterias uterinas a las 11-14 semanas para la predicción de preeclampsia/RCIU y la prevención de complicaciones materno-fetales en la población española
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061312
Funding: 137,335 €
Duration: 2007 to 2010

PI: Elena Carreras Moratonas
Prevención del parto pretérmino mediante pesario cervical en gestantes con longitud cervical disminuida
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI071086
Funding: 132,011 €
Duration: 2008 to 2011

PI: Mª Teresa Higueras Sanz
Sistema Nervioso Central Fetal: desarrollo de un programa interactivo de segmentación asistida de imágenes ecográficas
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI08/90912
Funding: 18,150 €
Duration: 2009 to 2010

PI: Elena Carreras Moratonas
Neurografía fetal: sustituye a la resonancia magnética?
Funding Agency: Fundació Santiago Dexeus Font
Reference: FSDF2009/05
Funding: 6,000 €
Duration: 2009 to 2011

PUBLICATIONS
(Impact Factor: 22.134)

Alijotas-Reig J, Ferrer-Oliveras R, Rodrigo-Anoro MJ, Farrán-Codina I, Cabero-Roura L, Vilardell-Tarrés M. Anti-beta(2)-glycoprotein-I and anti-phosphatidylserine antibodies in women with spontaneous pregnancy loss. *Fertil Steril* 2010 May 1; 93 (7): 2330-6. ➲ IF: 3.970.

Brieno-Enriquez MA, Robles P, García-Cruz R, Roig I, Cabero L, Martínez F, Garciía Caldes M. A new culture technique that allows in vitro meiotic prophase development of fetal human oocytes. *Hum Reprod* 2010 Jan; 25 (1): 74-84. ➲ IF: 3.859.

Campoy C, Cabero L, Sanjurjo P, Serra-Majem L, Anadon A, Morán J, Fraga JM. [Update of knowledge, recommendations and full consensus about the role of long chain polyunsaturated fatty acids in pregnancy, lactating period and first year of life.] *Med Clin (Barc)* 2010 Jun 12; 135 (2): 75-82. ➲ IF: 1.231.

García-Cruz R, Brieno MA, Roig I, Grossmann M, Velilla E, Pujol A, Cabero L, Pessarrodona A, Barbero JL, Caldes MG. Dynamics of cohesin proteins REC8, STAG3, SMC1 beta and SMC3 are consistent with a role in sister chromatid cohesion during meiosis in human oocytes. *Hum Reprod* 2010 Sep; 25 (9): 2316-27. ➲ IF: 3.859.

García-Cruz R, Casanovas A, Brieno-Enríquez M, Robles P, Roig I, Pujol A, Cabero L, Durban M, García Caldes M. Cytogenetic analyses of human oocytes provide new data on non-disjunction mechanisms and the origin of trisomy 16. *Hum Reprod* 2010 Jan; 25 (1): 179-91. ➲ IF: 3.859.

Khan K, Zamora J, Lamont RF, Geijn Hp H van, Svare J, Santos-Jorge C, Jacquemyn Y, Husslein P, Helmer HH, Dudenhausen J, Renzo GC Di, Cabero Roura L, Beattie B. Safety concerns for the use of calcium channel blockers in pregnancy for the treatment of spontaneous preterm labour and hypertension: a systematic review and meta-regression analysis. *J Matern Fetal Neonatal Med* 2010 Sep; 23 (9): 1030-8. ➲ IF: 1.362.

Marín RC, Bello-Muñoz JC, Martínez GV, Martínez SA, Moratonas EC, Cabero Roura L. Use of 3-dimensional sonography for prenatal evaluation and follow-up of fetal goitrous hypothyroidism. *J Ultrasound Med* 2010 Sep; 29 (9): 1339-43. ➲ IF: 1.181.

Sabadell J, Casellas M, Alijotas-Reig J, Arellano-Rodrigo E, Cabero L. Inherited antithrombin deficiency and pregnancy: Maternal and fetal outcomes. *Eur J Obstet Gynecol Reprod Biol* 2010; 149 (1): 47-51. ➲ IF: 1.582.

Vilca Yengle LM, Campins Martí M, Cabero Roura L, Rodrigo Pendás JA, Martínez Gómez X, Hermosilla Pérez E , Vaqué Rafart J. Influenza vaccination in pregnant women. Coverage, practices and knowledge among obstetricians. *Med Clin* (Barc). 2010 Feb 13; 134 (4): 146-151. ➲ IF: 1.231.

Area 8 Pathology, Cellular and Gene Therapy

8.4 Neuro-spinal Pathology Study

Group Leader
Carlos Villanueva Leal
Tel. 93 489 34 81 / 34 79
cvillanueva@vhebron.net

Researchers
Juan Bagó Granell
José Manuel Casamitjana Ferrandiz
M. José Clara Colomina Soler
Montserrat Domingo Sábat
Ferran Pellisé Urquiza
Carlos Villanueva Leal

Researcher in Training
Alba Vila Casademunt

OBJECTIVES

- International multicentric data base of adult scoliosis.
- Identification of peri-operative factors related to postoperative infection in spinal surgery.
- Data base of metastatic tumors of the spine. Scoliosis outcome after surgical deformity correction.

RESEARCH LINES

Perioperative anaesthesia management
M. José Clara Colomina Soler

Degenerative lumbar spine problems
Ferran Pellisé Urquiza

Scoliosis and other spinal deformities
Juan Bagó Granell

Thoracolumbar Fractures
Carlos Villanueva Leal

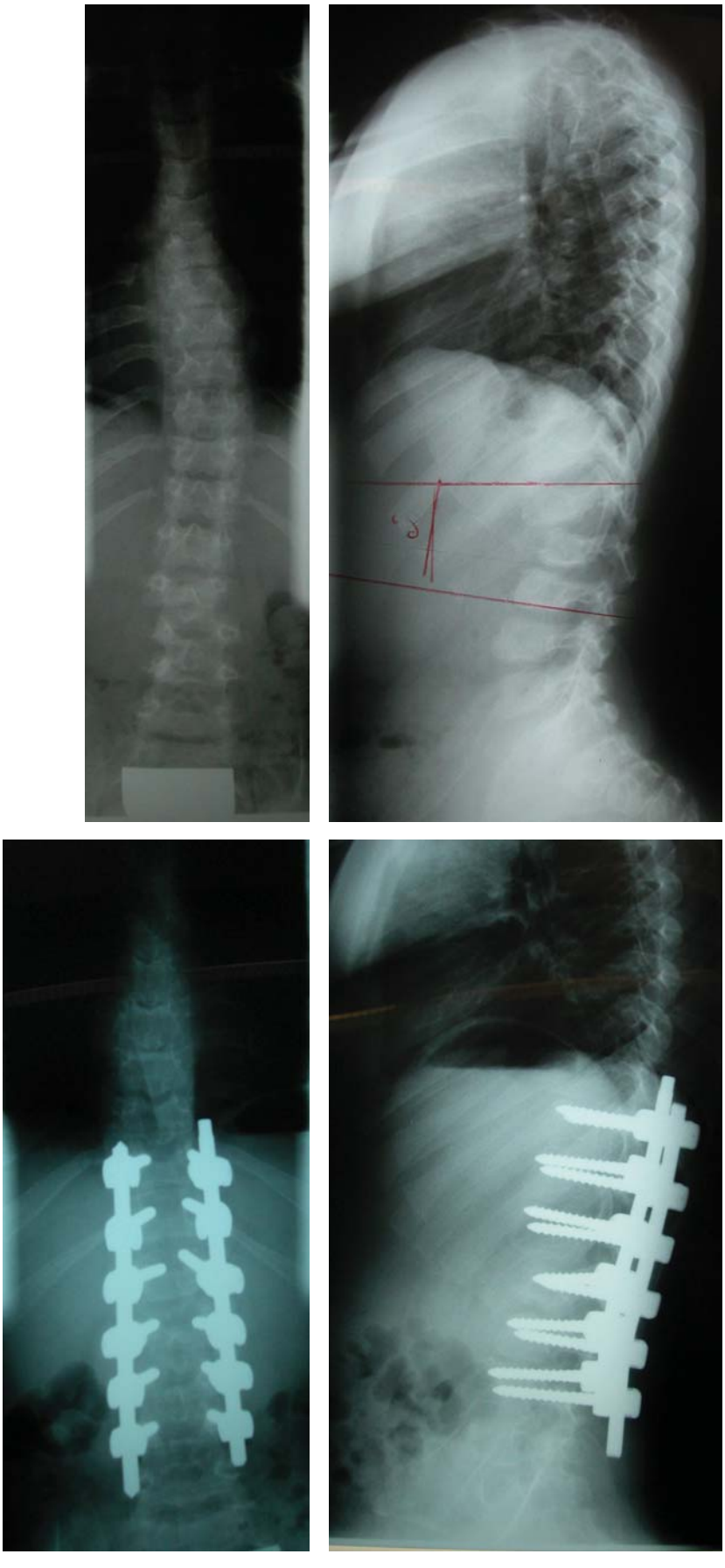
Cervical spine
José Manuel Casamitjana Ferrandiz

Spinal tumors
Ferran Pellisé Urquiza and Ainhoa Arias Baile

Postoperative Infections in Spinal Surgery
Ferran Pellisé Urquiza and Susana Núñez Pereira

Adult scoliosis
Ferran Pellisé Urquiza

2010 Impact Factor:
7.483



CURRENT RESEARCH PROJECTS

PI: M. José Clara Colomina Soler

Ensayo clínico, multicéntrico, aleatorizado y controlado con placebo para evaluar la eficacia de la utilización perioperatoria de ácido tranexámico sobre los requerimientos transfusionales y la hemorragia quirúrgica en la cirugía compleja de columna

Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-189
Funding: 78,611.40 €
Duration: 2010 to 2011

PUBLICATIONS
(Impact Factor: 7.483)

Martínez-Llorens J, Ramírez M, Colomina MJ, Bagó J, Molina A, Cáceres E, Gea J. Muscle dysfunction and exercise limitation in adolescent idiopathic scoliosis. *Eur Respir J* 2010 Aug; 36 (2): 393-400. ➲ IF: 5.527.

Nuñez S, Bagó J, Pellisé F. Posterior spinal instrumented fusion and decompression. *Eur Spine J* 2010 Mar; 19 (3): 513-4. ➲ IF: 1.956.

Figure 86
Surgical treatment of thoracolumbar kyphosis in Hurler's syndrome

Area 8 Pathology, Cellular and Gene Therapy

8.5 Ophthalmology

Group Leader
José García Arumí
Tel. 93 274 60 08
josgarci@vhebron.net

Researchers
Laia Bisbe López
Ana Boixadera Espax
Carme Macià Badia
Sara Martín Nalda
Vicente Martínez Castillo

Researchers in Training
Álvaro Barraza Meneses
Laura Distefano
Diana Paola Mora Ramírez
Andrea Reg Rodrigues Carvalho
Pau Tarrús Bozal

Nursing, Technical and Administrative Staff
Anna Salas Torras

OBJECTIVES

Our main areas of research include retinal vascular disease, inside which we are focused on the physiopathology of diabetic macular edema; physiopathology and treatment of retinal vein occlusions and new treatments for retinal artery occlusions through experimental models; retinal detachment, for which we are interested in the development of a new surgical technique for its treatment. The physiopathology of vitreoretinal proliferation; age-related macular degeneration (ADM), for which we are studying genetic risk factors and the role played by inflammation in the pathogeny of uveitis, concretely the pathogeny of uveitic macular edema and the role played by antiangiogenic drugs in the treatment of this disorder.

2010 Impact Factor:
24.126

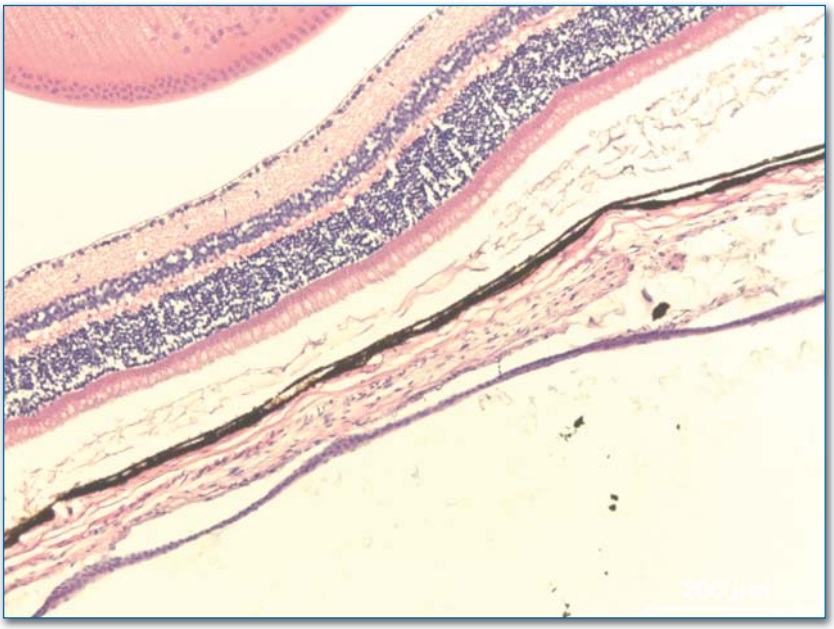


Figure 87
Rat model in the study of diabetic retinopathy. Ocular specimen stained by hematoxilin-eosin technique

RESEARCH LINES

Diabetic retinopathy research group

José García Arumí, Miguel Ángel Zapata Victori, Andrea Reg Rodrigues Carvalho and Anna Salas Torras

Our research group investigates new therapeutic approaches for diabetic retinopathy (DR). DR is one of the most prevalent and invalidated diseases present in the active age population.

Our research focus on clinic and basic science:

- Collaboration in multicentre clinical trials for new DR therapies.
- Research of angiogenic and anti-angiogenic factors in animal model of DR.
- "In vitro" and "in vivo" research of anti-angiogenic factors.
- Development of an anti-angiogenic gene therapy using non-viral vectors in an attempt to improve DR treatment and patient quality of life.

Retinal artery occlusion research group

José García Arumí, Miguel Ángel Zapata Victori, Andrea Reg Rodrigues Carvalho and Anna Salas Torras

Our research group investigates physiopathology as well as novel surgical approaches to retinal artery occlusion.

Our research focuses on clinic/surgery and basic science:

- Development and improvement of surgical treatment.
- Development of an animal model of branch retinal artery occlusion (BRAO).
- Research focusing on retinal neuronal death, structural changes and electrophysiology regarding time points of BRAO. Research on erythropoietin (EPO) and EPOr, VEGF and PEDF in ischemic retina.

Retinal vascular diseases

José García Arumí, Miguel Ángel Zapata Victori, Anna Boixadera and Carme Macià Badia

In diabetic retinopathy we are evaluating the efficacy of the new treatments that are used in this disease (anti-VEGF [vascular endothelial growth factor] agents) and designing new therapeutic approaches. In vascular retinal vein occlusions were are studying the vitreous factors that are related to the pathogenesis of macular edema. In retinal arterial occlusions we are evaluating foveal photoreceptor survival time after a branch retinal artery occlusion. For this purpose we are using an animal model (pig).

Age related macular degeneration

Miguel Ángel Zapata Victori

Our research group investigates one of the most prevalent and invalidated diseases present in the population over 50 years old.

Our research focuses on clinical and basic science:

- Collaboration in multicentre clinical trials for new exudative age related macular degeneration therapies, with both industry and public funds.
- Collaboration in multicentre studies of the macular degeneration genotype.
- Collaboration in multicentre studies in the progression of atrophic macular degeneration.
- Independent clinical trial research with new medications to treat exudative macular degeneration.
- Research of biomarkers and risk factors in intermediary macular degeneration.
- In vitro research into antiangiogenic and neuroprotective factors using primary and cell line retinal pigmentary epithelium cultures.

Uveitis

Carme Macià Badia

We are mainly investigating macular edema, which is a major important cause of vision loss in uveitis. We have not a completely effective treatment nowadays for this entity. A better understanding of the pathophysiology would allow a more successful therapeutical management. We are determinating intravitreal concentration of some interleukines and metalloproteinases in patients with macular edema secondary to these disease. We are evaluating the role of bevacizumab injections for the treatment of uveitic macular edema.

CURRENT RESEARCH PROJECTS

PI: José García Arumí

Expresión diferencial de citocinas y metaloproteinasas en el edema macular secundario a trastornos oclusivos venosos retinianos y el edema macular uveítico: análisis comparativo en humor vítreo

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI06/0803
Funding: 58,080 €
Duration: 2007 to 2011

PI: José García Arumí

Papel de la somatostatina-28 en la fisiopatología del edema macular secundario a uveítis

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070414
Funding: 94,985 €
Duration: 2008 to 2011

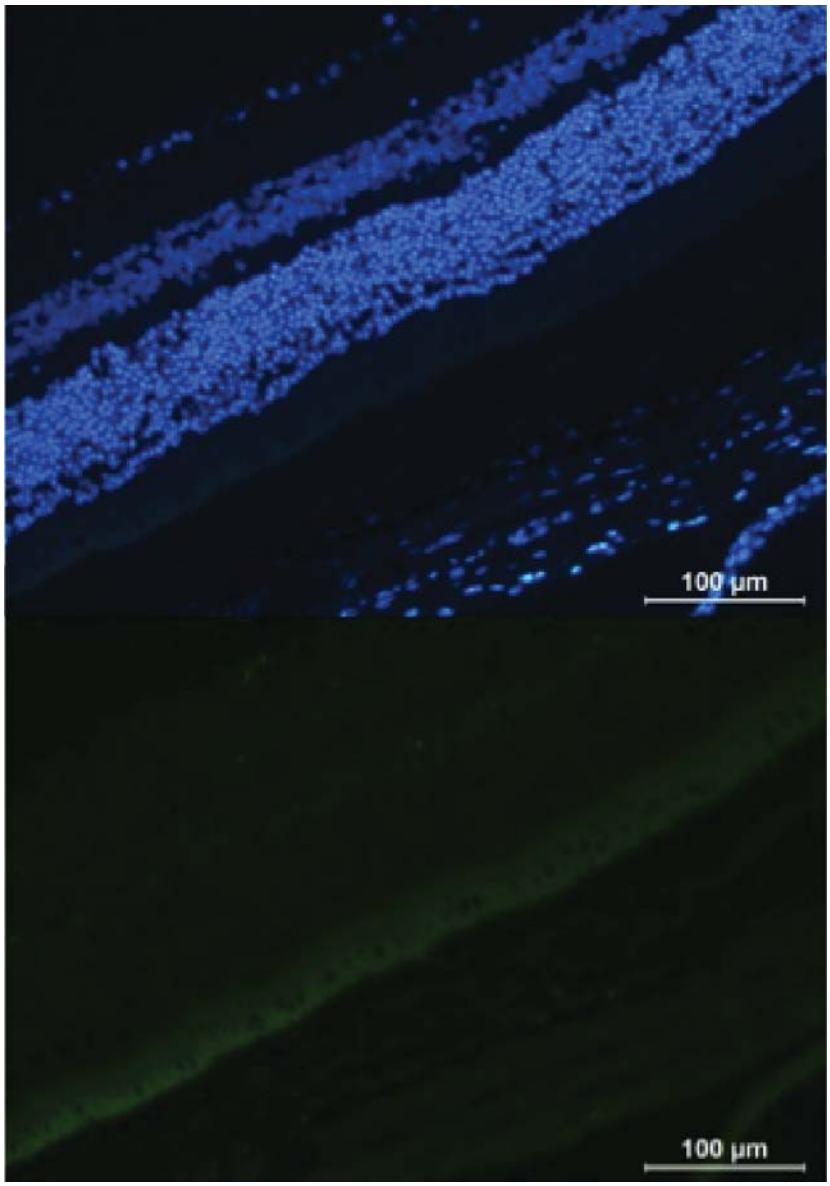
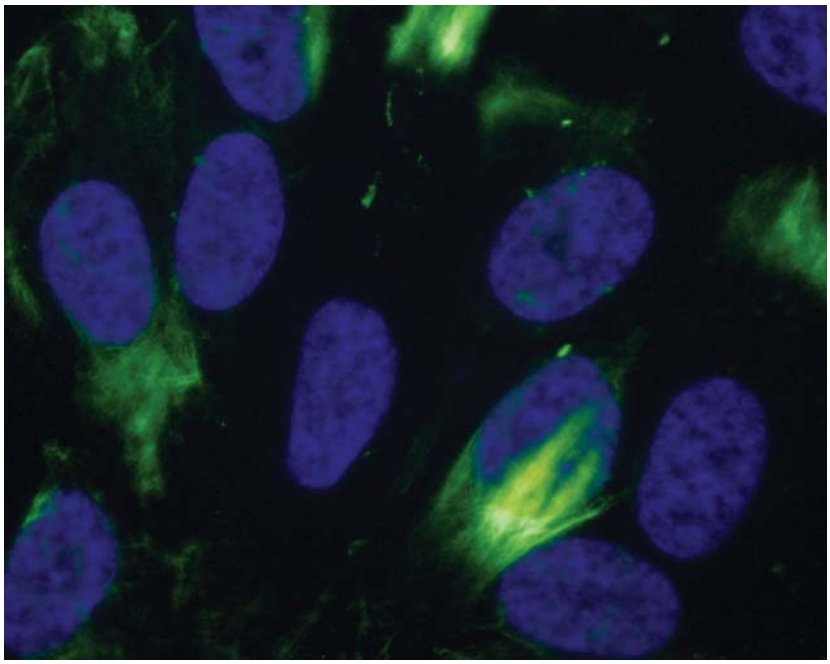


Figure 88
Immunofluorescence of transfected retina with non-viral vector

Figure 89
Immunofluorescence of retinal pigment epithelium cell line



PI: José García Arumí
Evaluación de la eficacia y seguridad de la inyección intravítrea de bevacizumab en el tratamiento de la neovascularización coroidea asociado a miopía magna
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90808
Funding: 39,204 €
Duration: 2007 to 2010

PI: José García Arumí
Estudio de la eficacia y seguridad de inyecciones intravítreas de bevacizumab en el edema macular secundario a obstrucciones venosas retinianas (EBOVER)
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00171
Funding: 42,737.20 €
Duration: 2009 to 2012

PI: Álex Fonollosa Calduch
Estudio aleatorizado y abierto de la eficacia, seguridad y tolerabilidad de dosis repetidas de bevacizumab intravítreo en pacientes con edema macular uveítico refractario
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00117
Funding: 3,025 €
Duration: 2009 to 2011

PI: Vicente Martínez Castillo
Roturas retinianas en las esclerotomías en el tratamiento del desprendimiento de retina rhegmatógeno primario mediante vitrectomía vía pars plana sin indentación escleral
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/01444
Funding: 19.965,00 €
Duration: 2010 to: 2012

PI: Miguel Ángel Zapata Victori
Ensayo clínico, abierto, de seguridad y eficacia de adalimumab intravítreo en pacientes con neovascularización coroidea secundaria a degeneración macular asociada a la edad no respondedores al tratamiento convencional con ranibizumab
Funding Agency: Ministerio de Sanidad y Política Social
Reference: TRA-196
Funding: 20,400 €
Duration: 2010 to 2011

PI: José García Arumí
OFTARED - Red de Patología Ocular del Envejecimiento, Calidad Visual y Calidad de Vida
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD07/0062/0010
Funding: 99,310.45 €
Duration: 2008 to 2011

PI: José García Arumí
Grup de Recerca en Oftalmologia Vall d'Hebron
Funding Agency: AGAUR
Reference: 2009 SGR 384
Funding: 0,00 €
Duration: 2010 to 2013

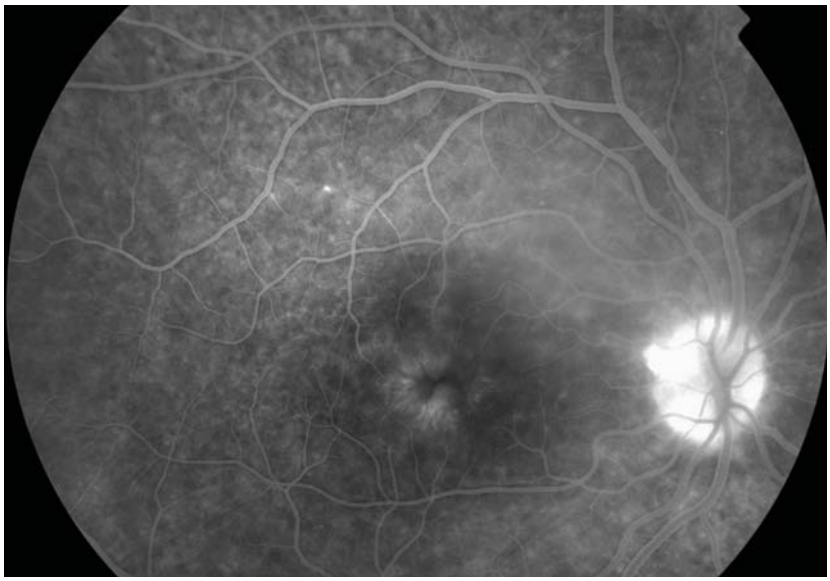


Figure 90
Fluorescein angiography of a patient with macular edema secondary to paunveítis

PUBLICATIONS (Impact Factor: 24.126)

Fonollosa A, García-Arumi J, Santos E, Macià C, Fernández P, Segura RM, Zapata MA, Rodríguez-Infante R, Boixadera A, Martínez-Castillo V. Vitreous levels of interleukine-8 and monocyte chemoattractant protein-1 in macular oedema with branch retinal vein occlusion. *Eye (Lond)* 2010 Jul; 24 (7): 1284-90. ➲ IF: 1.974.

Haller JA, Bandelló F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jacques ML, Jiao J, Li XY, Whitcup SM, García Arumí J, *et al.* Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010 Jun; 117 (6): 1134-1146.e3. ➲ IF: 5.491.

Hernández C, Zapata MA, Losada E, Villarroel M, García-Ramírez M, García-Arumí J, Simó R. Effect of intensive insulin therapy on macular biometrics, plasma VEGF and its soluble receptor in newly diagnosed diabetic patients. *Diabetes Metab Res Rev* 2010 Jul; 26 (5): 386-92. ➲ IF: 2.762.

Pavesio C, Zierhut M, Bairi K, Comstock TL, Usner DW, Abboud E, Amoaku W, Becker M, Brancato R, Benítez del Castillo JM, Calonge M, Carmona M, Marano RC, Caspers-Velu L, Díaz Llopis M, Smet M de, Dick A, Eldem B, Figueroa M, Forrester J, Frau E, García-Arumí J, et al. Evaluation of an intravitreal fluocinolone acetonide implant versus standard systemic therapy in noninfectious posterior uveitis. Ophthalmology 2010 Mar; 117 (3): 567-75, 575.e1. ➲ IF: 5.491.

Rojas J, Fernández I, Pastor JC, García-Gutiérrez MT, Sanabria MR, Brión M, Coco RM, Ruiz-Moreno JM, García-Arumí J, Elizalde J, Ruiz-Miguel M, Gallardo JM, Corrales RM, Carracedo A. A Strong Genetic Association between the Tumor Necrosis Factor Locus and Proliferative Vitreoretinopathy: The Retina 4 Project. Ophthalmology 2010 Dec; 117 (12): 2417-2423.e1-2. ➲ IF: 5.491.

Zapata MA, Badal J, Fonollosa A, Boixadera A, García-Arumí J. Insulin resistance and diabetic macular oedema in type 2 diabetes mellitus. *Br J Ophthalmol* 2010 Sep; 94 (9): 1230-2. ➲ IF: 2.917.

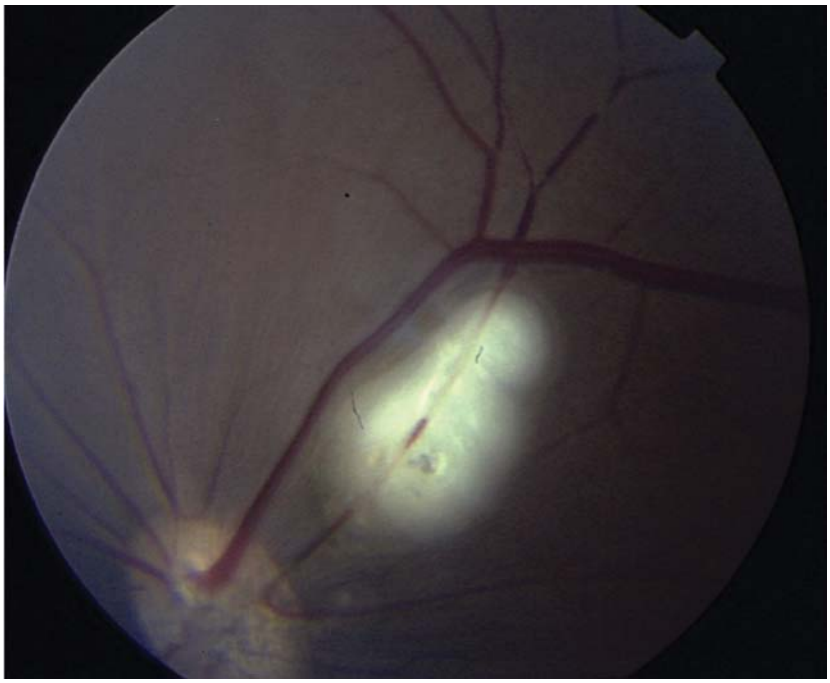


Figure 91
Retinography of a pig model in the study of branch retinal artery obstruction

AREA 8 PATHOLOGY, CELLULAR AND GENE THERAPY

8.6 Robotic and Craniofacial Surgery

Group Leaders
Guillermo Raspall Martín
Tel. 93 274 61 79
graspall@vhebron.net

Juan Antonio Hueto
Tel. 93 274 60 85
jahueto@vhebron.net

Researchers
Coro Bescós Atin
Javier Gutiérrez Santamaría
Juan Antonio Hueto Madrid
Jorge Pamias Romero
Guillermo Raspall Martín
Manuel Sáez Barba

OBJECTIVES

Research and development into the applications of robotics and information and image technologies in craniofacial surgery.

RESEARCH LINES

Robotics

Dr. Juan Antonio Hueto MD[1], Prof. Alícia Casals PhD[2], Prof. Josep Amat PhD[2], Dr. Javier Gutiérrez MD[1]

[1] Hospital General Universitario Vall d'Hebron.
[2] Departament d'Enginyeria de Sistemes, Automàtica i Informàtica Industrial (ESAII), Universitat Politècnica de Catalunya (UPC)

Imaging technologies and virtual reality

Dr. Juan Antonio Hueto MD[1], Prof. Isabel Navazo PhD[2], Prof. Pere Brunet PhD[2], Dr. Josep Rubio MD DDS[1]

[1] Hospital General Universitario Vall d'Hebron.
[2] Departament de Llenguatges i Sistemes Informatics (LSI), Universitat Politècnica de Catalunya (UPC)

Microsurgery

Dra. Coro Bescós MD PhD[1],
Dr. Jordi Pamias MD[1],
Dr. Manel Sáez MD PhD[1]
[1] Hospital General Universitario Vall d'Hebron

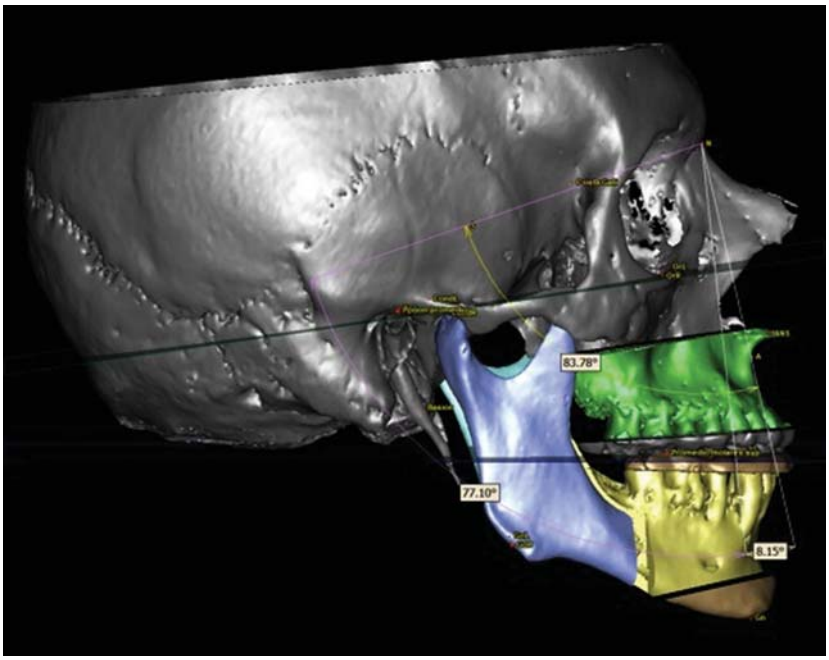
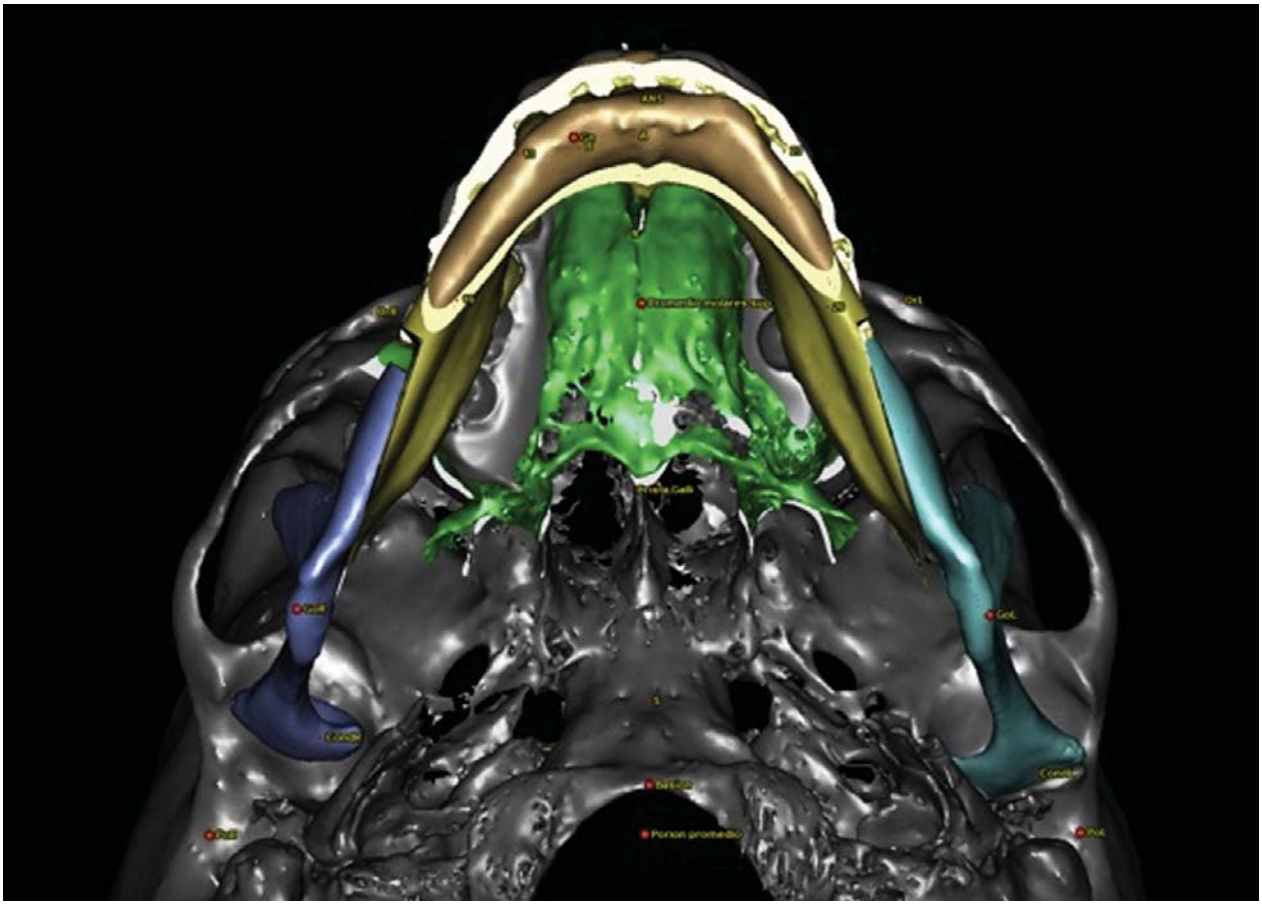


Figure 92
Example of craniofacial surgery

Figure 93
Imaging technology and virtual reality



AREA T1 EPIDEMIOLOGY, PHARMACOLOGY, NEW THERAPIES, CLINICAL RESEARCH

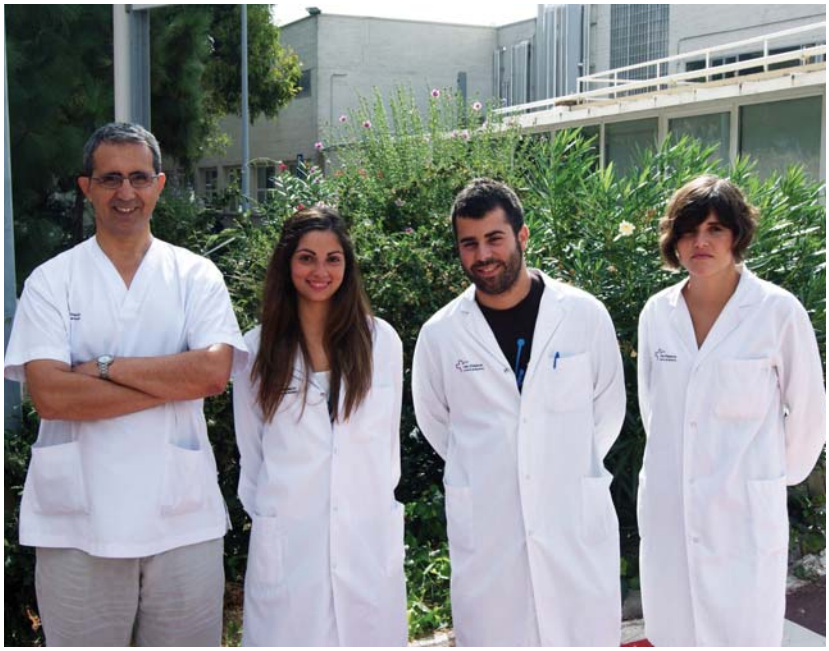
T1.1 Cell and Gene Therapy

Group Leader
Jordi Barquinero Mañez
Tel. 93 274 67 26
jbarquin@ir.vhebron.net

Researchers
Jordi Barquinero Mañez
Ramón Gimeno Martínez

Researchers in Training
Silvia Casacuberta Serra
Rebeca Sánchez Domínguez

Nursing, Technical and Administrative Staff
Sergio López Estévez



OBJECTIVES

- To investigate the mechanisms by which transplantation of hematopoietic cells expressing autoantigens induce tolerance in experimental autoimmune encephalomyelitis(EAE), a murine model of multiple sclerosis.
- To develop novel gene therapy strategies for MNGIE.
- To optimize hematopoietic differentiation from human induced pluripotent stem cells (iPSC).

2010 Impact Factor:
4.745

RESEARCH LINES

Immune tolerance induction through enforced expression of autoantigens in hematopoietic cells using gene therapy and non myeloablative strategies (in collaboration with Drs. C. Espejo, H. Eixarch and X. Montalban, Clinical Neuroimmunology Unit / CEM-Cat)
Jordi Barquinero

Applications of induced pluripotent stem cells (iPSC) on the diagnosis and therapy of diseases of the hematopoietic system (in collaboration with research groups at CIEMAT, CMRB and Hospital Niño Jesús)
Juan Bueren (CIEMAT, Madrid)

Preclinical development of a gene therapy strategy in hematopoietic cells for mitochondrial neurogastrointestinal encephalopathy (MNGIE) (in collaboration with Drs. R. Martí, J. Torres and A. Andreu, mitochondrial and neuromuscular pathology group)
Ramon Martí Seves

CURRENT RESEARCH PROJECTS

PI: Jordi Barquinero Mañez
Nuevas estrategias basadas en las células mieloides supresoras expresando autoantígenos para inducir tolerancia. Aplicación en un modelo experimental de esclerosis múltiple
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/00237
Funding: 134,915 €
Duration: 2010 to 2012

PI: Jordi Barquinero Mañez
Generación y diferenciación de células madre pluripotentes inducidas (IPS) de pacientes con enfermedades genéticas del sistema inmuno-hematopoyético
Funding Agency: Ministerio de Ciencia e Innovación
Reference: PLE2009-0100
Funding: 302,540 €
Duration: 2009 to 2012

PUBLICATIONS
(Impact Factor: 4.745)

Álvarez E, Moga E, Barquinero J, Sierra J, Briones J. Dendritic and tumor cell fusions transduced with adenovirus encoding CD40L eradicate B-cell lymphoma and induce a Th17-type response. *Gene Ther* 2010 Apr; 17 (4): 469-77. ➲ IF: 4.745.

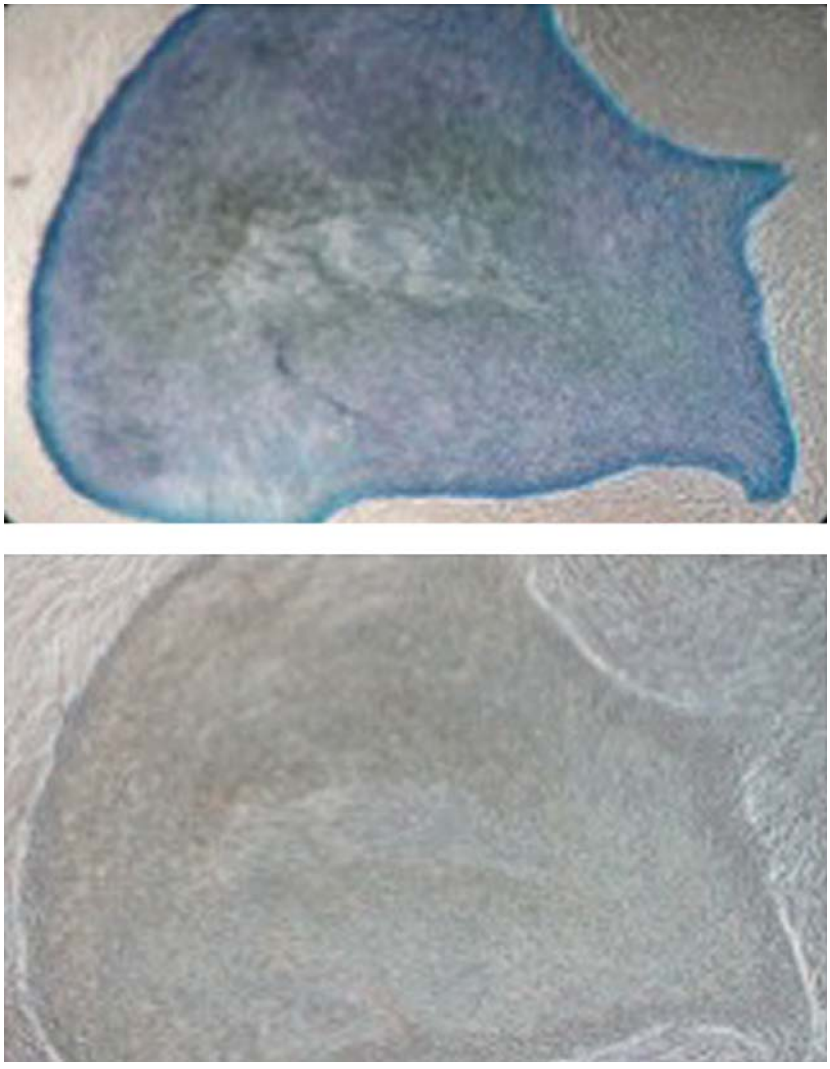


Figure 94
Human iPSC colony and the same colony after alkaline phosphatase staining

AREA T1 EPIDEMIOLOGY, PHARMACOLOGY, NEW THERAPIES, CLINICAL RESEARCH

T1.2 Clinical Pharmacology

Group Leader
Joan-Ramon Laporte Roselló
Tel. 93 489 41 05
jrl@icf.uab.es

Researchers
Cristina Aguilera
Maria Antònia Agustí Escasany
Josep Castel Llobet
Gloria Cereza García
Immaculada Danés Carreras
Eduard Diogène Fadini
Pili Ferrer Argelés
Albert Jesús Figueras Suñé
Immaculada Fuentes Camps
Núria García Dolade
Luisa Ibáñez Mora
Dolores Rodríguez Cumplido
Mònica Sabaté Gallego
Xavier Vidal Guitart

Nursing, Technical and Administrative Staff
Elena Ballarín Alins
José J Barroso García
Eulàlia Pérez Esquirol
Montserrat Pérez González
Ramón Puig Tressera
Lourdes Vendrell Bosch

OBJECTIVES

The main research field of the Foundation Catalan Institute of Pharmacology is pharmacoepidemiology, with a focus on research on effectiveness of medicine utilization and adverse effects of medicines in clinical practice. FICF is part of the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) research network, which is coordinated by the European Medicines Agency and of the PROTECT Group, a public-private consortium funded by the European Commission's IMI Initiative. It is also part of the Autonomous University of Barcelona Research Park.

2010 Impact Factor:
20.562

RESEARCH LINES

Risk of agranulocytosis associated with use of medicines
Joan-Ramon Laporte Roselló
In collaboration with all the Haematology services of the Metropolitan Area of Barcelona, and with support from the Spanish Agency on Medicines and Health Products and Sanofi-Aventis. This is a scheme for the case-control surveillance of agranulocytosis and aplastic anaemia.

Study on drug-induced liver disease
Luisa Ibáñez Mora and Mònica Sabaté Gallego
In collaboration with 12 Hepatology Units in the Metropolitan Area of Barcelona, the group performed a case-population study with the aim of estimating the risk of acute hepatitis associated with the use of medicines. A study of a cohort of patients who initiate treatment or prophylaxis with antituberculous drugs, and with the

aim of identifying those presenting a high risk of developing hepatotoxicity is being developed. The serum proteomic profiles of these patients will be analyzed.

Acute renal failure
Maria Antònia Agustí Escasany
In collaboration with three hospitals of the Metropolitan Area of Barcelona the group performs two studies to identify hospital admissions due to acute renal failure and hospital-acquired acute renal failure related to rennin-angiotensin-aldosterone system and other drugs with in-hospital use. The aim is to estimate the incidence rate and severity, describe the clinic characteristics and clinical course, the drugs involved, other associated risk factors, the length of the hospital stay, and the economical impact of acute renal failure.

PROTECT (Pharmacoepidemiological Research on Outcome of Therapeutics by a European ConsorTium
Joan-Ramon Laporte Roselló and Luisa Ibáñez Mora
The goal of this project is to strengthen the benefit-risk monitoring of medicines in Europe by developing innovative methods that will enhance the early detection and assessment of adverse drug reaction from different data sources (clinical trials, spontaneous reporting and observational studies). Our group is responsible for working on the use of national drug utilisation data. The specific tasks are to build and update an inventory of data sources on the consumption of the medicines of interest, to evaluate and disseminate methodologies for drug utilisation studies in order to estimate the potential public health impact of adverse drug reactions.

CURRENT RESEARCH PROJECTS

PI: Maria Antònia Agustí Escasany
Estudio prospectivo multicéntrico de la incidencia, relevancia clínica, factores de riesgo y preventibilidad del ingreso hospitalario por fracaso renal agudo asociado al uso de fármacos
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00244
Funding: 43,318 €
Duration: 2009 to 2011

PI: Luisa Ibáñez Mora
Caracterización de perfiles proteómicos predictivos de hepatotoxicidad asociada a medicamentos antituberculosos: un estudio exploratorio
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00250
Funding: 150,645 €
Duration: 2009 to 2011

Figure 96
We use standard and up to date web technologies and tools to build and run our products

PI: Joan-Ramon Laporte Roselló
Fundació Institut Català de Farmacologia
Funding Agency: AGAUR
Reference: 2009 SGR 412
Funding: 42,640 €
Duration: 2010 to 2013

Figure 95
On the FICF website informative materials, databases and publications are freely accessible

Figure 97
We design databases and develop electronic forms that can be accessed via the Internet

PUBLICATIONS (Impact Factor: 20.562)

Bosch Ferrer M, Lalueza Broto P. New oral anticoagulants for the prevention of venous thromboembolism. *Med Clin (Barc)* 2010 Mar 6; 134 (6): 279-81. ➲ IF: 1.231.

Cartoafa M, Agustí MA. Beta-blocking agents in the perioperative period of the non-cardiac surgery. *Med Clin (Barc)* 2010 Apr 24; 134 (12): 544-6. ➲ IF: 1.231.

Castells X, Casas M, Pérez-Mana C, Roncero C, Vidal X, Capella D. Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev* 2010 Feb 17; 2 : CD007380. ➲ IF: 5.653.

Cereza G, Agustí A, Pedros C, Vallano A, Aguilera C, Danés I, Vidal X, Arnau JM. Effect of an intervention on the features of adverse drug reactions spontaneously reported in a hospital. *Eur J Clin Pharmacol* 2010 Sep; 66 (9): 937-45. ➲ IF: 2.743.

Duran M, Pérez E, Abanades S, Vidal X, Saura C, Majem M, Arriola E, Rabanal M, Pastor A, Farré M, Rams N, Laporte JR, Capella D. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol* 2010 Nov; 70 (5): 656-63. doi: 10.1111/j.1365-2125.2010.03743.x. ➲ IF: 3.246.

Hereu P, Pérez E, Fuentes I, Vidal X, Suñé P, Arnau JM. Consent in clinical trials: What do patients know? *Contemp Clin Trials* 2010 Sep; 31 (5): 443-6. ➲ IF: 1.506.

Ruiz-Antorán B, Agustí Escasany A, Vallano Ferraz A, Danés Carreras I, Riba N, Mateu Escudero S, Costa J, Sánchez Santiago MB, Laredo L, Duran Quintana JA, Castillo JR, Abad-Santos F, Payares Herrera C, Sadaba Díaz de Rada , Gómez Ontanón E. Use of non-specific intravenous human immunoglobulins in Spanish hospitals; need for a hospital protocol. *Eur J Clin Pharmacol* 2010 Jun; 66 (6): 633-41. ➲ IF: 2.743.

Secoli SR, Figueras A, Lebrao ML, Lima FD de, Santos JL. Risk of potential drug-drug interactions among Brazilian elderly: a population-based, cross-sectional study. *Drugs Aging* 2010 Sep 1; 27 (9): 759-70. doi: 10.2165/11538460-000000000-00000. ➲ IF: 2.209.

AREA T1 EPIDEMIOLOGY, PHARMACOLOGY, NEW THERAPIES, CLINICAL RESEARCH

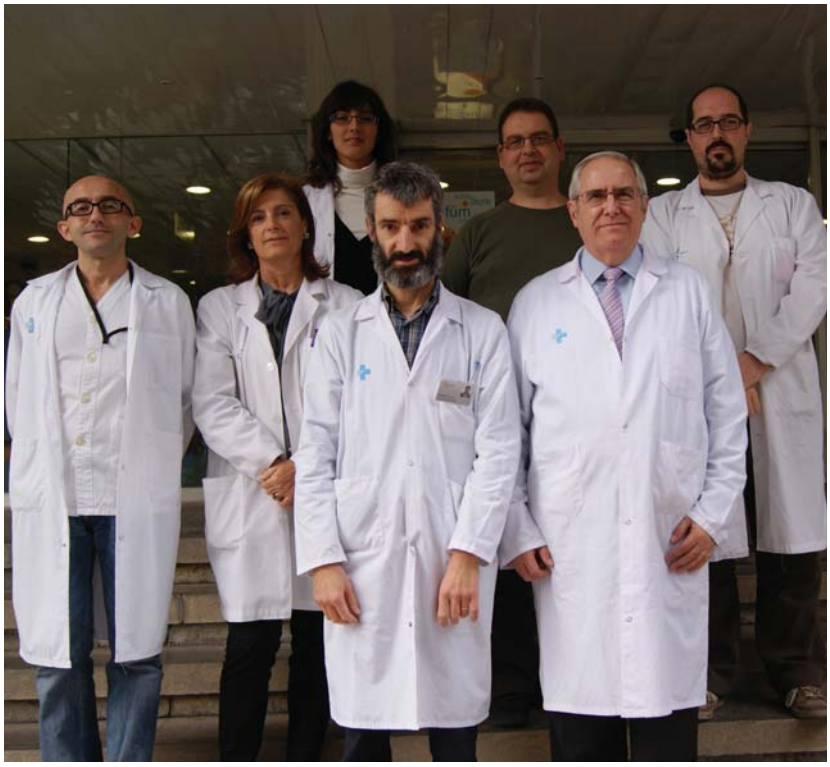
T1.3 Epidemiology and Public Health (EPIDEM)

Group Leader
Josep Vaqué Rafart
Tel. 93 489 42 10
jvaque@vhebron.net

Researchers
Lluis Armadans Gil
Magda Campins Martí
José Rosselló Urgell
Josep Vaqué Rafart

Researcher in Training
Susana Otero Romero

Nursing, Technical and Administrative Staff
Maria Elena Ballarín Alins
Eduard Hermosilla Pérez
Eva María López Guerrero
Santiago Pérez Hoyos



OBJECTIVES

Expand research on hospital epidemiology, preventive vaccines, health services and public health.

RESEARCH LINES

Nosocomial infections epidemiology
Josep Vaqué Rafart
Studying the evolution, features, host and healthcare-associated factors and impact of these infections.

Preventive vaccines
Magda Campins Martí
Developing studies on the effectiveness and characteristics of use of preventive vaccines in hospital and community contexts.

2010 Impact Factor:
42.287

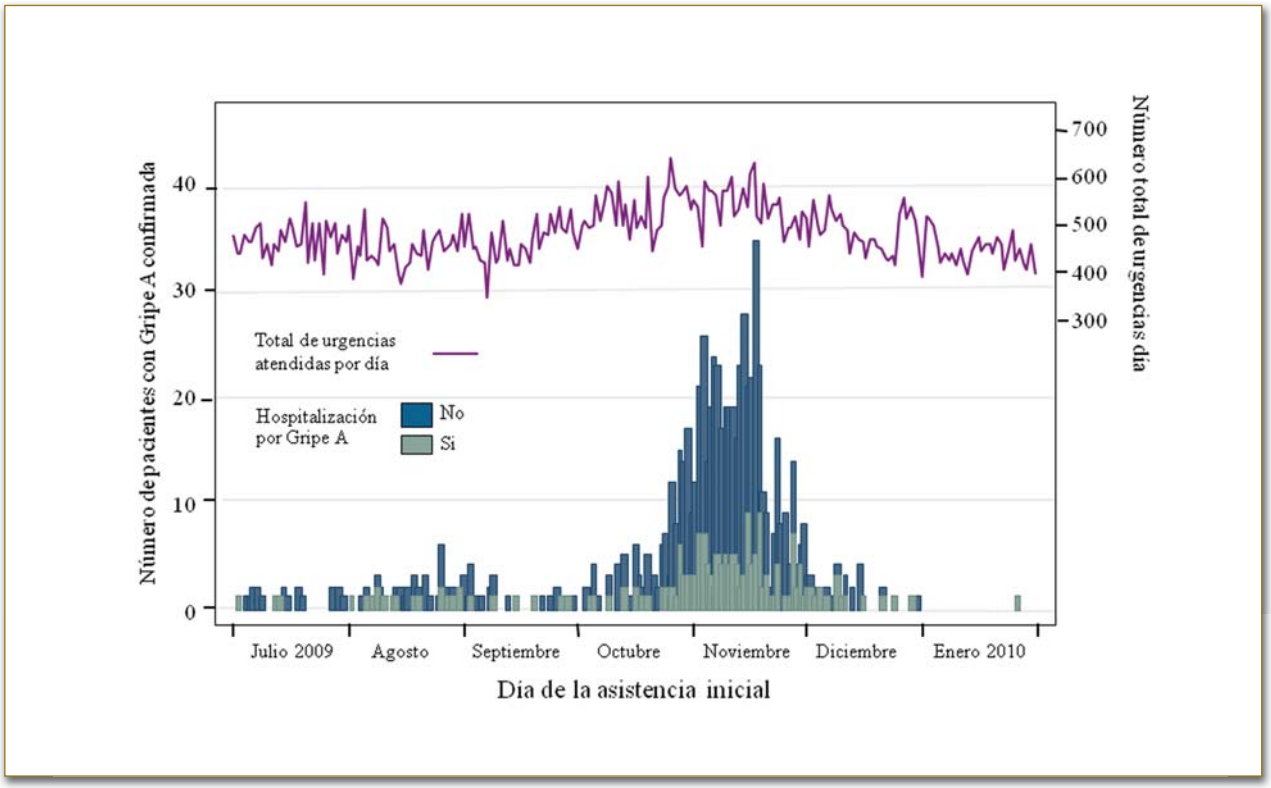
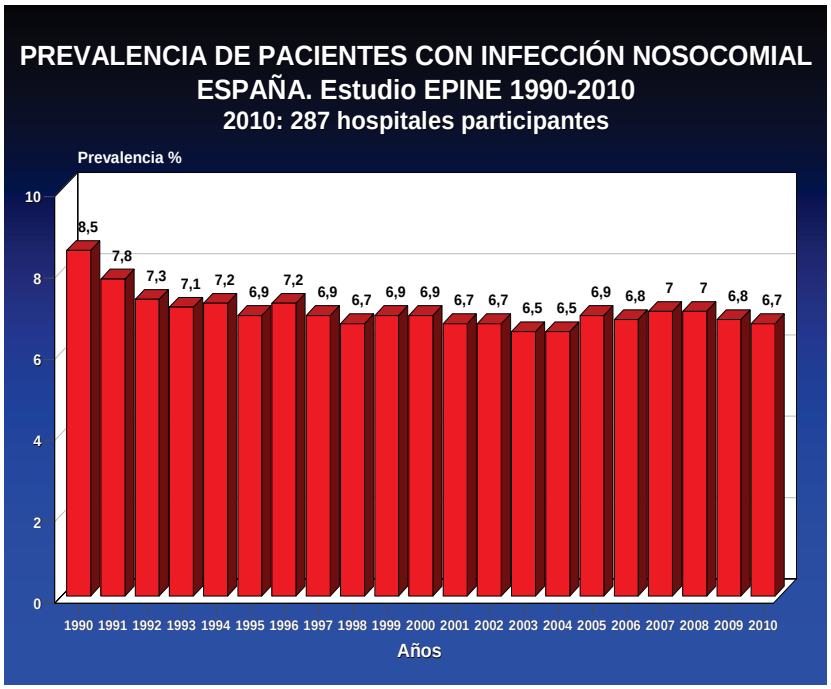


Figure 98
Distribution of confirmed cases of influenzavirus A (H1N1) which were seen at Hospital Universitari Vall d'Hebron, from 2nd July, 2009 until 22nd January, 2010



CURRENT RESEARCH PROJECTS

PI: Josep Vaqué Rafart

Estudio de la efectividad de la vacunación antigripal en la reducción del riesgo de muerte y hospitalizaciones en los ancianos

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070560
Funding: 63,525 €
Duration: 2008 to 2010

Figure 99
Evolution of prevalence of patients with nosocomial infection in Spain, EPINE Study 1990-2010

PUBLICATIONS
(Impact Factor: 42.287)

Brotons M, Campins M, Méndez L, Juste C, Rodrigo JA, Martínez X, Hermosilla E, Pinos L, Vaqué J. Effectiveness of varicella vaccines as postexposure prophylaxis. *Pediatr Infect Dis J* 2010 Jan; 29 (1): 10-3. ➲ IF: 2.854.

Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua J, Morán T, Astudillo J, Alonso G, Borro JM, González-Larriba JL, Torres A, Camps C, Guijarro R, Isla D, Aguiló R, Alberola V, Padilla J, Sánchez-Palencia A, Sánchez JJ, Hermosilla E, Massuti B. Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non-Small-Cell Lung Cancer. *J Clin Oncol* 2010 Jul 1; 28 (19): 3138-45. ➲ IF: 17.793.

Frick MA, Moraga-Llop FA, Bartolomé RM, Larrosa N, Campins M, Román Y, Vindel A, Figueras C. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in children. *Enferm Infecc Microbiol Clin* 2010 Jul 31. ➲ IF: 1.393.

López-Cano M, Manas MJ, Hermosilla E, Espín E. Multivisceral Resection for Colon Cancer: Analysis of Prognostic Factors. *Dig Surg* 2010 Aug; 27 (3): 238-45. ➲ IF: 1.372.

Otero S, Batlle J, Bonaventura I, Brieva L, Bufill E, Cano A, Carmona O, Escartín A, Marco M, Moral E, Munteis E, Nos C, Pericot I, Perkal H, Ramio-Torrenta L, Sastre-Garriga J, Tintoré M, Vaqué J, Montalban X, Pérez-Miralles F, *et al*. Multiple sclerosis epidemiological situation update: pertinence and set-up of a population based registry of new cases in Catalonia. *Rev Neurol* 2010 May 16; 50 (10): 623-33. ➲ IF: 1.234.

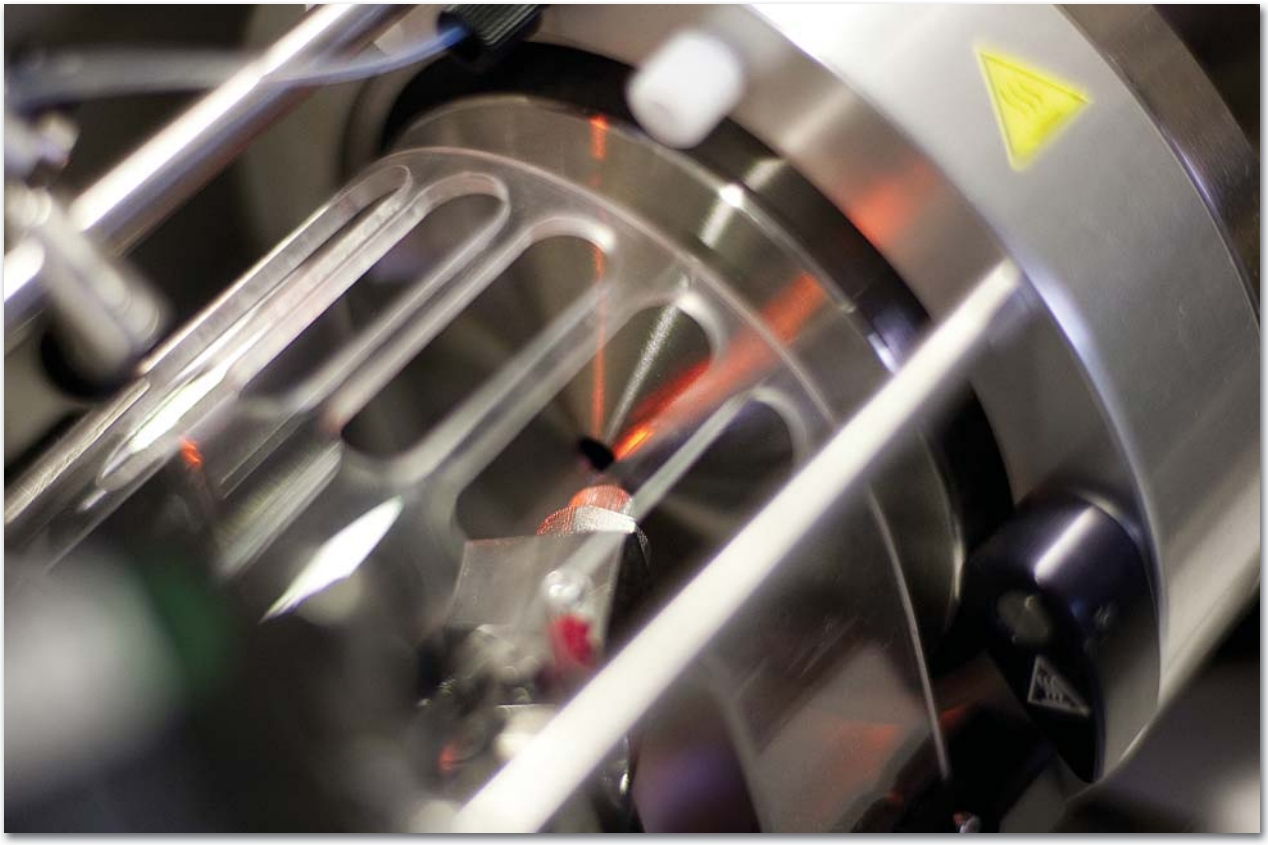
Selva-O'Callaghan A, Fonollosa-Pla V, Trallero-Araguas E, Martínez-Gómez X, Simeón-Aznar CP, Labrador-Horrillo M, Vilardell-Tarrés M. Nailfold capillary microscopy in adults with inflammatory myopathy. *Semin Arthritis Rheum* 2010 Apr; 39 (5): 398-404. ➲ IF: 4.724.

Selva-O'Callaghan A, Grau JM, Gámez-Cenzano C, Vidaller-Palacín A, Martínez-Gómez X, Trallero-Araguas E, Andia-Navarro E, Vilardell-Tarrés M. Conventional cancer screening versus PET/CT in dermatomyositis/polymyositis. *Am J Med* 2010 Jun; 123 (6): 558-62. ➲ IF: 4.466.

Trallero-Araguas E, Labrador-Horrillo M, Selva-O'Callaghan A, Martínez MA, Martínez-Gómez X, Palou E, Rodríguez-Sánchez JL, Vilardell-Tarrés M. Cancer-associated myositis and anti-p155 autoantibody in a series of 85 patients with idiopathic inflammatory myopathy. *Medicine (Baltimore)* 2010 Jan; 89 (1): 7-52. ➲ IF: 5.054.

Vaqué J. Epidemiology of influenza A (H1N1) worldwide and in Spain. *Arch Bronconeumol* 2010; 46S2: 3-12. ➲ IF: 2.166.

Vilca Yengle LM, Campins Martí M, Cabero Roura L, Rodrigo Pendas JA, Martínez Gómez X, Hermosilla Pérez E, Vaqué Rafart J. Influenza vaccination in pregnant women. Coverage, practices and knowledge among obstetricians. *Med Clin (Barc)* 2010 Feb 13; 134 (4): 146-151. ➲ IF: 1.231.



AREA T1 EPIDEMIOLOGY, PHARMACOLOGY, NEW THERAPIES, CLINICAL RESEARCH

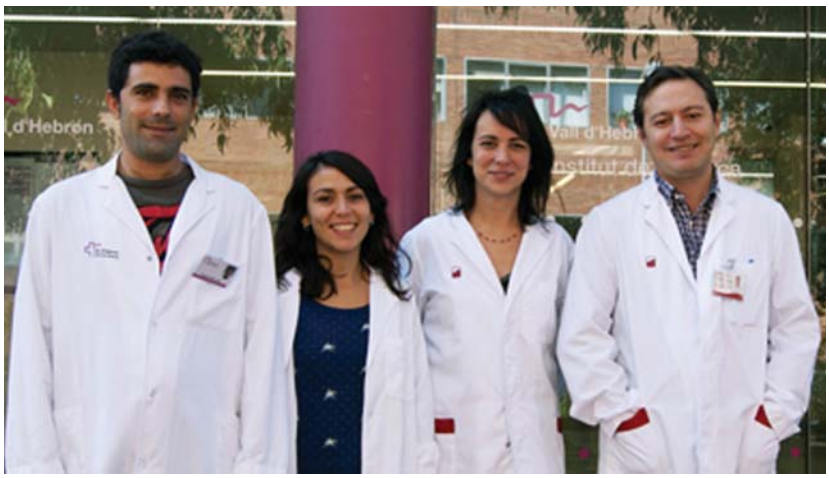
T1.4 Molecular Diagnosis and Therapy

Group Leader
Francisco Vidal Pérez
Tel. 93 274 67 26
fvidal@ir.vhebron.net

Researchers
Lluis Martorell Cedres
Francisco Vidal Pérez

Researcher in Training
Irene Corrales Insa

Nursing, Technical and Administrative Staff
Lorena Ramírez Orihuela



OBJECTIVES

Since its foundation in 1998 the Molecular Diagnosis and Therapy Unit (UDTM) of the Blood and Tissue Bank, has had a dual character providing-diagnostic support in congenital coagulation disorders as well as other hereditary diseases and research and development into new approaches in the field of medical diagnostics and therapeutics. In addition an important part of the current objectives are innovation in technological tools and their transfer to the laboratory routine. The research activity of the UDTM is linked to its commitment to the Hemophilia Unit of Vall d'Hebron Hospital (reference centre for congenital coagulopathies in Catalonia) in the development of molecular protocols applicable to genetic counselling, prenatal and preimplantation diagnosis. In-depth studies of the molecular events discovered in some affected individuals and the genotype-phenotype relationship constitute the most basic area of the team's goals.

RESEARCH LINES

Identification of the mutations responsible for hemophilia A and B in the Spanish population. Applications to therapeutic orientation, genetic counseling, prenatal and preimplantation diagnosis
Francisco Vidal Pérez

Molecular diagnosis of von Willebrand disease: study of genotype-phenotype relationship and application to clinical diagnosis
Francisco Vidal Pérez

Establishment of protocols and genetic study of the rare monogenic bleeding disorders: FXI deficiency, FXIII deficiency, combined deficit of FV and FVIII, FVII deficiency, the genetic platelet disorder Glanzmann's thrombasthenia, etc.
Francisco Vidal Pérez

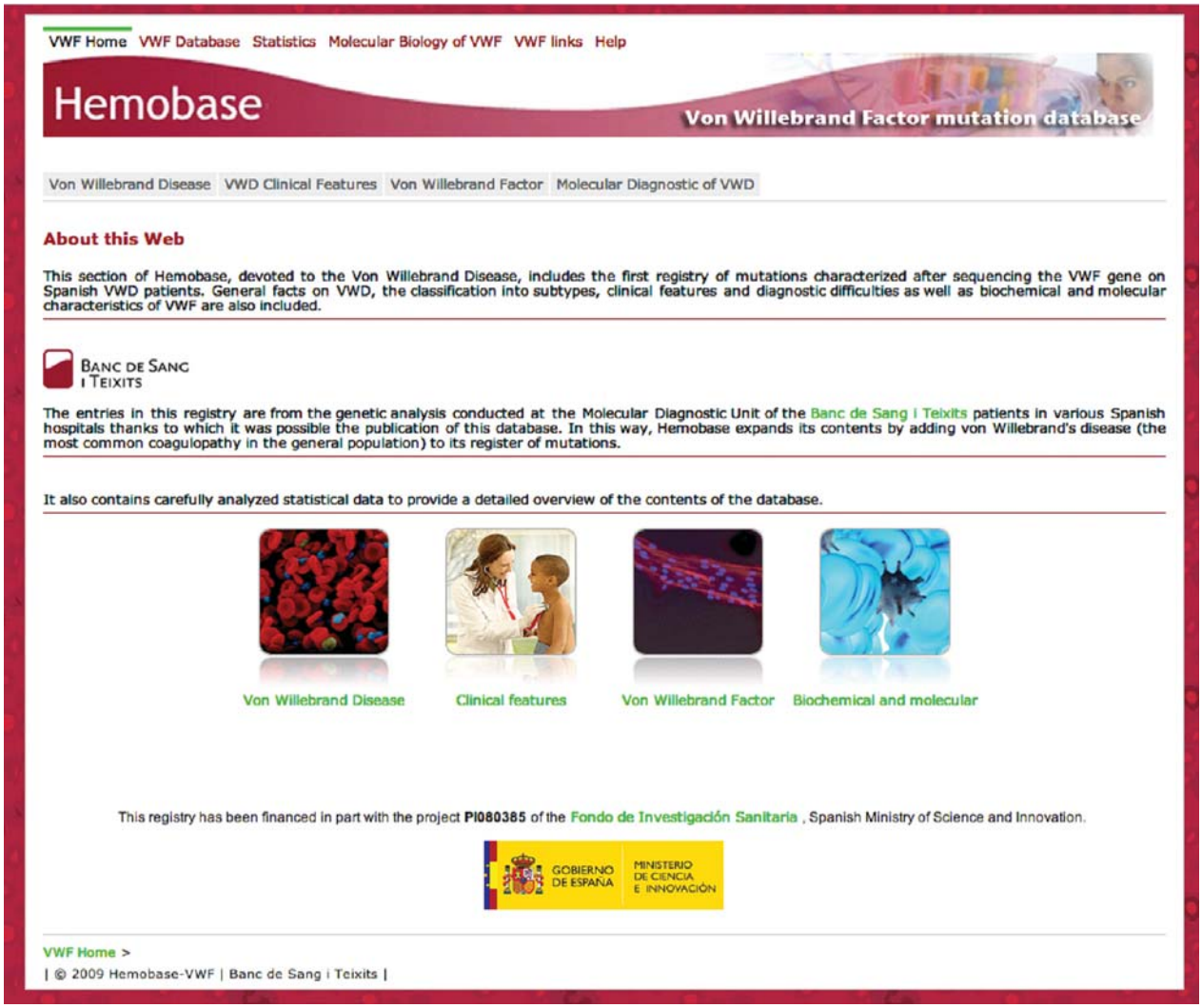


Figure 100
Home page of the website Hemobase (http://www.hemobase.com). Devoted to Hemophila and von Willebrand disease (VWD), it includes the first registry of mutations characterized from patients in the Spanish population. It is a dynamic registry with constant updates. General facts on coagulopathies, the classification, clinical features and diagnostic difficulties as well as biochemical and molecular characteristics of genes are also included. Design, development and maintenance of the website is carried out directly by the research team. The Hemobase website is recognized and linked, among others, by the NCBI and the Orphaned registries as locus specific mutation databases for the F8, F9 and VWF genes

Exploring alternatives for the recombinant human factor VIII production by means of novel yeast expression systems
Francisco Vidal Pérez

CURRENT RESEARCH PROJECTS

PI: Francisco Vidal Pérez
Aplicación de tecnologías optimizadas al diagnóstico molecular de la enfermedad de Von Willebrand: Análisis de la heterogeneidad genética
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080385
Funding: 91,113 €
Duration: 2009 to 2011

PUBLICATIONS

Corrales I, Ramírez L, Ayats J, Altisent C, Parra R, Vidal F. Integration of molecular and clinical data of 40 unrelated von Willebrand Disease families in a Spanish locus-specific mutation database: first release including 58 mutations. *Haematologica* 2010 Nov; 95 (11): 1982-4.

Ramírez L, Altisent C, Parra R, Vidal F. The 'royal disease' mutation in a Spanish patient. *J Thromb Haemost* 2010 Oct; 8 (10): 2316-7.

Area T2 Nanomedicine

Molecular Biology and Biochemistry Research Center for Nanomedicine (CIBBIM-Nanomedicine)

Director
Simón Schwartz Riera
Tel. 93 489 40 60
sischwartz@ir.vhebron.net

Coordinator
Simó Schwartz Jr.

Secretary Direction
Montserrat Capella Tomás
Silvia Vellosillo Almajano

Laboratory Monitoring
Isabel Mougan Albela

The CIBBIM was created in 1995 as the result of a joint effort by several scientists from different fields of research, surgeons and clinicians, in which the complementation of their respective expertises ensure the achievement of higher goals and top quality standards.

In 2007 the CIBBIM opened a new and very successful Nanomedicine Research Program which allowed the center to get involved in several national and International nanomedicine research networks and industrial partnerships. As a consequence, the CIBBIM re-oriented its main research purpose and goals towards the fast-emerging field of nanomedicine and nanotechnology in biomedicine and became the new CIBBIM-Nanomedicine.

The research effort of CIBBIM-Nanomedicine has been focused on two main fields, nanodiagnosis and nanotherapy. The final mission of the CIBBIM-Nanomedicine is to foster basic research on biomarker discovery and new therapeutic agents, as well as to provide the industry and other research groups with the optimal technology for preclinical validation of new nanomedicines. The center is now organized in three interconnected experimental areas covering different aspects of nanomedicine research and biomedical applications: i) Biomarkers and Therapeutics Targets, ii) Experimental Chemistry and Applied Nanotechnology and iii) Functional Validation and Preclinical Studies

AREA 1

Biomarkers and Therapeutic Targets

Obtention of new disease specific biomarkers is a must to achieve success in "nanodiagnostics", as well as in "targeted delivery". There is an increasingly growing need for them to confront several diseases and clinical conditions (i.e. markers for treatment response, immune system activation or disease stratification). These biomarkers are also essential for developing targeting strategies needed to biofunctionalyze nanoparticles against them to deliver traceable particles (imaging) and therapeutic drugs (drug delivery).
Research Groups:

- Drug Delivery and Targeting
- Molecular Oncology
- Immunobiology
- Cellular Physiopathology and Lisosomal Diseases
- Renal Physiopathology
- Neuromuscular and Mitochondrial Diseases
- Basic Aging Research

AREA 2

Experimental Chemistry and Applied Nanotechnology

This is a new area, which currently focuses on the development of its own biodegradable polymers (based on polyglutamic acid) for drug delivery. The study of nanomedicines of polymeric nature is more easily affordable from the view of chemical synthesis and has a promising potential, not just for the delivery of conventional drugs, but also for genomic therapies (iRNA). It is also worth mentioning that these polymers are completely biodegradable and have been proved to be non-toxic in *in vivo* approaches.
We also collaborate with external groups on the design and validation of nanoparticles of alternative natures, such as dendrimers, liposomes, silica nanoparticles, carbon nanotubes or magnetic nanoparticles.

AREA 3

Functional Validation and Preclinical Research

Besides providing the field with top scientific research on biomarker discovery and new therapeutic targets, one additional aim of CIBBIM Nanomedicine is to provide the Industry and other research groups with an optimal in vitro and in vivo validation platforms for "proof of concept" demonstrations and initial preclinical studies of new nanotechnological based approaches. To this end this area is formed by two technological platforms, one for *in vitro* analyses *(In vitro Experimental Platform),* and another for those studies requiring animal experimentation *(In vivo Experimental Platform).*

2010 Impact Factor:
113.587

AREA T2 NANOMEDICINE

CIBBIM-Nanomedicine

T2.1 Drug Delivery and Targeting

Group Leader
Simó Schwartz Navarro
Tel. 93 489 40 60
simo.schwartz@vhir.org

Researchers
Ibane Abasolo Olaortua
Manuel Armengol Carrasco
Eloy Espín Basany
Yolanda Fernández Amurgo
Manuel López Cano
Simó Schwartz Navarro
Simó Schwartz Riera

Researchers in Training
José Higinio Dopeso González
Lucía Lima Correia
Helena Plà Solans
Yuko Saruta

Nursing, Technical and Administrative Staff
Josefa Argadoña Escribano
Montse Capella Tomás
Laura García Latorre
Natalia García Aranda
Mª Eugenia López Sánchez
Sonia Miranda Blázquez
Isabel Mougan Albela
Anna Pujol Esclusa
Ramon Roca Puig

OBJECTIVES

The Drug Delivery and Targeting group has two main goals; first, the identification of new disease biomarkers and therapeutic targets, with special focus on cancer molecular pathways; second, the development of new delivery strategies in applied nanomedicine, with a particular interest in new delivery and targeting approaches for clinical applications.

2010 Impact Factor:
49.014

RESEARCH LINES

Identification of new disease biomarkers and therapeutic targets

There are several research lines dedicated to the study of oncogenic molecular pathways related with:

i) Genomic and microsatellite instability in gastrointestinal tumors;

ii) Condensin complexes in colorectal tumorigenesis,

iii) Molecular alterations caused by defects in the DNA repair system (basically, mismatch repair –MMR- pathway and repair of double strand breaks –DSB-)

and their relationship with tumor resistance to chemotherapy, and

iv) Identification and validation of new biomarkers and therapeutic targets by means of high-throughput screening (HTS).

Genomic and microsatellite instability in gastrointestinal tumors

Simó Schwartz Navarro

This project aims to explain the striking contrast in survival and metastatic capacity between chromosomal instable (CIN, 85% incidence), and microsatellite instable (MSI, 15% incidence) colorectal carcinomas, of the different aggressiveness among tumors bearing diverse *K-ras* point mutants, and of the distinct mutational selectivity of the *K-ras* and *B-raf* oncogenes. To that purpose, whole-body optical imaging will be used to perform a longitudinal analysis of metastatic dissemination, as well as an evaluation of the requirement for *K-ras* and/or *B-raf* oncogene expression in maintaining metastatic foci growth. This model will allow the dissection of the molecular pathways activated by *B-raf* and *K-ras* mutants, as well as the transition from dormant micrometastases to expansive metastases at the different target sites.

Condensin complexes in colorectal tumorigenesis

Simó Schwartz Navarro

We focus on the involvement of chromatin remodelling and chromosomal condensation complexes and protein partners in the development of colorectal tumors and cancer progression. We also address functional studies related to the involvement of these complexes in gene transcriptional regulation and their interactions with DNA repair complexes and the histone code.

DNA repair system and tumor resistance to chemotherapy

Simó Schwartz Navarro

This research line focuses on the identification of new signal transducers involved in DNA damage control pathways which are the main responsible of controlling cell death and repair mechanisms. We are also studying their alterations and biological involvement in tumor cell development and metastasis spread, together with the consequences excerted at the level of tumor treatment response to classical and non-classical chemotherapy. Validation of new checkpoint targets are also done in *C. elegans* models by using hydroxylurea treatments and specific transgenic mutants and siRNA of target genes.

Applied Nanomedicine: new drug delivery and targeting strategies for biomedical applications

We focus on new targeting strategies to ensure a specific delivery of therapeutic compounds into the most appropriate target cell to improve treatment response and achieve lower toxicity and higher therapeutic activities in several human diseases, with particular interest in delivery of chemotherapeutic drugs to cancer cells and enzyme replacement therapies for rare diseases. In addition, alternative targeting strategies are being designed to improve imaging-based diagnostics by using

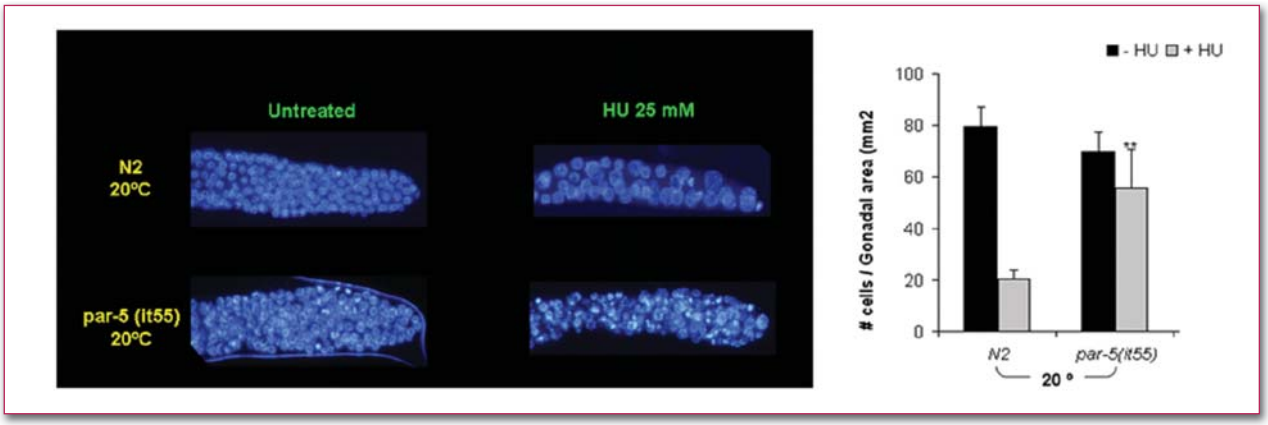


Figure 101
Par-5 inactivation disrupts HU-induced cell cycle arrest. Staged Wild Type (N2) or par -5 mutant (it55) young adults were treated with Hydroxyurea (HU) (replication inhibitor during 24 h at 20ºC. After the treatment the gonads were dissected and DAPI stained to conunt the cell number in the mitotic region of the germline. The images on the left show representative mitotic regions used for the counting. in WT worms HU induces a cell cycle arrest that can be observed as a decrease in the number of germ cells comparing with the untreated (–HU). Par-5 mutation significantly compromise this checkpoint-induced arrest, suggesting a role of these gene in the DNA damage response pathway

new cell-targeted nanoconjugates. Some of the projects explained bellow are developed in collaboration with other groups at CIBER-BBN *(Centro de Investigaciones en Red en Biomateriales, Bioingeniería y Nanomedicina, Instituto de Salud Carlos III)* or within specific European consortiums.

Enzyme replacement therapy for storage diseases: new therapeutic strategies

Simó Schwartz Navarro

Fabry disease is an X-linked recessive disorder caused by a deficiency of lysosomal hydrolase α-galactosidase A (GLA). This enzymatic defect causes the progressive cellular accumulation of neutral glycosphingolipids, giving rise to a multisystemic clinical symptomatology. Current enzyme replacement therapy (ERT) has a limited treatment efficacy in patients with advanced stages of the disease.

The objective of this research line is to improve the ERT by using new therapeutic compounds (nanoparticles or specifically designed proteins) of GLA targeted to the endothelial cells, one of the main cell type affected by GLA substrate accumulation. In addition, we also collaborate in a project focused on the validation of new integrated, multi-host approaches for the improved microbial production of high quality GLA enzymes for industrial purposes (IMAPPROT).

NANOSTEM: Targeting Combined Therapy to Cancer Stem Cells

Simó Schwartz Navarro

In many solid tumors, resistance to therapy and metastatic disease seem to be sustained by the presence within the tumors of cancer stem cells (CSC) capable of regenerating a tumor after chemotherapy and/or radiation treatment. In breast cancer, these cells correspond to a small fraction of cells within the tumor that express stem cell markers (CD44+/CD24-/low/lin-) which provides a useful target to the delivery of therapeutic agents to CSC. In this network project some of the partners will focus on the design of specific vehicles for the simultaneous delivery of chemotherapeutic drugs and/or shRNAs with known antitumor activity on breast CSC. To this end, different types of nanoparticles will be directed at the CSC compartment by using the CD44 receptor as a target. Such systems will allow specific CSC-targeting, and together with enhanced retention, a permeability effect (EPR) will improve accumulation of drugs in the tumor area and should yield a better therapeutic response. At CIBBIM-Nanomedicine, therapeutic activity, nanoparticle internalization and toxicology of these nanoparticulated systems will be addressed by using adequate in vitro and in vivo CSC models.

ONCONANOTARGET: Advancing the field of drug delivery - combined targeted treatments against human breast cancer and human leukemia

Simó Schwartz Navarro

The idea of the ONCONANOTARGET Network is to selectively abrogate tumour-protective functions aiming at either improving sensitivity of tumor cells to chemotherapy or finding synergistic combinations that may improve the clinical outcome for the treatment of breast cancer or leukaemia patients.

Therefore, the main objectives of this project are:

- To design and characterise ligand-targeted nanosystems for nucleic acid (siRNA) and drug delivery.
- To compare, in vitro, the gene-silencing efficiency of the developed targeted lipid-based or polymeric-based nanosized systems containing nucleic acids against Bcl-2 oncogene in breast cancer leukaemia and cells.
- To evaluate the cytotoxic activity of individual treatments with ei-

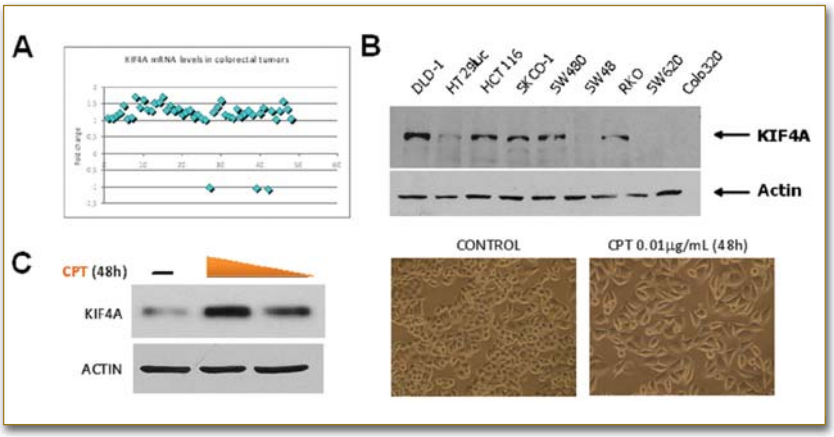


Figure 102
Condensin interactors. Expression and its sensitivity to camptothecin.
A. Condensin-interactor was found to be overexpressed in 24 out of 48 colorectal cancer (CRC) samples analyzed by expression microarrays. **B.** protein expression was further confirmed by Western Blot analysis in a panel of CRC cell lines. **C.** Furthermore, camptothecin (CPT), a drug commonly used in the treatment of CRC, increased the expression of the protein in HeLa cells, suggesting that this interactor could be used as a response prediction factor for CPT treatments

ther gene silencing with targeted system previously selected or targeted polymer-anticancer drug conjugate as compared to combined treatments (targeted gene silencing combined with targeted polymer-anticancer drug conjugates) against leukaemia and breast tumour cells, and

- Therapeutic evaluation of the treatment modality previously selected in an animal model of human breast cancer. In this project, in vivo proof of concept will be limited to breast cancer.

Treatment of advanced colorectal cancer by novel drug delivery systems, sensitive to metalloproteinases

Simó Schwartz Navarro

Current chemotherapeutic treatment for colorectal cancer implies the use of high doses of cytotoxic medications, specifically adjuvant combinations of 5-fluorouracil and Irinotecan, which cause the affected patient many adverse effects. This project proposes a program centred on the development of new nanomedicines, based on polymers of multifunctional character that bring together different chemotherapeutic agents, allowing a combined double or triple therapy using much lower systemic doses and significantly reducing undesirable side-effects. In this case, we will focus on increasing these advantages with the utilization of synthetic peptides sensitive to degradation by matrix metalloproteases (MMP), which will bind the polymeric nanocarrier to the chemotherapeutic drug. The activity of MMPs favours the liberation of the drug and its activity in MMP rich environments, such as primary tumors and metastatic sites. The project includes the processes of synthesis, chemical characterization and optimization of nanomedicines, as well as their in vitro and in vivo validation.

CURRENT RESEARCH PROJECTS

IP: Manuel Armengol Carrasco
Cambios en las características del tejido conectivo abdominal de pacientes con hernia incisional. Activación de fibroblastos. Integración a biomateriales blandos.
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070507
Funding: 73,205 €
Duration: 2008 to 2010

PI: Julian Cerón Madrigal
Modelling cancer in Caenorhabditis elegans. *GRANT number 206584MIRG-CT-2007-206584*
Funding Agency: European Commission
Reference: CANCEROMICS-206584
Funding: 100,000 €
Duration: 2007 to 2011

PI: Simó Schwartz Navarro
Activación de vías dependientes del oncogén BRAF *en la tumorogénesis y metástasis del cáncer colorectal en modelos in vivo*
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080771
Funding: 219,252 €
Duration: 2009 to 2011

PI: Simó Schwartz Navarro
Integrated approach for the improved microbial production of high quality therapeutic enzymes (IMAPPROT)
Funding Agency: Ministerio de Ciencia e Innovación
Reference: EUI2008-03741
Funding: 164,000 €
Duration: 2009 to 2012

PI: Simó Schwartz Navarro
Advancing on drug delivery-combined targeted treatments against human breast cancer and Leukemia (Oncotarget/Nano)
Funding Agency: Ministerio de Ciencia e Innovación
Reference: EUI2008-0170
Funding: 28,300 €
Duration: 2009 to 2011

PI: Ibane Abasolo Olaortua
POLYSFERA: Nanocápsulas poliméricas para liberación controlada y dirigida de fármacos antitumorales
Funding Agency: Ministerio de Ciencia e Innovación
Reference: IPT-090000-2010-0001
Funding: 505,955 €
Duration: 2010 to 2013

PI: Manuel López Cano
Development of a robotic manipulator of human tubular tissues for suture and support in anastomosis surgery interventions
Funding Agency: European Commission
Reference: ECHORD-231143
Funding: 52,181.74 €
Duration: 2010 to 2014

PI: Simó Schwartz Navarro
Direccionament i alliberament farmacològic
Funding Agency: AGAUR
Reference: 2009 SGR 758
Funding: 43,680 €
Duration: 2010 to 2013

PI: Simó Schwartz Navarro
Nanostem (targeting combined therapy to cancer stem cells)
Funding Agency: Euronanomed
Funding: 1.8 M € for the partners: 3 academic and 1 SME
Duration: 2009 to 2011

PI: Simó Schwartz Navarro
Funding for Research Groups of Excellence (2009SGR 758)
Funding Agency: AGAUR. Dept of science and universities. Catalonia
Funding: 44.720 €
Duration: 2010 to 2013

CIBER-BBN Projects

Targeting combined therapy to cancer stem cells (NANOTEMNESS)

Development of a nanoparticles as vehicles for the treatment of metastatic colorectal cancer (NANOCOMETS)

Bacterially produced nanopills, dor a novel, protein-based cancer therapy (NANOPILLS)

Improving diagnosis, prognosis and therapy response in human glioma. Preclinical and translational studies (PROGLIO)

New orthotopic/ectopic nude mice model of human thyroid undifferentiated/analplastic carcinoma: useful tool for new cell-therapies, drug testing and validation in humans (CELL-NANO_THYROID)

PUBLICATIONS
(Impact Factor: 49.014)

Dopeso H, Mateo-Lozano S, Elez E, Landolfi S, Ramos Pascual FJ, Hernández-Losa J, Mazzolini R, Rodrigues P, Bazzocco S, Carreras MJ, Espín E, Armengol M, Wilson AJ, Mariadason JM, Ramon y Cajal S, Tabernero J, Schwartz S Jr, Arango D. Aprataxin tumor levels predict response of colorectal cancer patients to irinotecan-based treatment. *Clin Cancer Res* 2010 Apr 15; 16 (8): 2375-82. ➲ IF: 6.747.

López-Cano M, Manas MJ, Hermosilla E, Espín E. Multivisceral Resection for Colon Cancer: Analysis of Prognostic Factors. *Dig Surg* 2010 Aug; 27 (3): 238-45. ➲ IF: 1.372.

Manchon Walsh P, Borrás JM, Ferro T, Espinás JA, Alfaro J, Arnau JM, Artigas V, Aunon MC, Barrios P, Bellmunt J, Biondo S, Bolibar I, Cambray M, Canals E, Caro M, Casado E, Castells A, Companys A, Darnell A, Torres IM de, Espín E, Estévez M, Figueras J, Gallén M, González D, Lema L, Losa F, Lloreta J, Macías V, Marcuello E, Manzano JL, Martin-Richard M, Maurel J, Membrive I, Mira M, Moreno de Vega V, Murio JE, Panadés A, Pericay C, Pujol J, Queralt B, Ramos E, Reig A, Roca JM, Rodríguez F, Saigi E, Salas A, Salazar R, Sanjuan X, Serra X, Solé JM, Tabernero J, Targarona EM, Torras J. Colorectal Cancer OncoGuia. *Clin Transl Oncol* 2010 Mar; 12 (3): 188-211. ➲ IF: 1.146.

Martínez-Barriocanal, Comas-Casellas E, Schwartz S, Martín M, Sayos J. CD300 heterocomplexes, a new and family-restricted mechanism for myeloid cell signaling regulation. *J Biol Chem* 2010 Dec 31; 285 (53): 41781-94. ➲ IF: 5.328.

Melo SA, Moutinho C, Ropero S, Calin GA, Rossi S, Spizzo R, Fernández AF, Dávalos V, Villanueva A, Montoya G, Yamamoto H, Schwartz S Jr, Esteller M. A genetic defect in exportin-5 traps precursor microRNAs in the nucleus of cancer cells. *Cancer Cell* 2010 Oct 19; 18 (4): 303-15. ➲ IF: 25.288.

Sanjuan X, Salas A, Lloreta J, Manchon Walsh P, Alfaro J, Arnau JM, Artigas V, Aunon MC, Barrios P, Bellmunt J, Biondo S, Bolibar I, Cambray M, Canals E, Caro M, Casado E, Castells A, Companys A, Darnell A, Torres IM de, Espín E, Estévez M, Figueras J, Gallen M, Gonzalez D, Lema L, Losa F, Lloreta J, Macias V, Marcuello E, Manzano JL, Martin-Richard M, Maurel J, Membrive I, Mira M, Moreno de Vega V, Murio JE, Panadés A, Pericay C, Pujol J, Queralt B, Ramos E, Reig A, Roca JM, Rodríguez F, Saigi E, Salas A, Salazar R, Sanjuan X, Serra X, Solé JM, Tabernero J, Targarona EM, Torras J. Colorectal Cancer OncoGuia: surgical pathology report guidelines. *Clin Transl Oncol* 2010 Mar; 12 (3): 211-214. ➲ IF: 1.146.

Velho S, Oliveira C, Paredes J, Sousa S, Leite M, Matos P, Milanezi F, Ribeiro AS, Mendes N, Licastro D, Karhu A, Oliveira MJ, Ligtenberg M, Hamelin R, Carneiro F, Lindblom A, Peltomaki P, Castedo S, Schwartz S Jr, Jordan P, Aaltonen LA, Hofstra RM, Suriano G, Stupka E, Fialho AM, Seruca R. Mixed lineage kinase 3 gene mutations in mismatch repair deficient gastrointestinal tumours. *Hum Mol Genet* 2010 Feb 15; 19 (4): 697-706. ➲ IF: 7.386.

Vilallonga R, Stoica RA, Cotirlet A, Armengol M, Iordache N. Single incision laparoscopic surgery (SILS) cholecystectomy. A novel technique. *Chirurgia (Bucur)* 2010 Mar-Apr; 105 (2): 239-41. ➲ IF: 0.601.

AREA T2 NANOMEDICINE

CIBBIM-Nanomedicine

T2.2 Molecular Oncology

Group Leader
Diego Arango Corro
Tel. 93 274 67 39
diego.arango@vhir.org

Researchers
Hafid Alazzouzi
Silvia Mateo Lozano

Researchers in Training
Sarah Bazzocco
Paulo André Gonçalves Rodrigues
Rocco Mazzolini
Erica Serrano Barbero

OBJECTIVES

The main interest of our Laboratory is the study of molecular events underlying the oncogenic process, especially in colorectal cancer. Colorectal cancer is the second leading cause of cancer related deaths in the western world. In 2004 colorectal cancer accounted for approximately 13% of all cancer cases and cancer-related deaths in the European Union, with over 375,000 new cases and more than 200,000 deaths due to this disease. Understanding of the molecular mechanisms underlying the tumorigenic process is a key step that will allow the identification of new prognostic markers, response to therapy and therapeutic targets. These in turn will lead to an improvement of the survival and quality of life of a large number of patients with colorectal cancer.

2010 Impact Factor:
18.452

RESEARCH LINES

Identification of new prognostic markers and response to treatment for colorectal cancer patients

Diego Arango Corro

Colorectal cancer is the second leading cause of cancer related deaths in the western world and represents a serious health concern. To put the magnitude of the problem posed by colorectal cancer in perspective it is important to highlight that approximately one in 17 EU citizens will develop malignant tumors in their colon or rectum in the course of their lifetime. Patients diagnosed with early stage (I and II) tumors have a good prognosis (more than 80% have a survival rate of 5 years). However, the majority of patients

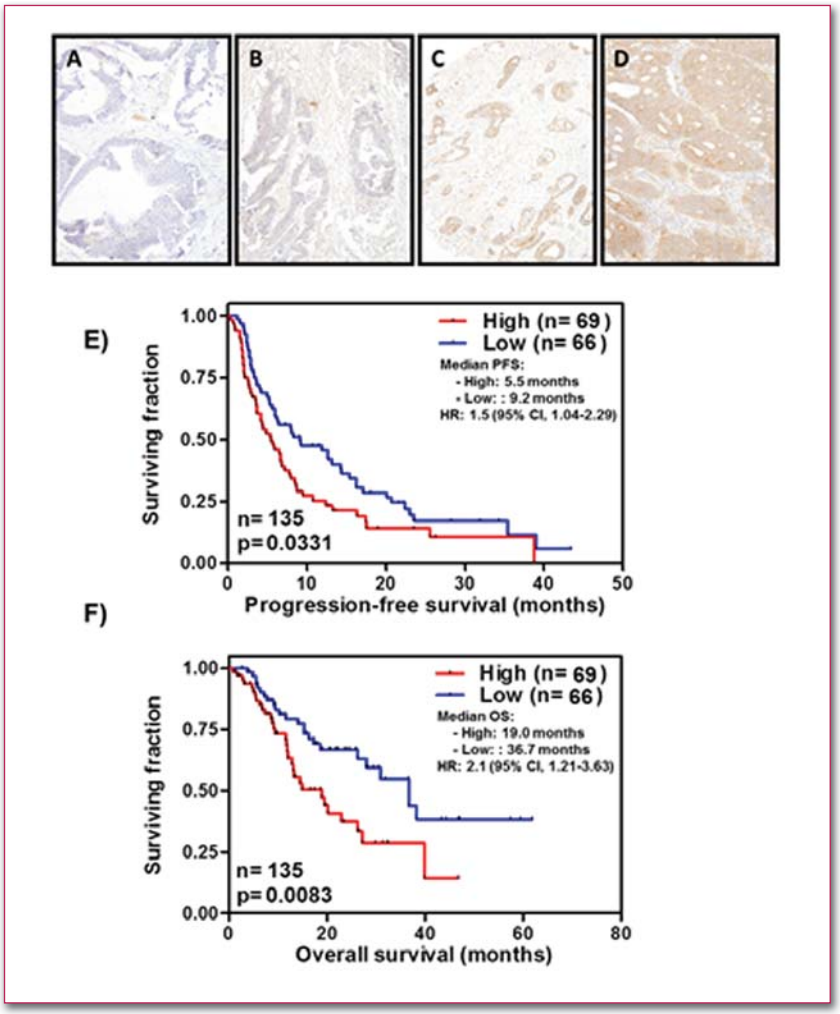


Figure 103
Aprataxin tumor levels and survival of patients with advanced colorectal cancer receiving irinotecan-based treatment. Immunohistochemical staining of colorectal tumors demonstrates a gradient of expression, with some tumors having no detectable Aprataxin (A), high levels (D) or intermediate levels of expression (B-C). Progression-free (E) and overall survival (F) protein levels according to Aprataxin are shown (Kaplan-Meier plots). Log-rank p-values are shown

have advanced disease (stage III or IV) at the moment of their initial diagnosis and the 5-year survival rates for these patients' ranges from 40% to less than 5%. There is, therefore, great need to improve the treatment of these patients.

We use high throughput techniques to find new markers that when used alone or in combination with other markers, can be used to discriminate between patients that have high and low probability of recurrence after treatment. We then follow up these experiments using in vitro and in vivo experiments to investigate the functional relevance of these new markers for colorectal cancer initiation and progression.

Role of EPH signaling in cancer

Diego Arango Corro

EPH receptors are the largest family of tyrosine kinases receptor (RTKs) proteins, which play a crucial role in many biological processes such as embryonic development, cell proliferation and differentiation. The first member of the EPH family was identified and cloned in 1987 by Hirai *et al.* from an Erytropoietin Producing Hepatocellular carcinoma cell line (EPH). To date, 16 receptors (14 found in mammals) and 9 ligands (8 in mammals) have been described. EPH receptors and ephrins (ligands) are implicated in a great variety of processes such as regulation of cell proliferation, migration, cell attachment and shape, axon guidance and synaptic plasticity.

EPH receptors play important roles in tumorigenesis and metastasis and high levels of EPH have been related to angiogenesis in many tumor types including breast and lung. Although overexpression of EPHB2 is observed in some tumor types, in gastrointestinal cancers, low levels of EPHB2 expression have been reported and found to be significantly associated with advance disease stage and poor survival (Lugli *et al.*, 2005).

In colorectal carcinoma (CRC), a progressive reduction in EPHB2 levels has been reported in the progression from normal epithelial cells to benign adenomas and to low and high stage tumors as well as lymph node and liver metastases, demonstrating a clear tendency to decreasing EPHB2

levels as CRC progresses towards a more aggressive and metastatic phenotype. The loss of EPHB2 expression is also significantly associated with poor tumor differentiation and shorter patient survival. We have made some contributions towards increasing our understanding of the mechanisms responsible for this EPHB2 down-regulation in CRC (Alazzouzi *et al.* 2005 Cancer Res 65:10170; Dávalos *et al.* 2007 Oncogene 26:308). Similarly, EPHB4 expression in cancer is up- or down-regulated depending on the tumor type. A drastic increase of EPHB4 protein has been observed in endometrial hyperplasias and carcinomas, suggesting EPHB4 as an early indicator of malignant development. Moreover, EPHB4 overexpression has been associated with high histological grade and certain clinical stages in endometrial cancer. An increase in breast carcinoma has been also reported and high levels of EPHB4 correlated with histological grade and stage. In addition, strategies to block EPHB4 expression, both using siRNA and antisense led to dose-dependent reduction in cell survival and increased apoptosis in breast. In the normal colonic mucosa, we revealed a gradient of EPHB4 expression from the lower crypt to the colonic flat mucosa, and a substantial variability of EPHB4 expression in colorectal tumors from complete lack of immunoreactivity to very high levels of expression (Dávalos *et al.* 2006 Cancer Res 66:8943). Furthermore, our group has shown that low EPHB4 tumor levels identify a subset of colorectal cancer patients with poor prognosis and high risk of recurrence, and demonstrated that promoter hypermethylation was a common mechanism associated with the loss of EPHB4 expression. Moreover, reintroduction of EPHB4 into EPHB4-deficient tumor cells significantly reduced their long-term clonogenic potential, which taken together have contributed to es-

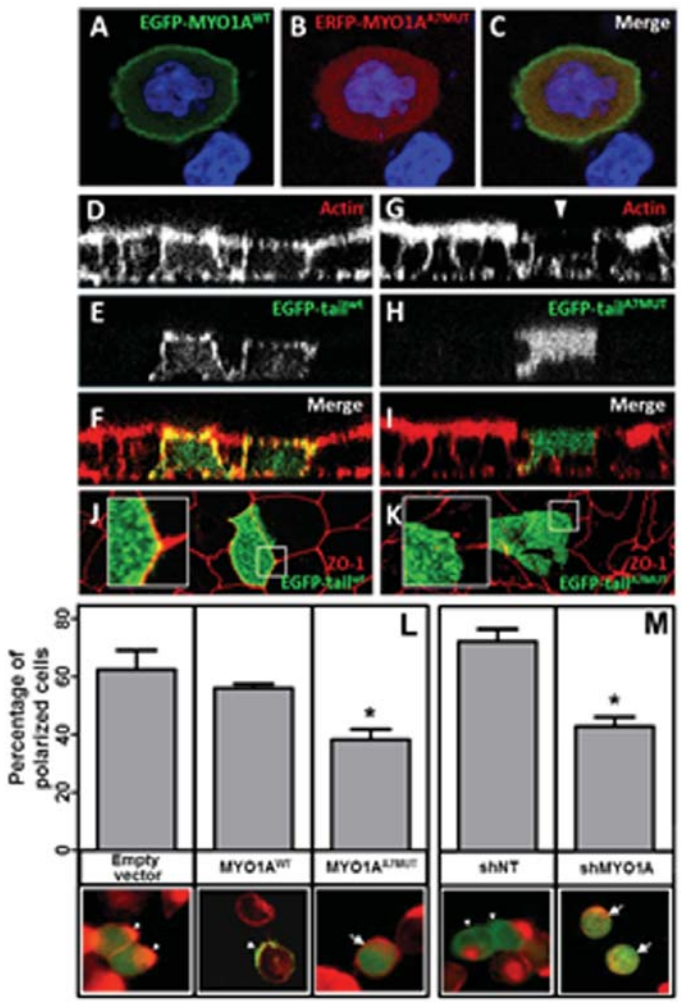


Figure 104
MYO1A A8->A7 mutations affect the localization of the protein and the polarization of colon cancer cells. A-C) Co-transfection of wild type EGFP-MYO1A^{wt} and mutant ERFP-MYO1A^{A7MUT} demonstrated that the mutant protein mislocalized to the cytoplasm of undifferentiated Caco2 cells. Panels D-I show an orthogonal view of differentiated Caco2BBe cells. Alexa 568 labeled Phalloidin was used to visualize F-actin. Wild type MYO1A EGFP-tail^{wt} showed membrane localization (D-F) compared to the cytoplasmic localization of mutant MYO1A EGFP-tail^{A7MUT} (G-I). F-actin was reduced in the apical membrane of MYO1A EGFP-tail^{A7MUT}-expressing cells (G; white arrow head). ZO-1 immunostaining demonstrated that MYO1A EGFP-tail^{A7MUT}-expressing Caco2BBe cells exhibit loss of tight junctional integrity (Z-axis stack; J-K). The inset shows higher magnification of the indicated areas demonstrating loss of ZO-1 membrane staining in EGFP-Tail^{A7MUT} transfected cells. Induction of LKB1/STK11 expression resulted in the polarization of most LS174T-W4 cells characterized by the apical accumulation of actin within 24h (white arrowheads in L and M). The number of polarized cells 24h after LKB1/STK11 activation was significantly reduced following transfection of either mutant EGFP-MYO1A^{A7MUT} (L; mean ± SE; Student's t-test, p=0.03) or co-transfection of EGFP and shMYO1A (M; mean ± SE; Student's t-test, p=0.01), compared to the corresponding pEGFP-C3 empty vector, EGFP-MYO1A^{WT} and non-target shRNA (shNT) controls. Rhodamine-Phalloidin was used to visualize F-actin (red). White arrows show un-polarized transfected cells. The average (±SE) of 3 independent experiments is shown

tablish EPHB4 as a new putative tumor suppressor gene, and a useful prognostic marker in colorectal cancer (Dávalos *et al.* 2006 Cancer Res 66:8943).

Identification of new genetic and epigenetic causes predisposing to colorectal cancer

Diego Arango Corro

A significant proportion of colorectal cancers are hereditary. Hereditary Nonpolyposis Colorectal Cancer (HNPCC) and Familial Adenomatous Polyposis (FAP) are the two most common forms of hereditary predisposition to colorectal cancer.

FAP is characterized by the presence of hundreds to thousands of adenomatous polyps in the colon and rectum of affected individuals and would lead to colorectal cancer in virtually all the patients if left untreated. An attenuated form of FAP (AFAP) is characterized by a reduced number of polyps compared to classical FAP and a later age of onset. Together, FAP and AFAP affect up to 1 in 5,000 individuals. Inherited mutation or deletion of one allele of the adenomatous polyposis coli *(APC)* gene is responsible for 80% of FAP or AFAP cases. A small proportion of FAP/AFAP individuals that do not have germline mutations in *APC* carry homozygous mutations in the gene *MutY* homolog *(MUTYH).* However, the underlying genetic cause of FAP/AFAP is not known for approximately 20% of affected families. Precise identification of the genetic cause of this condition has a profound impact on the management of FAP/AFAP family members, and there is therefore an acute need to identify new genetic abnormalities that could be responsible for a significant number of these adenomatous polyposis syndromes in *APC/MUTYH* mutation negative families. We are actively investigating new genetic and epigenetic causes of colorectal cancer predisposition, both to FAP and HNPCC.

Role of small GTPAses in colorectal cancer

Diego Arango Corro

RhoA is a member of the small GTPase family that regulates cytoskeletal remodeling, protein and lipid trafficking, transcriptional activation and cell growth. We have recently demonstrated that patients whose tumors have low levels of RhoA have a significantly worse prognosis than patients with high RhoA tumor levels (Arango *et al.,* 2005). The membrane-bound small GTPase *RAS* was one of the first oncogenes to be identified (Sukumar *et al.,* 1983). Activating mutations in *KRAS* have been found in more than one third of the human tumors of the colon and rectum (Oliveira *et al.*, 2004), highlighting the importance of this protein in promoting tumor initiation and progression. The role of RhoA and other members of the small GTPase super-family on colorectal carcinogenesis have not been as extensively studied. In contrast to the high frequency of *KRAS* mutations in colorectal

tumors, no mutations have been identified in RHOA in this tumor type (Arango *et al.,* 2005; Rihet *et al.,* 2001). However, RhoA signaling regulates an important signal transduction pathway linking plasma membrane receptors to the assembly of focal adhesions and actin stress fibers. This signaling cascade can regulate cell morphology, attachment to the substrate and motility, and this regulation is cell type dependent (Van Aelst & D'Souza-Schorey, 1997). In addition, RhoA signaling has been shown to regulate the expression and activity of multiple key members of the cell cycle machinery. Thus, inhibition of RhoA activity can lead to either cell cycle arrest or increased growth, depending on the cellular contest (Bellovin *et al.,* 2005; Bellovin *et al.,* 2006; Pille *et al.,* 2005). We are studying the molecular mechanism underlying our previous observation showing that low RhoA levels are associated with poor prognosis of colorectal cancer patients. For this purpose, we are using in vitro isogenic systems as well as animal studies and analysis of materials obtained from human tumor samples.

CURRENT RESEARCH PROJECTS

PI: Diego Arango Corro
Los receptores EPH y el cáncer colorrectal
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-00789
Funding: 169,400 €
Duration: 2009 to 2011

PI: Diego Arango Corro
La GTPasa RhoA en cáncer colorrectal
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/12/2008
Funding: 50,000 €
Duration: 2008 to 2011

PI: Diego Arango Corro
Marcadores de respuesta a Irinotecan en pacientes con cáncer colorrectal
Funding Agency: Ministerio de Ciencia e Innovación
Reference: TRA2009-0093
Funding: 230,478.80 €
Duration: 2010 to 2012

PI: Diego Arango Corro
Grup d'Oncologia Molecular
Funding Agency: AGAUR
Reference: 2009 SGR 157
Funding: 40,560 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 18.452)

Alhopuro P, Bjorklund M, Sammalkorpi H, Turunen M, Tuupanen S, Bistrom M, Niittymaki I, Lehtonen HJ, Kivioja T, Launonen V, Saharinen J, Nousiainen K, Hautaniemi S, Nuorva K, Mecklin JP, Jarvinen H, Orntoft T, Arango D, Lehtonen R, Karhu A, Taipale J, Aaltonen LA. Mutations in the Circadian Gene CLOCK in Colorectal Cancer. Mol Cancer Res 2010 Jul; 8 (7): 952-60. ➲ IF: 4.162.

Dopeso H, Mateo-Lozano S, Elez E, Landolfi S, Ramos Pascual FJ, Hernández-Losa J, Mazzolini R, Rodrigues P, Bazzocco S, Carreras MJ, Espín E, Armengol M, Wilson AJ, Mariadason JM, Ramon y Cajal S, Tabernero J, Schwartz S Jr, Arango D. Aprataxin tumor levels predict response of colorectal cancer patients to irinotecan-based treatment. *Clin Cancer Res* 2010 Apr 15; 16 (8): 2375-82. ➲ IF: 6.747.

Wilson AJ, Chueh AC, Togel L, Corner GA, Ahmed N, Goel S, Byun DS, Nasser S, Houston MA, Jhawer M, Smartt HJ, Murray LB, Nicholas C, Heerdt BG, Arango D, Augenlicht LH, Mariadason JM. Apoptotic sensitivity of colon cancer cells to histone deacetylase inhibitors is mediated by a Sp1/Sp3-activated transcriptional program involving immediate-early gene induction. *Cancer Res* 2010 Jan 15; 70 (2): 609-20. ➲ IF: 7.543.

Area T2 Nanomedicine

CIBBIM-Nanomedicine

T2.3 Immunobiology

Group Leader
Juan Sayós Ortega
Tel. 93 489 37 53
joan.sayos@vhir.org

Researchers
Aroa Ejarque Ortiz
Águeda Martínez Barriocanal

Researcher in Training
Emma Comas Casellas

OBJECTIVES

The CD300 family of immunoreceptors is composed of six members, CD300a/IRP60, CD300b/IREM3, CD300c/CMRF35, CD300d, CD300e/IREM2 and CD300f/IREM1. All of them share an extracellular region comprising a single Ig-like domain and, with the exception of CD300a, a myeloid linage restricted pattern of expression. In addition to the expression on myeloid cells, CD300a is found in some subsets of T, B and NK cells. The Immunobiology group is focused on the study of the structure and function of the CD300 family of immune receptors, as well as in their involvement in different human pathologies.

RESEARCH LINES

Molecular and functional characterization of the family of immunoreceptors CD300

In the last few years the existence of a number of multigenic families of activating and inhibitory immune receptors belonging to the immunoglobulin superfamily has been shown. The physiologic ligand of some of these receptors has been identified, though the ligand of most of them remains unknown. The importance of these receptors for immune system regulation was revealed by showing that dysfunction in some of them increases their susceptibility to autoimmune disorders in experimental models. Our main goal will be the molecular and functional characterization of a new family of activating/inhibitory immune receptors called CD300. This novel immunoglobulin superfamily gene cluster maps to a region of human chromosome 17q25 that has been linked to psoriasis susceptibility. The analysis of the structure, distribution and function of the members of this family of immune receptors may provide clues to understanding the mechanisms involved in the development of autoimmune disorders.

2010 Impact Factor:
5.328

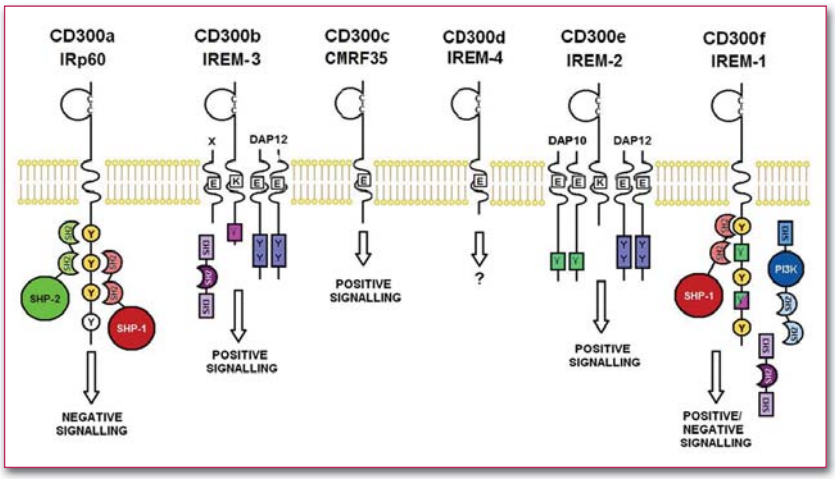


Figure 105
Schematic representation of the CD300 family of Immunoreceptors

The role of the CD300 family of immunoreceptors in the function of microglial cells

In the last few years we have been working on the identification and functional characterization of the CD300 family of immunoreceptors. We have described these molecules as being expressed by cells of myeloid lineage and with some of them activating receptors while others act as negative regulators. We want to analyze the expression and possible role of CD300 molecules in the function of microglial cells in the central nervous system (CNS). We expect that the data generated by this project could help to understand how CD300 receptors modulate microglia function and how to use these molecules as a therapeutic target in processes of acute brain damage.

The involment of CD300 immunoreceptors in the pathogenesis of demyelinating processes

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (SNS) that affects more than 2.5 million individuals worldwide. The first symptoms appear between 20 and 30 years and it is the main neurological disease in young adults, with higher incidence in women. Although the mechanisms underlying MS pathogenesis are still unclear, it is well known that patients' blood-brain barrier allows the passage of macrophages and lymphocytes to the NHS, thereby initiating an inflammatory process. This inflammatory response includes activation of microglial cells and autoimmune attack against white matter oligodendrocytes.

We propose, based on previous experimental data, the study of the role of the CD300f in the patho-

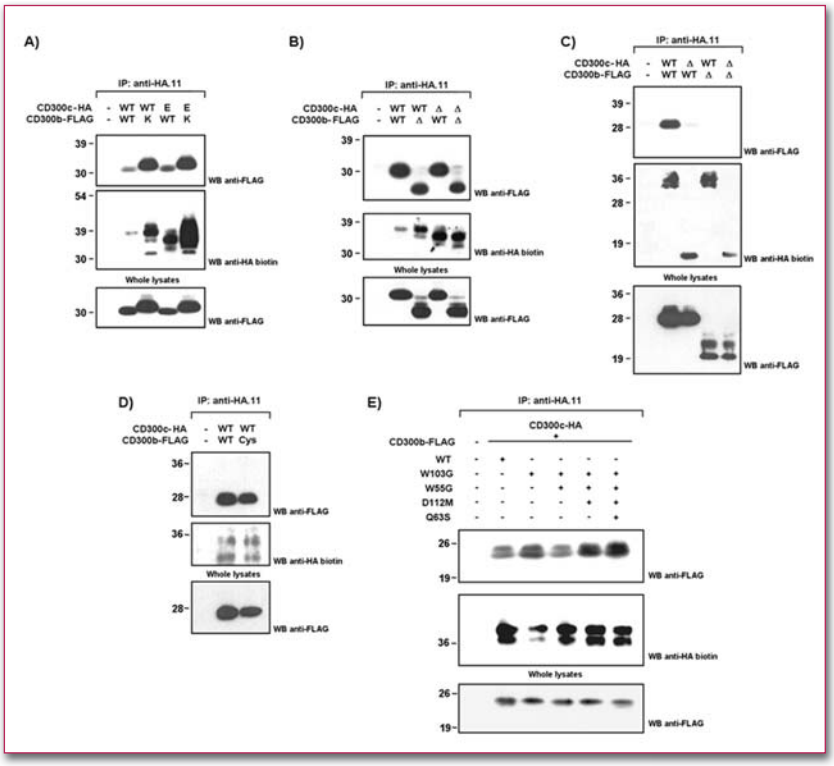


Figure 106
CD300c and CD300b interact through their Ig-like domains. COS-7 cells were transiently transfected with HA-tagged CD300c in combination with FLAG-tagged CD300b. Wild type forms were tested against transmembrane substitution mutants (A), intracellular deletion mutants (B), extracellular deletion mutants (C), cysteine substitution mutants (D) or point mutants affecting the protruding body in the Ig fold (E) in order to map the interaction between both molecules

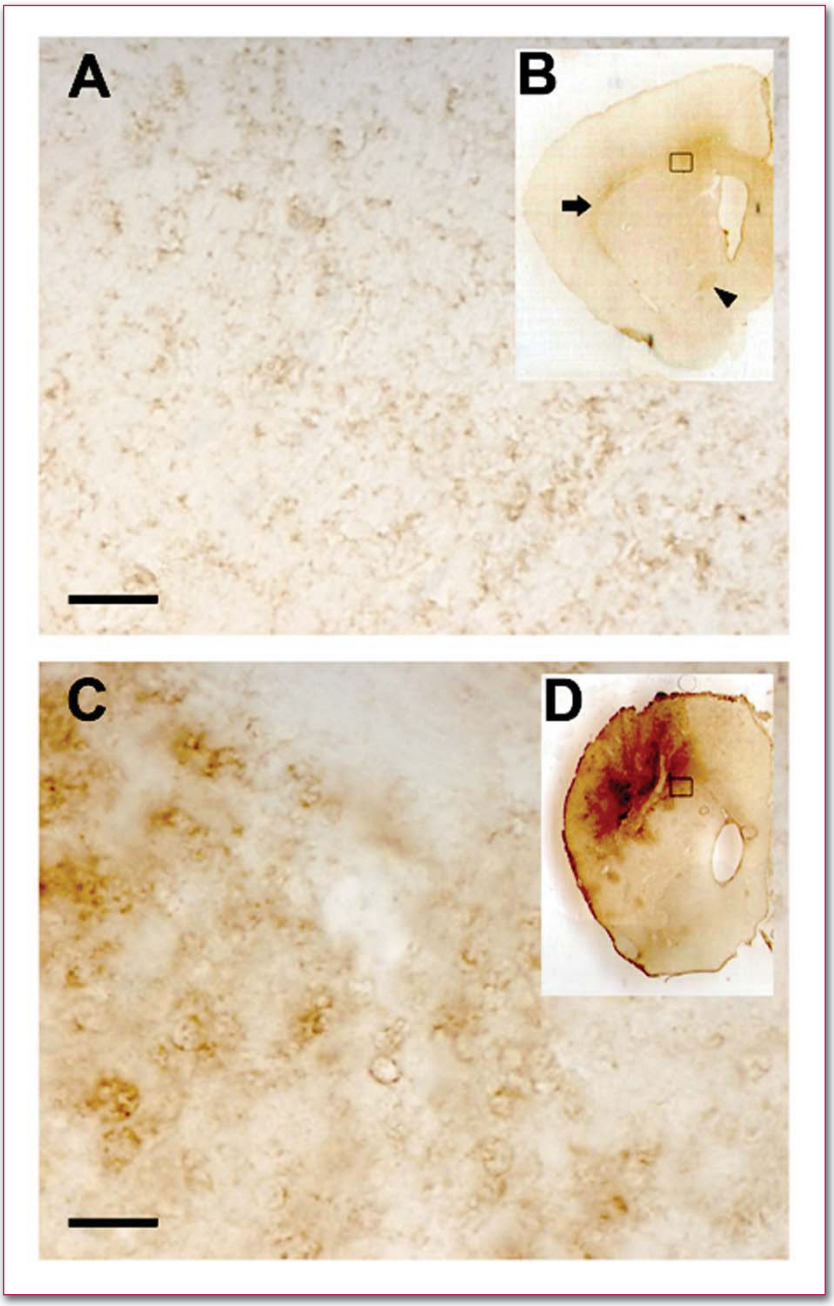


Figure 107
Increased staining for the ligand of CD300f in lesioned rat brain. Normal brain (A-B) showed a dotted staining with hCD300f-IgG2a fusion protein mainly in white matter areas like corpus callosum, external capsule (B: arrow) or the anterior commisure (B: arrowhead). Brains subjected to intra-striatal injection of NMDA showed an increased hCD300f-IgG2a staining in the lesion core (C, D) in comparison to the non-injured brain (A, B)

physiology of this disease. First, we are working in the identification of the physiological ligand for this receptor that we know is expressed by certain cells in the SNS. Secondly, the analysis of the role of soluble forms of CD300f in the development of the disease by studying their expression in fluid samples of multiple sclerosis patients. Since activation of microglia and macrophages is critical in the development and expansion of MS lesions, the study of the mechanisms that regulate the activation of these cells may be of vital importance in the development of new therapeutic agents for the treatment of this disease.

CURRENT RESEARCH PROJECTS

PI: Juan Sayós Ortega
Papel de la familia de inmunorreceptores CD300 en la función de las células microgliales
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080366
Funding: 220,825 €
Duration: 2009 to 2011

PI: Juan Sayós Ortega
Immunobiologia
Funding Agency: AGAUR
Reference: 2009 SGR 493
Funding: 42,620 €
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 5.328)

Martínez-Barriocanal, Comas-Casellas E, Schwartz S, Martín M, Sayós J. CD300 heterocomplexes, a new and family-restricted mechanism for myeloid cell signaling regulation. *J Biol Chem* 2010 Dec 31; 285 (53): 41781-94. ➲ IF: 5.328.

AREA T2 NANOMEDICINE

CIBBIM-Nanomedicine

T2.4 Lysosomal Storage Disease and Cell Pathophysiology

Group Leader
Mª Carmen Domínguez Luengo
Tel. 93 489 40 66
mcdominguez@vhebron.net

Researchers
Mª Carmen Domínguez Luengo
Elisa Llurba Olivé
Víctor Manuel Rodríguez Sureda
Olga Sánchez García

Researcher in Training
Ángel Vilches García

OBJECTIVES

- Diagnosis and study of critical cellular mechanisms in the pathogenesis of lysosomal storage diseases.
- Involvement of oxidative stress in the pathophysiology and evolution of type 1 diabetes mellitus, gestational diabetes and metabolic syndrome in children. Molecular mechanisms of cellular toxicity of oxidative hyperglycaemia and toxic dyslipidaemia.
- Study of pathogenic mechanisms and cellular stress response in preeclampsia, congenital heart defects and intrauterine growth restriction. Identification of maternal risk factors for these diseases.
- In vitro study of pathogenic mechanisms of endothelial and neuronal damage in cerebral ischaemia: relationship with in vivo oxidative processes in acute stroke patients.

RESEARCH LINES

Role of angiogenic factors in fetal heart development: congenital heart disease and fetal programming. Study of early markers of endothelial damage, cardiac dysfunction and angiogenesis regulation in pregnancy

Mª Carmen Domínguez Luengo, Elisa Llurba Olivé, Olga Sánchez García and María del Mar Goya Canino

2010 Impact Factor:
19.774

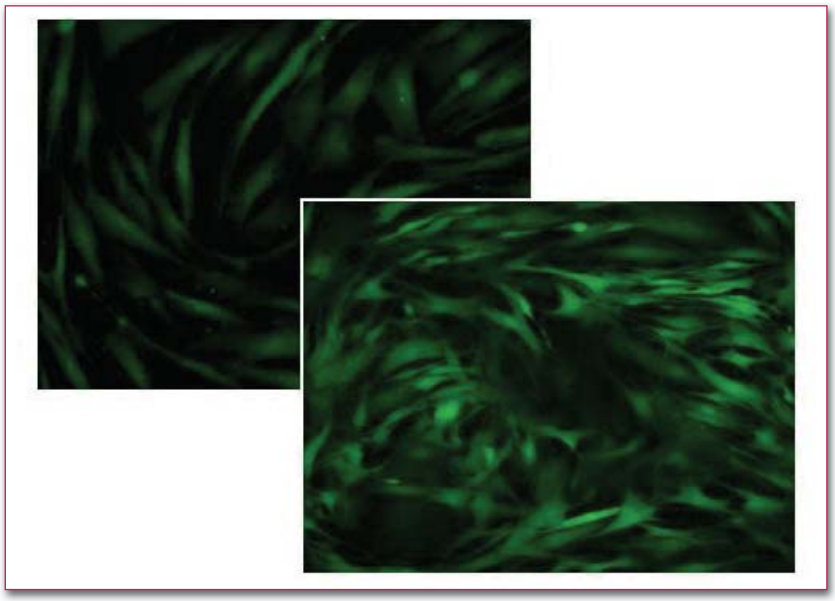


Figure 108
Free radical generation in dermal fibroblasts with and without pro-oxidant treatment

Diagnostic and disease progression biomarkers in lysosomal storage diseases, ischaemic stroke and multiple sclerosis

Mª Carmen Domínguez Luengo, Víctor Manuel Rodríguez Sureda and Ángel Vilches García

Study of new therapeutic options in some lysosomal storage diseases: substrate reduction therapy, enzyme replacement therapy and chaperone enzyme activation

Mª Carmen Domínguez Luengo, Víctor Manuel Rodríguez Sureda, Olga Sánchez García and María Pilar Martín Gallán

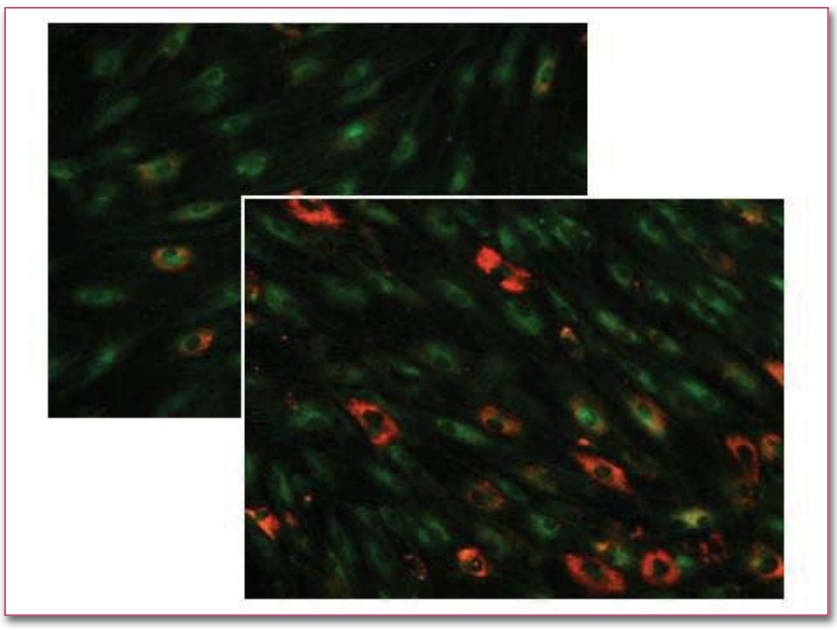


Figure 109
Dermal fibroblasts of control and patient with a lysosomal disorder. Mitochondria staining (green, Mitotracker) and lysosomes (orange, Lysotracker)

CURRENT RESEARCH PROJECTS

PI: Elisa Llurba Olivé

La gestación como situación de estrés para el desarrollo de enfermedad cardiovascular: Evaluación de marcadores de riesgo hemodinámicos y bioquímicos para la enfermedad arterioesclerótica en madres y fetos con preeclampsia y/o retraso de crecimiento

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/1095
Funding: 61,226 €
Duration: 2008 to 2011

PUBLICATIONS (Impact Factor: 19.774)

Alijotas-Reig J, Ferrer-Oliveras R, Rodrigo-Anoro MJ, Farran-Codina I, Llurba-Olivé E, Vilardell-Tarrés M, Casellas-Caro M. Anti-annexin A5 antibodies in women with spontaneous pregnancy loss. *Med Clin (Barc)* 2010 Apr 10; 134 (10): 433-438. ➲ IF: 1.231.

Córdoba O, Llurba E, Cortés J, Sabadell MD, Lirola JL, Ferrer Q, Xercavins J. Complete pathological remission in a patient with hormone-receptor positive and c-erbB-2 expression-negative breast cancer treated with FAC chemotherapy during pregnancy. *Tumori* 2010 Jul-Aug; 96 (4): 629-32. ➲ IF: 0.863.

Domínguez C, Delgado P, Vilches A, Martín-Gallán P, Ribó M, Santamarina E, Molina C, Corbeto N, Rodríguez-Sureda V, Rosell A, Álvarez-Sabín J, Montaner J. Oxidative Stress After Thrombolysis-Induced Reperfusion in Human Stroke. *Stroke* 2010 Apr; 41 (4): 653-60. ➲ IF: 7.041.

Hernández-Guillamón M, García-Bonilla L, Solé M, Sosti V, Parés M, Campos M, Ortega-Aznar A, Domínguez C, Rubiera M, Ribó M, Quintana M, Molina CA, Álvarez-Sabín J, Rosell A, Unzeta M, Montaner J. Plasma VAP-1/SSAO Activity Predicts Intracranial Hemorrhages and Adverse Neurological Outcome After Tissue Plasminogen Activator Treatment in Stroke. *Stroke* 2010 Jul; 41 (7): 1528-35. ➲ IF: 7.041.

San Millan B, Teijeira S, Domínguez C, Vieitez I, Navarro C. Chorionic villi ultrastructure in the prenatal diagnosis of glycogenosis type II. *J Inherit Metab Dis* 2010 Feb 16. ➲ IF: 3.598.

AREA T2 NANOMEDICINE

CIBBIM-Nanomedicine

T2.5 Renal Pathophysiology

Group Leader
Anna Meseguer Navarro
Tel. 93 489 40 61
ameseguer@ir.vhebron.net

Researchers
Joan López Hellín
Anna Meseguer Navarro
Eduard Sarró Tauler

Researchers in Training
Beatriz Bardají de Quixano
Andrea Caballero Garralda
Antoni Cuevas Alcalà
Conxita Jacobs Cachà
Haizea Lekuona Gómez

Nursing, Technical and Administrative Staff
María Fernández Escobar

OBJECTIVES

A major foucs of our laboratory has been to investigate the role of androgens in kidney pathophysiology, by identifying androgen-regulated genes whose expression is restricted to the proximal tubule cells of the kidney. The molecular mechanisms that control specific expression of those genes in tubular epithelia have been studied in different mouse models and in androgen-responsive proximal tubule derived cell lines. Some of these novel identified genes have also been investigated at the functional level. The interaction found between the kidney androgen-regulated (KAP) gene and Cyclophilin B (CypB), one of the receptors of the potent immunossupressant Cyclosporine A (CsA), prompted us to investigate the molecular and cellular mechanisms underlying kidney tubular injury induced by renal nephrotoxicants and isquemia-reperfusion processes. The role of KAP, CypB and other members of the immunophylin family in processes related with kidney injury and regeneration are currently being investigated by using genomic approaches in proximal tubule derived cell lines and in Tg and KO mice. Recent data from our laboratory has shown that Tg mice overexpressing the KAP protein in proximal tubule cells develop hypertension mediated by oxidative stress and focal segmental glomeruloesclerosis. We are currently working with this Tg model

2010 Impact Factor:
4.351

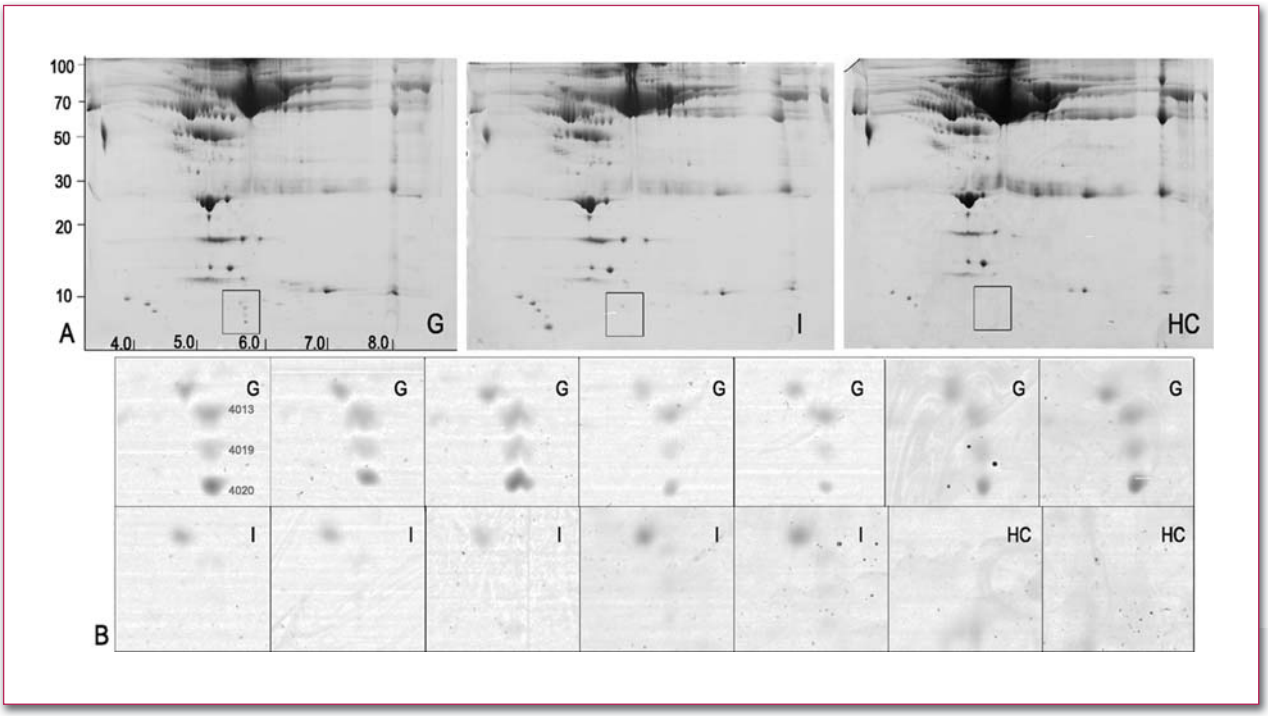


Figure 110
(A) Two-dimensional gels of pooled plasma from patients with focal segmental glomerulosclerosis in the genetic group (G), in the group without podocyte protein mutations (idiopathic group [I]), and in healthy control individuals (HC). The vertical scale shows the molecular weight (kDa) and the horizontal scale shows the isoelectric point. (B) Magnification of the boxed regions indicated in (A). Results are shown for 7 replicate gels of the genetic group pooled sample, 5 replicates of the idiopathic group pooled sample, and 2 replicates of the healthy control sample. In the first genetic group gel, the differential spots are labeled with their corresponding spot numbers

and producing KAP KO mice to further investigate the role of KAP in renal pathophysiology.
Another gene of interest is the one coding for the hepatitis A viral receptor (hHAVR), first identified in our laboratory by its overexpression in clear cell renal cell carcinomas (ccRCC), the most malignant and frequent form of renal cancer that arises in proximal tubule cells and is more prevalent in men than women. We are currently investigating the role of hHAVR in the development and progression of human ccRCC. An important part of the group's efforts is focused on the identification of early, specific and sensitive biomarkers of renal dysfunction by means of high-throughput proteomic analyses in urine and blood samples of transplanted patients under different immunosuppressant regimes. These techniques are also used for the identification of putative plasma permeabilizating factors in patients suffering idiopathic non-familial focal segmental glomeruloesclerosis and in ccRCC patients. Our close relationship with nephrologists, urologists and pathologists from our Institution promotes collaborations aiming towards the identification of potential biomarkers and therapeutical targets that might be useful for future clinical interventions. Finally, the possibility of using nanoconjugates for drug delivery opens new perspectives for targeted therapy.

RESEARCH LINES

Role of Hepatitis A viral receptor (HAVR) / kidney injury molecule-1 (KIM-1) in the development and progression of clear-cell renal carcinoma (ccRCC), as well as, in the renal tubule injury/regeneration processes

Overexpression of this protein in 60% of the ccRCCs has already been described. HAVR/KIM-1 overexpression in human ccRCC cell lines blocks cell differentiation and promotes cell scattering. We aim to determine the role of HAVR/KIM-1 in the development and progression of ccRCC, and its possible value as a diagnostic and prognostic biomarker.
We also focus on KIM-1's role in ischemia/reperfusion- or ne-

phrotoxic-induced renal tubular injury. Overexpression of this protein in kidney injury has been described. However, whether its involvement is associated with processes enabling tubular epithelium to recover, or potentially increasing damage is not known to this date. With the assistance of cultured renal tubular cell models, we are now investigating whether KIM-1 expression shifts are correlated with renal proximal tubule regeneration ability and, as a consequence, investigating its potential therapeutic application.

Androgen activity in renal pathophysiology. Identification of androgen-regulated kidney-specific genes and their role in the pathogenesis of renal, cardiovascular disease and metabolic disorders

Among the genes identified in our laboratory that are kidney-specific and regulated by androgens at the transcriptional level we are particularly focused on the one that codes for the kidney androgen-regulated protein (KAP). Besides characterization of the functional promoter elements that enable KAP expression in proximal tubule epithelial cells, we have generated a transgenic (Tg) mouse model that overexpresses KAP in proximal tubule cells under the presence of androgens, in order to mimick the endogenous KAP expression pattern. KAP Tg mice show altered lipid metabolism, glycosuria, proteinuria and hypertension, as well as focal segmental glomerulosclerosis mediated by increased oxidative stress. We are currently working in this Tg model and also preparing conditional knock-out mice to further characterize the role of KAP in renal pathophysiology.

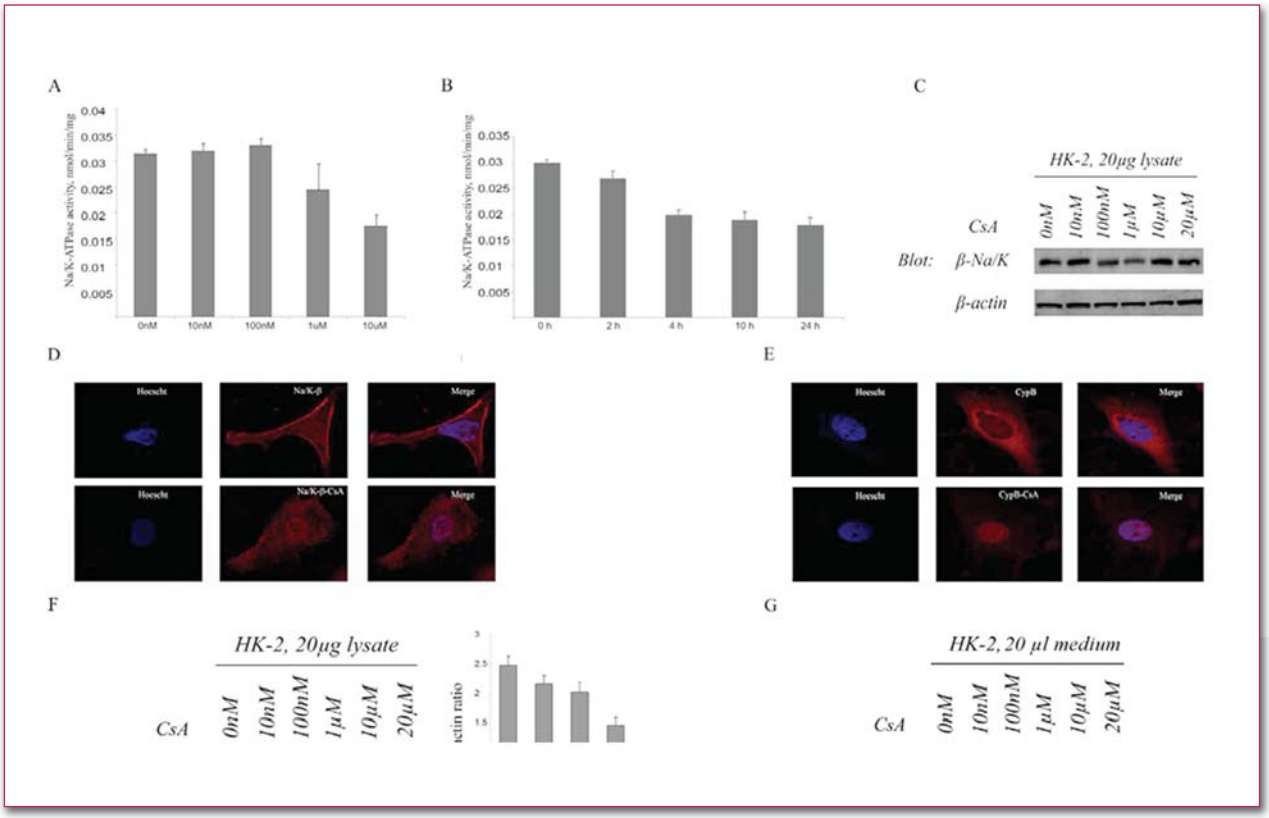


Figure 111
Effects of CsA on Na/K-ATPase in HK-2 cells
A–B: Dose-and time-response effects of CsA on Na/K-ATPase activity. CsA inhibited Na/K-ATPase activity at concentrations of 10 mM (A). Time course inhibition of Na/K-ATPase activity after 2 h, 4 h, 10 h and 24 h, at 10 mM CsA (B).
C: Na/Kb1 stady-state levels after CsA treatment. Effects of different doses of CsA on Na/K-b1 protein expression levels. b-actin was used as a loading control.
D–E: Effects of CsA on Na/K-b1 and CypB localization. Immunocitochemistry assays using anti-CypB and anti-Na/K-b1 rabbit polyclonal antibodies were performed on untreated (upper panel) and 10 mM CsA treated (lower panel) HK-2 cells.
F–G: Effects of CsA on CypB expression. Intracellular (F) and secreted (G) CypB levels in HK-2 cells treated with different doses of CsA. Ratios between CypB and actin signals in cell lysates have been represented upon quantification. Figures are representative of at least three independent experiments.
doi:10.1371/journal.pone.0013930.g003

Pathological mechanisms leading to chronic allograft disease and its potential mediators. Detection of early markers of the chronic kidney disease of the graft

Chronic allograft nephropathy (CAN) is one of the major causes of graft loss in kidney-transplanted patients. The pathogenetic mechanisms of CAN are probably multifactorial, including early noxious agents as a consequence of ischemia / reperfusion of the graft or high loading doses of anticalcineurinics (aCN), and also chronic damage following aCN therapy, rejection or for other reasons. We want to determine the proteomic and genomic changes occurring in tubular cells after different noxious agents are applied (cyclosporine, tacrolimus, other renal toxicants, hypoxia), and also the effects caused by immunophilin silencing (anticalcineurin receptors) in the renal proximal tubule cells. Our objective is to identify specific markers of kidney injury that would be useful to anticipate toxicity or injury in early stages. These putative markers will be clinically validated in collaboration with the Nephrology and the Pathology services of Vall d'Hebron Hospital.

Focal segmental glomerulosclerosis

Idiopathic nonfamilial focal segmental glomerulosclerosis (FSG) is a disease with no treatment, whose usual outcome is end-stage renal disease frequently recidivating after transplantation. In close cooperation with the Nephrology and Paediatric Nephrology services of Vall d'Hebron hospital together with hospitals throughout the country providing a significant number of patients, we intend to identify the hypothetical blood factor that causes the proteinuria observed in this disease. Identification of such a plasma factor, by means of differential proteomic analysis, would allow the definition of therapeutic targets for the disease, which currently lacks an effective treatment. Our second objective is to find biomarkers that enable us to foresee a potential recidivation and the consequent loss of the graft following renal transplantation to FSG patients.

CURRENT RESEARCH PROJECTS

PI: Anna Meseguer Navarro

Implicacions del receptor del virus de l'hepatitis A humà (hHAVcr-1) en el desenvolupament i la progressió del carcinoma renal. Valor com a marcador diagnòstic i pronòstic en els carcinomes de bufeta i renals

Funding Agency: Fundació La Marató de TV3
Reference: TV3/052410
Funding: 204,625 €
Duration: 2006 to 2010

PI: Anna Meseguer Navarro

Acción androgénica y función renal: Implicación de la Kidney androgen-regulated protein (KAP)

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI081351
Funding: 441,045 €
Duration: 2009 to 2011

PI: Anna Meseguer Navarro

Acción androgénica y función renal: Implicación de la Kidney androgen-regulated protein (KAP)

Funding Agency: Sociedad Española de Nefrología (S.E.N.)
Reference: SENEFRO/01/08
Funding: 18,000 €
Duration: 2009 to 2011

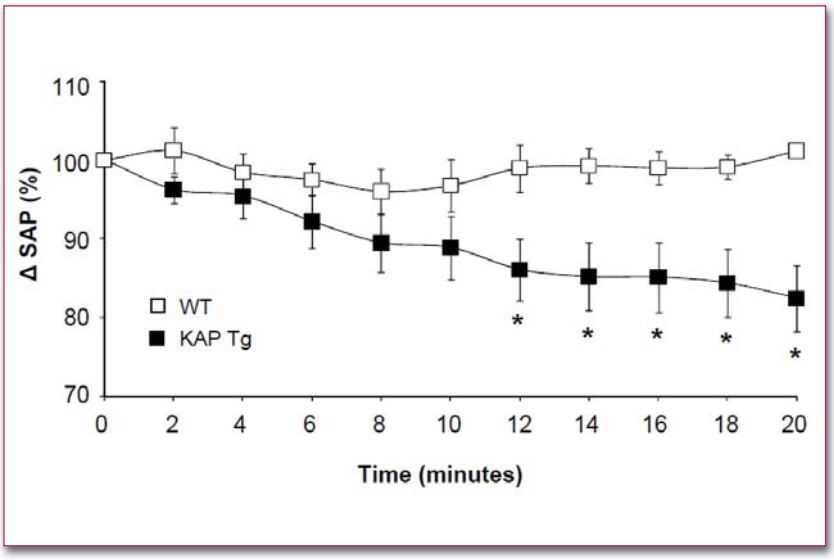


Figure 112
Changes in arterial pressure in response to intracerebroventricular injections of tempol
■ WT mice (*n*=5)
■ KAP Tg mice (*n*=6)
SAP, Systolic arterial pressure

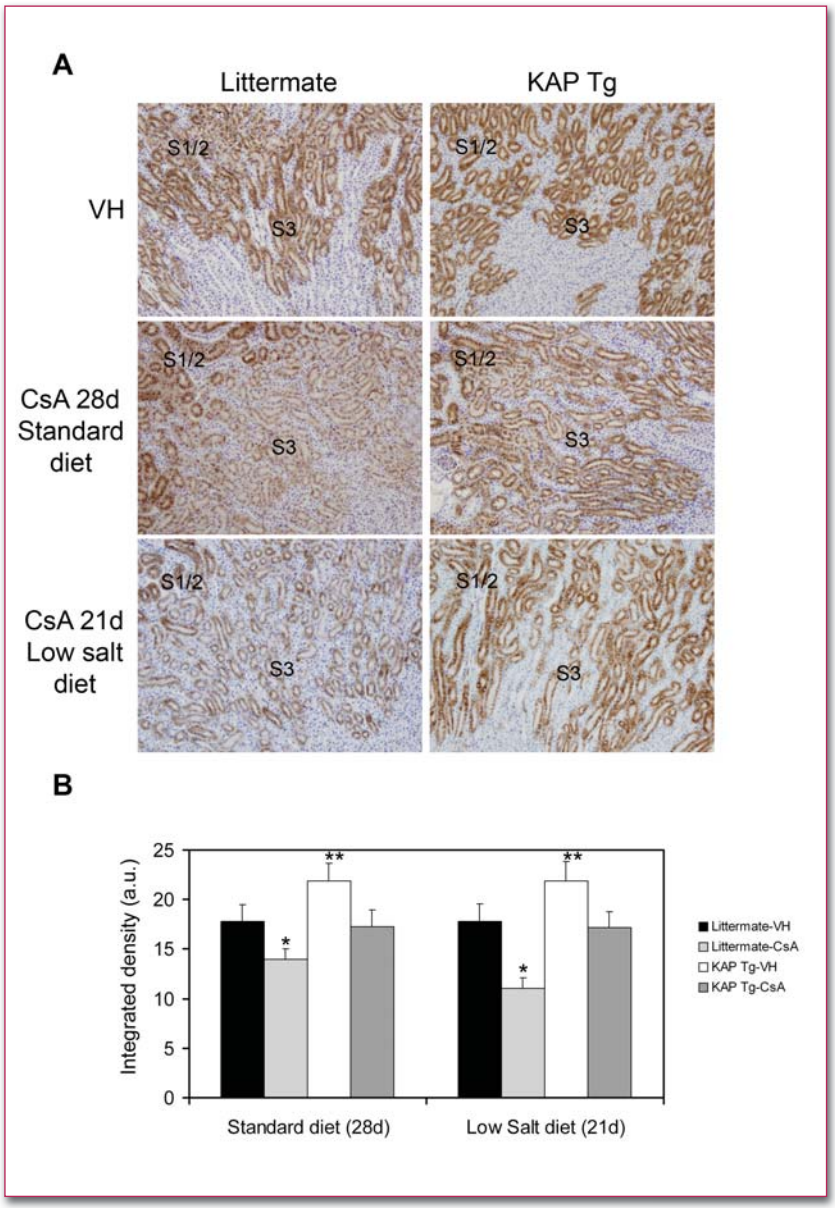


Figure 113
KAP levels in KAP Tg and control littermates after CsA treatment.
(A) KAP expression levels were assessed by immunohistochemical staining in kidney sections of KAP Tg and control littermates using specific anti-KAP antibodies. Polyclonal antibodies against KAP were raised by rabbit immunization with the NH2-CPKIPLAGNPVSPTS-CONH2 KAP peptide. Mice were treated with CsA (50 mg/kg/day) for 28 days with standard diet or 21 days with a low-salt diet, as indicated in Fig 1. Vehicle-treated mice are marked as VH. Data shown are representative of six animals per group. Magnification: 40x.
(B) Quantification of KAP levels in Tg and littermates, under control conditions and following different injuries, using the Image J software (Image J 1.44p, National Institutes of Health, Bethesda, Maryland, USA). Data represent means ± SD of six animals per group. There are statistically significant differences for both standard (p<0.0001) and low salt (p<0.0001) diets, being littermate-CsA KAP levels (*) lower than the others groups, and KAP Tg-VH KAP levels (**) higher than the other groups (ANOVA, with Turkey post-hoc test)

PI: Anna Meseguer Navarro
Role of the kidney androgen-regulated protein (KAP) as a mediator of cardiometabolic syndrome
Funding Agency: Fundación Renal íñigo Álvarez de Toledo
Reference: FRIAT-2009-01
Funding: 9,000 €
Duration: 2010 to 2010

PI: Anna Meseguer Navarro
Patologia cel·lular
Funding Agency: AGAUR
Reference: 2009 SGR 75
Duration: 2010 to 2013

PUBLICATIONS
(Impact Factor: 4.351)

Suñé G, Sarró E, Puigmule M, López-Hellín J, Zufferey M, Pertel T, Luban J, Meseguer A. Cyclophilin B Interacts with Sodium-Potassium ATPase and Is Required for Pump Activity in Proximal Tubule Cells of the Kidney. *PLoS One* 2010 Nov 10; 5 (11): e13930.
➲ IF: 4.351.

AREA T2 NANOMEDICINE

CIBBIM-Nanomedicine

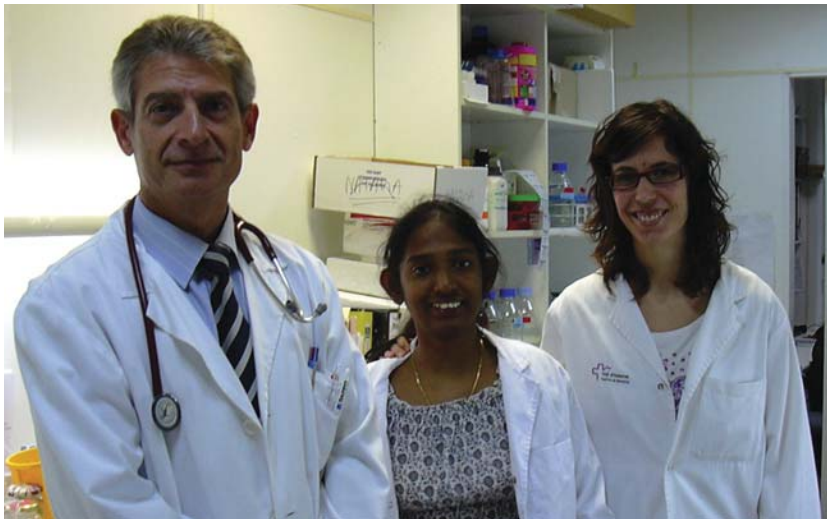
T2.6 Basic Research in Aging

Group Leader
Jaune Alijotas Reig
Tel. 93 489 31 85
jalijota@vhebron.net

Researcher
Jaume Alijotas Reig

Researcher in Training
Renuka Kandhaya Pillai

Nursing, Technical and Administrative Staff
Natalia García



OBJECTIVES

Our goal is the study of the molecular and immunological alterations associated with the aging process. In particular, the association and correlation of cellular aging and endothelial cell senescence with epigenetic and telomeric alterations, taking the immunological alterations as the basis of cellular immunosenescence. Identification of such alterations might provide us with new candidates for therapeutic intervention.

2010 Impact Factor:
16.668

RESEARCH LINES

Immunological alterations as the basis of immunosenescence in pathological aging

Jaume Alijotas Reig

This research line is centred on the study of the role of cross-reactivity among oxidized lipoproteins (oxLDL), antiB2-GP1 and membrane phospholipids, as well as between these complex and heat shock proteins. We also focus on the role of proinflammatory (IL2 / IL6 / TNFα) and anti-inflammatory (IL4 / IL-10) cytokines, as well as on the different activation profiles of TCR and/or CD14 (TLR4) and the role of hormones such as melatonin and growth hormone.

Endothelial senescence and its pleiotropic effects on inflammatory processes, immunological response and angiogenesis

Jaume Alijotas Reig

Identification at the molecular level of pathways and proteins associated with the senescence of endothelial cells linked to aging and inflammatory responses. New candidate targets for therapeutic intervention at the clinical level and as new molecular moieties for nanomedicine approaches to improve aging related pathologies caused by endothelial inflammatory based senescence.

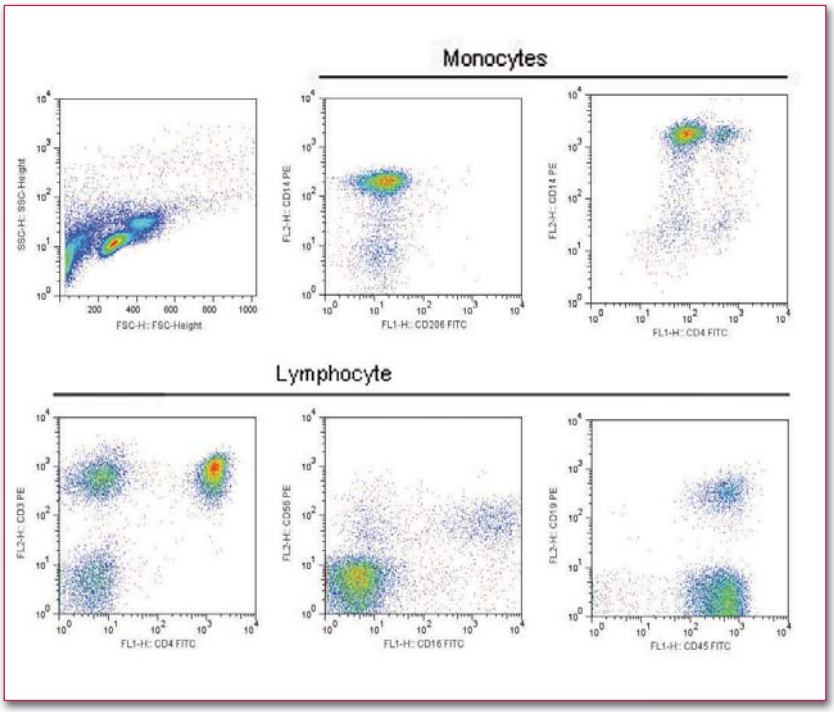


Figure 114
Characterization of monocytic and lymphocytic populations in healthy and pathological donors

CURRENT RESEARCH PROJECTS

PI: Francesc Miró Mur

Envejecimiento endotelial y sus efectos pleiotrópicos sobre procesos inflamatorios, de la respuesta inmune y angiogénesis

Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/05/2008
Funding: 36,000 €
Duration: 2008 to 2011

PI: Jaume Alijotas-Reig

Estudio de las reacciones inflamatorias inmuno-mediadas relacionadas con los materiales de relleno de uso médico.

Funding Agency: SEMCC

PUBLICATIONS
(Impact Factor: 16.668)

Alijotas-Reig J. [The complement system as a main actor in the pathogenesis of obstetric antiphospholipid syndrome.] *Med Clin (Barc)* 2010 Jan 23; 134 (1): 30-4. ➲ IF: 1.231.

Alijotas-Reig J, Ferrer-Oliveras R, Rodrigo-Anoro MJ, Farrán-Codina I, Llurba-Olivé E, Vilardell-Tarrés M, Casellas-Caro M. Anti-annexin A5 antibodies in women with spontaneous pregnancy loss. *Med Clin (Barc)* 2010 Apr 10; 134 (10): 433-438. ➲ IF: 1.231.

Alijotas-Reig J, Ferrer-Oliveras R, Rodrigo-Anoro MJ, Farrán-Codina I, Cabero-Roura L, Vilardell-Tarrés M. Anti-beta(2)-glycoprotein-I and anti-phosphatidylserine antibodies in women with spontaneous pregnancy loss. *Fertil Steril* 2010 May 1; 93 (7): 2330-6. ➲ IF: 3.970.

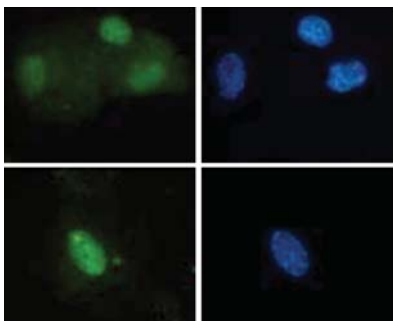


Figure 115
Accumulation of p21 and p53 within senescent endothelial cell nucleis

Alijotas-Reig J, Hindie M, Kandhaya-Pillai R, Miró-Mur F. Bioengineered hyaluronic acid elicited a nonantigenic T cell activation: Implications from cosmetic medicine and surgery to nanomedicine. *J Biomed Mater Res A* 2010 Oct; 95 (1): 180-90. ➲ IF: 2.816.

Alijotas-Reig J, Miró-Mur F, Planells-Romeu I, García-Aranda N, García-Giménez V, Vilardell-Tarrés M. Are Bacterial Growth and/or Chemotaxis Increased by Filler Injections? Implications for the Pathogenesis and Treatment of Filler-Related Granulomas. *Dermatology* 2010; 221 (4): 356-64. ➲ IF: 2.741.

Alijotas-Reig J, Vilardell-Tarrés M. Is obstetric antiphospholipid syndrome a primary nonthrombotic, proinflammatory, complement-mediated disorder related to antiphospholipid antibodies? *Obstet Gynecol Surv* 2010 Jan; 65 (1): 39-45. ➲ IF: 3.097.

Sabadell J, Casellas M, Alijotas-Reig J, Arellano-Rodrigo E, Cabero L. Inherited antithrombin deficiency and pregnancy: Maternal and fetal outcomes. *Eur J Obstet Gynecol Reprod Biol* 2010 Mar; 149 (1): 47-51. ➲ IF: 1.582.

Other Research Units

CURRENT RESEARCH PROJECTS

PI: María Inmaculada Bori de Fortuny
L'ictus a Catalunya: anàlisi de la situació funcional al 4rt dia i als 6 mesos. Necessitats de rehabilitació i recursos disponibles
Funding Agency: Agència d'Informació Avaluació i Qualitat en Salut
Reference: AATRM047/04/2006
Funding: 61,200 €
Duration: 2007 to 2010

PI: Daniel Pacha Vicente
Estudio in vivo de la resistencia a la tensión de una sutura estriada para tendones flexores comparada con el punto de Kessler con hilo convencional
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070093
Funding: 20,110.20 €
Duration: 2008 to 2010

PI: Eduardo Muñiz Díaz
Implementación y desarrollo de una nueva estrategia para la prevención de la trombocitopenia fetal/neonatal aloinmune incluyendo un protocolo de diagnóstico preimplantacional
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070758
Funding: 34,668.92 €
Duration: 2008 to 2010

PI: Claudia Marhuenda Irastorza
Estudio exploratorio multicéntrico para comparar la eficacia de la uroquinasa con la videotoracoscopia en el tratamiento del empiema paraneumónico complicado en la infancia
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90385
Funding: 50,215 €
Duration: 2007 to 2011

PI: Jordi Teixidor Serra
Valoración coste-efectividad del tratamiento quirúrgico con enclavado endomedular o clavo-placa dinámico en las fracturas pertrocantéricas estables de fémur en el anciano
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI081212
Funding: 10,406 €
Duration: 2009 to 2011

PI: Daniel Pacha Vicente
Estudio clínico prospectivo y randomizado comparando la inyección subacromial de plasma rico en plaquetas, o de betametasona y bupivacaina en la tendinosis del manguito rotador del hombro
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00284
Funding: 36,905 €
Duration: 2009 to 2011

PI: Concepción Figueras Nadal
VOR-IIG-49: Invasive fungal infection in children: clinical presentation, management with Voriconazole and therapeutic drug monitoring
Funding Agency: Pfizer SA
Reference: PFIZER_01-2008
Funding: 42,000 €
Duration: 2008 to 2010

PI: María Amparo Cuxart Fina
Rehabilitation Garning System
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI08/90941
Funding: 196,625 €
Duration: 2009 to 2011

PI: Óscar González López
Evaluación y validación clínica de la biopsia selectiva del ganglio centinela en el diagnóstico de extensión ganglionar del cáncer papilar de tiroides
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI09/90440
Funding: 41,436 €
Duration: 2010 to 2011

PI: Antoni Julià Font
REIPI - Red Española de Investigación en Patología Infecciosa
Funding Agency: Fondo de Investigación Sanitaria
Reference: RD06/0008/0030
Funding: 20,940 €
Duration: 2007 to 2010

PUBLICATIONS
(Impact Factor: 53.946)

Canet J, Gallart L, Gomar C, Paluzie G, Vallés J, Castillo J, Sabaté S, Mazo V, Briones Z, Sanchís J, Roige J, Sala R, Bascunana P, Rodríguez A, Serrano E, Ribas M, Cortiella P, Medel J, Márquez E, Salgado I, Lozano C, Serrat A, Morros C, Pérez D, Serra JM, Lorenzo JP, *et al.* Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010 Dec; 113 (6): 1338-50. ➲ IF: 5.354.

Carnero A. The PKB/AKT Pathway in Cancer. *Curr Pharm Des* 2010; 16 (1): 34-44. ➲ IF: 4.414.

Esteban C, Pérez P, Fernández-Llamazares J, Surinach JM, Camafort M, Martorell A, Monreal M. Clinical outcome in patients with peripheral artery disease and renal artery stenosis. *Angiology* 2010 Feb-Mar; 61 (1): 58-65. ➲ IF: 1.097.

Ferran C, Sanz J, Delacamara R, Sanz G, Bermudez A, Valcárcel D, Rovira M, Serrano D, Caballero D, Espigado L, Morgades M, Heras I, Solano C, Duarte R, Barrenetxea C, García-Noblejas A, Diez-Martín JL, Iriondo A, Carreras E, Sierra J, Sanz MA, Ribera JM. Unrelated Transplants For Poor Prognosis Adult Acute Lymphoblastic Leukemia: Long-Term Outcome Analysis And Study Of The Impact Hematopoietic Graft Source. *Biol Blood Marrow Transplant* 2010 Jul; 16 (7): 957-66. ➲ IF: 3.149.

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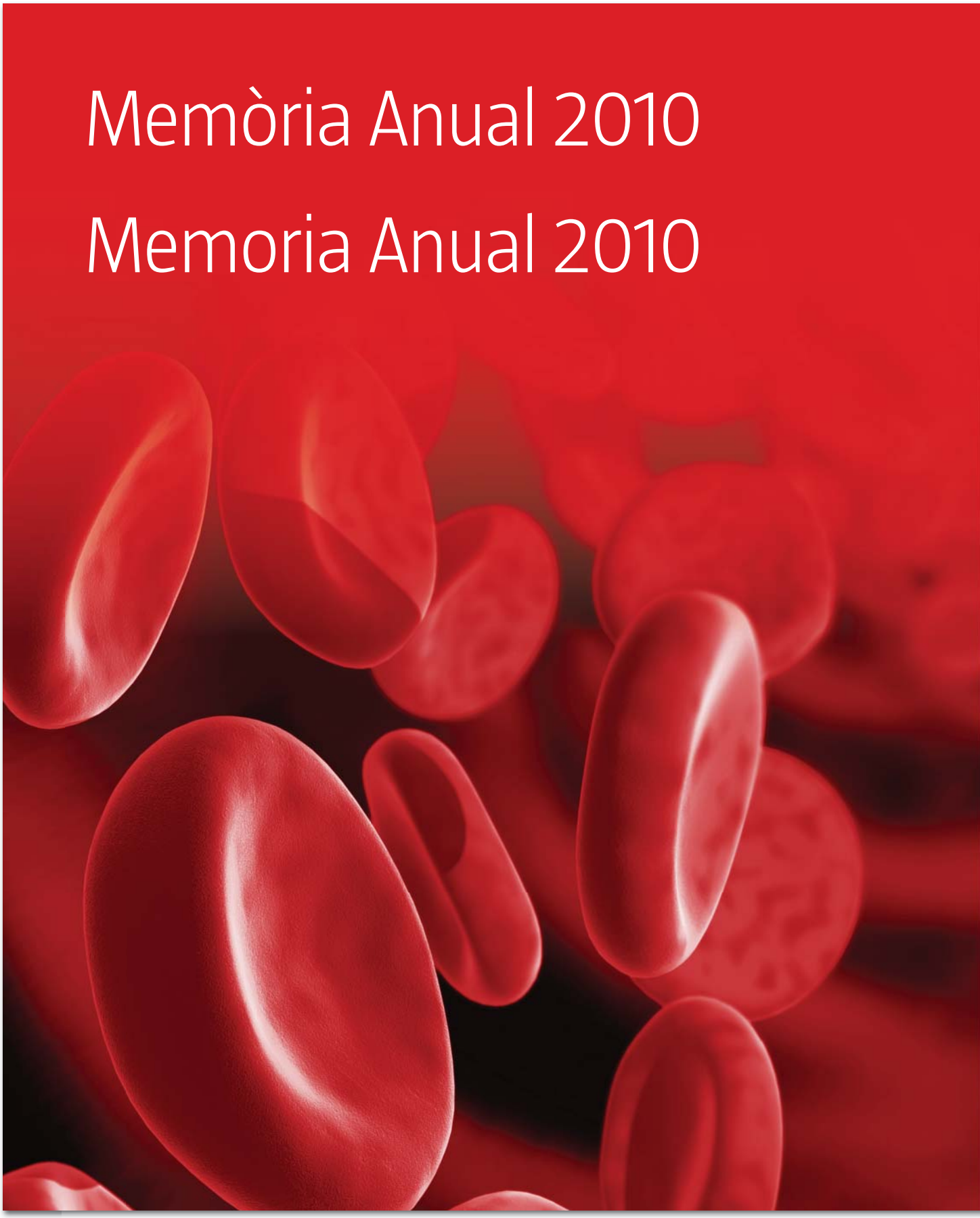
2010 Impact Factor:
53.946

8 Presentation
13 VHIR Information
69 VHIR Research Activity

Memòria Anual 2010

Memoria Anual 2010



Memòria Anual 2010

OBJECTIUS

Vall d'Hebron Institut de Recerca (VHIR) es una institució del sector públic que promou i desenvolupa la investigació i la innovació biosanitària de l'Hospital Universitari Vall d'Hebron, estant orientada a trobar solucions als problemes de salut de la ciutadania i amb la voluntat de contribuir al desenvolupament científic, docent, social i econòmic del seu àmbit de competència.

Volem que la nostra recerca i innovació, realitzada per les persones que conformen la institució, amplïi la frontera del coneixement i es consolidi com un actiu rellevant i referent per a la nostra societat, el nostre sistema de salut i la seva ciutadania, sent un pol d'atracció de talent i aconseguint que la nostra activitat, en termes d'excel·lència, qualitat i translació, respongui a la posició de lideratge que ha de tenir l'Hospital Universitari Vall d'Hebron.

ÒRGANS DE DIRECCIÓ

La infraestructura de direcció i presa de decisió del VHIR pertany a la Fundació Institut de Recerca Hospital Universitari Vall d'Hebron i inclou, des del patronat del 16 de desembre 2010, els òrgans de direcció següents: el Patronat, la Comissió delegada, la Direcció, i els Consells Científics Interns i Externs.

Direcció

El director s'encarrega de desenvolupar la direcció executiva de la Fundació. Té les següents funcions:

a) Dirigir, organitzar i gestionar les activitats de recerca de la Fundació.
b) Proposar al Patronat la programació d'activitats que ha de concretar les línies de recerca, el seu cost i les fonts de finançament previstes.
c) Proposar al Patronat el pressupost anual de la Fundació.
d) Proposar al Patronat el nomenament de persones que assumeixin la gerència, i subdireccions i assessories, si s'escau.
e) Coordinar les actuacions encaminades a l'obtenció dels recursos necessaris perquè es puguin dur a terme els objectius de la Fundació.
f) Informar i retre comptes al Patronat del desenvolupament de les activitats i programes de recerca de la Fundació.
g) Dirigir el procés selectiu del personal investigador i de suport a la recerca, o per a l'acceptació de l'adscripció del personal investigador i científic i tècnic d'altres institucions a la Fundació.
h) Proposar els serveis que calguin perquè la Fundació desenvolupi les activitats i funcions que li corresponen.
i) Proposar al Patronat les normes de funcionament intern.
j) Formalitzar els convenis de col·laboració amb institucions públiques o privades d'import inferior al màxim que expressament li hagi autoritzat el Patronat.
k) Qualsevol altres funcions que li siguin expressament encomanades o delegades pel Patronat, en els termes previstos en aquests Estatuts.

Patronat

El Patronat és l'òrgan de govern i d'administració de la Fundació, la representa i gestiona, i assumeix totes les facultats i funcions necessàries per a la consecució dels fins fundacionals.

De Junta de Govern a Comissió delegada

Des del 16 de desembre de 2010 la Junta de Govern es converteix en Comissió delegada i té les següents funcions:

a) Dur a terme els acords adoptats pel Patronat que aquest òrgan l'encomani.
b) Fer el seguiment periòdic de les tasques de direcció i de gestió del centre.
c) Elaborar la proposta d'ordre del dia de les sessions del Patronat i revisar la documentació a presentar, si escau.
d) Proposar al Patronat l'adopció dels acords que corresponguin a aquest òrgan.
e) Realitzar el seguiment dels convenis i acords subscrits per la Fundació.
f) Informar de les necessitats d'endeutament de la Fundació.
g) Facilitar les tasques de direcció i gestió de la Fundació, especialment en allò relatiu a les seves relacions amb les entitats fundadores.

De Comitè Científic Intern a Consell Científic Intern

Des del 16 de desembre de 2010 el Comitè Científic Intern es converteix en Consell Científic Intern.

El Patronat nomena, a proposta de la Direcció, un Consell Científic Intern format per un mínim de tres i un màxim de vint Investigadors dels Grups de Recerca de la Fundació, que té per objecte assessorar la Direcció en el desenvolupament de les seves funcions. Aquest òrgan no ostenta, en cap cas, funcions de gestió o de representació de la Fundació.

De Comitè Científic Extern a Consell Científic Extern

Des del 16 de desembre de 2010 el Comitè Científic Extern es converteix en Consell Científic Extern.

El Consell Científic Extern és l'òrgan encarregat d'assessorar sobre les activitats científiques de la Fundació i de vetllar per la seva qualitat científica. Aquest òrgan no ostenta, en cap cas, funcions de gestió o de representació de la Fundació.

El Consell Científic Extern està format per un mínim de tres i un màxim de vint persones científiques de prestigi internacional i competència reconeguda en els àmbits de recerca de la Fundació. En cap cas, els membres del Consell Científic Extern poden ser persones investigadores vinculades a la Fundació o que hi col·laborin habitualment.

UNITATS DE SUPORT A LA RECERCA

L'activitat de la Fundació s'articula a través de múltiples Unitats de Suport a la Recerca, coordinades des de la Direcció dividida en tres blocs principals: Innovació, Estructura administrativa i Serveis.

1. Innovació

L'Hospital Universitari Vall d'Hebron, mitjançant l'Institut de Recerca, vol impulsar un pla d'innovació que permeti estructurar i ordenar les accions pròpies d'aquest àmbit, concretades amb les següents línies d'actuació: detecció d'iniciatives d'innovació, el seu registre i la cerca de sinergies entre elles, recolzament als professionals de l'organització en la identificació d'oportunitats i en la seva concreció, anàlisi de la innovació tecnològica susceptible de ser transferida i avaluació i priorització de les innovacions transferides.

2. Estructura administrativa

L'estructura administrativa de suport a la recerca del VHIR, amb capacitat per a gestionar, generar recursos i contractar personal tècnic, s'articula en diferents unitats:

Agència d'Assaigs Clínics

Organisme independent que vetlla per la protecció de drets, la seguretat i el benestar dels subjectes que participen en un assaig i projectes d'investigació en humans o en aquells que utilitzen mostres humanes. Ofereix garantia pública al respecte mitjançant un dictamen sobre el protocol de l'assaig, la idoneïtat dels investigadors i l'adequació de les instal·lacions, així com els mètodes i els documents que s'utilitzin per informar als subjectes de l'assaig per a obtenir el seu consentiment informat.

Unitat Bàsica de Prevenció de Riscos Laborals

La Unitat Bàsica de Prevenció de Riscos Laborals assessora i vetlla per la seguretat i salut dels llocs de treball, d'acord amb els preceptes de la Llei 31/95 de Prevenció de Riscos Laborals, avaluant i controlant els riscos, elaborant instruccions de seguretat, analitzant els accidents, informant i formant als treballadors, vigilant i promocionant la salut i prevenint les malalties laborals dels professionals.

Unitat de Comunicació i Imatge

Vincula la recerca científica i la resta d'activitats de l'Institut i la societat a través dels mitjans de comunicació. Dóna a conèixer les activitats de l'Institut i els seus investigadors mitjançant notes i rodes de premsa, entrevistes, vídeos divulgatius i campanyes de comunicació concretes, desenvolupa i fa servir la web institucional com a eina fonamental per comunicar-se de manera interna i externa.

Unitat de Fundraising

Impulsa i promou un model de mecenatge per tal de cercar la participació i la generositat de persones, empreses, fundacions, obres socials i entitats públiques i privades que desitgin recolzar econòmicament i invertir en recerca biomèdica. Identifica l'univers de donants i possibles finançadors i defineix una estratègia de captació de fons per a la Fundació VHIR. Dóna suport als investigadors en les seves relacions amb els donants i entitats col·laboradores.

Unitat de Gestió de Projectes

La Unitat de Gestió de Projectes gestiona la sol·licitud i el seguiment dels projectes de recerca que es duen a terme a l'HUVH i al VHIR, finançats per agències públiques i privades, autonòmiques, nacionals i internacionals. Selecciona i difon la informació sobre recursos i ajuts econòmics, canalitza el seguiment dels recursos i ajuts finançats, optimitza i promou la gestió dels recursos de personal, instal·lacions i serveis implicats en el desenvolupament dels projectes de recerca que es duen a terme al VHIR, i promou activitats formatives sobre recursos i ajuts.

Unitat de Gestió Informàtica

Els Serveis Informàtics del VHIR coordinen tots els aspectes informàtics relacionats amb l'Institut i donen suport als investigadors. Un dels objectius principals ha estat la creació d'una base de dades centralitzada per a la gestió del coneixement integral de la institució que cobreix tant l'àmbit dels processos interns com el de relació amb els agents externs d'interès.

Unitat de Gestió Econòmica

La Unitat de Gestió Econòmica rep els ingressos i donacions, realitza els pagaments de factures ordenades pels investigadors, realitza els procediments de contractació pública per a les grans compres, subministra informació econòmica, des de dades agregades per serveis o grups de recerca fins a la confecció de memòries econòmiques per projectes, i assessora jurídicament quant a contractes, convenis, etc.

Unitat de Recursos Humans

La Unitat de Gestió de Recursos Humans promou i facilita les relacions laborals del VHIR. Adequa els recursos laborals a les directrius i necessitats de l'Institut tot respectant els marcs jurídics, legals i ètics.

3. Serveis

Amb la finalitat de proporcionar els complexos mitjans que requereix la biomedicina actual, el Vall d'Hebron Institut de Recerca disposa d'un seguit de serveis importants per donar suport a la Recerca. Són la Unitat Científico-Tècnica de Suport (UCTS), la Unitat d'Estadística i Bioinformàtica (UEB), la Unitat de Suport en Metodologia per a la Investigació Biomèdica (USMIB), l'Estabulari i la Coordinació de Laboratoris de Recerca. Els dos últims serveis incorporats són el Biobanc i la Unitat Central d'Investigació Clínica i Assaigs Clínics (UCICAC). D'aquesta forma, a més de facilitar als investigadors la tecnologia i els serveis més actuals, s'augmenta la rendibilitat i es millora l'autosuficiència.

Unitat Científico-Tècnica de Suport

La Unitat Científico-Tècnica de Suport (UCTS) és un conjunt de serveis de tecnologia puntera que donen suport a les activitats docents i de recerca de l'àmbit biomèdic. El caràcter centralitzat de la UCTS permet posar a l'abast de qualsevol investigador les eines més avançades en les àrees de genòmica, bioinformàtica, proteòmica, citòmica i microscòpia a un cost reduït, amb una actualització constant i amb l'assessorament de personal especialitzat. La UCTS ofereix les següents plataformes: Citòmica, Diagnòstic Molecular, Genòmica, Microscòpia, Proteòmica, Metabolòmica, i d'Estadística i Bioinformàtica (UEB).

UEB

La Unitat d'Estadística i Bioinformàtica (UEB) es crea dins de l'Institut de Recerca de l'Hospital Universitari Vall d'Hebron amb l'objectiu de potenciar l'ús i el desenvolupament dels moderns recursos estadístics i bioinformàtics en la recerca efectuada en el seu entorn.

Així doncs, els objectius principals de la UEB, són:

- Proporcionar suport estadístic i bioinformàtic especialment per al tractament de dades d'alt rendiment *(high troughput)* generades en la investigació en el nostre centre i l'àmbit biomèdic.
- Desenvolupar línies pròpies de recerca en el camp de l'estadística i la bioinformàtica i particularment en aquells camps que puguin revertir en una millora dels serveis proporcionats per la Unitat.
- Establir un programa de formació en estadística i bioinformàtica per a la recerca biomèdica.

Biobanc

El Biobanc de l'Hospital Universitari Vall d'Hebron (BBHUVH) és una unitat de suport a la recerca que acull mostres biològiques d'origen humà amb finalitats d'investigació biomèdica en compliment amb la legislació vigent, i l'objectiu del qual és posar a disposició de la comunitat científica el material biològic necessari per a la recerca en unes òptimes condicions que assegurin la competitivitat i excel·lència de la investigació.

Estabulari

La recerca i la docència vinculades a l'ús d'animals de laboratori es centralitzen a l'Estabulari de l'Institut de Recerca de l'Hospital Universitari Vall d'Hebron. Ubicat a l'edifici Mediterrània, ocupa una superfície construïda de 745 m^2 i una superfície útil de 683 m^2 en una sola planta. L'Estabulari compleix amb la legislació vigent i està registrat en el Departament de Medi Ambient i Habitatge amb el número de registre B9900062. La instal·lació està dividida en dues àrees: l'Àrea de Rosegadors amb una zona convencional neta, una quarantena passiva, una zona de barrera per allotjar ratolins immunodeficients, sis sales de manipulació i la Plataforma d'Imatge Molecular; i l'Àrea de Grans Animals amb espai per allotjar conills, porcs i ovelles amb quiròfans experimentals complets per realitzar projectes de cirurgia experimental i docència. L'Estabulari disposa d'una Comissió que es compon per investigadors de l'Institut que assessoren en temes científics relacionats amb l'Estabulari. La Plataforma d'Imatge Molecular (PIM) està situada dins de l'Estabulari del VHIR, i està equipada amb un sistema Xenogen IVIS® Spectrum d'imatge òptica no invasiva i un macroscopi Leica MacroFluo, manipulats per personal especialitzat.

Unitat Central d'Investigació Clínica i Assaigs Clínics

La UCICAC, constituïda per un equip de professionals multidisciplinars, ofereix un programa de serveis integrals *(start-to-end)* als investigadors per al desenvolupament de projectes d'investigació clínica així com assaigs clínics, garantint l'atracció i la competitivitat de la investigació biomèdica de l'HUVH. La UCICAC genera i promou tant projectes com instruments per facilitar la recerca clínica. Addicionalment, la UCICAC promou activitats formatives en recerca clínica i assaigs clínics. En un futur oferirà la centralització de les seves funcions en un espai únic a la planta 13a. de l'Hospital Materno-Infantil i en la que s'hi ubicaran les unitats:

- Unitat de Recerca i Assaigs Clínics (URAC).
- Unitat de Suport Metodològic per a la Investigació Biomèdica (USMIB).

USMIB

La Unitat de Suport en Metodologia per a la Investigació Biomèdica (USMIB) està promoguda per la Fundació Institut de Recerca de l'Hospital Universitari Vall d'Hebron (VHIR) amb el suport institucional de la Gerència de l'Hospital Universitari Vall d'Hebron (HUVH) i la col·laboració del Servei de Farmacologia Clínica i del Servei de Medicina Preventiva i Epidemiologia. La Unitat de Suport en Metodologia per a la Investigació Biomèdica (USMIB) proporciona serveis en metodologia científica per facilitar, promoure i potenciar la investigació biomèdica en l'Hospital Universitari Vall d'Hebron, l'àrea d'atenció primària corresponent i usuaris externs que demanin els seus serveis. Així mateix, dins les seves tasques hi ha l'establiment d'un programa de formació en metodologia per a la investigació biomèdica.

URAC

La Unitat de Recerca i Assaigs Clínics (URAC) dóna recolzament a la realització d'assaigs clínics i estudis postautorització amb medicaments, productes sanitaris i altres teràpies promoguts per investigadors de la institució o de promoció pública, en aspectes ètics, metodològics, regulatoris i logístics. Addicionalment, la Unitat de Recerca i Assaigs Clínics té l'objectiu de promoure la formació continuada en recerca clínica i assaigs clínics.

Coordinació de Laboratoris

La coordinació de laboratoris té com a finalitat gestionar els recursos i vetllar pel funcionament dels laboratoris que formen l'Institut de Recerca, així com la gestió del personal d'infermeria, tècnics i auxiliars d'infermeria que donen suport a la investigació biomèdica. Les activitats que depenen d'aquesta coordinació són: exercir com a nexe d'unió entre els laboratoris i la Direcció, facilitar el coneixement, la implantació i seguiment de les normatives tant pel que fa a l'àmbit hospitalari com a l'Institut de Recerca, així com centralitzar la borsa de treball en els àmbits anteriorment mencionats.

COMITÈS ÈTICS

Comitè Ètic d'Investigació Clínica (CEIC)

Dependent de l'HUVH, el CEIC col·labora i proporciona el seu suport a l'Institut de Recerca. El CEIC és un organisme independent, constituït per professionals sanitaris i membres no sanitaris, encarregat de vetllar per la protecció dels drets, la seguretat i el benestar dels subjectes que participen en un assaig i d'oferir garantia pública al respecte mitjançant un dictamen sobre el protocol de l'assaig, la idoneïtat dels investigadors i l'adequació de les instal·lacions, així com els mètodes i els documents que s'utilitzin per informar als subjectes de l'assaig amb la finalitat d'obtenir el seu consentiment informat.

Comitè Ètic d'Experimentació Animal (CEEA)

Creat el 8 de gener de 1998, el Comitè Ètic d'Experimentació Animal (CEEA) va ser format per vetllar per la cura i el benestar dels animals d'experimentació. Entre les seves funcions es troben: informar sobre la realització dels procediments d'experimentació, eliminar el patiment innecessari i proporcionar eutanàsia humanitària, contrastar la competència del personal que hi participa, així com l'adequació dels procediments emprats.

RESUM DE L'ACTIVITAT INVESTIGADORA

Les activitats de recerca del VHIR que es presenten en aquesta *Memòria* de l'any 2010 queden reflectides de forma resumida en els següents apartats:

Personal Investigador i tècnic

El 2010 el VHIR tenia un total de 57 grups de recerca amb 489 investigadors (metges, biòlegs, psicòlegs, bioquímics, farmacèutics, químics, veterinaris, i altres) amb 77 investigadors postdoctorals, 213 investigadors en formació i 417 personal de suport a la recerca (infermers, tècnics de laboratori, administratius i altres).

Dades Financeres

El finançament total de recerca ha estat de 36,2 milions d'euros format per organitzacions oficials, donacions, assaigs clínics, convenis amb la indústria, ingressos d'infraestructura i altres contribucions.

Publicacions Internacionals i Nacionals

Un total de 595 publicacions han estat realitzades per investigadors del VHIR, i s'han publicat en revistes científiques el 2010, amb un factor d'impacte total de 3149,576. El factor d'impacte mig per publicació ha estat de 5,293. La distribució d'aquestes publicacions queda de la manera següent: 440 articles, 41 revisions, 29 editorials en revistes internacionals, i 69 articles, 8 revisions, 8 editorials en revistes nacionals. El factor d'impacte del 2010 es calcula utilitzant el *Journal Citation Reports* (JCR) del 2010, amb el càlcul basat en articles originals, revisions i editorials. Les cartes i abstracts s'exclouen del càlcul.

Projectes de Recerca

El 2010, hi havia 242 projectes de recerca en curs, completament finançats per agències oficials i institucions privades.

Estudis Clínics

Un total de 238 assaigs clínics se sotmetien al Comitè Ètic d'Investigació Clínica per a la seva aprovació, dels quals 205 (un 86 %) eren estudis multicentre i el resta 33 (14 %) eren estudis unicentre. Dels 238 assaigs presentats, 199 (84 %) eren patrocinats per la indústria farmacèutica, 8 (3 %) per investigadors del VHIR, i la resta, 31 (13 %), eren patrocinats per uns altres hospitals.

Nous Contractes a Investigadors i Tècnics Finançats per Diferents Organismes i Programes

Al 2010, se signaven 10 contractes d'investigadors sèniors, 11 contractes d'investigadors postdoctorals, 16 contractes d'investigadors predoctorals i 8 contractes de tècnics de suport, fi nançats per diverses institucions públiques i privades.

Centre de Recerca Biomèdica en Xarxa (CIBER)

El Centre de Recerca Biomèdica en Xarxa (CIBER) és un organisme de recerca, dotat de personalitat jurídica pròpia, i que té com a missió la recerca monogràfica sobre una patologia o un problema de salut concret. Els CIBER pretenen generar grans Centres de Recerca traslacional, de caràcter multidisciplinari i multiinstitucional on s'integri la recerca bàsica, clínica i poblacional a fi de desenvolupar un únic programa comú de recerca, focalitzat en certes patologies que són rellevants per al Sistema Nacional de Salut per la seva prevalença o que degut a la seva repercussió social, són considerades estratègiques per al mateix. Tretze projectes del VHIR participen en set CIBER.

Xarxes Temàtiques de Recerca Cooperativa de l'*Instituto De Salud Carlos III*

Les Xarxes Temàtiques són estructures organitzatives, afavorides per l'*Instituto de Salud Carlos III* (ISCIII), d'un conjunt variable de centres i grups de recerca en biomedicina, de caràcter multidisciplinari, l'objectiu dels quals és la realització de projectes de recerca cooperativa d'interès general. Respon a les prioritats del Pla Nacional (2000-2003) en l'àmbit sanitari i l'integren els diferents tipus de recerca com a estratègia per retallar la distància entre la producció d'un nou coneixement i la seva transferència i aplicabilitat a la pràctica mèdica. El VHIR participa en deu Xarxes Temàtiques de Centres i setze de projectes.

Grups de Recerca Reconeguts per la Generalitat de Catalunya

Un dels objectius de la Generalitat de Catalunya, dins dels seus plans de recerca, ha estat el de proporcionar suport a aquells grups de recerca d'universitats i de centres de recerca de Catalunya que s'articulen al voltant d'una dimensió mínima estable d'investigadors, amb una trajectòria convergent, mitjançant la participació en projectes de recerca conjunts, la realització de publicacions o d'activitats comunes que impulsin la formació de joves investigadors. El VHIR compta amb el reconeixement de 28 d'aquests grups en les àrees d'Oncologia i genètica; Endocrinologia, creixement, metabolisme i diabetis; Fisiopatologia digestiva i hepatologia; Malalties cardiovasculars, hemostàsia i hipertensió; Neurociències, salut mental i envelliment; Malalties infeccioses i SIDA; Immunologia: malalties respiratòries, genètiques i sistèmiques; i Patologia i teràpia cel·lular i gènica, R+D, noves tecnologies i cirurgia experimental.

Tesis Doctorals

Un total de 62 tesis doctorals supervisades i dirigides per personal del VHIR es llegeixen al 2010. D'aquestes, 55 pertanyen a la Universitat Autònoma de Barcelona (UAB), 6 a la Universitat de Barcelona (UB), i 1 a la Universitat de Navarra.

Memoria Anual 2010

OBJETIVOS

Vall d'Hebron Institut de Recerca (VHIR) es una institución del sector público que promueve y desarrolla la investigación y la innovación biosanitaria del Hospital Universitari Vall d'Hebron, orientada a hallar soluciones a los problemas de salud de la ciudadanía y con la voluntad de contribuir al desarrollo científico, docente, social y económico de su ámbito de competencia.

Queremos que nuestra investigación e innovación, realizada por las personas que conforman la institución, amplíe la frontera del conocimiento y se consolide como un activo relevante y referente para nuestra sociedad, nuestro sistema de salud y su ciudadanía, siendo un polo de atracción de talento y consiguiendo que nuestra activitad, en términos de excelencia, calidad y translación, responda a la posición de liderazgo que debe tener el Hospital Universitari Vall d'Hebron.

ÓRGANOS DE DIRECCIÓN

La infraestructura de dirección y toma de decisión del VHIR pertenece a la *Fundació Institut de Recerca Hospital Universitari Vall d'Hebron,* e incluye, desde el 16 de diciembre de 2010, los siguientes órganos de dirección: el Patronato, la Comisión delegada, la Dirección, y los Consejos Científicos Internos y Externos.

Dirección

El director se encarga de desarrollar la dirección ejecutiva de la Fundación. Tiene las siguientes funciones:

a) Dirigir, organizar y gestionar las actividades de investigación de la Fundación.
b) Proponer al Patronato la programación de actividades que debe concretar las líneas de investigación, su coste y las fuentes de financiación previstas.
c) Proponer al Patronato el presupuesto anual de la Fundación.
d) Proponer al Patronato el nombramiento de personas que asuman la gerencia, y subdirecciones y asesorías, si fuera necesario.
e) Coordinar las actuaciones encaminadas a la obtención de los recursos necesarios para que se puedan llevar a cabo los objetivos de la Fundación.
f) Informar y dar cuentas al Patronato del desarrollo de las actividades y programas de investigación de la Fundación.
g) Dirigir el proceso selectivo del personal investigador y de apoyo a la investigación, o para la aceptación de la adscripción del personal investigador y científico y técnico de otras instituciones a la Fundación.
h) Proponer los servicios que hagan falta para que la Fundación desarrolle las actividades y funciones que le correspondan.
i) Proponer al Patronato las normas de funcionamiento interno.
j) Formalizar los convenios de colaboración con instituciones públicas o privadas de importe inferior al máximo que expresamente le haya autorizado el Patronato.
k) Otras funciones que le sean expresamente encomendadas o delegadas por el Patronato, en los términos previstos en estos Estatutos.

Patronato

El Patronato es el órgano de gobierno y de administración de la Fundación, la representa y gestiona, y asume todas las facultades y funciones necesarias para la consecución de los fines fundacionales.

De Junta de Gobierno a Comisión delegada

Desde el 16 de diciembre de 2010, la Junta de Gobierno se convierte en Comisión delegada y tiene las siguientes funciones:

a) Llevar a cabo los acuerdos adoptados por el Patronato que este órgano le encomiende.
b) Hacer el seguimiento periódico de las tareas de dirección y de gestión del centro.
c) Elaborar la propuesta de orden del día de las sesiones del Patronato y revisar la documentación a presentar, si procede.
d) Proponer al Patronato la adopción de los acuerdos que correspondan a este órgano.

e) Realizar el seguimiento de los convenios y acuerdos suscritos por la Fundación.
f) Informar de las necesidades de endeudamiento de la Fundación.
g) Facilitar las tareas de dirección y gestión de la Fundación, especialmente en aquello relativo a sus relaciones con las entidades fundadoras.

De Comité Científico Interno a Consejo Científico Interno

Desde diciembre de 2010 el Comité Científico Interno se convierte en Consejo Científico Interno.

El Patronato nombra, a propuesta de la Dirección, un Consejo Científico Interno formado por un mínimo de tres y un máximo de veinte investigadores de los Grupos de Investigación de la Fundación, que tiene por objeto asesorar a la Dirección en el desarrollo de sus funciones. Este órgano no ostenta, en caso alguno, funciones de gestión o de representación de la Fundación.

De Comité Científico Externo a Consejo Científico Externo

Desde diciembre de 2010 el Comité Científico Externo se convierte en Consejo Científico Externo.

El Consejo Científico Externo es el órgano encargado de asesorar sobre las actividades científicas de la Fundación y de velar por su calidad científica. Este órgano no ostenta, en caso alguno, funciones de gestión o de representación de la Fundación.

El Consejo Científico Externo está formado por un mínimo de tres y un máximo de veinte personas científicas de prestigio internacional y competencia reconocida en los ámbitos de investigación de la Fundación. En ningún caso los miembros del Consejo Científico Externo pueden ser personas investigadoras vinculadas a la Fundación o que colaboren habitualmente.

UNIDADES DE APOYO A LA INVESTIGACIÓN

La actividad de la Fundación se articula a través de múltiples Unidades de Apoyo a la Investigación, coordinadas desde la Dirección y divididas en tres bloques principales: Innovación, Estructura administrativa y Servicios.

1. Innovación

El Hospital Universitari Vall d'Hebron, mediante el Institut de Recerca, quiere impulsar un plan de innovación que permita estructurar y ordenar las acciones propias de este ámbito, concretadas con las siguientes líneas de actuación: Detección de iniciativas de innovación, su registro y búsqueda de sinergias entre ellas, apoyo a los profesionales de la organización en la identificación de oportunidades y en su concreción, análisis de la innovación tecnológica susceptible de ser transferida, y evaluación y priorización de las innovaciones transferidas.

2. Estructura administrativa

La estructura administrativa de apoyo a la investigación del VHIR, con capacidad para gestionar, generar recursos y contratar personal técnico, se articula en diferentes unidades:

Agencia de Ensayos Clínicos

Organismo independiente que vela por la protección de derechos, la seguridad y el bienestar de los sujetos que participan en un ensayo y proyectos de investigación en humanos o en aquellos que utilizan muestras humanas. Ofrece garantía pública al respecto mediante un dictamen sobre el protocolo del ensayo, la idoneidad de los investigadores y la adecuación de las instalaciones, así como los métodos y los documentos que se utilicen para informar a los sujetos del ensayo para obtener su consentimiento informado.

Unidad Básica de Prevención de Riesgos Laborales

La Unidad Básica de Prevención de Riesgos Laborales asesora y vela por la seguridad y salud de los puestos de trabajo, de acuerdo con los preceptos de la Ley 31/95 de Prevención de Riesgos Laborales, evaluando y controlando los riesgos, elaborando instrucciones de seguridad, analizando los accidentes, informando y formando a los trabajadores, vigilando y promocionando la salud y previniendo las enfermedades laborales de los profesionales.

Unidad de Comunicación e Imagen

Vincula la investigación científica y el resto de actividades del Instituto y la sociedad a través de los medios de comunicación. Da a conocer las actividades del Instituto y sus investigadores mediante notas y ruedas de prensa, entrevistas, vídeos divulgativos y campañas de comunicación concretas, desarrolla y utiliza la página web institucional como herramienta fundamental para comunicarse tanto interna como externamente.

Unidad de Fundraising

Impulsa y promueve un modelo de mecenazgo con el fin de buscar la participación y la generosidad de personas, empresas, fundaciones, obras sociales y entidades públicas y privadas que deseen apoyar económicamente e invertir en investigación biomédica. Identifica el universo de donantes y posibles financiadores y define una estrategia de captación de fondos para la Fundación VHIR. Da soporte a los investigadores en sus relaciones con los donantes y entidades colaboradoras.

Unidad de Gestión de Proyectos

La Unidad de Gestión de Proyectos gestiona la solicitud y el seguimiento de los proyectos de investigación que se llevan a cabo en el HUVH y en el VHIR, financiados por agencias públicas y privadas, autonómicas, nacionales e internacionales. Selecciona y difunde la información sobre recursos y ayudas económicas, canaliza el seguimiento de los recursos y ayudas financiadas, optimiza y promueve la gestión de los recursos de personal, instalaciones y servicios implicados en el desarrollo de los proyectos de investigación que se llevan a cabo en el VHIR, y promueve actividades formativas sobre recursos y ayudas.

Unidad de Gestión Informática

Los Servicios Informáticos del VHIR coordinan todos los aspectos informáticos relacionados con el Instituto y ofrecen apoyo a los investigadores. Uno de los objetivos principales ha sido la creación de una base de datos centralizada para la gestión del conocimiento integral de la institución que cubre tanto el ámbito de los procesos internos como el de relación con los agentes externos de interés.

Unidad de Gestión Económica

La Unidad de Gestión Económica recepciona los ingresos y donaciones, realiza los pagos de facturas ordenadas por los investigadores, realiza los procedimientos de contratación pública para las grandes compras, suministra información económica, desde datos agregados por servicios o grupos de investigación hasta la confección de memorias económicas para proyectos, y asesora jurídicamente en cuanto a contratos, convenios, etc.

Unidad de Recursos Humanos

La Unidad de Gestión de Recursos Humanos promueve y facilita las relaciones laborales del VHIR. Adecua los recursos laborales a las directrices y necesidades del Instituto respetando los marcos jurídicos, legales y éticos.

3. Servicios

Con la finalidad de proporcionar los complejos medios que requiere la biomedicina actual, el Vall d'Hebron Institut de Recerca dispone de una serie de importantes servicios para prestar apoyo a la Investigación. Son la Unidad Científico-Técnica de Soporte (UCTS), la Unidad de Estadística y Bioinformática (UEB), la Unidad de Soporte en Metodología para la Investigación Biomédica (USMIB), el Estabulario y la Coordinación de Laboratorios de Investigación. Los últimos servicios incorporados son: el Biobanco y la Unidad Central de Investigación Clínica y Ensayos Clínicos (UCICAC). De esta forma, además, de facilitar a los investigadores la tecnología y los servicios más actuales, se aumenta la rentabilidad y se mejora la autosuficiencia.

Unidad Científico-Técnica de Soporte

La Unidad Científico-Técnica de Soporte (UCTS) es un conjunto de servicios de tecnología puntera que dan soporte a las actividades docentes y de investigación del ámbito biomédico. El carácter centralizado de la UCTS permite poner al alcance de cualquier investigador las herramientas más avanzadas en las áreas de genómica, bioinformática, proteómica, citómica y microscopia a un coste reducido, con una actualización constante y con el asesoramiento de personal especializado.

La UCTS ofrece las siguientes plataformas: Citómica, Diagnóstico Molecular, Genómica, Microscopia, Proteómica, Metabolómica, y de Estadística y Bioinformática (UEB).

UEB

La Unidad de Estadística y Bioinformática (UEB) se crea dentro del Institut de Recerca del Hospital Universitari Vall d'Hebron con el objetivo de potenciar el uso y el desarrollo de los modernos recursos estadísticos y bioinformáticos en la investigación efectuada en su entorno. Así pues, los objetivos principales de la UEB, son:

– Proporcionar soporte estadístico y bioinformático especialmente para el tratamiento de datos de alto rendimiento *(high troughput)* generados en la investigación en nuestro centro y el ámbito biomédico.

– Desarrollar líneas propias de investigación en el campo de la estadística y la bioinformática y particularmente en aquellos campos que puedan revertir en una mejora de los servicios proporcionados por la Unidad.

– Establecer un programa de formación en estadística y bioinformática para la investigación biomédica.

Biobanco

El Biobanco del Hospital Universitari Vall d'Hebron (BBHUVH) es una unidad de soporte a la investigación que acoge muestras biológicas de origen humano con fines de investigación biomédica en cumplimiento con la legislación vigente, y cuyo objetivo es poner a disposición de la comunidad científica el material biológico necesario para la investigación en unas óptimas condiciones que aseguren la competitividad y excelencia de la investigación.

Estabulario

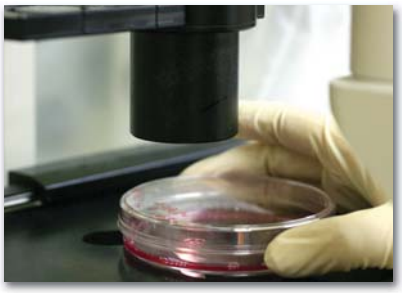
La investigación y la docencia vinculadas al uso de animales de laboratorio se centralizan en el Estabulario del Institut de Recerca del Hospital Universitari Vall d'Hebron. Ubicado en el edificio Mediterrània, ocupa una superficie construida de 745 m^2 y una superficie útil de 683 m^2 en una sola planta. El Estabulario cumple con la legislación vigente y está registrado en el Departamento de Medio Ambiente y Vivienda con el número de registro B9900062. La instalación está dividida en dos áreas: el Área de Roedores con una zona convencional limpia, una cuarentena pasiva, una zona de barrera para alojar ratones inmunodeficientes, seis salas de manipulación y la Plataforma de Imagen Molecular; y el Área de Grandes Animales, con espacio para alojar conejos, cerdos y ovejas con quirófanos experimentales completos para realizar proyectos de cirugía experimental y docencia. El Estabulario dispone de una Comisión compuesta por investigadores del Instituto que asesoran en temas científicos relacionados con el mismo. La Plataforma de Imagen Molecular (PIM), situada dentro del Estabulario del VHIR, está equipada con un sistema Xenogen IVIS® Spectrum de imagen óptica no invasiva y un macroscopio Leica MacroFluo, manipulados por personal especializado.

Unidad Central de Investigación Clínica y Ensayos Clínicos (UCICAC)

La UCICAC, constituida por un equipo de profesionales multidisciplinares, ofrece un programa de servicios integrales *(start-to-end)* a los investigadores para el desarrollo de proyectos de investigación clínica así como ensayos clínicos, garantizando la atracción y la competitividad de la investigación biomédica del HUVH. La UCICAC genera y promueve tanto proyectos como instrumentos para facilitar la investigación clínica. Adicionalmente, la UCICAC promueve actividades formativas en investigación clínica y ensayos clínicos. En un futuro ofrecerá la centralización de sus funciones en un espacio único en la planta 13ª del Hospital Materno-Infantil y en la que se ubicarán las unidades:

– Unidad de Investigación y Ensayos Clínicos (URAC).

– Unidad de Soporte Metodológico para la Investigación Biomédica (USMIB).



USMIB

La Unidad de Soporte en Metodología para la Investigación Biomédica (USMIB) está promovida por la Fundació Institut de Recerca Hospital Universitari Vall d'Hebron (VHIR) con el soporte institucional de la Gerencia del Hospital Universitari Vall d'Hebron (HUVH) y la colaboración del Servicio de Farmacología Clínica y del Servicio de Medicina Preventiva y Epidemiología. La Unidad de Soporte en Metodología para la Investigación Biomédica (USMIB) proporciona servicios en metodología científica para facilitar, promover y potenciar la investigación biomédica en el Hospital Universitari Vall d'Hebron, el área de atención primaria correspondiente y usuarios externos que pidan sus servicios. Asimismo, dentro de sus tareas está el establecimiento de un programa de formación en metodología para la investigación biomédica.

URAC

La Unidad de Investigación y Ensayos Clínicos da apoyo a la realización de ensayos clínicos y estudios postautorización con medicamentos, productos sanitarios y otras terapias promovidos por investigadores de la institución o de promoción pública, en aspectos éticos, metodológicos, regulatorios y logísticos. Adicionalmente, la URAC tiene el objetivo de promover la formación continuada en investigación clínica y ensayos clínicos.

Coordinación de Laboratorios

La Coordinación de Laboratorios tiene como finalidad gestionar los recursos y velar por el funcionamiento de los laboratorios que forman el Instituto de Investigación, así como la gestión del personal de enfermería, técnicos y auxiliares de enfermería que dan soporte a la investigación biomédica. Las actividades que dependen de esta coordinación son: ejercer como nexo de unión entre los laboratorios y la Dirección, facilitar el conocimiento, la implantación y seguimiento de las normativas tanto con respecto al ámbito hospitalario como al Institut de Recerca, así como centralizar la bolsa de trabajo en los ámbitos anteriormente mencionados.

COMITÉS ÉTICOS

Comité Ético de Investigación Clínica (CEIC)

Dependiente del HUVH, el CEIC colabora y proporciona apoyo al Institut de Recerca. Se trata de un organismo independiente, constituido por profesionales sanitarios y miembros no sanitarios, que se encarga de velar por la protección de los derechos, la seguridad y el bienestar de los sujetos que participan en un ensayo y de ofrecer garantía pública al respecto mediante un dictamen sobre el protocolo del ensayo, la idoneidad de los investigadores y la adecuación de las instalaciones, así como los métodos y los documentos que se utilicen para informar a los sujetos del ensayo con la finalidad de obtener su consentimiento informado.

Comité Ético de Experimentación Animal (CEEA)

Creado el 8 de enero de 1998, el Comité Ético de Experimentación Animal se formó para velar por el cuidado y el bienestar de los animales de experimentación. Entre sus funciones se encuentran: informar sobre la realización de los procedimientos de experimentación, eliminar el padecimiento innecesario y proporcionar eutanasia humanitaria, contrastar la competencia del personal que participa, así como la adecuación de los procedimientos utilizados.

RESUMEN DE LA ACTIVIDAD INVESTIGADORA

Las actividades de investigación del VHIR que se presentan en esta *Memoria* del 2010 quedan reflejadas de forma resumida en los siguientes apartados:

Personal Investigador y Técnico

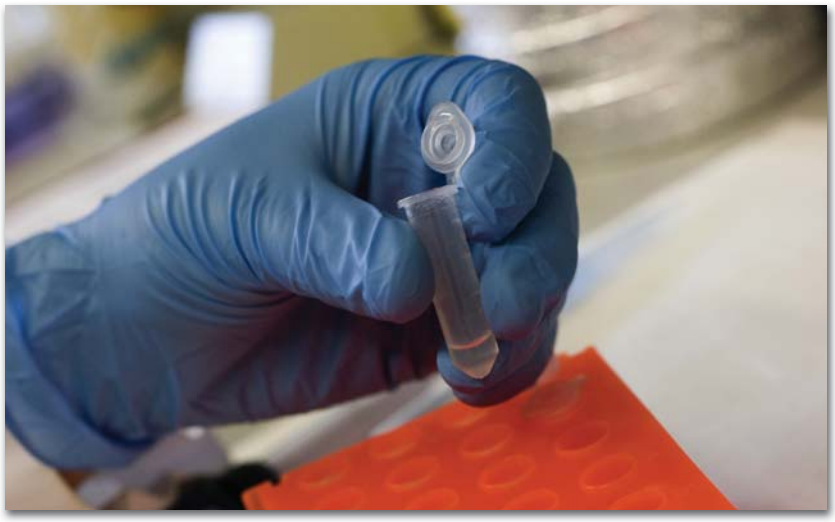
En 2010, el VHIR tenía un total de 57 grupos de investigación con 489 investigadores (médicos, biólogos, psicólogos, bioquímicos, farmacéuticos, químicos, veterinarios, y otros) con 77 investigadores postdoctorales, 213 investigadores en formación y 417 personal de apoyo a la investigación (enfermeros, técnicos de laboratorio, administrativos y otros).

Datos Financieros

La financiación total de investigación ha sido de 36,2 millones de euros, formada por organizaciones oficiales, donaciones, ensayos clínicos, convenios con la industria, ingresos de infraestructura y otras contribuciones.

Publicaciones Internacionales y Nacionales

Un total de 595 publicaciones han sido realizadas por investigadores del VHIR, y se han publicado en revistas científicas en el 2010, con un factor de impacto total de 3149,576. El factor de impacto medio por publicación ha sido de 5,293. La distribución de estas publicaciones es la siguiente: 440 artículos, 41 revisiones, 29 editoriales en revistas internacionales, y 69 artículos, 8 revisiones, 8 editoriales en revistas nacionales, El factor de impacto del 2010 se calcula utilizando el *Journal Citation Reports* (JCR) del 2010, con el cálculo basado en artículos originales, revisiones y editoriales. Las cartas y *abstracts* se excluyen del cálculo.



Proyectos de Investigación

En el 2010, hubo 242 proyectos de investigación en curso, completamente financiados por agencias oficiales e instituciones privadas.

Estudios Clínicos

Un total de 238 ensayos clínicos se sometieron al Comité Ético de Investigación Clínica para su aprobación, de los cuales 205 (un 85 %) eran estudios multicéntricos y el resto 33 (14 %) eran estudios unicéntricos. De los 238 ensayos presentados, 199 (84 %) fueron patrocinados por la industria farmacéutica, 8 (3 %) por investigadores del VHIR, y el resto, 31 (13 %), fueron patrocinados por otros hospitales.

Nuevos Contratos a Investigadores y Técnicos Financiados por Diferentes Organismos y Programas

En el 2010, se firmaron 10 contratos de investigadores seniors, 11 contratos de investigadores postdoctorales, 16 de investigadores predoctorales y 8 de técnicos de soporte, financiados por diversas instituciones públicas y privadas.

Centro de Investigación Biomédica en Red (CIBER)

El Centro de Investigación Biomédica en Red (CIBER) es un organismo de investigación, dotado de personalidad jurídica propia, y que tiene como misión la investigación monográfica sobre una patología o un problema de salud concreto. Los CIBER pretenden generar grandes Centros de Investigación traslacional, de carácter multidisciplinar y multiinstitucional donde se integre la investigación básica, clínica y poblacional con el fin de desarrollar un único programa común de investigación, focalizado en ciertas patologías que son relevantes para el Sistema Nacional de Salud por su prevalencia o que debido a su repercusión social, son consideradas estratégicas para lo mismo. Trece proyectos del VHIR participan en siete CIBER.

Redes Temáticas de Investigación Cooperativa del Instituto de Salud Carlos III

Las Redes Temáticas son estructuras organizativas, auspiciadas por el Instituto de Salud Carlos III (ISCIII), de un conjunto variable de centros y grupos de investigación en biomedicina, de carácter multidisciplinar, el objetivo de los cuales es la realización de proyectos de investigación cooperativa de interés general. Responde a las prioridades del Plan Nacional (2000-2003) en el ámbito sanitario y lo integran los diferentes tipos de investigación como estrategia para recortar la distancia entre la producción de un nuevo conocimiento y su transferencia y aplicabilidad a la práctica médica. El VHIR participa en diez Redes Temáticas de Centros y dieciséis de proyectos.

Grupos de Investigación Reconocidos por la Generalitat de Catalunya

Uno de los objetivos de la Generalitat de Catalunya, dentro de sus planes de investigación, ha sido el de proporcionar soporte a aquellos grupos de investigación de universidades y de centros de investigación de Cataluña que se articulan en torno a una dimensión mínima estable de investigadores, con una trayectoria convergente, mediante la participación en proyectos de investigación conjuntos, la realización de publicaciones o de actividades comunes que impulsen la formación de jóvenes investigadores. El VHIR cuenta con el reconocimiento de 28 de estos grupos en las áreas de Oncología y genética; Endocrinología, crecimiento, metabolismo y diabetes; Fisiopatología digestiva y hepatología; Enfermedades cardiovasculares, hemostasia e hipertensión; Neurociencias, salud mental y envejecimiento; Enfermedades infecciosas y SIDA; Inmunología: enfermedades respiratorias, genéticas y sistémicas; y Patología y terapia celular y génica, I+D, nuevas tecnologías y cirugía experimental.

Tesis Doctorales

Un total de 62 tesis doctorales supervisadas y dirigidas por personal del VHIR se leen en 2010. De estas, 55 pertenecen a la Universidad Autónoma de Barcelona (UAB), 6 a la Universidad de Barcelona (UB), y 1 a la Universidad de Navarra (UN).

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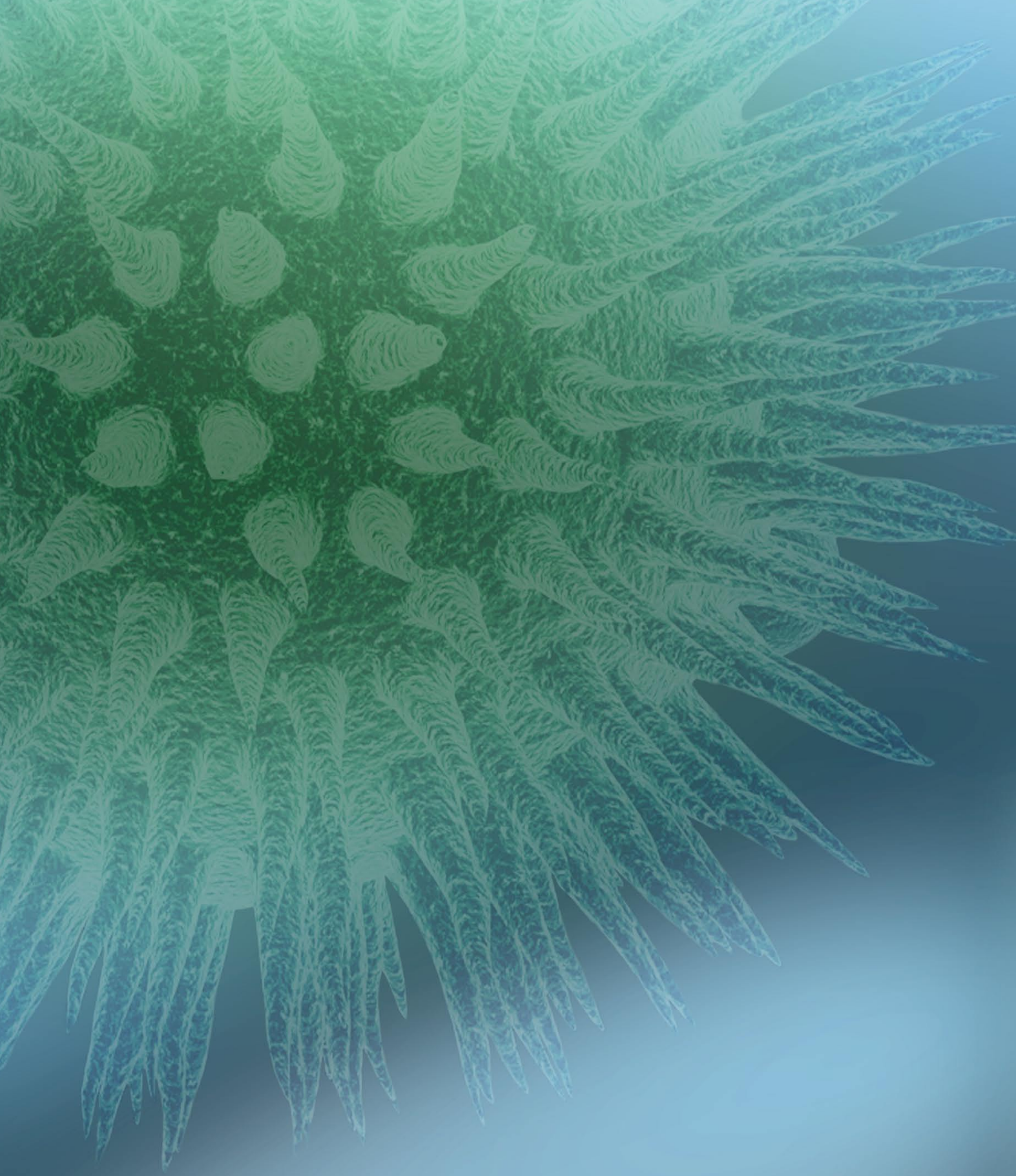

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