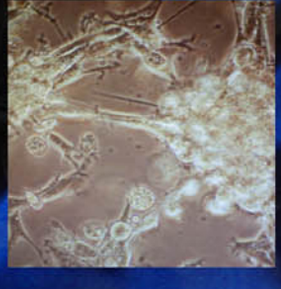
Vall d'Hebron Institut de Recerca (VHIR)

ANNUAL REPORT 2009



Vall d'Hebron
Institut de Recerca
VHIR

Vall d'Hebron Institut de Recerca

ANNUAL REPORT 2009

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

Vall d'Hebron Institut de Recerca

ANNUAL REPORT 2009

Generalitat de Catalunya
Departament de Salut

Institut Català de la Salut

Vall d'Hebron
Institut de Recerca
VHIR

UAB
Universitat Autònoma de Barcelona

Instituto de Salud Carlos III

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www.vhir.org

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Index

Presentation

Marina Geli i Fàbrega
Catalonian Regional Minister of Health

The report of Vall d'Hebron Research Institute (VHIR) I have the honor to present you shows the strong commitment of this institution to grow and promote its status as a leading biomedical research center.

2009 was a year of great change for the institution with the addition of a new management team at the Institute, headed by Dr. Joan Comella, who has maintained – and even improved – the same direction of excellence in scientific production of previous years.

Among the numerous actions carried out, it should be mentioned the inclusion of over sixty researchers, which has enabled to create more working groups and a new restructuring of research areas. We have also launched more new projects, more publications have been made, always with a high prestige, and a hard work has been done to increase their impact, both in science, education and the media.

To accommodate this increase in research activity, the Institute began the construction of the new Collserola building in 2009, which was inaugurated in September 2010. The investment, which exceeds M€6.5, extends the facilities devoted to research in Vall d'Hebron premises in 2,500 m2. In addition, close to the Collserola building, the Multiple Sclerosis Center of Catalonia (CEM-Cat) was build, which will allocate 1,800 m2 to multiple sclerosis comprehensive care.

It is also remarkable that the Institute is fully committed to clinical and translational research. Its leadership in this area resulted in its participation as coordinator of centers throughout Spain in such an important European research project as EATRIS.

It is necessary to congratulate, therefore, the Research Institute of the Hospital Vall d'Hebron, and all those who work to make it possible, to help build a knowledge-based society in Catalonia, which will allow us to tackle with confidence the challenges of the future.

Marina Geli i Fàbrega
Catalonian Regional Minister of Health

Presentation

José Luis de Sancho
Executive Vice President and General Manager of Vall d'Hebron University Hospital

The 2009 Report of the Vall d'Hebron Research Institute (VHIR) reflects, once again, the image of research main characters and all the activities carried out at Vall d'Hebron University Hospital (HUVH).

At HUVH, patients are the core of our health care activities and, consequently, they are also the core of the research carried out at VHIR. Our hospital, the most important in Catalunya regarding medical care volume, is at the same time the most productive regarding scientific research in the Institut Català de la Salut, and the second one throughout Spain.

In 2009, Research Institute launched ambitious translational and clinical research projects whose results will be published in the coming years. However, it has not neglected at all its scientific production.

As HUVH manager, I do assess the magnitude of the evolution in the context of efficiency required in public resources management. Results achieved during the last year have been obtained due the 5.5% funding increase compared to 2008. It reflects an efficiency of which we feel especially proud.

Regarding economic resources, VHIR obtained 38.5 million euros funding in 2009, with a major contribution of the private sector, particularly from agreements with industry, donation and clinical trials. It shows the social prestige of Research Institute. The hospital contribution to VHIR was of 4.8 million euros last year. The importance of these data in time of economic difficulties shows that commitment to research at Vall d'Hebron Hospital has a great support.

Our center is increasingly present in the best research networks, improving exchanges and collaborations among centers and leading some of these initiatives.

The excellent results of this annual scientific report show that VHIR is still evolving; carrying out quality research at the service of citizens, for whom we will keep on working.

In 2009, we started some changes that have been implemented once and for all in 2010. With the new management team the commitment to innovation has been strengthened and new research support units have been created to make the project more ambitious.

The new building project, conceived in 2009, is already real since the second half of 2010. More space to carry out more research. Although it is not our limit, it is only a further step to achieve the Vall d'Hebron Biohealth Research Park.

With these results, objectives and perspectives, it is an honor to be part of this premium project where magnificent professionals working at VHIR offer to our patients, and the whole society, diagnostic, preventive, therapeutic and technological solutions in order to beat diseases.

As I am sure they will keep working with the same strength and dedication, I want to congratulate them and offer them my whole support.

José Luis de Sancho
Executive Vice President and General Manager of Vall d'Hebron University Hospital

Introduction

David García-Dorado
VHIR's former Director

It was indeed an honor and a privilege to serve our institution as the Director during most of 2009. It was also a huge challenge and an exciting and intense experience. I had the opportunity to get a more direct experience of the strong, convinced commitment of the General Manager and the Directive Board of our Hospital with research and innovation, and of the dedication and professional skills of the administrative and technical staff of the institute.

During a relatively short period of time many important developments took place in our institution. It deserves particular mention the reception of the accreditation as a Health Research Institute of the Instituto de Salud Carlos III, which gives a new role to our hospital as a highest level Research Center with the participation of the Autonomous University of Barcelona and the Research Institute and Hospital itself.

Clinical Research received a big impulse from the organization new and important support facilities included the Biobank and the Clinical Research Unit. The final design of the new research building, the Collserola building, was concluded. The new space available was allocated to different groups according to objective criteria agreed by the representatives and coordinators of the different research areas. A set of advisory committees (Animal House matters, technical and scientific support facilities, equipment, laboratories, library, intellectual property) was organized, and the system for co-funding of scientific personnel by the research groups was modified. All this was done with the help of the Internal Scientific Committee, and in particular of its Vice-President, Joan Montaner, acting all that time as Subdirector of the institute. Finally, but most importantly, the process of election of the new Director of the institute took place during that period through public and transparent concourse in which the Internal and External Scientific Committees had an important role.

Thanks to the effort and enthusiasm of everybody, in the middle of these changes, the funding and the scientific production continued to grow steadily during 2009. I am convinced that the new Director will succeed in finding new ways to impulse our research activities and the transference of our results to the Society. It is not exaggerated to say that our Institute is now at the verge of a new and exciting era.

David García-Dorado
VHIR's former Director

Introduction

Joan X. Comella
VHIR's Director

2009, the first year of our new management, has supposed the launching of a project whose mid-range goal is to achieve that all research carried out at Vall d'Hebron University Hospital reaches the leadership that it deserves regarding the human and professional quality of its researchers and support personnel. We have worked, we work and we will work to maintain the leadership regarding our publications' quantity and quality, but, specially, to maintain our leadership regarding the solutions to human health issues. We are leaders in innovation, but also leaders in bringing the results of our research closer to the society to which we are devoted.

We have more researchers, more research groups and more space than the last year, but it is only the starting point of a project that will not stop growing. 2009 implied the arrival of our new management that inherited an historical legacy which is now further developed. One year and a half later, this adventure is still a challenge for those who, directly or indirectly, work in Vall d'Hebron research projects.

As you can see on the content of this report, during 2009, Vall d'Hebron Research Institute (VHIR) has published 540 papers, with an impact factor of 2,474.709, which means an increase of 6.6% regarding the same data for 2008. If quantity is significant, quality of our publications is even more important. The average impact factor of 2009 scientific publications has been around 4.58. As additional reference we need to state that 48.52% of our publications have been placed in the upper quartile and the 21.48% in the upper decile, which strengthens the relation between quantity and quality.

13 of our 46 research groups existing in 2009 took part in seven projects of the Biomedical Research Networking Centers (CIBER), and 16 groups took part in 10 Health Thematic Networks and Cooperative Research (RETICS) of the Instituto de Salud Carlos III (ISCIII). Altogether, 230 projects of the VHRI have been externally funded. It has to be highlighted that 28 of our research groups have been recognized by the Generalitat de Catalunya.

Our idea of increasing our working space planned in 2009, has become a reality during 2010, with 2,500 m2 devoted to research. Our researchers deserve the best infrastructures, and the new Collserola Building is the seed of what has to become the new Biomedical Research Park, which, in the future, will group all Vall d'Hebron scientific activities.

We have built up new structures and units to grow up according to modern times. We resolutely encourage the appreciation tasks and the transfer of research results to manufacturing sector. Innovation is the core of our activity. We are committed to innovation by promoting a Plan in order to detect innovation initiatives, its records and the synergies among them. We also support management professionals to identify opportunities and the way they should be carried out; we analyze technological innovations that can be transferred and assess and prioritize already transferred innovations.

We strongly believe in the need of bringing the results of our research closer to our society; for this rea-

son our communicative activities are constantly increasing. We look for new allies among the society to create a friend network of support to research, for this reason fundraising has become one of our new main goals.

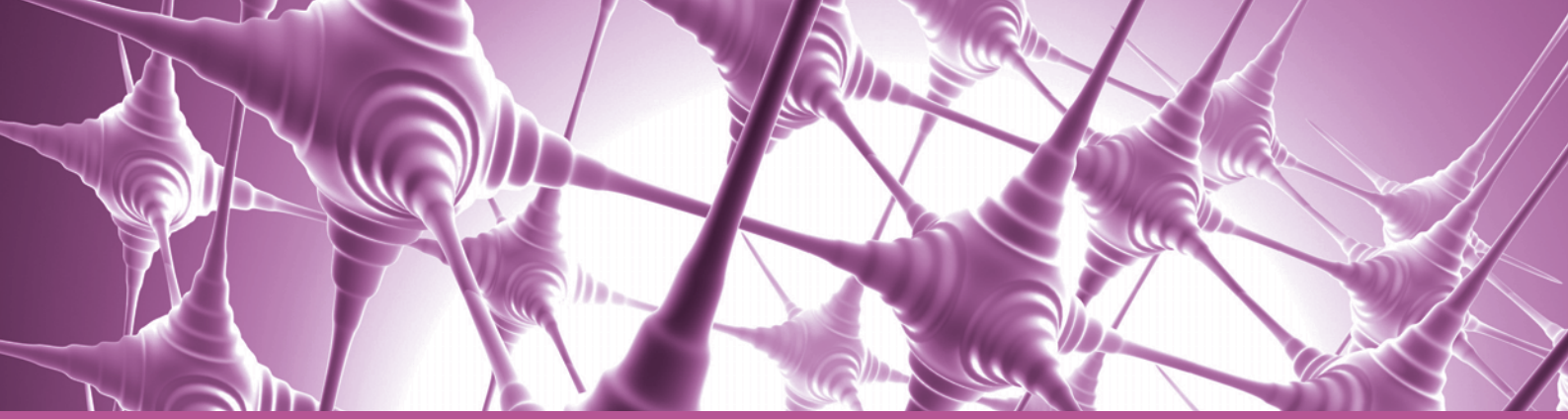
The global objective of all this work is to create a scenario to find out the solutions for the citizens health issues. Everyone has to know that in Vall d'Hebron we work at laboratories with animal models and at the hospital we solve the patients problems. From the hospital bed to our laboratories and from our laboratories back to the hospital. It is clinical and translational research, going from theory to practice and viceversa. Research became a basic healthcare tool in society's daily life.

Clinical research is part of our DNA, so it cannot be apart in our definition as Research Institute of a healthcare center. For this reason, we have created the Central Unit of Clinical Research and Clinical Trials (UCICAC), which offers a program of integral services (start-to-end) to researchers while developing clinical research projects, as well as clinical trials, guaranteeing attraction and competitiveness of biomedical research at Vall d'Hebron.

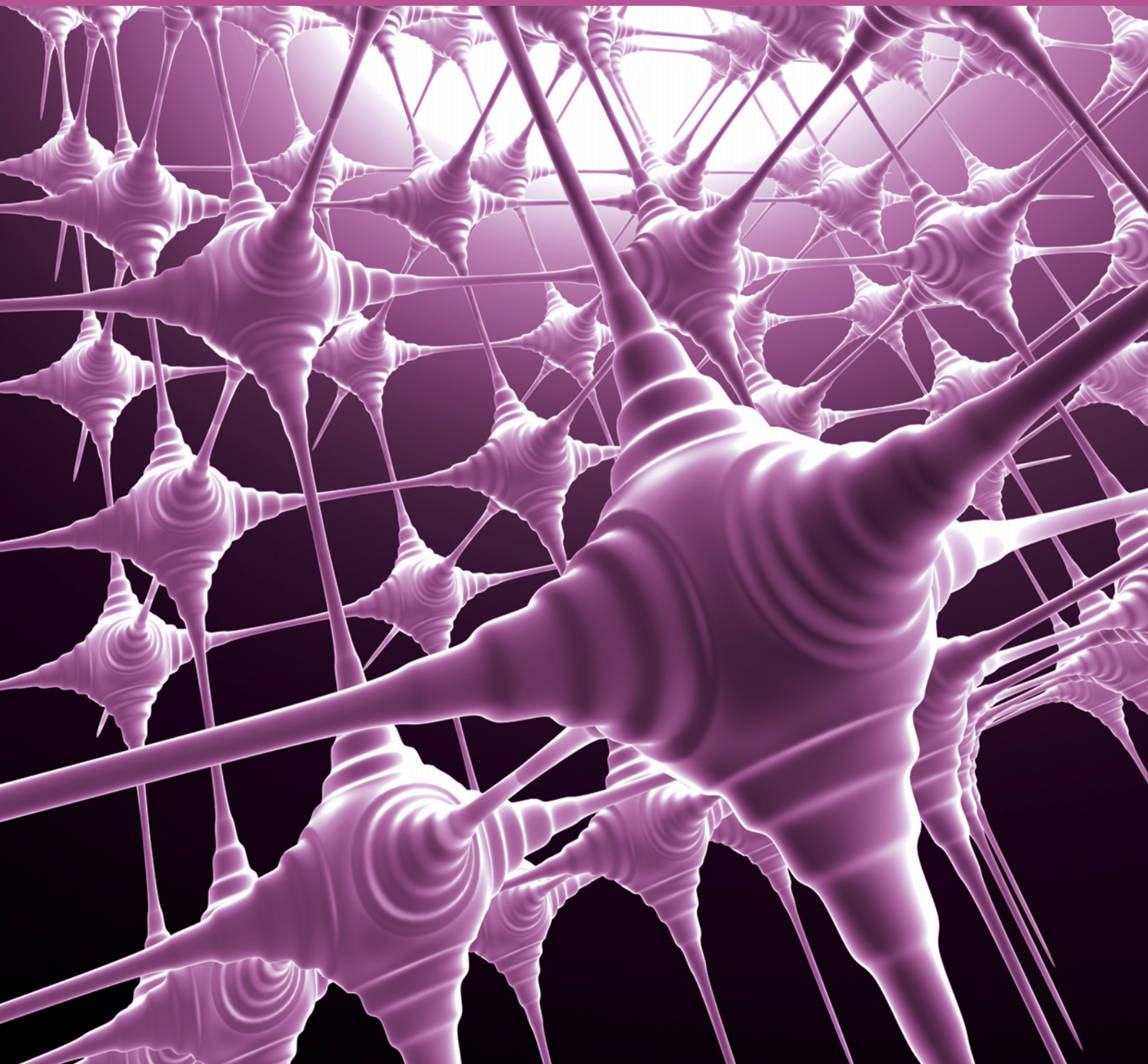
We want and we can be the leaders in translational research in our country, and for this reason we are recognized by Spanish and European institutions, that have decided that VHIR should be the Spanish coordinator of the EATRIS, a global project that tries to bring investigations to daily treatment of patients. A network composed by 25 hospitals and research centers that is institutionally leaded in Spain by the Instituto de Salud Carlos III, and Vall d'Hebron acts as scientific coordinator.

To sum up, 2009 report reflects the activity for this year, but it also shows the present state of VHIR, with its new research groups, added to those already existent, and new units, added to those that were already supported. All of them share the same common goal: to overcome themselves to achieve outstanding challenges that await in the future. Without them it would not be possible, but with them nothing is impossible.

Joan X. Comella
VHIR's Director



Vall d'Hebron Institut de Recerca (VHIR)



1.1 Vall d'Hebron Institut de Recerca (VHIR)

1.1 VALL D'HEBRON INSTITUT DE RECERCA (VHIR)

The general purpose of Vall d'Hebron Research Institute (VHIR) is to support, promote, and foster research, scientific and technological knowledge, teaching, and training in the setting of the Hospital Universitari Vall d'Hebron (HUVH), of the University Autònoma de Barcelona (UAB), and their areas of influence. The basic mission of VHIR is the biomedical research development and promotion of its application to improve citizens' heath. VHIR is a leader centre in biomedical research at a national and European scope. Because of its advantage from its privileged relation with the third-level hospital, it achieves a highly competitive position. It also deepens collaborative relationships with other science parks, universities and research institutes.

1.1.1 Governing Bodies

The infrastructure of management and decision of VHIR falls in the Foundation University Hospital Vall d'Hebron Research Institute, where the organs managing are:

1.1.1.1 Trustees

Government and representation of the VHIR correspond to the Board. It has all the required faculties for the realization of its objectives, without prejudice of the delegation faculties given by laws and statutes. It shall consist of at least 8 people and a maximum of 25.

President
Marina Geli Fàbrega
Catalonian Regional Minister of Health

1st Vice President
Enric Argelagués Vidal
Director
Catalonian Institute of Health (ICS)
(From 25/2/09)

Francesc José María Sánchez
Director
Catalonian Institute of Health (ICS)
(Until 25.02.09)

2nd Vice President
Ana Ripoll Aracil
Rector
Universitat Autònoma de Barcelona (UAB)
(From 25.02.09)

Lluís Ferrer Caubet
Rector
Universitat Autònoma de Barcelona (UAB)
(Until 25.02.09)

3rd Vice President
José Luis de Sancho Martín
General Manager
Vall d'Hebron University Hospital (HUVH)

Treasurer
Eduard Jaurrieta i Mas
Deputy Director Professional Development Catalonian Institute of Health (ICS)

Members

Jesús Acebillo Marín
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)
(From 25.02.09)

Francesc Moreu Orobitg
Chief Executive Officer
Imaging Diagnostic Institute (IDI)
(Until 25.02.09)

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
(From 25.02.09)

José J. Navas Palacios
Director of the Plan of Research in Sciences of the Health
Department Health
(Until 25.02.09)

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

José Sánchez de Toledo Sancho
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
(From 25.02.09)

Attendees

Joan X. Comella Carnicé
Director
Vall d'Hebron Research Institute (VHIR)
(From 01.09.09)

Secretary

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

1.1.1.2 Governing Board

Executive Board consists of at least 5 people designated by the Board. The Vall d'Hebron University Hospital and the Universitat Autònoma de Barcelona will be represented in it.

President

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

Vice President

Joan X. Comella Carnicé
Director, VHIR
(From 01.09.09)

David García-Dorado
Director, VHIR
(Until 31.08.09)

1.1.1.3 Management

Members

Manuel Armengol Carrasco
Coordinator of the Educational Unit, HUVH

Joan Fernández Náger
Director of Medical Processes, HUVH

David García-Dorado
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

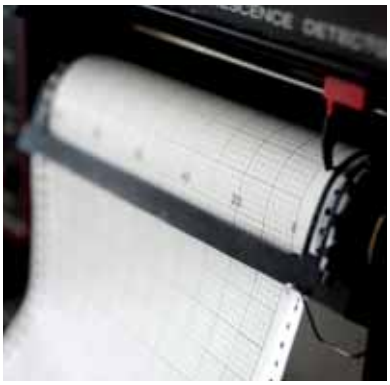
Rafael Simó Canonge
Clinical Trials Unit (UCICAC) Scientific Responsible, HUVH
(From 30.10.09)

Pilans Solans Julián
Director of Health Care, HUVH

Miquel Vilardell i Tarrés
Chief of Service Internal Medicine, HUVH

Secretary

Sr. Lluís Massó i Guitart
VHIR Manager



Director

Joan X. Comella
direccio@ir.vhebron.net

Hierarchically depending on the 3d executive vice president of the Board and the president of the Executive Board, he will be responsible of the strategic and operational direction of the scientific structure of the Fundació.

- To carry out and enforce decisions of the Board and the Executive Board.
- To represent the Fundació in institutional and scientific meetings.
- To propose the Scientific Policy of the Institut to the Executive Board and the Board, taking into account the opinion of the Internal Scientific Committee.
- To propose the Strategic Plan to the Executive Board and the Board, taking into account the opinion of the Internal Scientific Committee. Strategic Plan must include all activities of the Fundació, specially activities of research, development and innovation of the Fundació.
- To propose the Investment Plan both in physical and instrumental resources of the Fundació to the Executive Board and the Board, taking into account the opinion of the Internal Scientific Committee.
- To propose the research infrastructure of the Fundació: physical, instrumental and human resources infrastructure.
- To execute the scientific strategy of the Strategic Plan.
- To manage all research activities of the Fundació.
- To propose and manage the scientific organization model of the Fundació.
- To formulate the alliances' policy of the Fundació, which must be approved by the Board.
- To propose the Communication Plan and the Results Diffusion Plan of the Fundació.
- To propose the mechanisms of selection and recruitment of researchers.
- To elaborate the annual scientific report of the Fundació.
- To track the scientific indicators of the Fundació.
- To formulate the Training Plan for the scientific personnel.
- To manage the external relations model of the Fundació, at regional, national, European and global level.

– To elaborate the Quality Plan and the Policy, which should be approved by the Executive Board and the Board.

– To ensure the good practices in research.

– To coordinate together with the CEIC President, the different functions of the CEIC and the contract execution in clinical trials, in basic and clinical research of the Fundació.

Director Assistant in Clinical Research
Joan Genescà
jgenesca@ir.vhebron.net

Direction Secretariat
Irene Sendiu Gubianes
Tel. 93.489.38.63
isendiu@ir.vhebron.net

Manager

Lluís Massó Guitar
lmasso@ir.vhebron.net

The manager has the following functions of economic and financial management, as well as administrative services management:

– To manage, organize and execute management and administrative activities of resources of the Fundació, according to the guidelines approved by the Executive Board and the Scientific Director of the Fundació.

– To elaborate the annual budget proposal of the Fundació, as well as its possible modifications, together with the Scientific Director, and present it to the Executive Board and the Board for its formulation and approval.

– To propose the Human Resources Policy to the Executive Board and the Board. The Manager will have to implement and manage this policy.

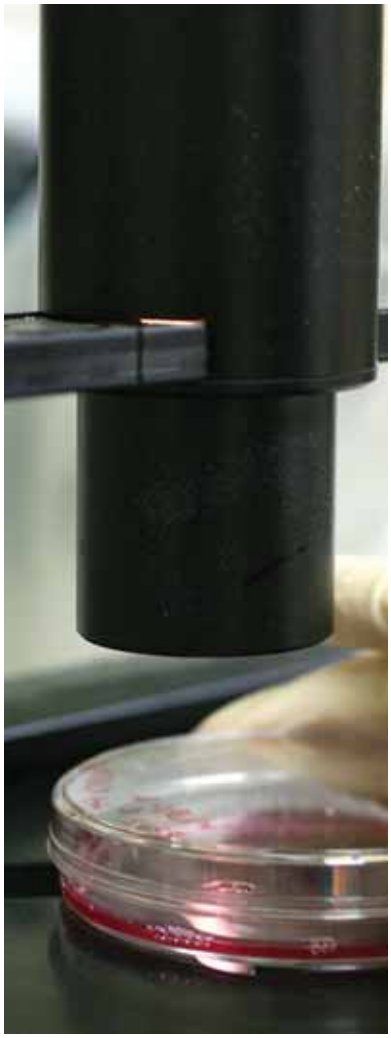
– To present the annual accounts of the Fundació: balances, accounts, activities reports and investment plans.

– To propose the Budget Projects to the Executive Board and the Board, taking into account the opinion of the Internal Scientific Committee.

– To supervise budget execution, accounting and inventory of the Fundació.

- To take care of administrative management, ensuring its proper coordination with all research activities.
- To order payments, according to what has been assigned by the Board and the Executive Board.
- To inform about the Investment Plans in works, facilities and services.
- To grant work contracts, services and supplies, as well as handling their contracts.
- Subject to the Board criteria and according to the Scientific Director, undertake recruitment, separation and termination of contrast of temporary or permanent staff, approve the category change of staff and agree with the staffs about salaries, work and staff moves.
- To ensure the introduction of information systems and technological innovation.
- To ensure the preservation and the maintenance of the facilities and equipment of the Fundació.
- To support Scientific Director in the task of obtaining funds to achieve the main objectives of the Fundació.

Secretary
Trinidad Gutiérrez Morente
Tel. 93.489.41.01
tgutierrez@ir.vhebron.net



1.1.1.4 Internal Scientific Committee

Designated by the Board, Internal Scientific Committee shall consist of at least 3 researchers. It is an advisory committee of the Direction and their decisions are not binding. It may act in committees.

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 01.09.09)

María Jesús Cruz Carmona
Research Group in Pneumology

Joan Genescà Ferrer
Research Group in Hepatic Diseases

1.1.1.5 External Scientific Committee

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

External Scientific Committee will consist of at least of 4 members designated by the Board at a Governing Board proposal. There will be 4 people of worldwide renowned scientific and professional prestige in biochemistry health sciences and live sciences research.

Members

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

1.1.2 Where we are

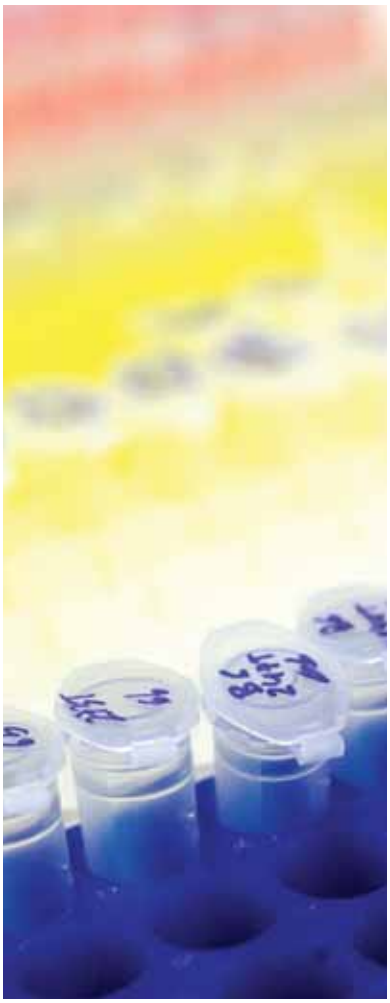
Vall d'Hebron Research Institute
Passeig Vall d'Hebron, 119-129
08035 Barcelona

Figure 1
VHIR's two buildings are inside Vall d'Hebron University Hospital, near "Vall d'Hebron" and "Montbau" stations

1.2 Research Support Units

1.2 RESEARCH SUPPORT UNITS

Everybody at VHIR works to support our research. Innovation, administrative staff and services are always available to improve the work of our researchers.



1.2.1 Research Support Units

1.2.1.1 Innovation

Director
Francesc Iglesias García
Tel. 93 489 45 23
figlesias@ir.vhebron.net

Secretary Innovation
Ana Lucía Román Mora
alroman@ir.vhebron.net

Business Development and commercialization
Cecília López García
clopez@ir.vhebron.net

Legal Advisor
Lourdes Salomón Sancho
lsalomon@ir.vhebron.net

1.2.1.1.1 Innovation Model

The Hospital Vall d'Hebron, through the Institut de Recerca, wants to promote an Innovation Plan, that will structure and manage all activities related to this field. All proposed activities must be included in the following action lines:

- Detection of innovation initiatives, their register and the synergy among them.
- Support to management professionals in order to identify innovation opportunities.
- Analysis of technological innovation that may be transferred: protection and marketing.
- Assessment and prioritization and transferred innovations: strategic marketing and business development.

1.2.1.2 Administrative Structure

1.2.1.2.1 Clinical Trials Agency

Director
Mireia Navarro Sebastian
Tel. 93 489 46 51
mirenavarro@ir.vhebron.net

Clinical Essays and Ethics Committee
Vanessa Rojas Sotomayor
Tel. 93 489 38 91
vrojas@ir.vhebron.net

Administrative Suport
Immaculada Pérez Gladiador
Tel. 93 489 46 51
iperez@ir.vhebron.net

Montserrat Fernández Recio
Tel. 93 489 40 10
montsefernandez@ir.vhebron.net

This unit supports clinical trials and post-authorization studies with medicines, medical devices and other therapies. It also supports projects promoted by researchers from the institution or by public agencies. It takes into account ethical, methodological and logistical aspects. Service Portfolio

1.2.1.2.2 Communication Management Unit

Director
Franc García Morales
Tel. 93 489 30 00 (Ext. 4835)
fgarcia@ir.vhebron.net

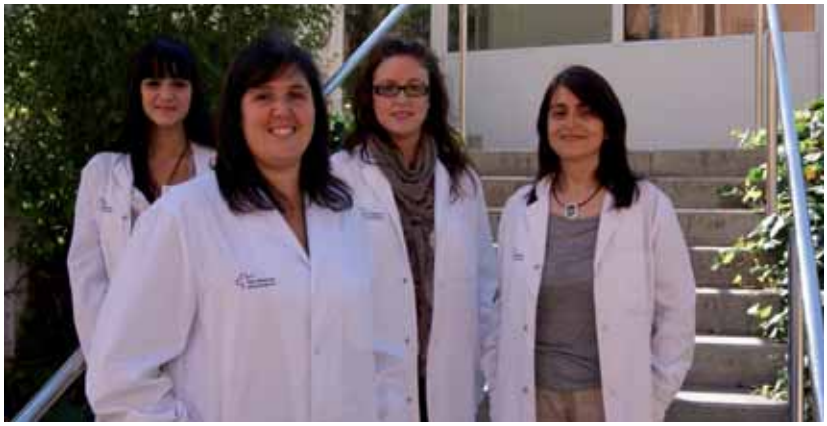
Website and Image
Elena Casaldàliga Albisu
Tel. 93 489 46 68
ecasaldaliga@ir.vhebron.net

Multimedia and Image
Roland Peralta Díez
Tel. 93 489 40 59
roperalt@ir.vhebron.net

Secretary/Communication
Montserrat Ferrando Pastor
Tel. 93 274 67 28
mferrando@ir.vhebron.net

The Communication Management Unit has the following functions assigned:

- Linking scientific research and other activities of the Institute to society through media.
- Announcing all Institute activities and their researchers through brief news and press conferences, interviews, divulgative media and other communication campaigns.
- Developing and using institutional webpage as essential tool to internal and external communication.
- Communicating, internally to whole Institute, different researches, publications and activities carried out by our researchers. Internal communication, intranet, web 2.0.
- Creating an essential tool for this institution that annually analyses the scientific production of the Institute, by means of a report.
- Betting for the internationalization publishing most of information in English.



1.2.1.2.3 Computer Management Unit

Project Manager
Domenec Far Macia
Tel. 93 489 45 64
dfar@ir.vhebron.net

System Manager
Jesús María Vicente Pérez
Tel. 93 489 41 27
jmvicente@ir.vhebron.net

Computer Assistance
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Programming Technician
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VHIR Computer Services coordinate all computer issue related with VHIR and support our researchers. A major objective was the creation of a centralized database in order to manage integral knowledge of the institution, which involves the fields of internal processes and external agents. From this database, many useful tools for researchers have been developed:
GIR platform (www.vhir.org/gir) integrates on-line services, and it also allows researchers to interact with information in real time, anywhere and anytime. This is an interactive and participative tool that will grow up dynamically.

1.2.1.2.4 Financial Management Unit

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Biddings and Contractings
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Teaching
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Treasury
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The Financial Management Unit supports the economic management of the different research projects and clinical trials developed at HUVH and at the VHIR, both for tracking and elaboration of financial statements (financial reports). It has the following functions assigned, directed to researchers:

- Receiving revenues and donations, linking laboratories.
- Paying invoices, minutes of fees, course inscriptions, etc., or any payment ordered on-line by researchers, through Econet application.
- Elaborating public contracting procedures for big purchase.
- Giving financial information, both giving aggregate data for research groups or services and elaborating financial reports for projects.
- Giving legal advice regarding contracts, agreements, etc.

1.2.1.2.5 Fundraising Unit

Director
Carmen Netzel
Tel. 93 489 30 00 (Ext. 4931)
mcnetzel@ir.vhebron.net

- Fosters and promotes a fund-raising model to seek the generosity of individuals, corporations, foundations, private and public institutions and request their philanthropic giving and financial support for biomedical research.
- Identifies the potential donors and financial partners and outlines a fund-raising strategy for the Vall d'Hebron Research Institute Foundation.
- Provides support for the researchers in their relationships with donors and sponsoring partners.
- Participates in the design and implementation of guidelines to be followed in the relationship with donors and financial sponsors.
- Draws up a portfolio of projects and defines different possibilities for donation and ways to give.
- Monitors follow-up of the impact of donations received.

1.2.1.2.6 Human Resources Unit

Director
Roger Verdejo Torras
Tel. 93 489 43 39
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Human Resources
Laia Pérez Lasarte
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Miriam Izquierdo Sans
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Natàlia Tibau Llarden
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The Human Resources Unit promotes and facilitates VHIR working relationships. It adapts working resources to VHIR guidelines and needs, respecting ethic and legal frameworks.

1.2.1.2.7 Occupational Risks Prevention Unit

Safety at Work
Ana Elena Ruiz Querol
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Mª Teresa de la Campa Alonso
Tel. 93 489 48 71
mtcampa@vhebron.net

The Occupational Risks Prevention Unit advice and work for health and safety at work, according to what is stated in the Law 31/95 in Occupational Risks Prevention. It assesses and controls risks, elaborating safety instructions, analyzing work accidents, training and informing employees and promoting healthy habits and preventing professional from occupational diseases.

1.2.1.2.8 Project Management Unit

Director
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International Projects
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Project Monitoring
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Research Grants and Fellowships
Maribel Corral Zabala
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macorral@ir.vhebron.net

Project Management Unit manages the applications and the tracking of research projects at HUVH and VHIR, funded by regional, national and international private and public agencies.
Project Management Unit:

- Its main functions are selection and dissemination of information about resources and financial support.
- Managing resources and financial support tracking.
- Optimizing and promoting human resources and facilities management, as well as management of other services related with research project development at VHIR.
- Promoting training activities about resources and financial support.

1.2.1.3 Services

Serving Research
In order to provide the complex environments requiring current biomedicine, Vall d'Hebron Research Institute has a number of important services to support research. They are 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 Laboratories Coordination.
The last two recent created services are the biobank and the Central Unit of Clinical Research and Clinical Trials (UCICAC). Thus, in addition, to enable researchers to technology and most current services, increasing profitability and improving self-sufficiency.

1.2.1.3.1 Scientific and Technical Support Unit (UCTS)

The Scientific and Technical Support Unit (UCTS) offers a set of high-tech services that support teaching activities and research activities in biomedical field.
The centralized character of STSU allows to offer researchers the most advanced tools in genomics, bioinformatics, proteomics, cytomics and microscopy fields at a reduced cost with constant updates and with advising of specialized personnel.

Director

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Josep Lluís Mosquera Mayo
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Genomics Unit

Real-Time Quantitative PCR System

Responsible
Francisca Gallego Valadés
Tel. 93 489 41 78
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Scientific Advisor
Joan Seoane Suárez
Tel. 93 274 60 26
jseoane@ir.vhebron.net

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

Responsible
Rosa Arjona Martos
Tel. 93 489 41 81
rarjona@ir.vhebron.net

Scientific Advisor
Antoni Lluís Andreu Périz
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Equipment
- 1 Automatic sequencer ABI PRISM 3100 by Applied Biosystems.

Bioanalyzer Service

Responsible
Ricardo Gonzalo Sanz
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Rosa Arjona Martos
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Equipment
- 1 Bioanalyzer 2100 by Agilent.

Molecular Diagnostic Platform

Ultrasequencing Service

Responsible
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Rosa Mª Prieto Sánchez
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Equipment
- 1 GS-FLX system by Roche/454.

Genetic Expression Analysis Service

Responsible
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Scientific Advisor
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Equipment
- 1 Microarrays system by Affymetrix GeneChip with two fluid stations and automatic array charger.
- 1 GeneTitan system by Affymetrix to process arrays automatically.
- 1 Nimblegene microarray system (NimbleGen Microarray Scanner MS 200)
- 1 sequence enrichment system on a solid bracket

Protein Microarray Service

Responsible

Marta Valeri Sala
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Equipment

- 1 system for high-density microarrays - Zeptosens Reverse Array System (it includes Scanner Zepto Reader and NanoPlotter)

Proteomics Platform

Proteomics Service

Responsible

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Researchers

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Marta Monge Azemar
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mmonge@vhio.net

Equipment

- 1 System for two-dimensional electrophoresis of proteins by Amersham Bio -Sciences, composed by:
  - 2 units a pH-gradient strip for isoelectric focusing IPGPHOR.
  - 2 electrophoresis units DALT VI for gels of 26 x 20 cm.
- 1 scanner and imaging analysis software Image Master Platinum by Amersham BioSciences.
- 1 DIGE System *(Differential Gel Electrophoresis, Amersham)* by GE Healthcare, composed by:
  - 1 Typhoon 9400 scanner to obtain fluorescence images of 2D electrophoresis gels.
  - 1 DeCyder by GE Healthcare to quantitative analysis of differences.
  - 1 Nonlinear Dynamics SameSpots software to quantitative analysis of images.
- 1 Spot Picker robot by GE Healthcare.
- 1 Proteineer DP robot by Bruker.
- 1 mass spectrometry MALDITOF/TOF Autoflex Speed by Bruker.
- 1 Ettan LC system by Amersham of liquid chromatography from micro- to analytical scale.
- 1 nano-HPLC system by LC-Packings.
- 1 nano-HPLC Proxeon system.
- 1 Ionic trap-electrospray mass spectrometry Esquire Ultra-ETD Bruker.
- 1 mass spectrometry Ultra High Resolution Q-TOF Maxis by Bruker.

Metabolomics Platform

Metabolomics Service (Cardiocirculatory Pathology)

Responsible
Ignasi Barba Vert
Tel. 93 489 41 86
ibarba@ir.vhebron.net

Group Leader
David García-Dorado
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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)

Staff
M.ª Ángeles Artaza Marino
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maartaza@ir.vhebron.net

Ricardo Gonzalo Sanz
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rgonzalo@ir.vhebron.net

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

Citomics Platform

Cytometry Analysis and Cell Sorting Service

Staff
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Scientific Advisors
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Jordi Pétriz González
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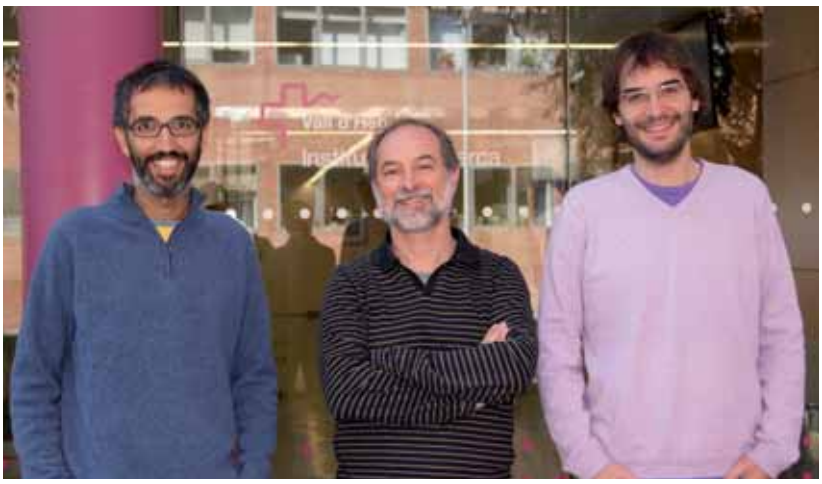
Equipment
- 2 flow cytometers:
  - 2 FACScalibur flow cytometer analyzers by Becton & Dickinson.
- 2 high-speed cell sorters:
  - FacsAria by Becton & Dickinson.
  - MOFLO by Beckman Coulter.

Microscopy Platform

Confocal Microscopy Service



Technicians

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Scientific Advisor

Rosanna Paciucci
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Equipment

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

Microdissection Service

Staff

Mª Ángeles Artaza Marino
Tel. 93 489 41 80
maartaza@ir.vhebron.net

Scientific Advisor

Santiago Ramón y Cajal
Tel. 93 274 68 09
sramon@vhebron.net

Equipment

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

1.2.1.3.2 Bioinformatics and Statistics Platform (UEB)

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

- Providing statistical and bioinformatics support specially to analyze high performance data *(high troughput)* generated in the research carried out in our center and in the biomedical field;
- Developing our own research lines in statistical and bioinformatics fields; particularly, in those fields that may represent an improvement in those services providedby this unit, and
- Establishing atraining program in statistics and bioinformatics to biomedical research.

Responsible

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Staff

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Offered Services

- High-performance data treatment.
- Advising when filling applications for funded projects or protocols of studies.
- Developing and maintaining bioinformatics applications.
- Carrying 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).
- Private software (i.e. Partek Genomics Suite or Ingenuity System).

1.2.1.3.3 Vall d'Hebron University Hospital Biobank (VHUHBB)

The Vall d'Hebron University Hospital Biobank (VHUHBB) is a unit of research support which collects biological samples from humans in order to carry out biomedical research obeying the legislation in force. Its main objective is to provide the scientific comunity all biological material needed in research in order to assure research competitivity and excellence.

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Coordinator and File Manager
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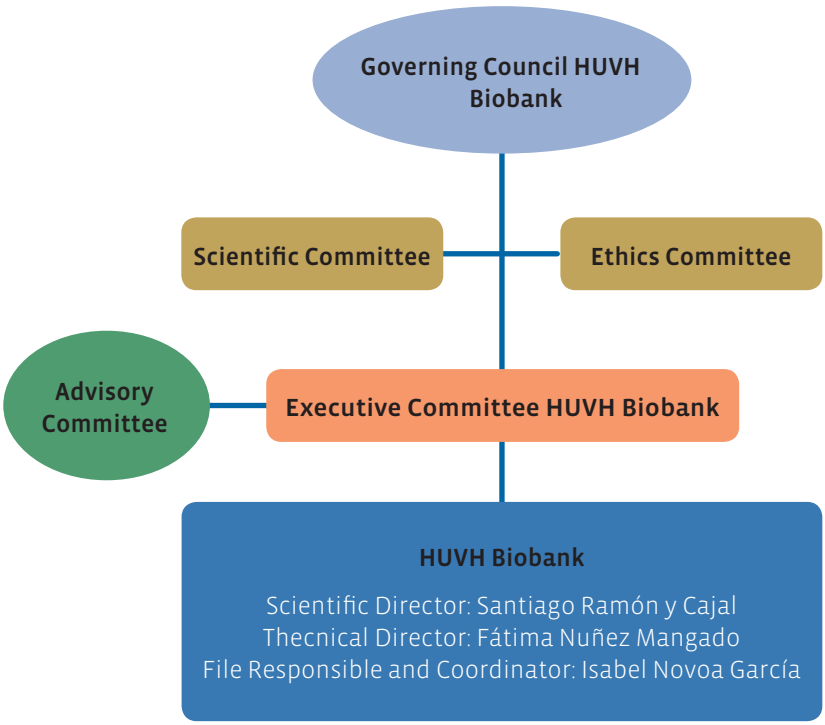
Services

- Advice for the proper collection, processing, storage and use of human biological samples for biomedical research.
- Service registration process (in development) and storage of laboratory samples in the biobank.

Figure 2
Structure / Organization Vall d'Hebron University Hospital Biobank (VHUHBB)



1.2.1.3.4 Animal Facility

Research and teaching related to the use of laboratory animals is focused on the animal house of the Vall d'Hebron Research Institute, located at Mediterrània Building, it occupies a built area of 745 m² and a useful area 683 m² in a single floor.

Animal house obey the legislation in force and it is registered at the "Departament de Medi Ambient i Habitatge" with register number B9900062.

Facilities are divided in two areas: Rodent Area with an standard clean area, a passive quarantine, a barrier area to accommodate immunodeficient mice, 6 manipulation rooms and the Molecular Imaging Platform; as well as the Big Animals Area with space enough to accommodate rabbits, pigs and sheep with complete experimental operating rooms to carry out teaching and experimental surgery projects.

Animal house has an Advisory Committee composed by researchers of the Institut with the objective of creating, improving and modifying different aspects related with animal testing.

Responsible
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Daniel Martínez Falconero
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Secretary
Montse Molano Flores
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Equipment
- Automatic system of control and environmental parameters regulation: ventilation and pressure, temperature, relative humidity and lighting.
- Support structures, cages and complements for animal maintenance.
- Autoventilated racks of positive pressure.
- Biological safety cabinets.
- Bottle and rack cleaners to automatically clean and disinfect shelves, cages and other complements.

- Autoclave.
- Micronebulizer to disinfect/sterilize all kind of 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 and 1 SPF
- 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.

1.2.1.3.4.1 Molecular Imaging Platform

Optical imaging system by bioluminescence and fluorescence, Molecular Imaging Platform (PIM) is established through the common efforts of CIBER-BBN, CIBBIM-Nanomedicine and VHIR as a service to research groups and pharmaceutical companies. Its mission consists in providing the capacity to develop noninvasive optical image *in vivo* at cellular, molecular and functional level, including fluorescence and bioluminescence. Main equipment has 3 items:

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

Responsible

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Technician

Anna Pujol Esclusa
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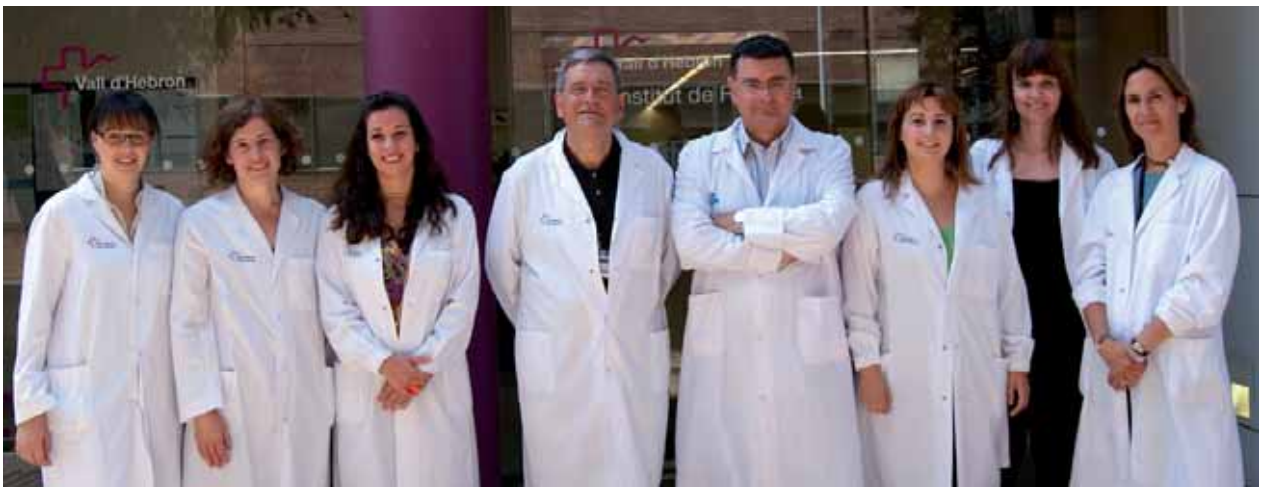
Location

Mediterrània Building, at Vall d'Hebron Research Institute, ground floor.
Vall d'Hebron University Hospital



1.2.1.3.5 UCICAC

The Central Unit of Clinical Research and Clinical Trials (UCICAC), that was established by a team of multidisciplinary professionals, offers integral services program (start-to-end) to researchers in order to develop clinical research projects, as well as clinical trials. It guarantees attraction and competitiveness of HUVH biomedical research.
UCICAC generates and promotes both projects and instruments to facilitate clinical research. Additionally, UCICAC promotes training activities in clinical research and clinical trials.
In the future, it will offer a centralization of its functions in a single location at 13th floor of the Hospital Materno-Infantil, where the following units will be located:

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

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Coordinator
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Project Manager
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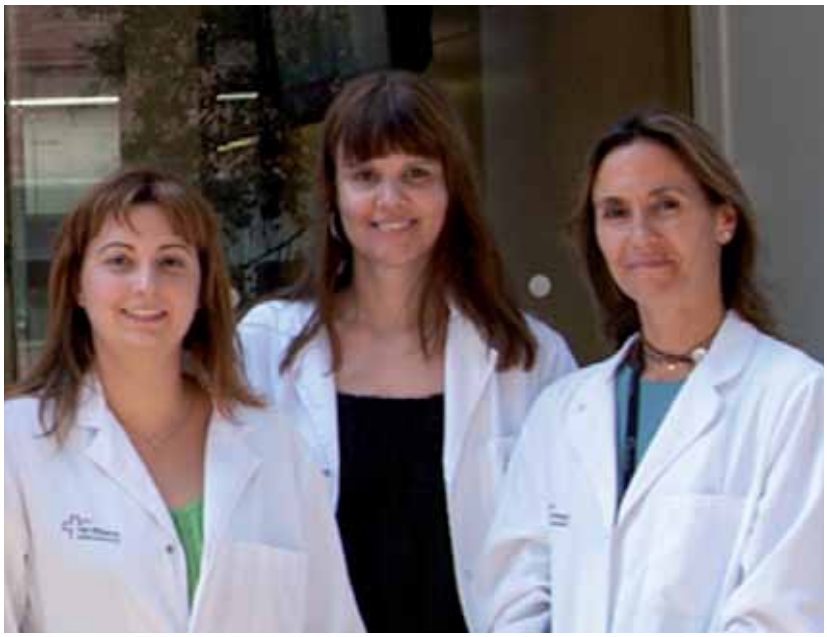

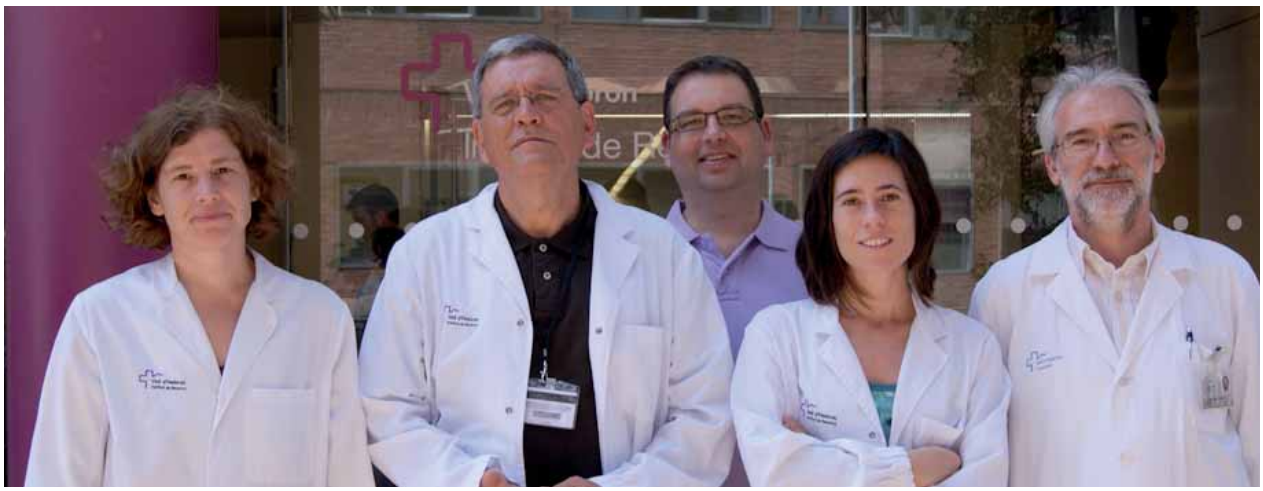

1.2.1.3.5.1 URAC

Research and Clinical Essays Unit (URAC)

Coordinator
Immaculada Fuentes Camps
ifuentes@ir.vhebron.net

Nursering
Patricia Fernández Vandellòs
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Instructor
Silvia Garcia Matas
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The Research and Clinical Essays Unit (URAC) supports clinical trials and post-authorization studies with medicines, medical devices and other therapies. It also supports projects promoted by researchers from the institution or by public agencies. It takes into account ethical, methodological and logistical aspects. Additionally, the The Research and Clinical Essays Unit aims to promote continuous training in clinical research and clinical trials.

1.2.1.3.5.2 USMIB

Methodological Support for the Biomedical Research Unit (USMIB)

Coordinators
Antonio Salgado Remigio
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Claudia Cases Langhoff
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Methodologists
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Santiago Pérez Hoyos
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Lluis Armadans Gil
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Eva López Guerrero
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The Methodological Support for the Biomedical Research Unit (USMIB) was promoted by 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" and the "Servei de Medicina Preventiva i Epidemiologia".
The USMIB offers services of scientific methodology to facilitate, provide and promote biomedical research at Hospital Universitari Vall d'Hebron, primary healthcare area and external users that request its services. Likewise, among its tasks there is the following: to establish a training program in methodology for biomedical research.

1.2.1.3.6 Laboratory Coordination

Responsible
Núria Prim Vilaró
Tel. 93 489 43 23
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Common Lab Technician
Fátima Jiménez Mamolar
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Eulàlia Joseph Munné
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Secretary
Anna Pedrol Clará
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Rosa Guillen Vidal
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Janitors
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Tao González Zaragoza
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Esther Mateos Mullor
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Raimundo Molina Martínez
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Joaquim Solà Santesmases
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Pablo Vilalta Gras
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Lab Cleaner
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Patricia Hinojosa Casanova
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Rosario Molano Flores
Tel. 93 489 30 00 (Ext. 4902)

The main objective of the coordination among laboratories is:

- Managing resources and ensuring the functioning of laboratories composing Institut de Recerca, as well as management of nursing personnel, nursing technicians and auxiliaries that support biomedical investigation.
- The activities depending on this coordination are: working as a link between laboratories and Direction, providing knowledge, implantation and monitoring of regulations regarding both hospital and Research Institute environment, as well as centralizing job vacancies in previously mentioned environments.

1.2.2 Ethics Committees

1.2.2.1 Animal Experimentation Ethics Committee (CEEA)

The Animal Experimentation Ethics Committee (CEEA) was created the 8th of January of 1998 to ensure experimentation animals care and welfare. Among its functions there are the following ones: reporting about experimental procedures realization, eliminating unnecessary pain and provide humanitarian euthanasia, contrasting involved personnel competence, as well as used procedures suitability.

President
Carmen Espejo Ruiz
Biologist
Researcher at the Neuroimmunologia Clínica group

Secretary
Marta Rosal Fontana
Veterinarian
Animal house responsible. Animal welfare adviser

Vocals
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

1.2.2.2 Clinical Research Ethics Committee (CREC)

Depending on the HUVH, the CREC collaborates and provides its support to the VHIR. The CREC is an independent body comprising health and non health professionals. It is responsible to ensure the protection of the rights, safety and welfare of subjects taking part on clinical trials and to offer public guarantee regarding the report about trial protocols, the suitability of researchers and the facilities adequacy, as well as methods and documents used to inform those subjects taking part on a trial in order to obtain their informed consent.

President
Francisco Latorre Arteche
Doctor

Secretary
J. Bruno Montoro Ronsano
Hospital Pharmacologist

Vocals
Lluís Armadans Gil
Doctor

Fernando Azpiroz Vidaur
Doctor

Joan Bagó Graell
Doctor

Arantxa Catalán Ramos
Primary Care Pharmaceuticals

Inés M de Torres Ramírez
Doctor

Carmen Fuentelsaz Gallego
Nursing Degree

Immaculada Fuentes Camps
Pharmacologist Doctor

Soledad Gallego Melcón
Doctor

Jaume Guardia Massó
Doctor

Juan Carlos Hortal Ibarra
Law University Profesor

Joan Ramon Laporte Roselló
Pharmacologist Doctor

Isabel Miró Muixi
Doctor

Alexis Rodríguez Gallego
Pharmacologist Doctor

Joan Segarra Sarries
Lawyer

Marta Solé Orsola
Nursing Degree

Pilar Suñé Martín
Hospital Pharmacologist

Josep Vaqué Rafat
Doctor

1.3 Summary of Research Activity

1.3 SUMMARY OF RESEARCH ACTIVITY

VHIR's research activities displayed on this Annual Report 2009 are summarized in the following parts.

1.3.1 Researchers and Technicians

Table 1
VHIR researchers and technicians
(During 2010 there has been a new redistribution of the groups, increasing to 56)

46 Research Groups		
Researcher staff (66%)		
Researchers		405
Doctors	340	
Biologists	22	
Biochemical	7	
Pharmacists	4	
Psychologists	4	
Chemical	4	
Veterinarians	3	
Other	21	
Postdocs		68
Predocs		173
Supporting research staff (34 %)		
Supporting research staff		328
Degrees	118	
Nursers, ATS, DUI	27	
Laboratory technicians	68	
Administrative	65	
Other	50	
Total		974

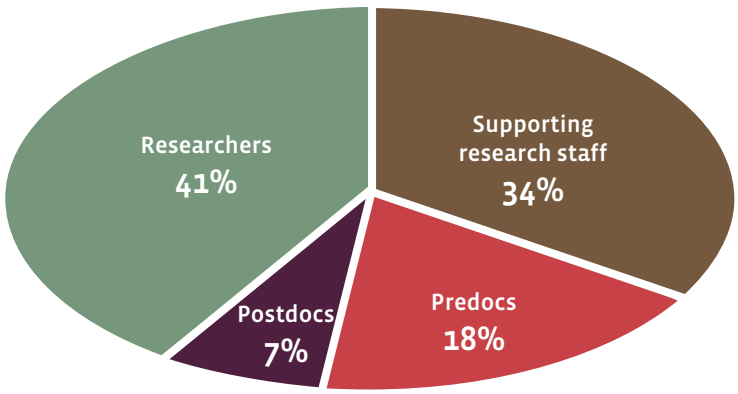


Figure 3
VHIR researchers and technicians

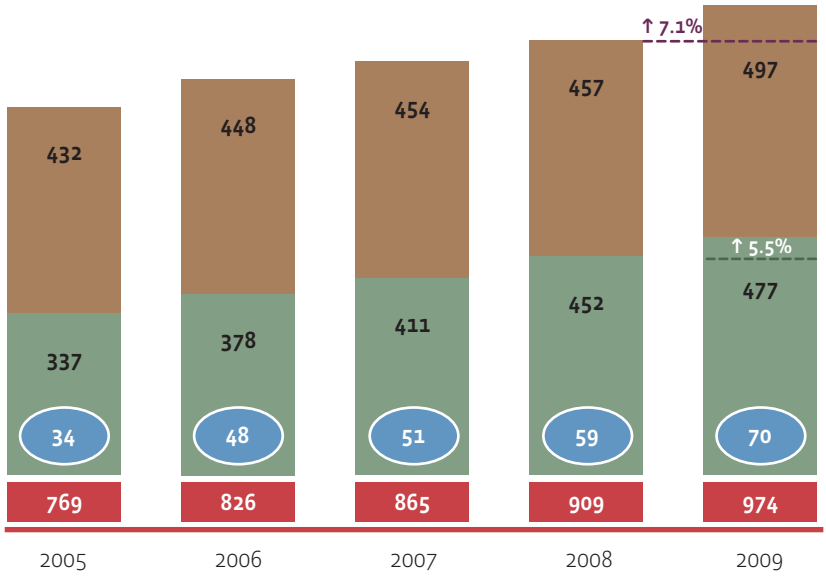


Figure 4
Evolution of the staff the last 5 years

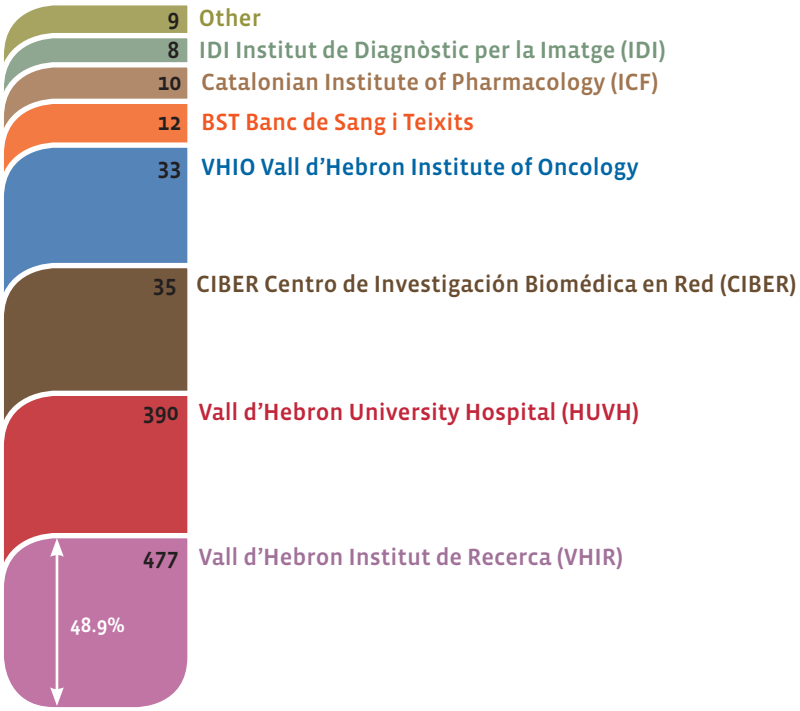


Figure 5
Contracting entities.
VHIR's funded staff: 477 (48.9%)

1.3.2 VHIR's Economic Summary

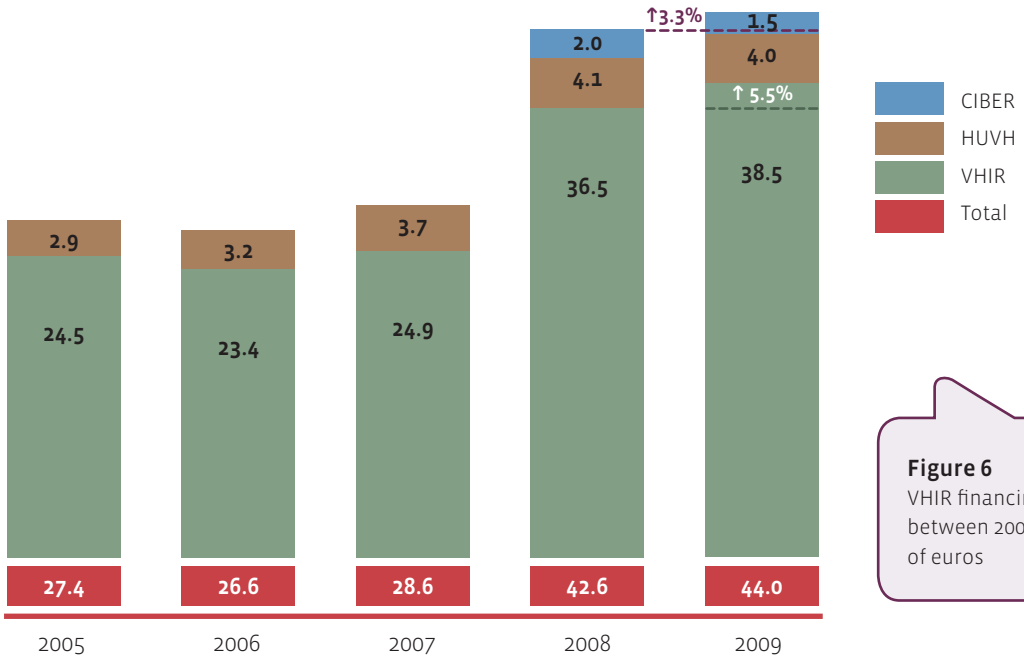
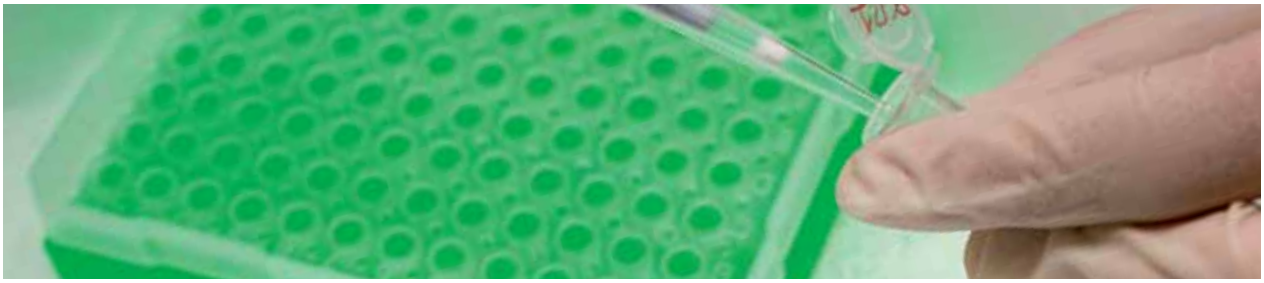


Figure 6
VHIR financing during the period between 2005 and 2009, in millions of euros

Table 2
2009 VHIR's Income Breakdown

2009 Income Breakdown	Milion of Euros
Projects funded by agencies	14.1
Agreements with industry	8.2
Donations	4.2
Clinical Trials	7.2
Teaching	1.8
Network	0.9
Other	2.1
Total	**38.5**
HUVH contributions (Staff, Goods and Direct Services and other €)	4.0



1.3.3 National and Internacional Publications reported in the *Journal Citation Reports* (JCR)

The number of publications in scientific magazines signed by VHIR's researchers in 2009 has been 540, with an impact factor of **2,474.709.** The average impact factor per review has been **4.58.**

To calculate the 2009 impact factor has been used the *Journal Citation Reports (JCR)* de l'any 2008. It includes original papers, reviews and editorials. Letters and communications for congresses has been excluded.

Table 3
VHIR's 2009 International and national publications

	Number	Impact Factor
Papers in international magazines	413	2,035.764
Papers in national magazines	56	84.503
Review or editorial in international magazines	49	323.300
Review or editorial in national magazines	22	31.142
Total	**540**	**2,474.709**

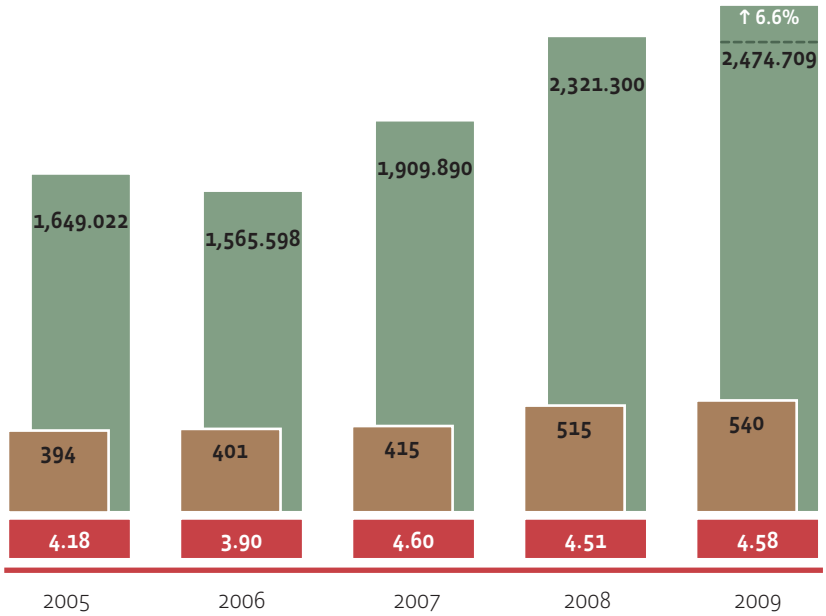


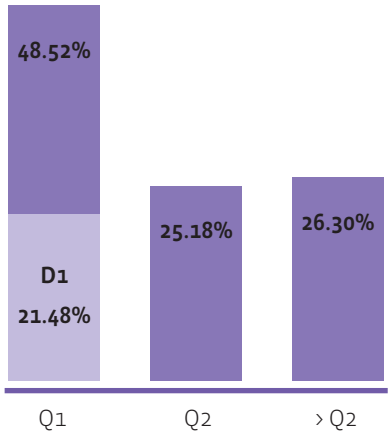
Figure 7
VHIR scientific production in the last five years

It's also important that 48.52% of the publications in scientific magazines by VHIR's researchers belong to the first quartile, according to the category and impact factor they belong to 21.48% of these publications belong to the first quartile.

Table 4
Publications per quartiles

Quartile	Number	%
Q1	262	48.52
First decile D1	*116*	*21.48*
Q2	136	25.18
› Q2	142	26.30
Total	**540**	**100.00**

Figure 9
Distribution of publications per quartiles and first deciles according to category and impact factor



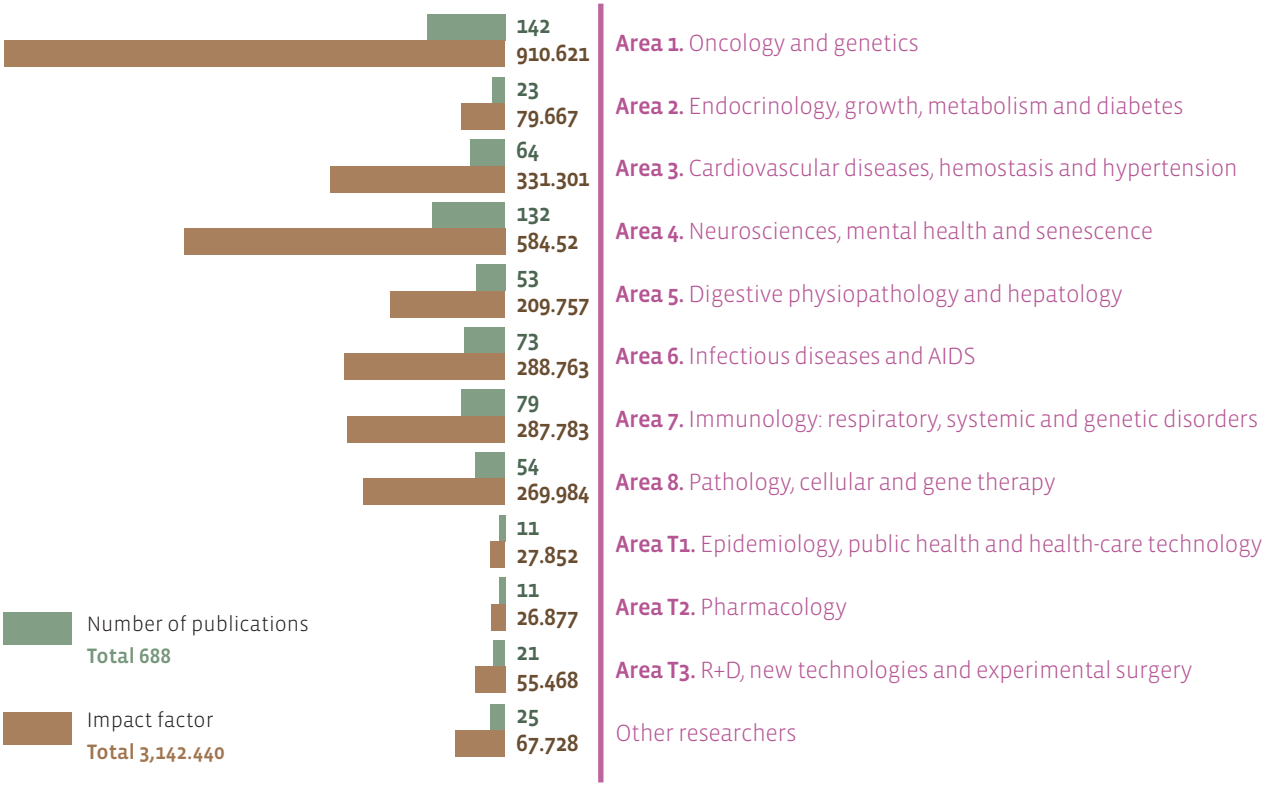


Figure 8
2009 Impact factor per research areas
Publications participated by two or more research areas are analyzed independently, counting the publication and its impact factor in each of the participant areas.

Table 5
2009 Impact factor per research groups

Research Groups	Total Publications	Impact Factor
Vall d'Hebron Institute of Oncology - VHIO	74	585.621
Cardiovascular Diseases	64	331.301
Clinical Neuroimmunology	38	215.417
CIBBIM - Nanomedicine	48	242.730
Molecular Pathology	35	170.860
Infectious Diseases	39	162.029
Systemic Autoimmune Diseases	39	132.773
Neurovascular Diseases	32	128.422
Liver Diseases	28	116.266
Pulmonology	31	116.153
Microbiology	28	106.993
Phisiology and Pathophisiology of the Digestive Tract	20	86.982
Diabetes and Metabolism	19	74.927
Neuro Magnetic Resonance	18	67.432
Research Unit in Biomedicine	18	65.481
Psychiatry and Mental Health	16	56.910
Alzheimer	10	42.716
Neurotraumatology and Neurosurgery	5	35.112
Immunology	5	34.403
Pediatric Neurology	12	33.108
Epidemiology and Public Health	11	27.852
Clinical Pharmacology	11	26.877
Ophtalmology	7	22.862
Paediatric Hemato-oncologic Diseases	6	20.658
Infectious, Sepsis and Organic Failure and Critical Patient Disease	6	19.741
Cell and Gene Therapy	4	17.481
Fetal Surgery, Congenital Malformations and Orthopedical Anomalies	8	17.247
Spinal Pathology Study	5	12.493
Molecular Diagnosis and Therapy	2	9.773
Paediatric Endocrinology	5	9.091
Digestive Transplants	5	6.509
Neurodegenerative Diseases	1	5.399
Ear, Nose and Throat Disorders	4	4.454
Robotic and Craniofacial Surgery	1	2.866

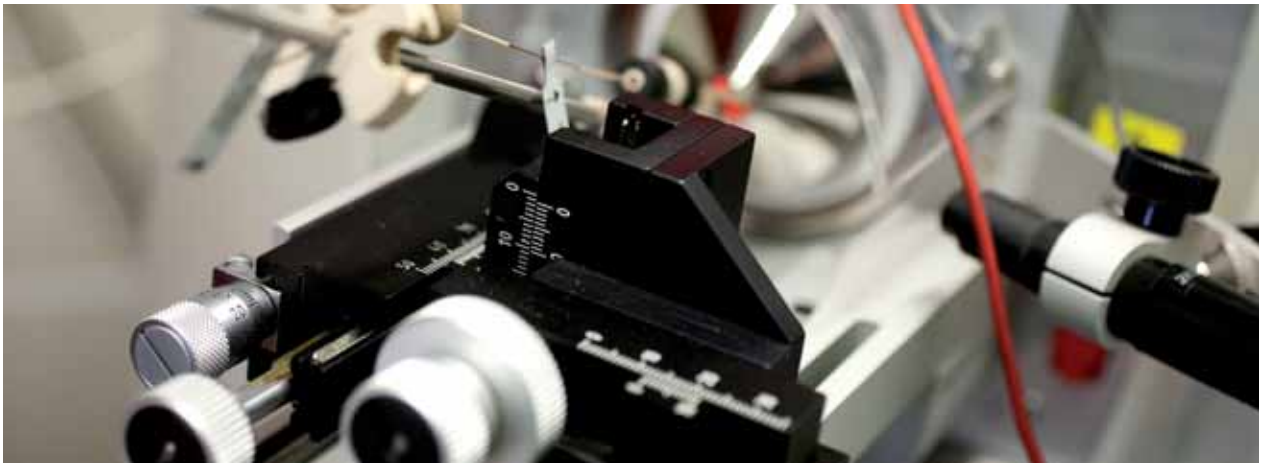


Table 6
Publications in International magazines

Publication	Impact Factor	Published Papers	Total Impact Factor	Decile (D)	Quartile (Q)
International Magazines (*n* = 273)					
Abdominal Imaging	1.485	1	1.485		Q3
Acta Paediatrica	1.517	1	1.517		Q2
Aids	5.46	1	5.46	1	Q1
Aids Research and Human Retroviruses	2.024	2	4.048		Q3
Alimentary Pharmacology & Therapeutics	1.215	2	2.43		Q4
Allergy	6.204	1	6.204		Q1
American Heart Journal	4.285	1	4.285		Q1
American Journal of Cardiology	3.905	1	3.905		Q1
American Journal of Gastroenterology	6.444	5	32.22		Q1
American Journal of Human Genetics	10.153	1	10.153	1	Q1
American Journal of Kidney Diseases	4.822	1	4.822		Q1
American Journal of Neuroradiology	2.745	3	8.235		Q2
American Journal of Ophthalmology	3.102	1	3.102		Q1
American Journal of Physiology-Heart and Circulatory Physiology	3.643	1	3.643		Q1
American Journal of Respiratory and Critical Care Medicine	9.792	1	9.792	1	Q1
American Journal of Surgery	2.605	1	2.605		Q1
American Journal of Transplantation	6.559	1	6.559	1	Q1
Analytical Biochemistry	3.088	1	3.088		Q2
Annals of Internal Medicine	17.457	2	34.914	1	Q1
Annals of Neurology	9.935	1	9.935	1	Q1
Annals of Oncology	4.935	12	59.22		Q1
Annals of the Rheumatic Diseases	7.188	4	28.752	1	Q1
Anticancer Research	1.39	1	1.39		Q4
Antimicrobial Agents and Chemotherapy	4.716	2	9.432		Q1
Archives of Internal Medicine	9.11	1	9.11	1	Q1
Archives of Microbiology	1.975	1	1.975		Q3
Archives of Neurology	5.874	3	17.622	1	Q1
Archives of Ophthalmology	3.242	1	3.242		Q1
Archives of Orthopaedic and Trauma Surgery	0.965	1	0.965		Q3
Archives of Pediatrics & Adolescent Medicine	4.32	1	4.32	1	Q1
Arthritis and Rheumatism	6.787	2	13.574	1	Q1
Arthritis Research & Therapy	4.485	1	4.85		Q1
Basic Research in Cardiology	5.407	2	10.814	1	Q1
Biochemical Journal	4.371	2	8.742		Q1
Biological Psychiatry	8.672	2	17.344	1	Q1
Biology of Blood and Marrow Transplantation	3.375	1	3.375		Q2
Bju International	2.704	3	8.112		Q2
Blood	10.432	2	20.864	1	Q1
Blood Cells Molecules and Diseases	2.749	1	2.749		Q2
Bmc Medical Genetics	2.762	1	2.762		Q2
Bmc Molecular Biology	2.81	1	2.81		Q2
Bmc Musculoskeletal Disorders	1.987	1	1.987		Q3
Brain	9.603	3	28.809	1	Q1
Breast Cancer Research	5.052	1	5.052		Q1
Breast Cancer Research and Treatment	5.684	1	5.684		Q1
British Journal of Haematology	4.478	1	4.478		Q1

Publication	Impact Factor	Published Papers	Total Impact Factor	Decile (D)	Quartile (Q)
British Journal of Nutrition	2.764	1	2.764		Q2
British Journal of Ophthalmology	2.859	1	2.859		Q1
British Journal of Oral & Maxillofacial Surgery	0.787	1	0.787		Q3
Canadian Journal of Cardiology	1.796	1	1.796		Q3
Cancer	5.238	1	5.238		Q3
Cancer Causes & Control	3.69	1	3.69		Q2
Cancer Cell	24.962	1	24.962	1	Q1
Cancer Chemotherapy and Pharmacology	2.74	2	5.48		Q2
Cancer Research	7.514	3	22.542	1	Q1
Cancer Treatment Reviews	4.729	1	4.729		Q1
Carcinogenesis	4.93	1	4.93		Q1
Cardiovascular and Interventional Radiology	1.721	2	3.442		Q3
Cardiovascular Research	5.947	8	47.576	1	Q1
Cell Cycle	4.12	1	4.12		Q2
Cell Stem Cell	16.826	1	16.826	1	Q1
Cerebrovascular Diseases	3.41	6	18.246		Q2
Circulation	14.595	2	29.19	1	Q1
Clinical and Experimental Immunology	2.853	1	2.853		Q2
Clinical and Experimental Rheumatology	2.364	4	9.456		Q3
Clinical Biochemistry	1.926	1	1.926		Q2
Clinical Cancer Research	6.488	7	45.416		Q1
Clinical Endocrinology	3.398	1	3.398		Q2
Clinical Gastroenterology and Hepatology	6.068	1	6.068		Q1
Clinical Immunology	3.606	3	10.818		Q2
Clinical Infectious Diseases	8.266	3	24.798	1	Q1
Clinical Microbiology and Infection	3.554	1	3.554		Q1
Clinical Nuclear Medicine	3.181	1	3.181		Q1
Clinical Rheumatology	1.559	1	1.559		Q4
Clinical Transplantation	1.915	1	1.915		Q3
Colorectal Disease	2.293	1	2.293		Q2
Computers in Biology and Medicine	1.272	1	1.272		Q3
Contact Dermatitis	3.47	1	3.47		Q2
Critical Care	4.553	1	4.553		Q1
Critical Reviews in Oncology Hematology	4.589	2	9.178		Q1
Current Alzheimer Research	4.132	1	4.132		Q1
Current Cancer Drug Targets	4.316	1	4.316		Q2
Current HIV Research	2.495	3	7.485		Q3
Current Medical Research and Opinion	2.596	2	5.192		Q2
Current Neurovascular Research	3.571	2	7.142		Q1
Current Opinion in Gastroenterology	3.877	1	3.877		Q1
Current Opinion in Oncology	4.116	1	4.116		Q2
Current Pharmaceutical Design	4.399	2	8.798		Q1
Chest	5.154	3	15.462	1	Q1
Dermatologic Surgery	2.102	2	4.204		Q2
Dermatology	2.227	1	2.227		Q2
Developmental Medicine and Child Neurology	2.561	1	2.561		Q1
Diabetes Care	7.349	1	7.349	1	Q1
Diabetes Obesity & Metabolism	4.259	1	4.259		Q1
Diabetes-Metabolism Research and Reviews	3.149	1	3.149		Q2

Table 6
Publications in International magazines *(Cont.)*

Publication	Impact Factor	Published Papers	Total Impact Factor	Decile (D)	Quartile (Q)
Diabetologia	6.418	2	12.836		Q1
Diagnostic Microbiology and Infectious Disease	2.139	1	2.139		Q3
Digestive Diseases	1.092	1	1.092		Q4
Digestive Diseases and Sciences	1.583	1	1.583		Q3
Diseases of the Colon & Rectum	2.615	1	2.615		Q2
Drug News & Perspectives	1.989	1	1.989		Q3
Drug Safety	3.537	1	3.537		Q1
Drugs & Aging	2.11	1	2.11		Q2
Environmental and Molecular Mutagenesis	2.181	1	2.181		Q3
Epidemiology and Infection	2.36	1	2.36		Q3
Europace	1.706	1	1.706		Q3
European Heart Journal	8.917	6	53.502	1	Q1
European Journal of Cancer	4.475	5	22.375		Q2
European Journal of Clinical Microbiology & Infectious Diseases	2.866	2	5.732		Q2
European Journal of Echocardiography	1.917	2	3.834		Q3
European Journal of Endocrinology	3.791	1	3.791		Q2
European Journal of Gastroenterology & Hepatology	2.08	2	4.16		Q3
European Journal of Internal Medicine	1.045	1	1.045		Q3
European Journal of Neurology	2.732	2	5.464		Q2
European Journal of Nuclear Medicine and Molecular Imaging	4.532	2	9.064	1	Q1
European Journal of Obstetrics Gynecology and Reproductive Biology	1.565	2	3.13		Q3
European Journal of Pediatrics	1.416	1	1.416		Q2
European Radiology	3.651	1	3.651		Q1
European Spine Journal	2.396	2	4.792		Q1
Experimental Cell Research	3.948	3	11.844		Q2
Experimental Eye Research	2.579	1	2.579		Q2
Experimental Hematology	3.203	1	3.203		Q2
Experimental Physiology	2.91	1	2.91		Q2
Expert Opinion on Biological Therapy	3.475	1	3.475		Q1
Expert Opinion on Investigational Drugs	4.058	1	4.058		Q1
Eye	2.064	2	4.128		Q2
Faseb Journal	7.049	1	7.049		Q1
Febs Journal	3.139	2	6.278		Q2
Free Radical Biology and Medicine	5.399	1	5.399		Q1
Frontiers in Bioscience	3.308	1	3.308		Q2
Gastroenterology	12.591	1	12.591	1	Q1
Genes and Immunity	4.006	1	4.006		Q1
Genome Research	10.176	1	10.176	1	Q1
Growth Hormone & Igf Research	2.008	1	2.008		Q3
Gut	9.766	1	9.766	1	Q1
Haematologica-The Hematology Journal	5.978	2	11.956		Q1
Heart	4.964	2	9.928		Q1
HIV Clinical Trials	1.735	1	1.735		Q3
HIV Medicine	3.103	2	6.206		Q2
Human Brain Mapping	5.395	1	5.395	1	Q1
Human Genetics	4.042	1	4.042		Q1

Publication	Impact Factor	Published Papers	Total Impact Factor	Decile (D)	Quartile (Q)
Human Molecular Genetics	7.249	3	21.747	1	Q1
Human Pathology	3.322	1	3.322		Q2
Human Reproduction	3.773	1	3.773		Q1
Inflammatory Bowel Diseases	4.975	1	4.975		Q1
Intensive Care Medicine	5.055	1	5.055		Q1
International Archives of Allergy and Immunology	2.131	1	2.131		Q3
International Journal of Cancer	4.734	1	4.734		Q1
International Journal of Cardiology	3.121	1	3.121		Q2
International Journal of Colorectal Disease	1.767	1	1.767		Q2
International Journal of Gynecological Pathology	1.766	1	1.766		Q2
International Journal of Radiation Oncology Biology Physics	4.639	2	9.278		Q1
International Journal of STD & AIDS	1.075	1	1.075		Q4
International Journal of Stroke	2	1	2		Q3
Jaids-Journal of Acquired Immune Deficiency Syndromes	4.57	6	27.42		Q1
Jama-Journal of the American Medical Association	31.718	1	31.718	1	Q1
Journal of Alzheimer's Disease	5.101	2	10.202		Q1
Journal of Andrology	2.396	1	2.396		Q2
Journal of Antimicrobial Chemotherapy	4.328	6	25.968		Q1
Journal of Biological Chemistry	5.52	1	5.52		Q1
Journal of Biomechanics	2.784	1	2.784		Q1
Journal of Biomedical Materials Research	2.03	1	2.03		Q2
Journal of Cellular and Molecular Medicine	5.114	1	5.114	1	Q1
Journal of Cerebral Blood Flow and Metabolism	5.741	2	11.482		Q1
Journal of Clinical and Experimental Neuropsychology	2.184	1	2.184		Q2
Journal of Clinical Endocrinology & Metabolism	6.325	2	12.65		Q1
Journal of Clinical Gastroenterology	2.775	1	2.775		Q2
Journal of Clinical Investigation	16.559	1	16.559	1	Q1
Journal of Clinical Microbiology	3.945	2	7.89		Q1
Journal of Clinical Oncology	17.157	10	171.57	1	Q1
Journal of Clinical Psychiatry	5.053	1	5.053	1	Q1
Journal of Chemotherapy	0.843	1	0.843		Q4
Journal of Experimental Medicine	15.219	1	15.219	1	Q1
Journal of Food Protection	1.763	1	1.763		Q2
Journal of Heart and Lung Transplantation	3.323	1	3.323		Q1
Journal of Hepatology	7.056	4	28.224	1	Q1
Journal of Hospital Infection	2.956	2	5.912		Q2
Journal of Infection	3.089	1	3.089		Q2
Journal of Inherited Metabolic Disease	2.691	1	2.691		Q2
Journal of Investigational Allergology and Clinical Immunology	1.254	1	1.254		Q4
Journal of Laparoendoscopic & Advanced Surgical Techniques	0.912	1	0.912		Q3
Journal of Laryngology and Otology	0.796	1	0.796		Q4
Journal of Medical Genetics	5.713	2	11.426		Q1
Journal of Molecular and Cellular Cardiology	5.054	1	5.054		Q1
Journal of Neurochemistry	4.5	1	4.5		Q1
Journal of Neuroimaging	1.811	1	1.811		Q3
Journal of Neuroimmunology	3.159	2	6.318		Q2
Journal of Neurology Sciences	2.536	2	5.072		Q2
Journal of Neuropathology and Experimental Neurology	5.14	1	5.14		Q1

Table 6
Publications in International magazines *(Cont.)*

Publication	Impact Factor	Published Papers	Total Impact Factor	Decile (D)	Quartile (Q)
Journal of Neuroscience Research	3.086	1	3.086		Q2
Journal of Nuclear Cardiology	2.442	2	4.884		Q2
Journal of Nutrition Health & Aging	2.321	1	2.321		Q2
Journal of Paediatrics and Child Health	1.124	1	1.124		Q3
Journal of Parenteral and Enteral Nutrition	1.97	1	1.97		Q2
Journal of Pathology	5.121	1	5.121		Q1
Journal of Pediatric Endocrinology & Metabolism	0.938	2	1.876		Q4
Journal of Pediatric Orthopaedics	1.569	2	3.138		Q2
Journal of Pharmacy and Pharmaceutical Sciences	1.887	1	1.887		Q3
Journal of Physiology-London	4.605	1	4.605	1	Q1
Journal of Proteome Research	5.684	3	17.052	1	Q1
Journal of Rheumatology	3.282	3	9.846		Q2
Journal of Telemedicine and Telecare	0.89	1	0.89		Q4
Journal of the American Society of Echocardiography	2.256	2	4.512		Q2
Journal of the International Medical Research	2.625	1	2.625		Q2
Journal of the Neurological Sciences	2.359	8	18.872		Q2
Journal of Thoracic and Cardiovascular Surgery	3.037	1	3.037		Q2
Kidney International	6.418	1	6.418	1	Q1
Lancet	28.409	3	85.227	1	Q1
Lancet Neurology	14.27	4	57.08	1	Q1
Leukemia	8.634	1	8.634	1	Q1
Liver Transplantation	4.085	1	4.085		Q1
Lung Cancer	2.97	1	2.97		Q2
Lupus	2.244	1	2.244		Q3
Larine Drugs	1.2	1	1.2		Q3
Metabolism-Clinical and Experimental	2.92	1	2.92		Q2
Microbes and Infection	2.801	1	2.801		Q2
Mitochondrion	4.262	2	8.524		Q2
Modern Pathology	4.678	1	4.678		Q1
Molecular and Cellular Biology	5.942	2	11.884		Q1
Molecular Cancer	5.362	1	5.362		Q1
Molecular Psychiatry	12.537	1	12.537	1	Q1
Molecular Therapy	5.97	3	17.91	1	Q1
Multiple Sclerosis	3.312	6	19.872		Q1
Muscle & Nerve	2.594	1	2.594		Q2
Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis	3.198	1	3.198		Q2
Nature Genetics	30.259	2	60.518	1	Q1
Nature Reviews Cancer	30.762	1	30.762	1	Q1
Nephrology Dialysis Transplantation	3.568	3	10.704		Q1
Neurobiology of Disease	4.852	1	4.852		Q1
Neurogastroenterology and Motility	3.48	1	3.48		Q2
Neurogenetics	3	1	3		Q2
Neuroimage	5.694	1	5.694		Q1
Neurology	7.043	7	49.301	1	Q1
Neuromuscular Disorders	2.932	1	2.932		Q2
Neuroscience Letters	2.2	1	2.2		Q3
Nutritional Neuroscience	1.092	1	1.092		Q4
Obesity Surgery	2.913	4	11.652		Q1

Publication	Impact Factor	Published Papers	Total Impact Factor	Decile (D)	Quartile (Q)
Ocular Immunology and Inflammation	0.919	1	0.919		Q4
Oncogene	7.216	1	7.216		Q1
Ophthalmology	5.296	1	5.296	1	Q1
Orthopedics	0.588	1	0.588		Q4
Parkinsonism & Related Disorders	1.907	1	1.907		Q3
Pediatric Allergy and Immunology	2.723	1	2.723		Q3
Pediatric Hematology and Oncology	0.897	1	0.897		Q4
Pediatric Infectious Disease Journal	3.176	1	3.176		Q2
Pediatric Radiology	1.186	1	1.186		Q3
Pflügers Archiv-European Journal of Physiology	3.526	1	3.526		Q2
Pharmacogenomics	3.551	2	7.102		Q1
Pharmacogenomics Journal	5.435	1	5.435		Q1
Philosophical Transactions of the Royal Society	2.282	1	2.282		Q1
Physiological Genomics	3.436	1	3.436		Q2
Pigment Cell & Melanoma Research	4.634	1	4.634	1	Q1
Planta	3.088	1	3.088		Q1
Plos Medicine	12.185	1	12.185	1	Q1
Research in Microbiology	2.055	1	2.055		Q3
Respiration	1.985	1	1.985		Q3
Respiratory Medicine	2.338	2	4.676		Q2
Respiratory Research	3.874	1	3.874		Q1
Reviews in Medical Virology	7.13	1	7.13	1	Q1
Rheumatology	4.136	2	8.272		Q2
Sarcoidosis Vasculitis and Diffuse Lung Diseases	1.267	1	1.267		Q4
Scandinavian Journal of Work Environment & Health	2.802	1	2.802		Q1
Sexually Transmitted Infections	2.571	1	2.571		Q2
Spine	2.793	1	2.793		Q1
Stroke	6.499	3	19.497	1	Q1
Thrombosis and Haemostasis	3.803	4	15.212		Q1
Transfusion	3.475	1	3.475		Q2
Transfusion Medicine	2.056	1	2.056		Q3
Transplantation	3.816	2	7.632		Q1
Transplantation Proceedings	1.055	7	7.385		Q4
Ultrasound in Obstetrics & Gynecology	2.69	2	5.38		Q1
Vaccine	3.298	1	3.298		Q2
World Journal of Gastroenterology	2.081	2	4.162		Q3
Total International Magazines		**462**	**2,359.064**		

Table 7
Publications in national magazines

Publication	Impact Factor	Published Papers	Total Impact Factor	Decile (D)	Quartile (Q)
Spanish Magazines (*n* = 11)					
Actas Españolas de Psiquiatría	0.446	3	1.338		Q4
Archivos de Bronconeumología	1.624	10	16.24		Q3
Enfermedades Infecciosas y Microbiología Clínica	1.432	8	11.456		Q3
Medicina Clínica	1.258	25	31.45		Q3
Neurocirugía	0.277	2	0.554		Q4
Neurología	0.933	5	4.665		Q4
Nutrición Hospitalaria	1.096	1	1.096		Q3
Revista Clínica Española	0.734	3	2.202		Q4
Revista de Neurología	1.083	5	5.415		Q4
Revista Española de Cardiología	2.88	13	37.44		Q2
Revista Española de Enfermedades Digestivas	1.263	3	3.789		Q4
Total Spanish Magazines		**78**	**115.645**		

1.3.4 Research Projects

The active research projects which have been funded by public and private institutions are short-listed below. During 2009, 77 projects were granted. There were 230 active research projects at 31st of December of 2009 and they are short-listed below.

Table 8
List of active research projects in 2009

Funder organizations	Number of active funded projects
Fondo de Investigación Sanitaria (FIS), Instituto de Salud Carlos III	121
European Commission	17
Ministerio de Ciencia e Innovación	22
Fundació La Marató de TV3	13
Fundación de la Investigación Médica – Mutua Madrileña Automovilista	15
Agència d'Avaluació de Tecnologia i Recerca Mèdiques (AATRM)	3
Fundación para la Investigación y la Prevención del Sida en España (FIPSE)	3
Fundación Ramón Areces	1
Obra Social "la Caixa"	1
Centro Nacional de Investigaciones Cardiovasculares (CNIC)	2
Asociación Española contra el Cáncer	2
Genoma España	1
Association for International Cancer Research	1
Fundació Santiago Dexeus Font	4
Other	24
Total	**230**

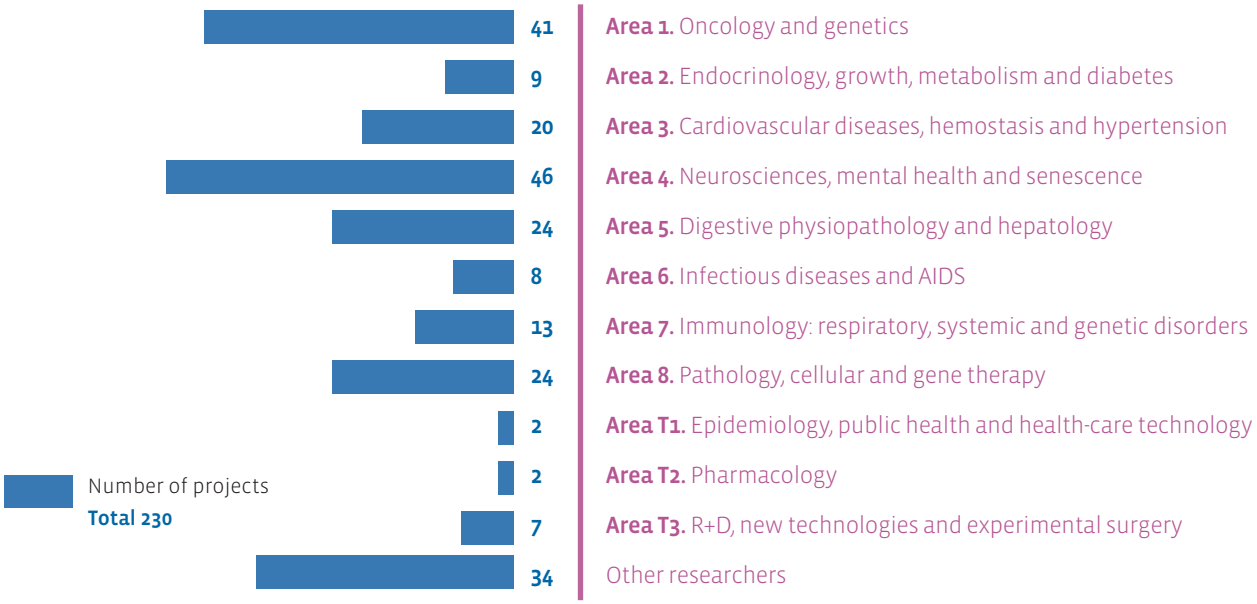


Figure 10
List of active research projects depending on its research area

1.3.5 Clinical Trials

203 clinical trials were submitted for their approval to the HUVH Clinical Research Ethical Committee (CREC), 173 (85%) of them were multicenter trials and 30 (15%) of them were unicenter trials. Of these 173 multicenter trials, 76 were acted as reference CREC (44%) and the other 97 were acted as involved CREC (56%). Of these 203 submitted trials, 171 (84%) were promoted by pharmaceutical industry, 14 (7%) were promoted by VHIR researchers and 18 (9%) were promoted by other hospitals. At 31st of December of 2009, there were 413 active clinical trials.

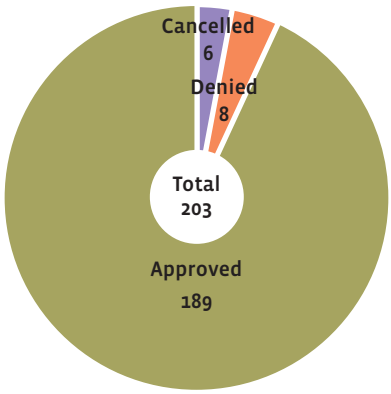


Figure 11
List of clinical trials submitted to CREC in the 2009

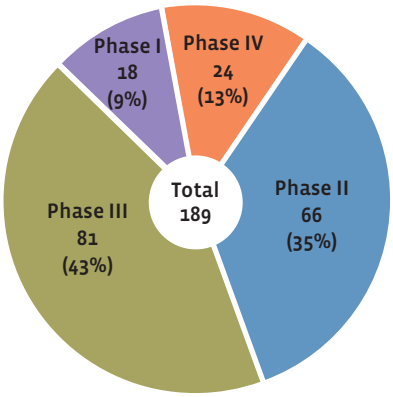


Figure 12
Clinical trials approved by CREC in the 2009, classified according to the trial phase

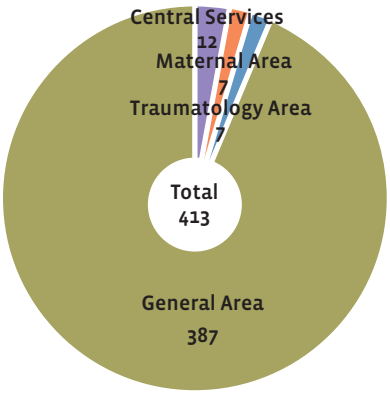


Figure 13
Active clinical trials at 31st of December of 2009, classified according services

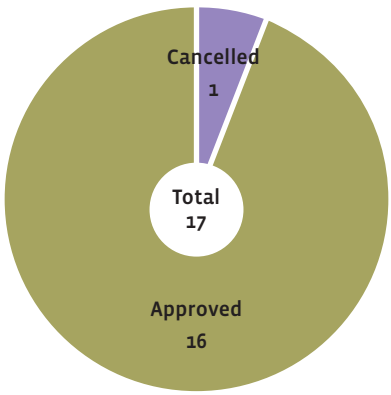
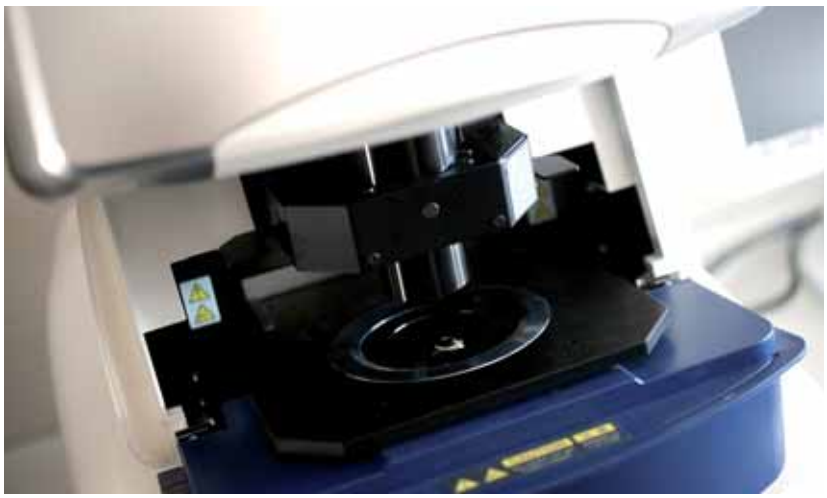


Figure 14
Post-authorization studies submitted to CREC in 2009

Table 9
List of active clinical trials at 31st of December of 2009, classified according services

Hospital Services		Number
General Area		**387**
Oncology	181	
Internal Medicine-Hepatology	21	
Neurotraumatology	6	
Internal Medicine-Infectious Diseases	10	
Cardiology	18	
Pulmonology	16	
Internal Medicine	20	
Nephrology	9	
Hematology	20	
General Surgery	7	
Endocrinology	12	
Digestive Apparatus	1	
Urology	5	
ICU	1	
Haemophilia	5	
Pain Clinics	2	
Neuroimmunology	37	
Allergies	1	
Internal Medicine-Rheumatology	8	
Ophthalmology	5	
Ear, Nose and Throat Disorders	2	
Maternal Area		**7**
Pediatrics	2	
Gynaecology	5	
Traumatology Area		**7**
Rehabilitation	2	
Traumatology	3	
Anesthesiology	2	
Central Services		**12**
Preventive Medicine	2	
Psychiatry	10	
Total		**413**



1.3.6 New Contracts to Researchers and Technicians Funded by Different Organizations and Programs

Table 10
VHIR's new contracts to researchers

Researchers' new contracts		Number
Senior Researchers		**9**
Research staff contracts - *Sistema Nacional de Salut*	4	
Intensification Programme contracts – *Instituto de Salud Carlos III*	4	
Research Retainment Programme – *Instituto de Salud Carlos III*	1	
Postdoc Researchers		**14**
Post-MIR contracts – *Instituto de Salud Carlos III*	5	
Postdoctoral contracts – *Instituto de Salud Carlos III*	1	
Juan de la Cierva Programme	4	
Beatriu de Pinós - Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)	1	
Postdoctoral contracts – *Fundació VHIR*	2	
Contracts stemming from Research Projects	1	
Predoc Researchers		**12**
Ministerio de Ciencia e Innovación	2	
Instituto de Salud Carlos III	2	
Fundació VHIR	3	
Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)	3	
Contracts stemming from Research Projects	2	
Support Staff		**8**
Ministerio de Ciencia e Innovación	1	
Instituto de Salud Carlos III	4	
Contracts stemming from Research Projects	3	
Total		**43**

1.3.7 Online Biomedical Research Center (CIBER)

The Online Biomedical Research Center (CIBER) is a research organization with its own legal entity, whose main objective is the monographic research of a pathology or a concrete health disorder. It is composed by different research groups, without physical contiguity, from different organizations, institutions and regions, from public or private sector and with its own research lines and objectives. CIBERs want to produce larger translational research centers, with multidisciplinary and multi-institutional character, where can be integrated basic, clinical and population research. They aim to develop a single common research program, focused on some pathologies which are relevant in the National Health System because of their prevalence or because of their social impact, they are considered strategic.

VHIR takes part in the following CIBERs:

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*

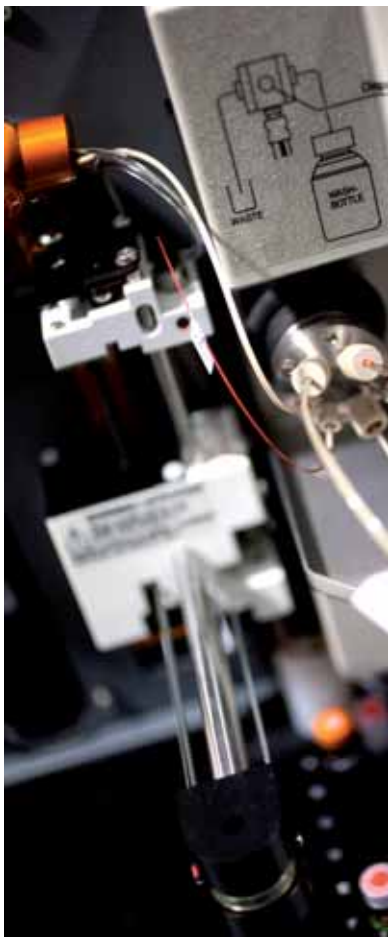


Table 11
List of CIBERs where VHIR takes part in

CIBER File	Title	Responsible
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

1.3.8 Thematic Networks of Cooperative Research of the *Instituto de Salud Carlos III*

Thematic Networks are organizational structures, promoted by the *Instituto de Salud Carlos III* (ISCIII), composed by different centers and research groups in biomedicine, with multidisciplinary character, that aims to carry out cooperative research projects of general interest. It is a response to the priorities of the *Plan Nacional (2000-2003)* in healthcare field and it is composed by different research projects as a strategy to reduce the existing distance between new knowledge production and its transfer and application to medical practice.

VHIR takes part in the ten following Thematic Networks of 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 Temàtica de Investigación Cooperativa de Biobancos.*

Table 12
List of ISCIII Thematic Network of Centers where VHIR takes part in

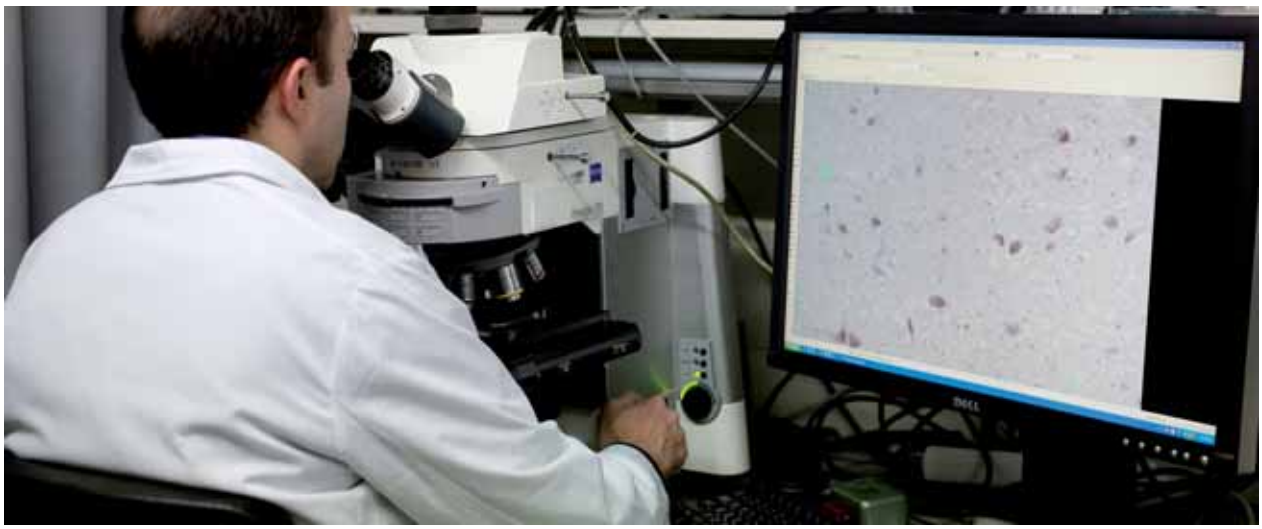
Nets of Centers File	Title	Responsible
RD06/0020/0022	*Red Temática de Investigación Cooperativa de Centros de Cáncer*	Joaquin Arribas López
RD06/0020/0075	*Red Temática de Investigación Cooperativa de Centros de Cáncer*	José Baselga Torres
RD06/0014/0025	*Factores de Riesgo, Evolución y Tratamiento de las Enfermedades Cardiovasculares (RECAVA)*	Antonio 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	*Patologia ocular del envejecimiento, calidad visual y calidad de vida*	José García Arumí
RD07/0060/0020	*Red Española de Esclerosis Múltiple (REEM)*	Xavier Montalbán 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 Temàtica de Investigación Cooperativa de Biobancos*	Santiago Ramón y Cajal Agüeras

1.3.9 Research Groups Recognized by the Generalitat de Catalunya

One of the objectives of the Generalitat de Catalunya, among their research programs, has been to provide support to those research groups of universities and research centers of Catalunya, which are articulated around a stable group of researchers, with convergent paths. This support is provided through taking part in cooperative research projects, publications and common activities promoting junior researchers' training.
VHIR has 28 groups recognized by the Generalitat de Catalunya.

Table 13
List of VHIR research groups recognized by the Generalitat de Catalunya

Area	File	Title	Responsible
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 Montalbán 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
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



Area	File	Title	Responsible
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

1.3.10 Thesis

The doctoral thesis read in 2009 by VHIR's researchers was 34: of which, 30 were read in several departments of the Autonomous University of Barcelona (UAB), 3 at the University of Barcelona (UB), and 1 at the Pompeu fabra University (UPF).

Table 14
Doctoral thesis read in 2009 or supervised by VHIR's staff

PhD	Title of the Thesis	Directors	Department	Qualification
Ares Rodríguez, Óscar	*El sangrado postoperatorio en cirugía artroplástica de rodilla*	Antoni Navarro Quilis	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Balmaña Gelpí, Judith	*Development and validation of predictive model for identification of MLH1 and MSH2 mutation carriers in lynch syndrome*	José Manuel Baselga Torres and Joan Brunet	Departament de Medicina (UAB)	Excellent *CumLaude*
Camats Tarruella, Núria	*Inestabilitat cromosòmica transgeneracional i radioprotecció en rata*	Montserrat Garcia Caldes and Francisca García Haro	Departament de Biologia Cel·lular, de Fisiologia i d'Immunologia (UAB)	Excellent *CumLaude*
Celma Domenech, Ana	*Valoración del daño renal producido por el neumoperitoneo en un modelo experimental*	Juan Morote Robles and Carles Raventós Busquets	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Coira Nieto, Amparo	*Beta-lactamasas de espectro extendido. Estudio comparativo del período 1989-1993 con la situación actual*	Guillem Prats Pastor	Departament de Genètica i de Microbiologia (UAB)	Excellent *CumLaude*
Cos Trullas, Joan	*Propuesta de un modelo experimental para la monitorización de la respuesta inmunitaria en pacientes sometidos a trasplante hepático*	Itxarone Bilbao and Josep Quer	Departament de Cirurgia (UAB)	*CumLaude*
Cuadrado Godia, Eloy	*Les metal·loproteïnases de matriu en la isquèmia cerebral: origen, localització cel·lular i contribució al dany tisular*	Joan Montaner, José Álvarez-Sabín and Anna Rosell	Departament de Medicina (UAB)	Excellent *CumLaude*
Garcia Miguel, Xavier	*Cambios en la microarquitectura ósea trabecular en osteoporosis normocalciúrica idiopática del varón y en la artritis reumatoide: análisis mediante microCT*	Adolfo Díez Pérez and Lluis Pérez-Edo	Departament de Medicina (UAB)	Excellent *CumLaude*

Table 14
Doctoral thesis read in 2009 or supervised by VHIR's staff *(Cont.)*

PhD	Title of the Thesis	Directors	Department	Qualification
García-Oria Serrano, Miguel	*Influencia del sobrepeso y la obesidad en la morbimortalidad perioperatoria y supervivencia a largo plazo de pacientes intevenidos electivamente por cáncer colorrectal*	Manuel Armengol Carrasco and Antoni Codina Cazador	Departament de Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva (UAB)	Excellent *CumLaude*
Gómez Martínez, Valentí	*Noves funcions de la proteïna Flotillin-1 en la regulació del procés de mitosi i la via de senyalització de Notch 1*	Rosanna Paciucci	Bioquímica i Biologia Molecular / Fac. Biologia (UB)	Excellent *CumLaude*
González López, Juan José	*Las beta-lactamasas cromosómicas de enterobacterias: regulación y difusión plasmídica*	Guillem Prats Pastor	Departament de Genètica i de Microbiologia (UAB)	Excellent *CumLaude*
González Santesteban, Cecilia Paula	*Caracterització de la glicoproteína CD8 mutante responsable de la deficiencia familiar de CD8. Estudios de otras inmunodeficiencias que afectan a la función de los linfocitos T citotóxicos*	Óscar de la Calle Martín	Departament de Biologia Cel·lular, de Fisiologia i d'Immunologia (UAB)	Excellent *CumLaude*
Hurtado Martínez, Mariano	*Función y mecanismo de acción de los activadores del plasminógeno en cáncer*	Rosanna Paciucci	Bioquímica i Biologia Molecular / Fac. Biologia (UAB)	Excellent *CumLaude*
Lozoya Trujillo, Roberto	*Cáncer de recto estadio IV. Factores predictivos*	Manuel Armengol Carrasco, Eloy Espín Basany and Cano Manuel López	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Martínez Barriocanal, Águeda	*Molecular and functional characterization of IREM3, a new activating member of the CMRF/ IREM family*	Joan Sayós Ortega	Departament de Ciències Experimentals i de la Salut (UPF)	Excellent *CumLaude*
Monge Azemar, Marta	*Caracterització del factor de transcripció ETV5 durant la infiltració miometrial i aproximacions proteòmiques al procés d'invasió en càncer d'endometri*	Jaume Reventós Puigjaner and Miguel Abal Posada	Bioquímica i Biologia Molecular / Fac. Biologia (UB)	Excellent *CumLaude*

Table 14
Doctoral thesis read in 2009 or supervised by VHIR's staff *(Cont.)*

PhD	Title of the Thesis	Directors	Department	Qualification
Montero Fernández, María Ángeles	*Factores moleculares predictivos en los GIST: correlación entre la expresión de las vías de señalización celular, estudio mutacional, localización y evolución clínica*	Inés de Torres and Santiago Ramón y Cajal	Ciències Morfològiques (UAB)	Excellent *CumLaude*
Morral Palau, Mercé	*Lentes intraoculares para ojo fáquico de fijación iridiana para la corrección de defectos de la refracción*	José García Arumí and José Luis Güell	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Naranjo Gómez, María del Mar	*Respuesta alogénica inducida por células dendríticas plasmacitoides. Factores implicados en su activación*	Ricardo Pujol Borrell and Francesc E Borras Seres	Departament de Biologia Cel·lular, de Fisiologia i d'Immunologia (UAB)	Excellent *CumLaude*
Padilla Gomes, Nelly Fabiola	*Seguimiento del desarrollo durante el primer año de vida de un grupo de neonatos con y sin antecedente de restricción de crecimiento intrauterino*	Antonio Carrascosa Lezcano	Departament de Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva (UAB)	Excellent *CumLaude*
Pérez Barcena, Juan	*Medidas terapéuticas de segundo nivel en pacientes con traumatismo craneoencefálico e hipertensión intracraneal refractaria*	Joan Sahuquillo Barris	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Ramos Quiroga, José Antonio	*TDAH en adultos: factores genéticos, evaluación y tratamiento farmacológico*	Miquel Casas Brugué and Bru Cormand	Departament de Psiquiatria i de Medicina Legal (UAB)	Excellent *CumLaude*
Reyes Ortiz, Leonardo José	*Enfermedad pulmonar intersticial (EPI) en el Hospital Universitario Vall d'Hebron de Barcelona, en los años 1995 a 2004.*	Ferran Morell Brotad	Departament de Medicina (UAB)	Excellent *CumLaude*
Saldivar Rodríguez, Donato	*Medición de cuerpos lamelares para valoración de la madurez pulmonar en pacientes con patología materna*	Lluis Cabero Moura	Departament de Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva (UAB)	Excellent *CumLaude*
Sánchez García, Jorge	*Diagnòstic genètic preimplantacional de malalties hereditàries: fibrosi quística i hemofilia*	Francisco Vidal Pérez, Jordi Benet Català and Joaquima Navarro Ferrete	Departament de Biologia Cel·lular, de Fisiologia i d'Immunologia (UAB)	Excellent *CumLaude*

PhD	Title of the Thesis	Directors	Department	Qualification
Santamaría Martínez, Albert	*Identificació, aïllament i caracterització de cèl·lules mare en models de càncer de pròstata*	Francina Munell Casadesús	Bioquímica i Biologia Molecular / Fac. Biologia (UB)	Excellent *CumLaude*
Santos Blanco, María Esther	*Cuantificación de interleucina-8 y MCP-1 intravítreas en el edema macular secundario a enfermedad oclusiva venosa*	José García Arumí and Àlex Fonollosa Calduch	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Soldado Carrera, Francisco Antonio	*Investigación traslacional en cirugía fetal de la brida amniótica en extremidades*	Vicenç Martínez Ibáñez, Marius Aguirre Canyadell and Joan Nardi Vilardaga	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Tost Valls, Josep Ramon	*Problemática de la hepatotoxicidad en el tratamiento de la tuberculosis en el siglo XXI*	Ferran Morell Brotad and Rafael Vidal Pla	Departament de Medicina (UAB)	Excellent *CumLaude*
Valdés Sánchez, Martha	*Integración de imágenes: tomografía axial computerizada y tomografía por emisión de positrones, en la planificación del tratamiento radioterápico en pacientes pediátricos con enfermedad de Hodking*	Jordi Giralt López de Sagredo and Maria Isabel Roca Bielsa	Departament de Medicina (UAB)	Excellent *CumLaude*
Valero Ventura, Sergi	*El modelo alternativo de los cinco grandes estudios de validez y fiabilidad del Zuckerman-Kuhlman Questionnaire (ZKPQ) en población general y clínica*	Montserrat Gomà Freixanet	Departament de Psiquiatria i de Medicina Legal (UAB)	Excellent *CumLaude*
Vallribera Valls, Francesc	*Influencia de la cirugía laparoscópica en la percepción de la calidad de vida después de apendicectomía. Ensayo clínico multicéntrico aleatorizado y abierto de comparación de dos técnicas quirúrgicas*	Manuel Armengol Carrasco and Joan Sala Pedrós	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Vilalta Saura, Anna	*Aplicación de la microdiálisis cerebral al estudio de la respuesta metabólica e inflamatoria en el traumatismo craneoencefálico moderado y grave*	Joan Sahuquillo Barris	Departament de Cirurgia (UAB)	Excellent *CumLaude*
Zamora Serrallonga, Elisabet	*Factores pronósticos en la insuficiencia cardíaca*	Rafael Simó Canonge and Josep Lupón Rosés	Departament de Medicina (UAB)	Excellent *CumLaude*

1.4 Scientific Report

1.4 SCIENTIFIC REPORT

The scientific activities organized during 2009 by VHIR were 135 (sale 134), stressing the great importance of teaching in our Institute.

Table 15
VHIR's activities

Activities	Number
Extraordinary conferences	
XIII Annual Conference HUVH	1
3rd Scientific Session of Postdoctoral and Predoctoral Researchers	1
6th Workshop on Biomedical Genomics and Proteomics	1
Scientific Seminar 'Biomedicine and Genomics'	1
Seminars	
VHIR	16
Oncology	6
Cardiology	23
Gastroenterology	33
Neuroscience	10
Neurosurgery	13
Courses	15
USMIB Teaching	9
UEB Teaching	5

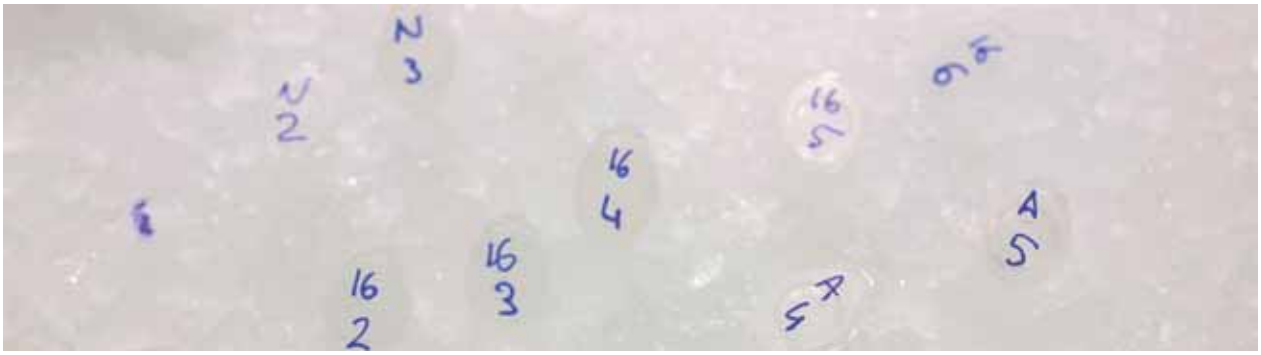


Table 16
Extraordinary Conferences

XIII Annual Conference Hospital Universitari Vall d'Hebron	Date
Scientif Session	03/12/2009
The Human Metagenome	
Stanislav Dusko Ehrlich Director de la Unitat de Recerca de Genètica Microbiana, Institut National de la Recherche Agronomique (INRA), Jouy en Josas, France	
• VIDEO: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/VIDEOS/xiiiconf/index.html • SUMMARY: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/Dusko_fg.pdf	

3rd Scientific Session of Postdoctoral and Predoctoral Researchers	Date
Predoctorals	02/12/2009
1st Award	
EPHB4 es un nuevo gen supresor de tumores en càncer colorrectal	
José Higinio Dopeso CIBBIM-Nanomedicina. Grup d'Oncologia Molecular	
• Abstract: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/predoc_higinio.pdf	
Accèssit	
HER2 611 Carboxy-Terminal Fragment Promotes Tumor Growth and Metastasis in vivo	
Pier Davide Angelini PROM- Factors de Creixement i Càncer	
• Abstract: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/predoc_angelini.pdf	
Postdoctorals	
1st Award	
The oncogenic effect of TGF-beta in human glioma. The TGF-beta pathway as a therapeutic target in cancer	
Silvia Peñuelas PROM-Expressió Gènica i Càncer	
• Abstract: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/posdoc_penuelas.pdf	
Accèssit ex-aequo	
HER2 carboxy-terminal fragments (CTFS)	
Kim Pedersen PROM-Factors de Creixement i Càncer	
• Abstract: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/posdoc_pedersen.pdf	

Table 16
Extraordinary Conferences *(Cont.)*

3rd Scientific Session of Postdoctoral and Predoctoral Researchers	Date
Postdoctorals *Accèssit ex-aequo* ***Inhibition of teh PI3K pathway as atarget for the treatment of glioblastoma multiforme*** Rosa María Prieto PROM-Expressió Gènica i Càncer • Abstract: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/posdoc_prieto.pdf	02/12/2009
3rd Scientific Session of Postdoctoral and Predoctoral Researchers • Abstracts book: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/3_jornadacientifica_programa.pdf	

6th Workshop on Biomedical Genomics and Proteomics	Date
Program: • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/final11.pdf	11/12/2009

Scientific Seminar 'Biomedicine and Genomics'	Date
Program: • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/posterSEQUENCERzzS.pdf	16/12/2009

Table 17
VHIR Seminars

VHIR Conferences	Date
Hereditary and Familial Colorectal Cancer: lessons learned from the EPICOLON study Antoni Castells Servei de Gastroenterologia Hospital Clínic de Barcelona. • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SesionesdeGastroenterolog%C3%ADa/epicolomangonic15102010/tabid/1096/Default.aspx	15/12/2009
Atrofia nerviosa simpática en las alteraciones hemodinámicas de la hipertensión portal María Martell Grupo de Hipertensión Portal, Laboratorio Enfermedades Hepáticas Institut de Recerca Hospital Universitari Vall d'Hebron • http://www.ir.vhebron.net/easyweb_irvh/Noticias/hipertens_atrof_martell/tabid/1102/Default.aspx	02/12/2009
Mecanismos genéticos que controlan la regionalización cerebral durante el desarrollo Salvador Martínez Pérez Grupo en Embriología Experimental Unidad de Investigación en Neurobiología del Desarrollo. Universidad Miguel Hernández-Elche (Alicante) • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/Conferencies/IR_24112009_Martinez/tabid/1083/Default.aspx	24/11/2009
Avaluació de linezolid, vancomicina, gentamicina i ciprofloxacina per al tractament de la infecció relacionada amb el catèter per* Staphylococcus aureus *mitjançant la tècnica del segellat antibiòtic Nuria Fernández Grup de Recerca en Malalties Infeccioses Institut de Recerca VHIR • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/dra_1/tabid/1108/Default.aspx	17/11/2009
Inhibition of IL-12 & IL-23 folding and assembly as novel route toward suppression of autoimmune disease Koen Vandenbroeck Head of the new Neurogenomiks laboratory Department of Neuroscience UPV-EHU.Bizkaia • http://www.ir.vhebron.net/easyweb_irvh/Neuroimmunologiaclinica/tabid/1076/Default.aspx	12/11/2009
Control del ciclo celular en la pared arterial: Mecanismos genético-moleculares e implicaciones clínicas Vicente Andrés Laboratorio Fisiopatología Cardiovascular Molecular y Genética Centro Nacional de Investigaciones Cardiovasculares (CNIC). Madrid • http://www.ir.vhebron.net/easyweb_irvh/vicand_ciclo_v2/tabid/1090/Default.aspx	03/11/2009

Table 17
VHIR Seminars *(Cont.)*

VHIR Conferences	Date
Efectes del tractament amb 6-metilprednisolona sobre un model animal de lesió pulmonar aguda induïda per l'administració de lipopolisacàrid Oriol Roca Grup de Recerca en Pneumologia Metge Adjunt-Servei de Medicina Intensiva HUVH • http://www.ir.vhebron.net/easyweb_irvh/Noticias/Pneum_oriolRoca/tabid/1077/Default.aspx	20/10/2009
La PGE2 intranasal induce tolerancia frente a aeroalergenos de los ácaros del polvo Rosa Torres Grupo de Investigación en Inmunoalergia Respiratoria Clínica y Experimental IDIBAPS (Barcelona) • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/IR_061009_torres/tabid/1065/Default.aspx	06/10/2009
Nuevos retos de la investigación del HIV: Nanomedicina y terapia génica Mª Ángeles Muñoz Unidad Immuno-Biología Molecular Hospital General Universitario Gregorio Marañon (Madrid) • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/Institut/IR_230909_munoz/tabid/1057/Default.aspx23/09/2009	23/09/2009
Mouse models of asthma – not only proteins, but also chemicals can act as allergens Jeroen Vanoirbeek K.U. Leuven Fac. Medicine Dep. Of Public Healh Occupational, Enviomental & Insurance Medicine • http://www.ir.vhebron.net/easyweb_irvh/Activitats/conf_ir_/tabid/1045/Default.aspx	07/07/2009
New Tricks for an old oncogene: Myc as inhibitor of cell differentiation Javier León Instituto de Biomedicina y Biotecnología de Cantabria (IBBTEC) Universidad de Cantabria-CSIC-IDICAN • http://www.ir.vhebron.net/easyweb_irvh/Activitats/conf_ir_/tabid/1032/Default.aspx	09/06/2009
Vitamin D, Snail1, Wnt and colon cancer Alberto Muñoz Instituto de Investigaciones Biomédicas, CSIC (Madrid) • http://www.ir.vhebron.net/easyweb_irvh/Activitats/conf_am_vd/tabid/1025/Default.aspx	21/05/2009
Alpha-Synuclein in Parkinson´s Disease: From genetics to pathogenesis Leonidas Stefanis Laboratory of Neurodegenerative Diseases Biomedical Research Foundation. Academy of Athens • http://www.ir.vhebron.net/easyweb_irvh/Activitats/acti_alpha_leonidas/tabid/1009/Default.aspx	21/04/2009

VHIR Conferences	Date
Genetic and Nutritional Interactions in Colon Tumorigenesis Leonard H. Augenlicht Albert Einstein Cancer Center • http://www.ir.vhebron.net/easyweb_irvh/Activitats/leonard_a_genetic/tabid/996/Default.aspx	03/04/2009
Regulación hipotalámica de la ingesta y peso corporal Carlos Dieguez Departamento de Fisiología. Instituto de Investigación Sanitaria (IDIS) Universidad Santiago Compostela (USC) • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/Conferencies/conferencies_ir_2009_dieguez/tabid/976/Default.aspx	10/03/2009
Structural Systems Biology: Modelling protein interactions and complexes Patrick Aloy ICREA Research Professor. Structural Bioinformatics Institut de Recerca Biomèdica de Barcelona (IRB Barcelona) • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/Aloy_270109/tabid/919/Default.aspx	27/01/2009

Table 18
Oncology Seminars

Oncology	Date
Computer modelling of proteins: how they may help a clinician Chandra Verma Head of the Structural/Functional Genomics Group at the Bioinformatics Institut, Singapore	29/01/2009
mTOR (the mammalian target of rapamycin)- a master regulator of cell functions Christopher Proud School of Biological Sciences Human Genetics Division.University of Southampton	17/02/2009
Transcriptional regulation of ERBB2 by estrogen receptor-Pax2 determines response to tamoxifen Antoni Hurtado Postdoc fellow Cancer Research UK Cambridge Research Institutte	26/02/2009
Myc inhibition in cancer: bright new hope or bad idea? Laura Soucek Assistant Research Molecular Biologist Evan Lab. Department of Pathology, UCSF	09/03/2009
Smad-dependent and Smad-independent pathways in TGF-b signaling as therapeutic targets in pancreatic cancer Davide Melisi Instructor, Department of Gastrointestinal Medical Oncology MD Anderson Cancer Center-University of Texas	19/03/2009
Conservation and divergence of transcription factor binding during mammalian evolution Michael D. Wilson Regulatory Circuitry Group Cancer Research UK Cambridge Research Institute	01/04/2009

Table 19
Cardiology Seminars

Cardiology	Date
Improved Outcomes with CABG versus PCI in Patients with Complex Three Vessel and/or Left Main Coronary Disease: Results from SYNTAX Pieter Kappetein, MD, PhD Erasmus Medical Center, Rotterdam. The Netherlands • http://www.ir.vhebron.net/easyweb_irvh/SYNTAXtwoyear/tabid/1089/Default.aspx	18/12/2009
Terapia génica para la insuficiencia cardíaca Sian Harding Imperial College. Londres • http://www.ir.vhebron.net/easyweb_irvh/cardio_041209_harding/tabid/1084/Default.aspx	04/12/2009

Table 19
Cardiology Seminars *(Cont.)*

Cardiology	Date
La proteolisis dependiente de calcio: una diana prometedora contra el daño por reperfusión en el infarto de miocardio Javier Inserte Hospital Universitari Vall d'Hebron. Barcelona • http://www.ir.vhebron.net/easyweb_irvh/Activitats/cardio_javie/tabid/1072/Default.aspx	06/11/2009
Vessament pericàrdic moderat-server en l'infart de miocardi amb elevació del ST. Tractament i seguiment a llarg termini Jaume Figueres Hospital Universitari Vall d'Hebron. Barcelona • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/cardio_figueres_301009/tabid/1071/Default.aspx	30/10/2009
Nuevas indicaciones y técnicas para la extracción de electrodos intracavitarios Maria Grazia Bongiorni University Hospital. Pisa • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/cardio_mariagb/tabid/1068/Default.aspx	16/10/2009
Valor del estudio electrofisiológico en pacientes portadores de tetralogía de Fallot intervenida Núria Rivas Hospital Universitari Vall d'Hebron. Barcelona • http://www.ir.vhebron.net/easyweb_irvh/Activitats/cardio_nrivas/tabid/1073/Default.aspx	09/10/2009
Correspondencia de los 17 segmentos del ventrículo izquierdo con las arterias coronarias en resonancia magnética José Rodríguez Palomares Hospital Universitari Vall d'Hebron. Barcelona • http://www.ir.vhebron.net/easyweb_irvh/RecercaHUVH2005/Cardiologia/cardio_jrodriguez/tabid/1067/Default.aspx	02/10/2009
Los primeros minutos de reperfusión: una segunda oportunidad para el paciente con infarto agudo de miocardio David García-Dorado Institut de Recerca, Hospital Universitari Vall d'Hebron. Barcelona • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/cardio_dgarciadorado/tabid/1042/Default.aspx	26/06/2009
Intervencionismo percutáneo del tronco común en el 2008: ¿Es posible hacerlo? Imad Sheiban San Giovanni Battista Hospital. Universidad de Torino • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/cardio_sheiban/tabid/1039/Default.aspx	29/05/2009

Table 19
Cardiology Seminars *(Cont.)*

Cardiology	Date
Presente y futuro de la implantación percutánea de válvulas para el tratamiento de la estenosis aórtica Josep Rodés Quebec Heart Institut/Laval Hospital. Quebec • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/cardio_rodes/tabid/1040/Default.aspx	22/05/2009
Fibrilación auricular. Un enfoque radical Barbara Casadei John Radcliffe Hospital. Oxford • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/ses_card_cas_fib/tabid/1028/Default.aspx	15/05/2009
Advances in camera and software technology in nuclear cardiology Ernest V. Garcia Emory University School of Medicine Atlanta, Georgia, USA • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/card_evg_adv/tabid/1018/Default.aspx	08/05/2009
30 años de REGICOR Joan Sala i Montero Hospital Josep Trueta. Girona • http://www.ir.vhebron.net/easyweb_irvh/card_jsm_esreg/tabid/1019/Default.aspx	24/04/2009
Antiaggregation and patients with irreversible appendage dysfunction, at high embolic risk, who need life-lasting anticoagulation Paolo Colonna Hospital Policlínico, Universidad de Bar. Italy • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/cardio_pcolomma/tabid/1043/Default.aspx	17/04/2009
El STENT coronari farmacoactiu a Espanya Gaietà Permanyer Miralda Unitat d'Epidemiologia, Servei de Cardiologia, Hospital Vall d'Hebron. Barcelona • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/sessions_cardiologia_perm_3_09/tabid/980/Default.aspx	20/03/2009
Reperfusión ácida en el infarto de miocardio. Estudios experimentales Antonio Rodríguez Sinovas Hospital Universitari Vall d'Hebron. Barcelona • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/sinovas_060309/tabid/963/Default.aspx	06/03/2009

Cardiology — Date

Precondicionamiento isquémico en pacientes — 27/02/2009
Derek Hausenloy
Hatter Institute. Londres

- http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/hausenloy_270209/tabid/962/Default.aspx

Muerte súbita en el infarto agudo de miocardio: ¿Un problema mecánico? — 13/02/2009
José Barrabés
Hospital Universitari Vall d'Hebron. Barcelona

- http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/Res_sesio_jab/tabid/937/Default.aspx

Ecocardiografía de estrés: Estado de la cuestión — 06/02/2009
Rosa Sicari
CNR, Institute of Clinical Physiology Pisa. Italy

- http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/060209_sicari.pdf

Catheter Ablation of Atrial Fibrillation: How to Balance between a Lot of Technology and Common Sense — 30/01/2009
Josef Kautzner
Institute for Clinical and Experimental Medicine, Prague, Czech Republic

- http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/cardio_jo_ka_cat/tabid/943/Default.aspx

Evolució de la incidència i mortalitat de la ruptura cardíaca en l'infart de miocardi amb elevació del segment ST durant un període de 30 anys — 23/01/2009
Jaume Figueras Bellot
Hospital Universitari Vall d'Hebron. Barcelona

- http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/dr_figeres_rs/tabid/921/Default.aspx

ARN y función cardíaca: una conexión inesperada — 16/01/2009
Gianluigi Condorelli
Consiglio Nazionale delle Ricerche. Italy

- http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/DrCondorelli160109/tabid/904/Default.aspx

Registros de síndrome coronario agudo: ¿Representan o distorsionan la realidad? — 09/01/2009
Ignacio Ferreira
Hospital Universitari Vall d'Hebron. Barcelona

- http://www.ir.vhebron.net/easyweb_irvh/Activitats/Confeiseminaris/SessionsdeCardiologia/DrFerreira090109/tabid/894/Default.aspx

Table 20
Gastroenterology Seminars

Gastroenterology	Date
Disfagia orofaríngea Jordi Serra Servei d'Aparell Digestiu, HUVH. Barcelona	12/01/2009
Modulación de la función barrera intestinal por bacterias de la flora comensal María Antolín Servei d'Aparell Digestiu, HUVH. Barcelona	19/01/2009
Microbiota transplantation under pharmacological treatments in rat model Chaysabanh Manichanh Servei d'Aparell Digestiu, HUVH. Barcelona	02/0272009
Dispepsia funcional versus gastroparesia Anna Accarino Servei d'Aparell Digestiu, HUVH. Barcelona	09/02/2009
Degranulación mastocitaria en la mucosa intestinal de pacientes con síndrome de intestino irritable María Vicario Servei d'Aparell Digestiu, HUVH. Barcelona	16/02/2009
Pseudoobstrucción intestinal y síndrome de intestino irritable Fernando Azpiroz Servei d'Aparell Digestiu, HUVH. Barcelona	23/02/2009
Protocolo de investigación: Evaluación de la motilidad intestinal mediante anàlisis computerizado de imágenes endoluminales Joan Ramon Malagelada Servei d'Aparell Digestiu, HUVH. Barcelona	02/03/2009
Efecto del cromoglicato disódico en la regulación de la barrera epitelial y su implicación en la fisiopatología del síndrome de intestino irritable Beatriz Lobo Servei d'Aparell Digestiu, HUVH. Barcelona	16/03/2009
Angiodisplasia intestinal Esteban Saperas Servei d'Aparell Digestiu, HUVH. Barcelona	23/03/2009
Estabilización del mastocito: Efecto antiinflamatorio ¿intestinal y sistémico? Laura Ramos Servei d'Aparell Digestiu, HUVH. Barcelona	30/03/2009
Protocolo de investigación: Evaluación de la motilidad intestinal mediante anàlisis computerizado de imágenes endoluminales Joan Ramon Malagelada Servei d'Aparell Digestiu, HUVH. Barcelona	20/04/2009
Seguridad clínica Joan Fernández Nàger HUVH. Barcelona	27/04/2009

Gastroenterology — Date

Efecto del cromoglicato disódico en la regulación de la barrera epitelial y su implicación en la fisiopatología del síndrome de intestino irritable — 04/05/2009
Beatriz Lobo
Servei d'Aparell Digestiu, HUVH. Barcelona

Psiquiatría y digestivo: nexos en común — 11/05/2009
Amanda Rodríguez
Servei de Psiquiatria, HUVH. Barcelona

Manejo de la rumiación — 18/05/2009
Daniel Cisternas
Universidad Pontificia Católica de Chile

In vitro studies of Salmonella Enterica serovar Typhimurium infection dynamics within bone marrow macrophages — 25/05/2009
Alicia Murcia
Servei d'Aparell Digestiu, HUVH. Barcelona

Protocolo de revisión: Enfermedad celíaca — 08/06/2009
Esther Beleta and Francesc Casellas
Servei d'Aparell Digestiu, HUVH. Barcelona

Tratamiento biológico en enfermedad inflamatoria intestinal — 15/06/2009
Natalia Borruel
Servei d'Aparell Digestiu, HUVH. Barcelona

Obesidad mórbida. Tratamiento médico. Indicación quirúrgica — 22/06/2009
Albert Lecube
Servei d'Endocrinologia, HUVH. Barcelona

***Papel de GEFH1 en la activacion de NOD1, dependiente de NFkB, iniciada por proteínas efectoras de* Shigella flexneri** — 29/06/2009
Carmen Alonso
Servei d'Aparell Digestiu, HUVH. Barcelona

Efecto de la desloxiglumida antagonista de los receptores CCK en dispepsia funcional y síndrome del intestino irritable — 06/07/2009
Beatriz Lobo
Servei d'Aparell Digestiu, HUVH. Barcelona

El inhibidor de COX-2 celecoxib induce muerte celular programada en células estrelladas activadas del páncreas — 13/07/2009
Meritxell Guil
Servei d'Aparell Digestiu, HUVH. Barcelona

Valoración de la fatiga en la enfermedad inflamatoria intestinal — 14/09/2009
Andrés Pelaez
Servei d'Aparell Digestiu, HUVH. Barcelona

Table 20
Gastroenterology Seminars *(Cont.)*

Gastroenterology	Date
Characterisation of the Microbial Diversity Associated with the Mucose of the Human colorectum Daniel Aguirre de Carcer Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO) Queensland Biosciences Precinct. St. Lucia, Australia	21/09/2009
Esofagitis eosinofílica María Vicario and Mar Guilarte Servei d'Aparell Digestiu, HUVH. Barcelona	28/09/2009
Actualización en encefalopatía hepática J. Córdoba Servei de Medicina Interna-Hepatologia, HUVH. Barcelona	19/10/2009
Protocolo de revisión: Estudio de LOE hepática Ana Adame and Jaime Vilaseca Servei d'Aparell Digestiu, HUVH. Barcelona	26/10/2009
Actuación metodológica en estadística Salvador Videla Esteve Laboratories	02/11/2009
Trastornos motores esofágicos Carlos Hernández and Anna Accarino Servei d'Aparell Digestiu, HUVH. Barcelona	09/11/2009
Protocolo de revisión: Diarrea crónica David Barquero and Francesc Casellas Servei d'Aparell Digestiu, HUVH. Barcelona	16/11/2009
Microflora y càncer de colon Francisco Guarner Servei d'Aparell Digestiu, HUVH. Barcelona	30/11/2009
Papel de la activación eosinofílica en la fisiopatología del síndrome del intestino irritable María Vicario Servei d'Aparell Digestiu, HUVH. Barcelona	07/12/2009
Actualización en hígado graso no alcohólico (NASH) Víctor Vargas Servei de Medicina Interna-Hepatologia. HUVH. Barceloan	14/12/2009

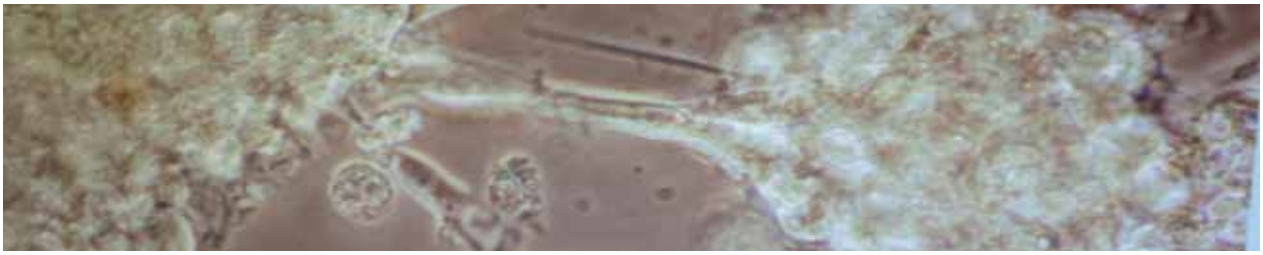


Table 21
Neuroscience Seminars

Neuroscience	Date
Implicació de les metal·loproteïnases de matriu en la angiopatia amiloide cerebral Mar Hernández Guillamón Grup de Recerca en Malalties Neurovasculars. Institut de Recerca VHIR. Barcelona	16/12/2009
Papel de la proteína mitocondrial Alex3 durante el desarrollo del Sistema Nervioso: Implicación en las vías de señalización asociadas a Wnts Guillermo López Neurobiologia del desenvolupament i de la regeneració cel·lular. Institut de Recerca Biomèdica de Barcelona, IRB barcelona	18/11/2009
Bases genètiques de la malformació de Chiari Aintzane Urbizu Grup de Recerca en Neurología infantil. Institut de Recerca VHIR. Barcelona	21/10/2009
Efecto de las mutaciones en el mtDNA sobre la expresión de genes involucrados en la función mitocondrial Marc Cuadros Grup de Recerca en Malalties neuromusculars i mitocondrials. Institut de Recerca HUVH. Barcelona	16/09/2009
DNA vaccines in multiple sclerosis Nicolás Fissolo Grup d'Immunologia Clínica. HUVH.Barcelona	17/06/2009
Fisiopatología de la migraña. Modelos experimentales Patricia Pozo Servei de Neurología (Unitat de Cefalees). HUVH. Barcelona	20/05/2009
Efecte del consum d'èxtasi sobre l'expressió gènica Noelia Fernàndez Grup de Recerca en Neurologia Infantil i Psiquiatria Genètica. Institut de Recerca VHIR. Barcelona	15/04/2009
Les metal·loproteïnases de matriu en la isquèmia cerebral: Origen, localització cel·lular i contribució al dany tissular Eloy Cuadrado Godia Grup de Recerca en Malalties Neurovasculars. Institut de Recerca VHIR. Barcelona	18/03/2009
Estudi del metabolisme anaerobi en pacients que han patit un traumatisme cranioencefàlic greu mitjançant la microdiàlisi cerebral M. Àngels Merino Servei de Neurotraumatologia. HUVH. Barcelona	18/02/2009
Estudi funcional del factor mitocondrial de terminació de la transcripció 4 (mTERF4) Yolanda Cámara Grup de Recerca en Malalties Neuromusculars i Mitocondrials. Institut de Recerca VHIR. Barcelona	21/01/2009

Table 22
Neurosurgery Seminars

Neurosurgery	Date
La calidad de vida en pacientes con gliomas de alto grado tratados quirúrgicamente M. Esquivel Servei de Neurocirurgia • http://www.ir.vhebron.net/easyweb_irvh/Activitats/neurocirugia_2009/tabid/974/Default.aspx	23-01-09
La segona opinió. Un dret del pacient i una obligació del metge? J. Jornet Servei de Neurocirurgia	09-02-09
Hydrodynamic shunt dysfunction in normal pressure hydrocephalus (NPH): Known and unknown risks and how to avoid them J. Sahuquillo Servei de Neurocirurgia • http://www.ir.vhebron.net/easyweb_irvh/Activitats/neurocirugia_2009/tabid/975/Default.aspx	23-02-09
Presentación del protocolo de revascularización cerebral para el tratamiento de la isquemia cerebral crónica F. Arikan Servei de Neurocirurgia • http://www.ir.vhebron.net/easyweb_irvh/Activitats/neuro_arikan_isquemia/tabid/1010/Default.aspx	09-03-09
Anticomicials i neurooncologia. Indicacions, interaccions i nous fàrmacs M. Castellví and P. Cano Servei de Neurocirurgia	27-04-09
Radiocirurgia: visió general i indicacions F.R. Martínez and J. Sahuquillo Servei de Neurocirurgia	11-05-09
Desenvolupament cranial normal i tècniques quirúrgiques actuals en el tractament de la craniosinostosi P. Cano and M.A. Poca Servei de Neurocirurgia	08-06-09
Actualitzacions i controvèrsies sobre l'ús del test de Katzman en el diagnòstic de la HCA M. Romero, D. Gandara and M.A. Poca Servei de Neurocirurgia	13-07-09
Protocol d'estudi del pacient amb sospita de metàstasis cerebrals D. Gandara and A. Arikan Servei de Neurocirurgia	10-08-09
Indicacions de la radiocirurgia en el tractament de les MAV J. Vilalta Servei de Neurocirurgia	14-09-09

Table 22
Neurosurgery Seminars *(Cont.)*

Neurosurgery	Date
Alteracions cognitives en la HCA idiopàtica. Presentació dels resultats en una sèrie de 240 pacients J. E. Solana and M.A. Poca Servei de Neurocirurgia	26-10-09
Baclofen intratecal en el tractament de l'espasticitat refractària en l'esclerosi múltiple J. R. Torné and M.A. Poca Servei de Neurocirurgia	10-11-09
Noves estratègies terapèutiques en la raquisquisi neonatal S. Núñez Servei de Neurocirurgia	29-12-08

Table 23
Courses

Courses	Date
Prevención de riesgos por el personal investigador • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/formacio_investigadors_241109.pdf	25/11/2009
Gestión y utilización del equipo de protección individual (EPI) • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/epis_201109.pdf	20/11/2009
V Curso nacional de ventilación mecánica • http://www.ventibarna.net/	16-19/11/2009
Prevención de riesgos para el personal auxiliar y celador • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/Riscos_231009.pdf	23/10/2009
Prevención de riegos para el personal técnico del laboratorio (2ª Edición) • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/prevencion_riscos.pdf	19/10/2009
Gestión y manipulación de los productos químicos en el laboratorio • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/productes_quimics_280909.pdf	28/09/2009
Prevención de riesgos en el trabajo con P.V.D • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/pvd_150909%20.pdf	15/09/2009
1ª Edición del curso: Prevención de riesgos para el personal investigador • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/curs_investigadors.pdf	17/06/2009
1ª Edición del curso: Prevención de riesgos para el personal técnico de laboratorio • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/curs_tecnics.pdf	27/05/2009

Table 23
Courses *(Cont.)*

Courses	Date
1ª Edición del curso: Prevención de riesgos en el trabajo con pantallas de visualización de datos (P.V.D.) • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/curs_pvd.pdf	30/04/2009
3ª Edición del curso: Operador de instalaciones radiactivas • http://www.ir.vhebron.net/easyweb_irvh/Activitats/Cursos/OperadorInstalacionsRadioactives/tabid/913/Default.aspx	12-27/03/2009
Amplifica a partir de una única célula y ahorra 25 veces en reactivos con la nueva plataforma de PCR que ha adquirido la UCTS • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/ucts_pcr.pdf	06/03/2009
1ª Edición del curso: Gestión y utilització de los equipos de protección individual (EPI) • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/curs_epis.pdf	05/03/2009
3ª Edición del curso: Gestión y manipulación de los productos químicos en el laboratorio • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/prod_quimics_3a.pdf	27/02/2009
Curso de coordinación y gestión de datos en ensayos clínicos oncológicos • http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/triptic_indscriipciocgdac.pdf	24/02/2009

Table 24
USMIB Teaching

Teaching	Date
Anàlisi crítica de la bibliografia biomèdica	
Tipus de publicacions científiques en biomedicina: Articles originals en recerca bàsica, recerca clínica, assaigs clínics, revisions i tesi Albert Selva Servei de Medicina Interna, HUVH. Redactor en Cap de Medicina Clínica. • Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_biblio_nov.pdf • Presentation: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_011209.pdf	01/12/2009
Llista guia PRISMA: Recomanacions per a la publicació de revisions sistemàtiques i metanàlisis d'estudis que evaluen intervencions en atenció de salut Xavier Vidal Fundació Institut Català de Farmacologia (FICF) Institut de Recerca VHIR. Barcelona • Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_biblio_nov.pdf • Presentation First part: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_101109.pdf • Presentation Second part: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_171109.pdf	10/11/2009 17/11/2009

Table 24
USMIB Teaching *(Cont.)*

Teaching	Date

Bibliografia científica en biomedicina i bibliometria 03/11/ 2009

Elvira Santamaria
Biblioteca. Àrea Materno-Infantil
HUVH. Barcelona

- Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_biblio_nov.pdf
- Presentation: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_031109.pdf

Introducció en el lideratge de projectes de recerca europeus del 7è Programa Marc (FP7). Convocatòria Health 2010

18/06/2009

Manuel Morillas
Gestió de Projectes Europeus
Unitat de Gestió de Projectes VHIR. Barcelona

- Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_180609.pdf
- Presentation and slide: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/presentaciomanel/presenter/index.htm

Cómo tener éxito en la presentación de un proyecto FIS'09

Aspectes pràctics per tenir èxit en la convocatòria FIS'09 2/04/2009

Anàlisi i estudi descriptiu dels projectes d'investigació presentats per l'Institut de Recerca al FIS'08
USMIB (Institut de Recerca VHIR). Barcelona

– *Aspectes formals. Requisits de la convocatòria*
Laura Casado
Unitat de Projectes.
Institut de Recerca VHIR. Barcelona

- Presentation: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_2_FIS09.pdf

– *Factors claus en l'avaluació de projectes de la convocatòria FIS'09*
Antoni Andreu
Grup de Recerca en Malalties Neuromusculars i Mitocondrials.
Institut de Recerca VHIR. Barcelona

- Presentation: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_3_tallerandreu2009.pdf

Aspectes metodològics en la presentació de projectes FIS'09 10/03/2009

Xavier Vidal
Fundació Institut Català de Farmacologia (FICF).
Institut de Recerca VHIR. Barcelona

Eduard Hermosilla
Servei de Medicina Preventiva i Epidemiologia
HUVH. Barcelona

- Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_100309.pdf
- Presentatión: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/taller_100309.pdf

Table 24
USMIB Teaching *(Cont.)*

Teaching	Date
Presentación de proyectos de investigación al CEIC. Memoria del proyecto y redacción de la hoja de información al paciente Lluis Armadans Servei de Medicina Preventiva i Epidemiologia HUVH. Barcelona • Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_100209_B.pdf • Presentation: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/taller_100209_presentacio.pdf • More información: http://www.ir.vhebron.net/easyweb_irvh/ComitesEtics/CEIC/Projectes/tabid/237/Default.aspx	10/02/2009
Investigación con muestras biológicas; requisitos en la Ley de investigación biomédica Lluís Armadans Servei de Medicina Preventiva i Epidemiologia HUVH. Barcelona • Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_240209_B.pdf • Presentation: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_240209_presentacio.pdf • More information: http://www.ir.vhebron.net/easyweb_irvh/ComitesEtics/CEIC/Projectes/tabid/237/Default.aspx	24/02/2009
Proyectos de investigación europea del 7 Programa Marco (FP7)	
Introducción en el liderazgo de proyectos de investigación europeos del 7 Programa Marco (FP7). Convocatoria Health 2010 Manuel Morillas Gestió de Projectes Europeus Unitat de Gestió de Projectes VHIR. Barcelona • Program: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/usmib_270109.pdf • Presentation and slide: http://www.ir.vhebron.net/easyweb_irvh/Portals/0/pdf/7FPhealthto90127_WEB_V3.pdf	27/01/ 2009

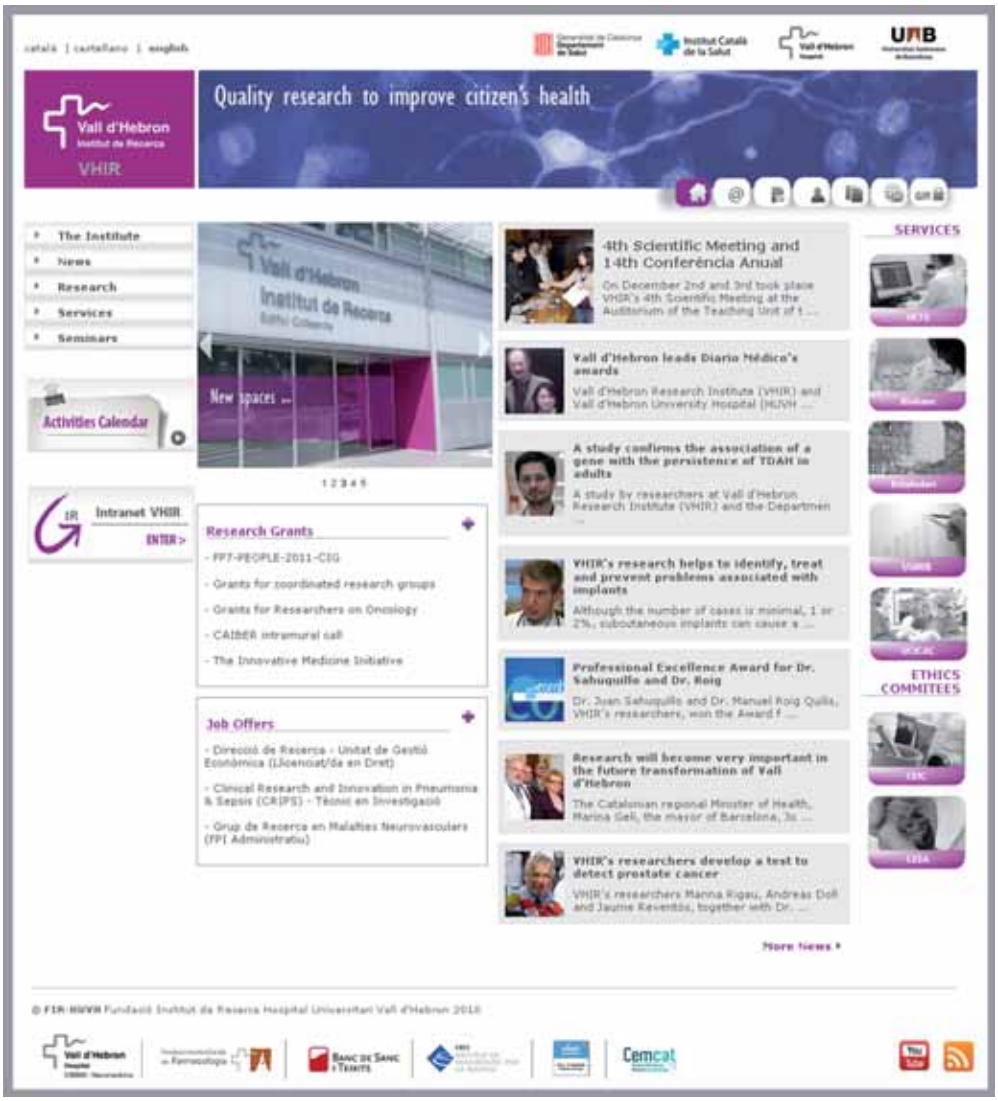
Table 25
UEB Teaching

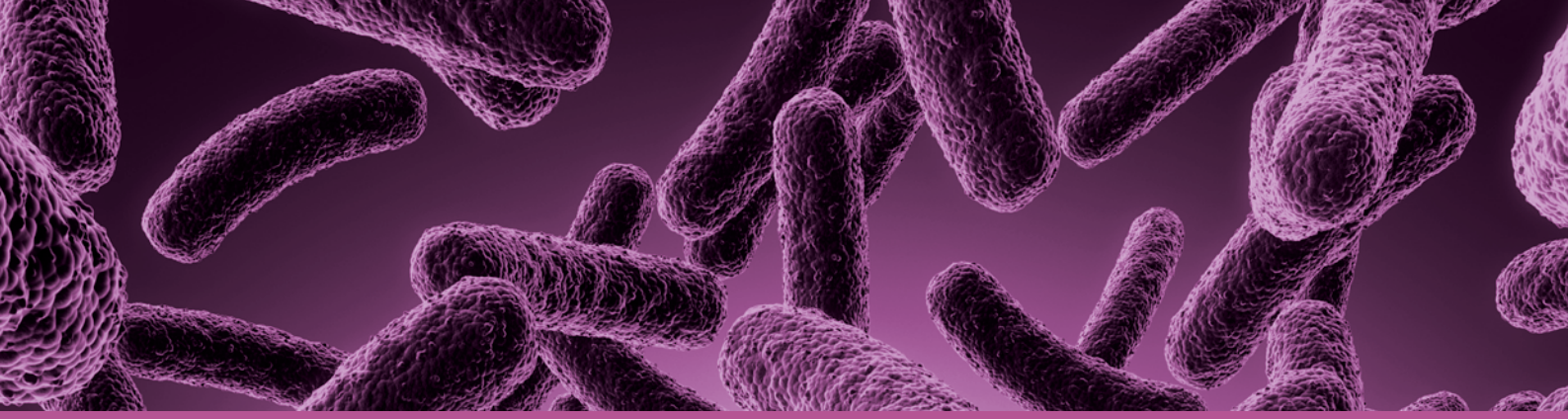
Teaching	Date
Eines bioinformàtiques i estadístiques per a la investigació biomèdica	
Introducció al programa estadístic lliure R/R Commander. Il·lustració d'algunes anàlisis habituals Àlex Sánchez • http://www.ir.vhebron.net/ueb/web/docencia/eines/index.htm	15/4/2009 13/5/2009
Introducció a l'anàlisi de dades amb el programa ingenuity Josep Lluís Mosquera and Àlex Sánchez • http://www.ir.vhebron.net/ueb/web/docencia/eines/index.htm	17/5/2009
Bioinformàtica bàsica. Bases de dades de biologia mol·lecular: cerca i explotació Israel Ortega and Àlex Sánchez • http://www.ir.vhebron.net/ueb/web/docencia/eines/index.htm	16/9/2009
Introducció a l'anàlisi de dades d'alt rendiment amb el programa Partek Genomics Suite Israel Ortega and Àlex Sánchez • http://www.ir.vhebron.net/ueb/web/docencia/eines/index.htm	14/10/2009
Consideracions sobre disseny d'experiments en biomedicina (o com dissenyar un experiment que després es pugui analitzar) Josep Lluís Mosquera and Àlex Sánchez • http://www.ir.vhebron.net/ueb/web/docencia/eines/index.htm	11/11/2009

1.5 VHIR's Website

1.5 VHIR'S WEBSITE

The new website aims to bring VHIR's research activity to society. The information of each group is more accessible, explaining our daily research and illustrating the highlights of our institution, we are opened to the world. English is the predominant language to tell what we do, who we are and which are our short, medium and long term projects. A new design and improved navigation to make it easy and affordable access to information. All Vall d'Hebron's research, all research groups and all researchers, in addition to our scientific activities and all service information. www.vhir.org





2 VHIR Research Activity

Find here all the information related to our 11 research areas. This is the information about our research groups, with their objectives, research lines and scientific production:

2.1 Area 1: Oncology and Genetics Institut de Recerca – VHIO Group

Vall d'Hebron Oncology Research (VHIO)

Group Leader
José Baselga
Tel. 93 274 60 85
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Vall d'Hebron Oncology Research (VHIO)

VHIO was established in 2006 in response to the need to bring together the basic, clinical and translational oncological research activities at the Vall d'Hebron University Hospital campus.

As a cancer center, VHIO is committed to cutting-edge research. The close collaboration between physicians and scientists is one of our unique strengths, and enables us to provide patients with the best care available today as we work to discover more effective strategies to prevent, control, and ultimately cure cancer.

The melding of research with patient care is at the heart of everything we do. At VHIO, ground breaking scientific research flourishes along side with clinical investigation and treatment at Vall d'Hebron University Hospital, one of the largest hospitals within Spain.

VHIO Research Groups

VHIO-Experimental Therapeutics

VHIO-Animal Models

VHIO-Breast Cancer

VHIO-Gastrointestinal Tumors

VHIO-Gene Expression and Cancer

VHIO-Genitourinary, CNS, Sarcoma and Cancer of Unknomwn Primary Site

VHIO-Growth Factors

VHIO-Head, Neck and Gynecological Tumors

VHIO-High Risk and Cancer Prevention

VHIO-Oncogenetics

VHIO-Proteomics

VHIO-Radiation Oncology

VHIO-Stem Cells And Cancer

VHIO-Thoracic Tumors

VHIO-Vall d'Hebron Oncology Research

Impact Factor:

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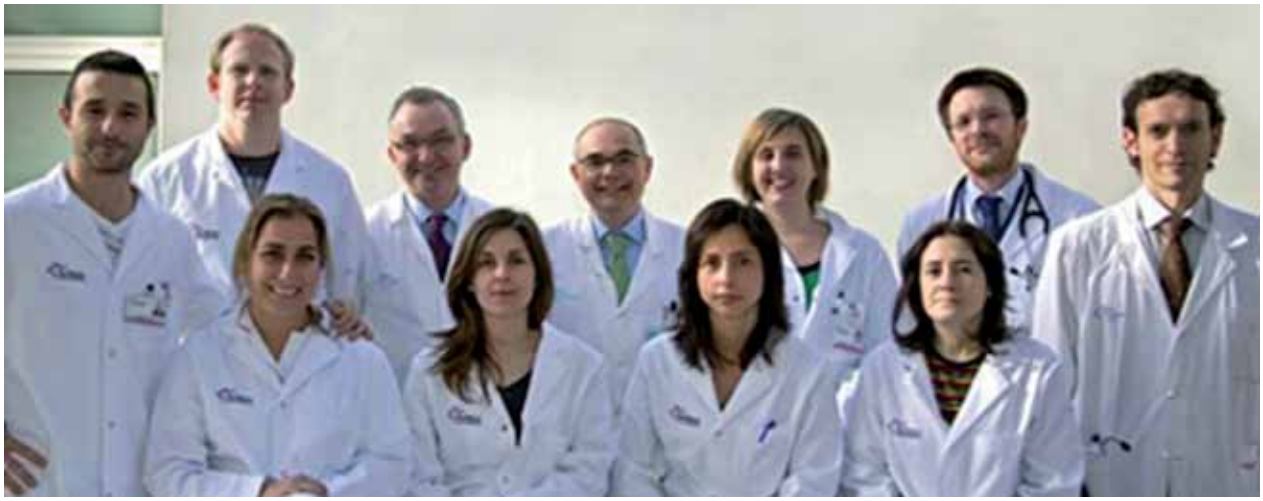
2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Experimental Therapeutics



Group Leader
José Baselga
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Staff Scientist
Maurizio Scaltriti PhD

Medical Oncologists
Jordi Rodón MD
Josep Tabernero MD

Post-doctoral Fellows
Pieter Eichhorn PhD
Celina García PhD
Yasir Ibrahim PhD
Violeta Serra PhD

Visiting Scholars
Michelangelo Russillo MD

Technicians
Pilar Antón
Magui Gili
Marta Guzmán
Olga Rodríguez

Objectives

- Translate to clinical practice the use of *CDK2* and *Hsp90* inhibitors.
- Study the efficacy of novel *Akt/mTOR* inhibitors.
- Predict genes/pathways responsible for resistance to *PI3K/Akt/mTOR* inhibitors.
- Study new therapeutic combinations such as *PI3K/Akt/mTOR* inhibitors with *MEK* inhibitors or *mTOR* inhibitors with anti-IGF-IR agents.
- Develop preclinical models based on tumor explants in immunocompromised mice.

Research Lines

Discovering novel mechanisms of anti-HER2 therapy resistance

Identifying mechanisms of resistance to PI3K/Akt/mTOR inhibitors

Hypothesis-based testing of new therapeutic strategies

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Animal Models

Group Leader
Juan Ángel Recio Conde
Tel. 93 274 60 26
jarecio@ir.vhebron.net

Researchers in Training
Pedro Antonio Andreu Pérez
Neia Naldaiz Gastesi
Ana Carolina Rhodes Cabrerizo

Nursing, Technical and Administrative Staff
Rosa Gil Villaverde

Objectives

LKB1 role in UVB-induced DNA damage response

Our own results and the previous literature revealed the role for *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 its mutational status in human tumors as a predictor of risk.

Protein arginine methylation and signal transduction

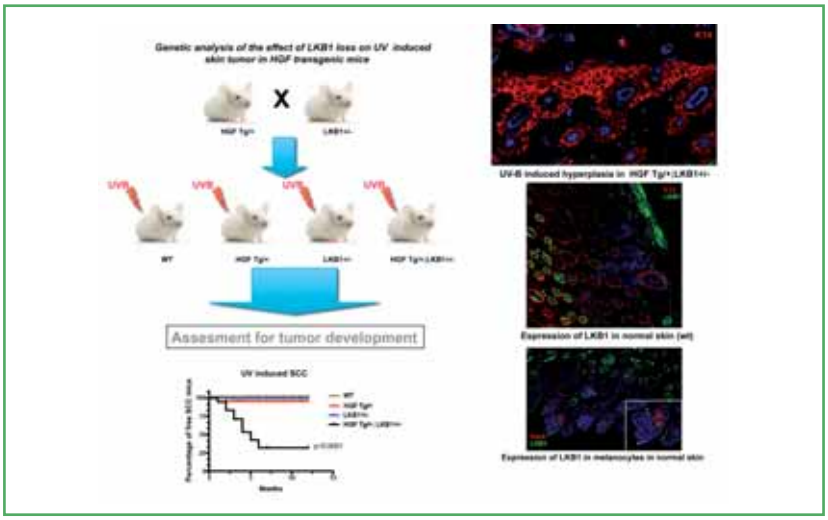
Through our proteomic screening, we revealed a novel regulation in signal transduction mediated by arginine methylation. Our data indicate that this post-translational modification is coordinated with phosphorylation to promote the appropriate biological response. This regulation is ligand-dependent and growth factor specific, adding a novel possible mechanism to explain how the activation of one pathway by different growth factors within the same system leads to a different biological response. We have identified the protein methyltransferase responsible for this modulation and the protein kinase activity regulated by this enzyme. We are currently investigating the role of methylation reactions in different biological responses and the possible deregulation of this mechanism in cancer. We are also investigating the therapeutic capabilities of the methyl-inhibitor Methylthioadenosine (MTA) in melanoma treatment.

Research Lines

Role of LKB1 in tumor biology

Discovery of novel molecules involved in melanoma

Novel therapeutic strategies for melanoma treatment



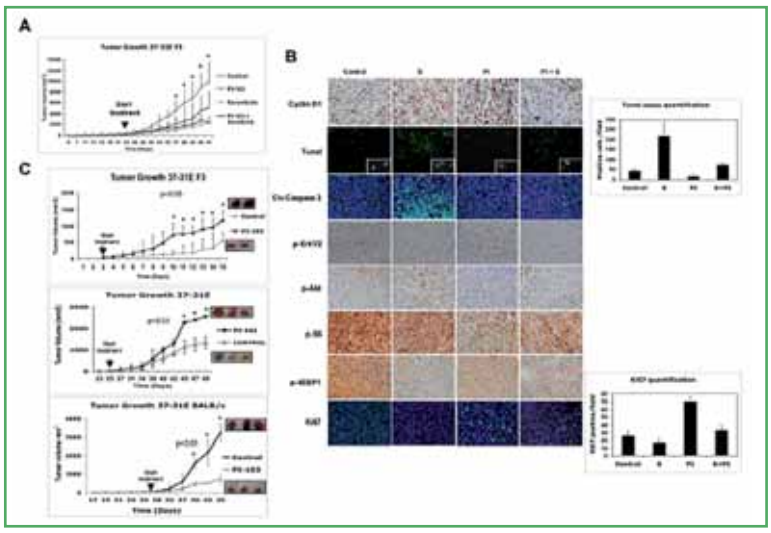


Figure 15
Crossing strategy to generate the HGF Tg/+;LKB1+/- mice to asses tumor development in response to UVB. Representative images of UVB induced skin hyperplasia, expression of LKB1 in normal skin and nuclear localization of LKB1 in melanocytes within the hair follicle

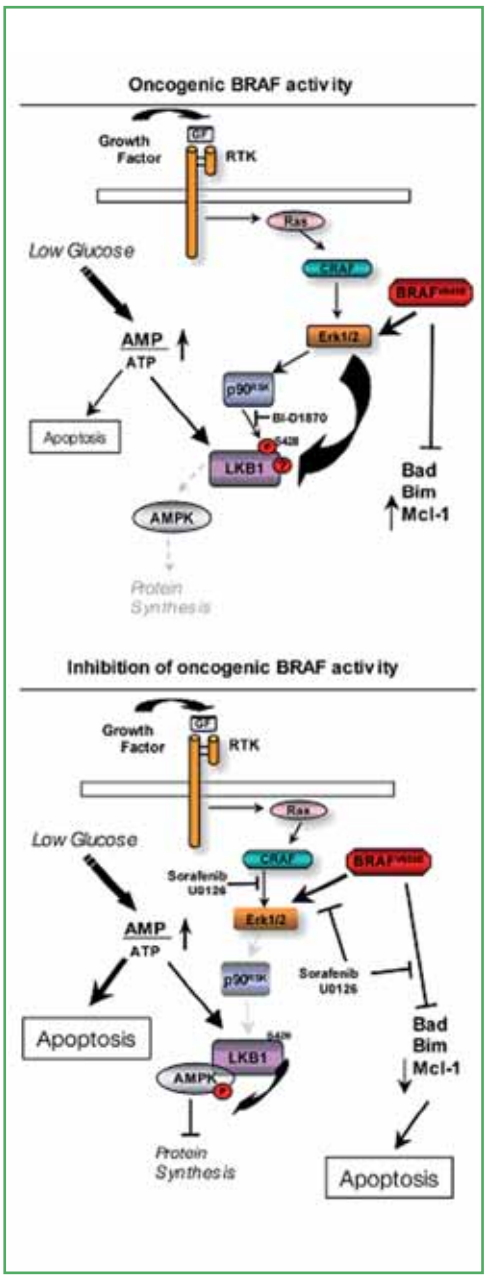


Figure16
A model of the metabolic stress response regulation by oncogenic BRAF in melanoma cells. Resistance to stress conditions is essential for melanoma cells survival. We propose that oncogenic BRAFV600E signaling (left panel) protects to apoptosis by regulating BH3-family members and confers resistance 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

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Breast Cancer

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Cristina Saura

Fellow
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Clinical Trials Coordinators
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.

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 proteomics and genomics platforms and platforms of circulating tumor cells in breast cancer studies.

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Gastrointestinal Tumors

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Teresa Macarulla Mercadé
Manuel Ruiz-Echarri Rueda

Objectives

Clinical Research

The development plans for the near future in the Gastrointestinal Tumors Program consider a as a key feature the integration of more translational endpoints in our clinical research. In this regard the group is participating in clinical trials mainly being carried out by collaborative groups (including the EORTC, the European Gastrointestinal Consortium and preliminary collaborations with US NCI-sponsored groups). The ultimate goal of this approach is to develop new strategies that could help in delimiting which populations of patients would benefit more from new therapeutic strategies with in the vision of "personalized medicine".

Early Clinical Research

The development plans for the next 3-5 years in this setting include preclinical and clinical development of new drugs targeting different cancer properties.

a) Growth signals, including receptors and downstream effectors:

EGFR family, HGF/cMET FGFR, PI3K-Akt-mTOR pathway, Ras-*Raf-MEK-MAPK* pathway, dual *PI3K* and *MAPK* pathway inhibition.

b) Apoptotic signaling: *HDM2 (MDM2)* inhibition.

c) Angiogenesis inhibitors: VEGFR pathway inhibition:

Molecular Markers in Gastrointestinal.

Malignancies: Our main achievement is this area is the set-up of European Consortium leaded by University Hospital Gasthuisberg in Leuven, Belgium and our institution to integrate different platforms for the development of prognostic and predictive biomarkers. This approach includes gene expression signatures as well that ultimately may allow us to define different populations of patients within each tumor type. This population may have different molecular characteristics that could be treated with different therapeutic strategies. In this setting we have applied to different EU calls for the continuation of this Consortium:

- EUFP7 Health 2010 call.
- IMI call. We are applying under different Consortiums to two IMI Efficacy Pillars, Oncology – Molecular Biomarkers and Oncology.
- Imaging Biomarkers

Basic Research

In collaboration with the Cell Signaling and Cancer Laboratory of the VHIO, as well with other International Research Groups:

The goals for the next 5 years are to consolidate our research laboratories and the collaborative projects we have with other Basic and Translational Research Groups. In this regard we are currently doing some experimental projects with the following Investigators/Institutions:

- Yossef Yarden at The Weizman Institute, Rehovot, Israel.
- Jordi Barretina and Mathew Meyersson at The Broad Institute, Cambridge, US.
- Eduardo Vilar and Stephen B. Gruber at The University of Michigan, Ann Arbor, US. Sabine Tejpar at The University of Leuven, Belgium.
- Iris Simon and Renè Bernards at the NKI/Agendia, Amsterdam, Holland.
- John Freshley and Arul Chinnaiyan at Compendia, Ann Arbor, US.
- Steve Shak at GenomicHealth, Redwood City, US.
- Alberto Barrolli, Torino, Italy.

In considering our Cell Signaling and Cancer Laboratories at VHIO, besides the preclinical studies devoted to better characterize new targeted agents in different cancer models we have contributed to setting up three different basic and translational research laboratories with special devotion to gastrointestinal malignancies:

Cancer stem cells

The main interest of this laboratory is to understand the molecular mechanisms that control the initiation and progression of colorectal cancer. In particular, we are focused on studying how rare populations of cancer stem cells retain the ability to perpetuate tumors and how they become the drug-resistant and long term source of cancer self-renewal. The project is leaded by Hector Garcia-Palmer, PhD, previously working at MCRC, London, UK.

Proteomics

The main focus of this laboratory is the discovery of biomarkers and drug targets using the proteomic profiling of sub-proteomes, 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; particularly from the primary culture of tumors. The project is lead by Josep Villanueva, PhD, previously working at MSKCC in New York, US.

Circulating Tumor Cells (CTCs) and Circulant DNA (cDNA) specimens

We are setting-up a platform for collecting CTCs and cDNA for the development of prognostic and predictive biomarkers, with special emphasis on filtration collection techniques.

Research Lines

Clinical research with more translational endpoints

Early clinical research with innovative targets

Collaboration with International Groups for translational research within the context of EUFP7 *and/or IMI calls but also in other settings*

Collaboration with the Proteomics, Genomics, Tumor Stem Cells and Circulating Tumor Cells Groups at VHIO

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Gene Expression and Cancer

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Andrea Sáez Borderías

Researchers in Training
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Alba González Junca
Dermot O'Sullivan
Laura Rodón Ahnert
Ada Sala Hojman
Francisco Torres Grande

Nursing, Technical and Administrative Staff
Alexandra Arias Piñeiro
Mª Isabel Cuartas Maza
Yasmina Mayugo Díez
Eva Paradell Salinas
Carolina Raventós Bernal

Objectives

- Study the role of the *TGFBeta* Shh, Notch and Wnt pathways in glioma.
- Extrapolate our discoveries in glioma to other tumor types.
- Characterize glioma-initiating cells, find new markers to identify them and study their regulation and biology.

Research Lines

Molecular mechanisms involved in the genesis and progression of glioma

Study of glioma-initiating cells, the cells responsible for the initiation, recurrence and resistance to conventional therapies in tumors

Study of the TGFβ *pathway as a therapeutic target in glioma*

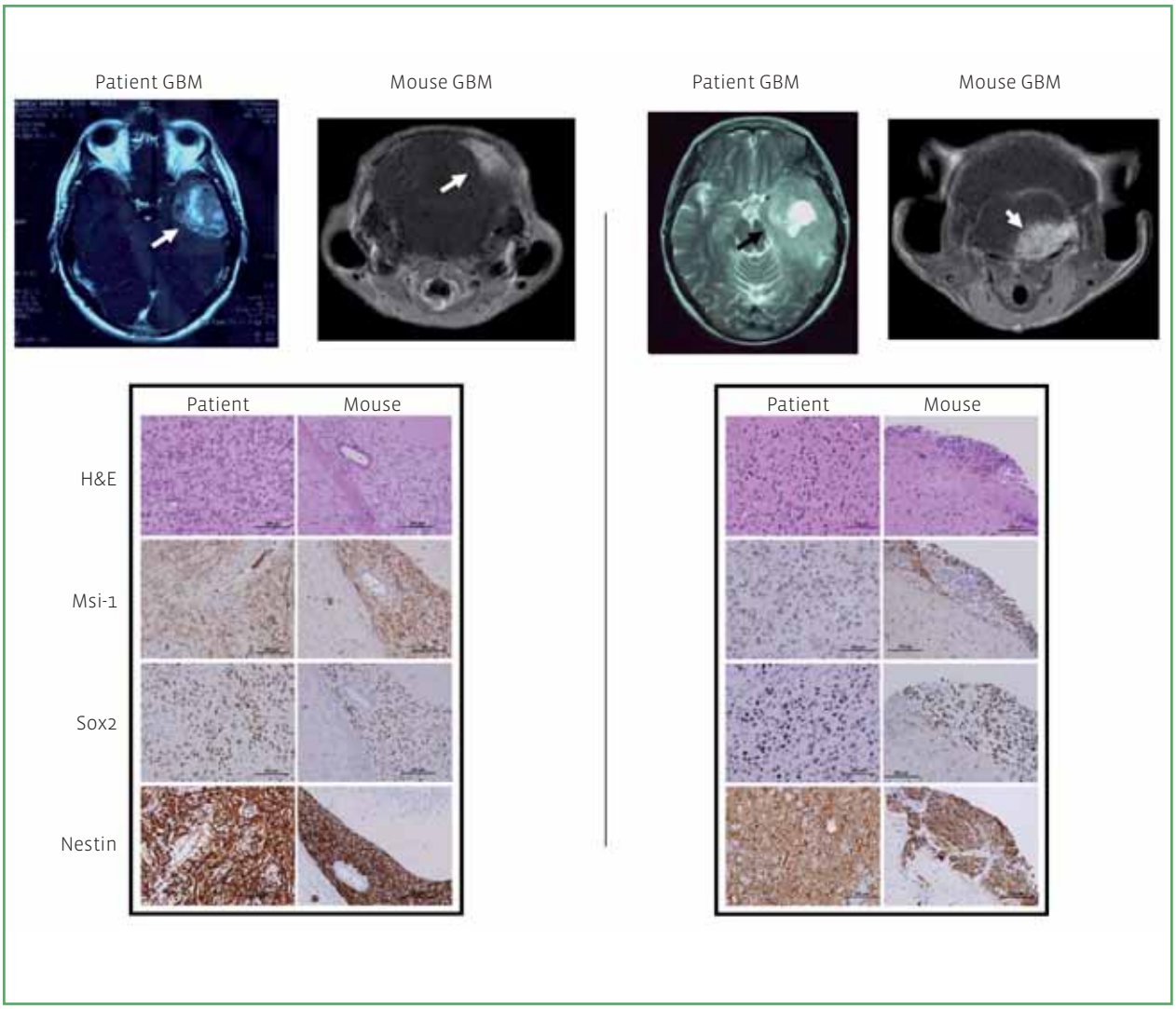

Figure 17
Image of nuclear magnetic resonance and histology of cerebral tumors of patients and their corresponding murins models

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Genitourinary, CNS, Sarcoma and Cancer of Unknomwn Primary Site

Group Leader

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Claudia Valverde

Clinical Fellows
Rafael Morales
Cristina Suárez

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.
- Consolidation of the CNS Committee with the development of several multidisciplinary clinical trials.
- Collaboration with the Spanish Sarcoma Group (GEIS) in order to conduct clinical trials at different stages of the disease with emphasis in 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 joint projects development.

Research Lines

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

Consolidation of the Committee on Nervous System Tumors

Consolidation of the Bone and Soft Tissue Sarcoma Committee

Development of a translational platform in prostate cancer

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Growth Factors

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Researchers in Training
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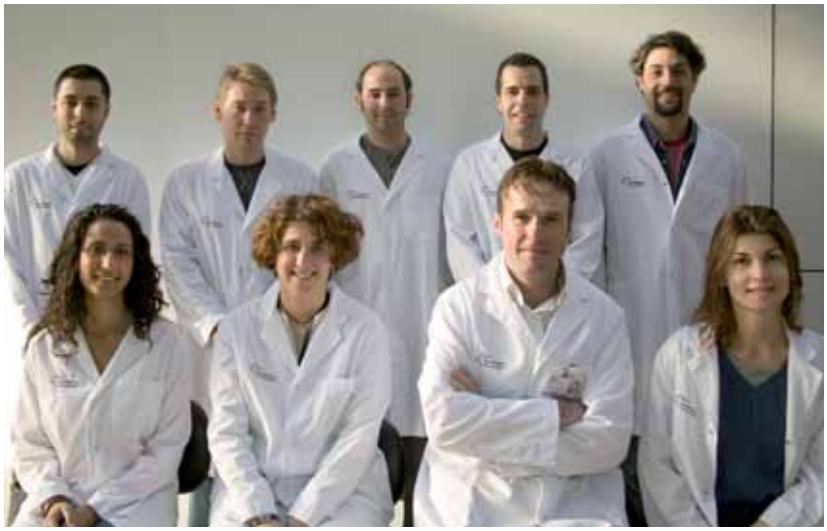
Mercè Fauqued Vázquez
Antonio Luque García
Sandra Mancilla Zamora
Susana Muñiz López
Sandra Porta Martínez
Isabel Vallvé Pardo



Objectives

To identify novel factors and mechanisms involved in the progression of *HER2*-positive breast cancers.

Research Lines

To identify novel mechanisms and factors leading to breast cancer progression

To develop novel anti-tumor therapies and improve current ones

To identify novel biomarkers to better manage breast cancer patients

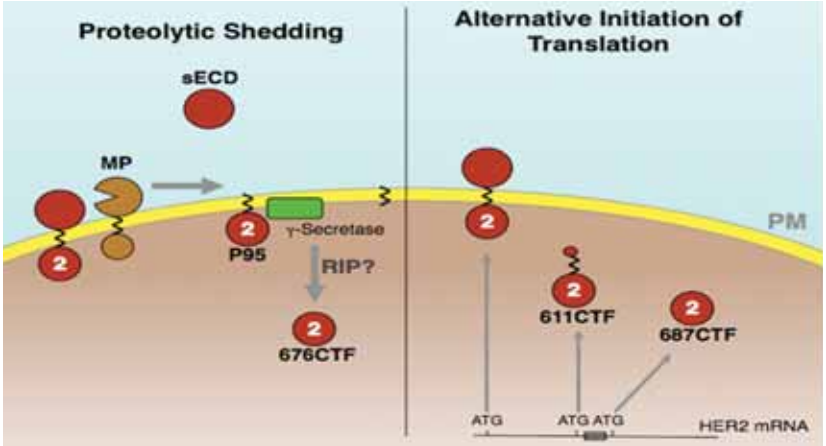


Figure 18
Carboxiterminals fragments (CTF) of HER2 generated by proteolytic processing or initiation of alternative translation

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Head, Neck and Gynecological Tumors

Goup Leader
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Marta Parera

Clinical Trials Coordinators
Cristina González
Mireia Sanchis

Objectives

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

- We will create a regional network of hospitals to facilitate patient access to novel treatments in clinical trials that are currently limited to reference centers.
- We aim to form part of the management structures of the cooperative groups of greatest international relevance (ENGOT, GCIG) and strengthen relations with highly specialized centers in our areas of interest (NCIC, Peter McCallum CC, Irvine MC, HSK Wiesbaden).
- We will develop our own database for each disease, which allows for exhaustive reviews of practical interest and of publishing potential.
- We will increase communications in international forums and publications in impact journals.

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 impact journals

Communications in international conferences

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: High Risk and Cancer Prevention

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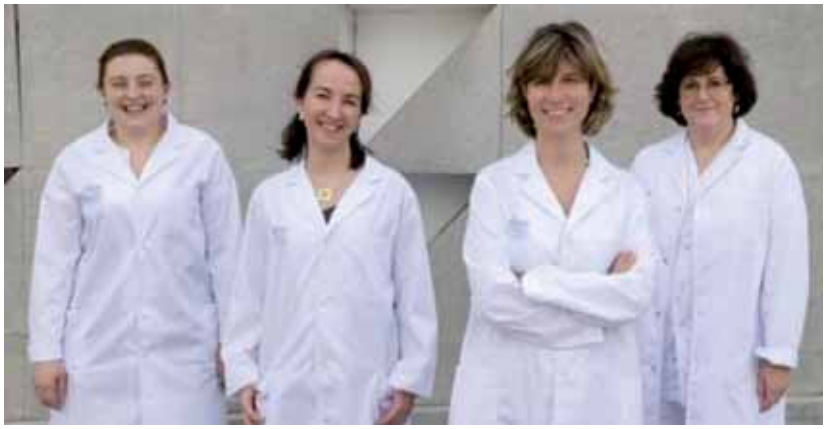
Nina Bosch

Clinical Nurse Specialist
Neus Gadea

Graduate Students
Daniel Fortuny
Irene Valenzuela



Objectives

We are due to validate the *PREMM1, 2,6* predictive model in a cohort of patients with populational endometrial cancer and validate the model in different populations of patients with colon cancer internationally, including a Spanish cohort. We are continuing with the process of developing specific new therapies for patients with hereditary cancer or patients with sporadic cancer and molecular abnormalities similar to those of hereditary cancer. We are expanding the analysis of the long-term psychosocial impact of genetic studies in hereditary syndromes, specifically in the male population. We are taking part in an international study to analyze the efficacy of early detection of prostate cancer in patients with a mutation in the *BRCA2* gene and 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 are scheduled to carry out ultrasequencing studies studies to search for mutations in new genes conferring predisposition to hereditary breast cancer.

Research Lines

Development of the clinical and molecular tools to identify people with suspected Lynch syndrome or hereditary breast and ovarian cancer syndrome associated with BRCA

Analysis of the medical and psychosocial impact of the genetic study of hereditary cancer (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 of adult patients with Fanconi anemia and survivors of other childhood syndromes with genetic predisposition to cancer

2.1 Area 1: Oncology and Genetics Institut de Recerca – VHIO Group

Research Group: Oncogenetics

Group Leader
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Staff Scientist
Sara Gutiérrez Enríquez

Technicians
Miriam Masas Castro
Anna Tenés Felipe

Objectives

- Analysis of variants with unknown biological significance and changes in untranslated regions in *BRCA1 /BRCA2* genes
- We also aim to identify and characterize germ line sequence variants en the *BRCA1*, *BRCA2* and *TP53* genes in breast cancer families

Research Lines

Molecular study of the genetic predisposition to hereditary breast/ovarian cancer

Identification and characterization of mutations and molecular alterations of genes of genetic predisposition to familiar breast/ovarian cancer of (BRCA1 *and* BRCA2, TP53, *among others)*

Identification of new genes for predisposition to familiar breast/ovarian cancer

Analysis of genetic modifiers of risk in BRCA1/BRCA2 *breast/ovarian cancer families*

Study of DNA repair capacity of cells with mutations in BRCA1 *or* BRCA2 *genes*

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Proteomics

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Researchers
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Nursing, Technical and Administrative Staff
Núria Colomé Calls
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Objectives

Continue to explore the role of ADAM and ADAMTS metalloproteases in tumor progression.

- Screening for new cell-surface markers of glioma-initiating cells to aid characterization of tumor heterogeneity and specific features of stem-like cells, such as tumor initiation ability or drug susceptibility.
- Implementing new quantitative proteomic analysis methodologies, such as iTRAQ and label-free strategies.
- Continuing to provide service on state-of-theart proteomic methodologies to other research groups.

Research Lines

Exploring the role of ADAM and ADAMTS metalloproteases in cancer through proteomic analysis

Proteomic screening for new biomarkers to assist cancer therapeutics

Providing services in proteomic techniques to other research groups as core facility

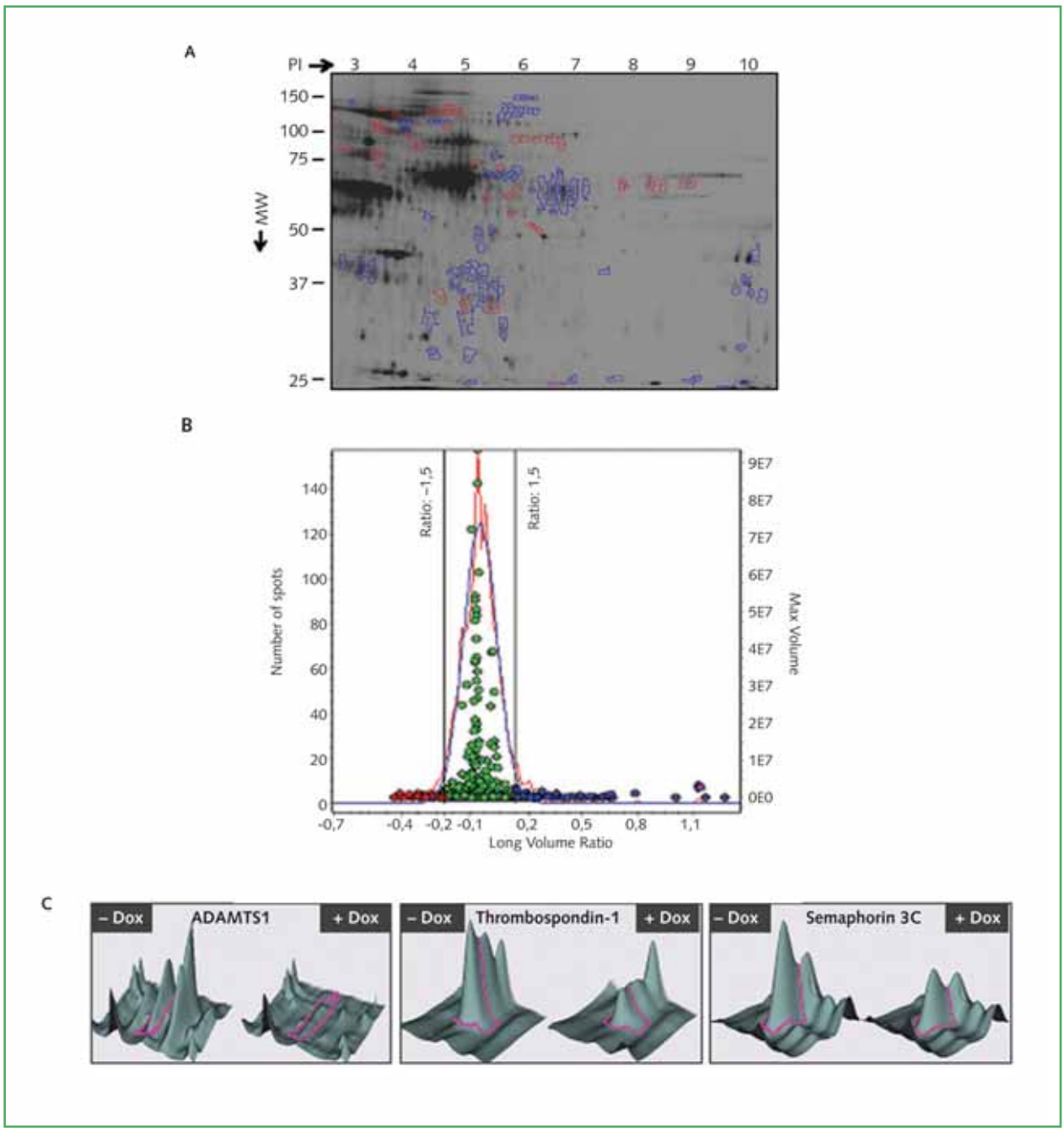
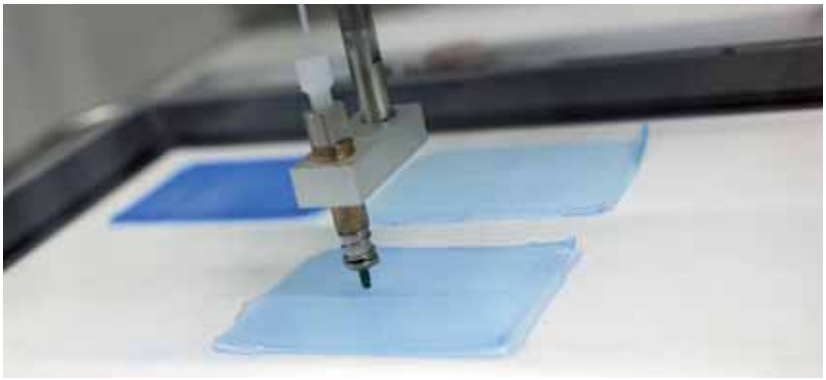
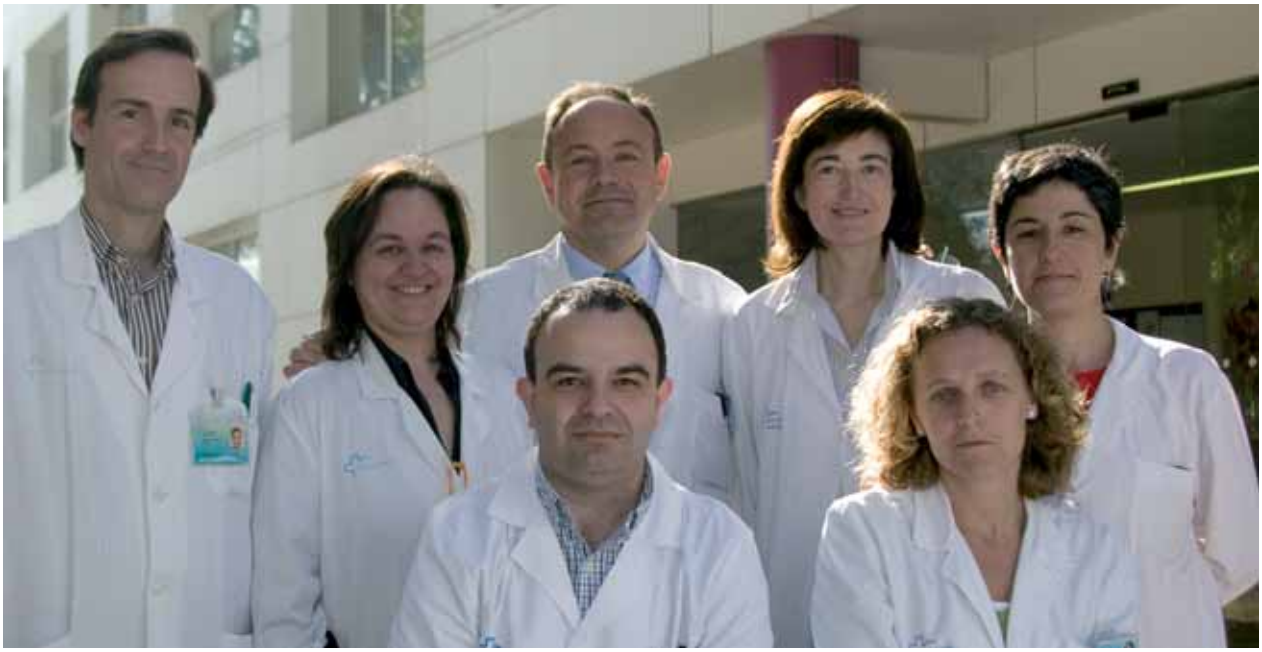


Figure 19
Proteomics analysis of substrata of the ADAMTS1 metaloproteasa in breast cancer cells through 2D-DIGE electroforesis



2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Radiation Oncology



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Ramón Bodi
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Meritxell Molla
Begoña Navalpotro
Mónica Ramos
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Ramona Vergés

Objectives

Continue with the IMRT program in pediatric, gynecology and gastrointestinal tumors.

- Develop the extracranial stereotactic radiotherapy program in lung cancer and liver metastases.
- 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

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Stem Cells and Cancer

Group Leader
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Researchers
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Stephan Tenbaum

Researchers in Training
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Nursing, Technical and Administrative Staff
Irene Chicote Ramos

Objectives

To characterize the gene expression profile specific to the new CoCSC populations described in our laboratory. This screening approach will allow us to identify new molecules specifically expressed by CoCSC, which could become effective biomarkers for predicting tumor progression and response to therapy.

- We plan to finish our first project relating to Wnt/beta-catenin and *PI3K/Akt/FOXO* pathways in colon cancer metastasis.
- Following our results with beta-catenin and FOXO molecular interplay, we will study the relevance of these mechanisms in the acquisition of stem cell properties and resistance to Akt inhibitors.

Research Lines

To describe the key molecular mechanisms responsible for the self-renewal of colon cancer stem cells (CoCSC)

To identify the central molecules responsible for the development of metastasis in colon cancer

To investigate the relevance of novel transcription factors as nuclear effectors of Wnt/betacatenin signal in colon cancer

To test the efficacy of known and new drugs on CoCSC, with special attention to the molecular mechanisms involved in chemoresistance and metastasis

2.1 Area 1: Oncology and Genetics
Institut de Recerca – VHIO Group

Research Group: Thoracic Tumors

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Pablo Martínez

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.
- Study 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 I-III cancer

Early integration of genetic determinations to personalize treatments

Participation in the development of new drugs

Active intervention in the fight against smoking

Current Research Projects Institut de Recerca – VHIO

PI: José Manuel Baselga Torres
Truncated intracellular HER2 C-terminal fragments and trastuzumab resistance
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061647
Funding: 259,545 €
Duration: from 2007 to 2010

PI: José Manuel Baselga Torres
Translating molecular knowledge into early breast cancer management: building on the BIG (Breast International Group) network for improved treatment tailoring Acrònim TRANS-BIGFP6: Network of ExcellenceContract No 503426
Funding Agency: European Comission
Reference: TRANS-BIG-503426
Funding: 0 €
Duration: from 2004 to 2011

PI: J Vicente Arribas López
Identificación del degradoma de la metaloproteasa desintegrina TACE: relevancia en el desarrollo de tumores de mama
Funding Agency: Obra Social "la Caixa"
Reference: BM05-208-0
Funding: 137,000 €
Duration: from 2006 to 2009

PI: J Vicente Arribas López
Identificación de mecanismos y factores involucrados en la sobreexpresión tráfico intracelular de ADAM17 (TACE). Relevancia para el desarrollo de tumores de mama
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/07/2006
Funding: 43,200 €
Duration: from 2007 to: 2010

PI: J Vicente Arribas López
The European Advanced Translational Research Infrastructure in Medicine EATRISGrant Agreement No: 212435
Funding Agency: European Commission
Reference: EATRIS-212435
Funding: 0,00 €
Duration: from 2008 to 2010

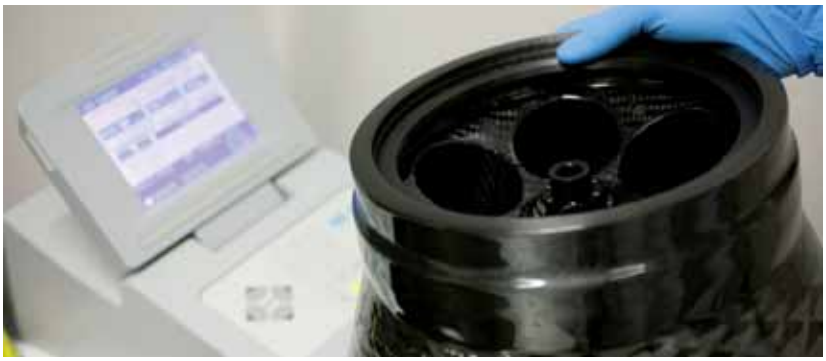
PI: Judith Balmaña Gelpí
Validation and extension of the PREMM model for mismatch repair gene mutations NIH Grant# r01ca132829-01A1
Funding Agency: NIH Consortium
Reference: R01CA132829
Funding: 13,332.79 €
Duration: from 2008 to 2009

PI: Francesc Canals Suris
Identificación y caracterización del degradoma de metaloproteasas implicadas en la progresión tumoral
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP06/00304
Funding: 42,000 €
Duration: from 2007 to 2009

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: PI071058
Funding: 286,770 €
Duration: from 2008 to 2010

PI: Orlando Díez Gibert
Desarrollo de un modelo predictivo de detección de mutaciones en los genes BRCA1 y BRCA2 en población española con sospecha de cáncer de mama familiar
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/03/2008
Funding: 14,000 €
Duration: from 2008 to 2010

PI: Sara Gutiérrez Enríquez
Identificación de genes predictores de susceptibilidad a los efectos secundarios de la radioterapia en cáncer de mama mediante estudios de variantes genéticas y expresión genómica
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI052181
Funding: 102,340 €
Duration: from 2006 to 2009



PI: Sara Gutiérrez Enríquez
Cáncer de mama y ovario hereditario: estudio de perfiles de expresión génica y proteómica de linfocitos irradiados como factor predictivo
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/09/2008
Funding: 40,000 €
Duration: from 2008 to 2011

PI: Juan Ángel Recio Conde
Mecanismos de actuación del Factor de Crecimiento Hepático (HGF) en la adquisición y progresión del melanoma cutáneo: aplicación del modelo animal de melanoma maligno basado en ratones transgénicos del HGF
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI050227
Funding: 171.360 €
Duration: from 2006 to 2009

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: from 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: from 2009 to 2011

PI: Joan Seoane Suárez
Role of FoxG1 in glioma
Funding Agency: Association for International Cancer Research
Reference: AICR 06-349
Funding: 159,424.12 €
Duration: from 2006 to 2009

PI: Joan Seoane Suárez
Papel del TGT-beta en la capacidad de auto-regeneración de las células madre tumorales del glioma
Funding Agency: Fondo de Investigación Sanitaria
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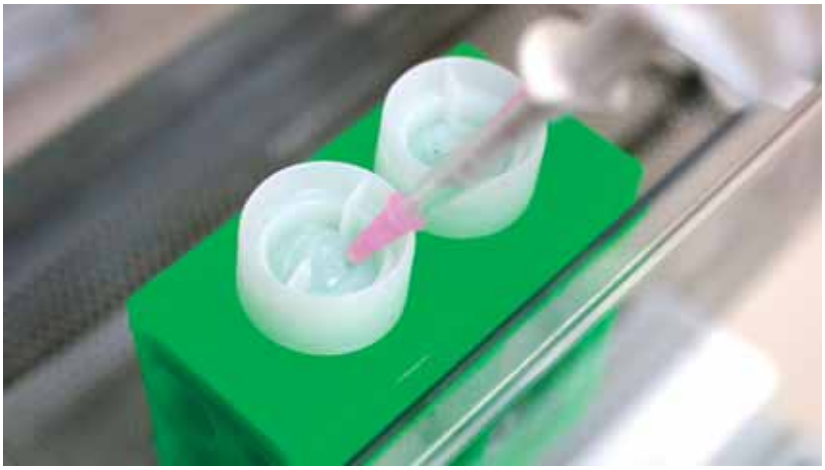

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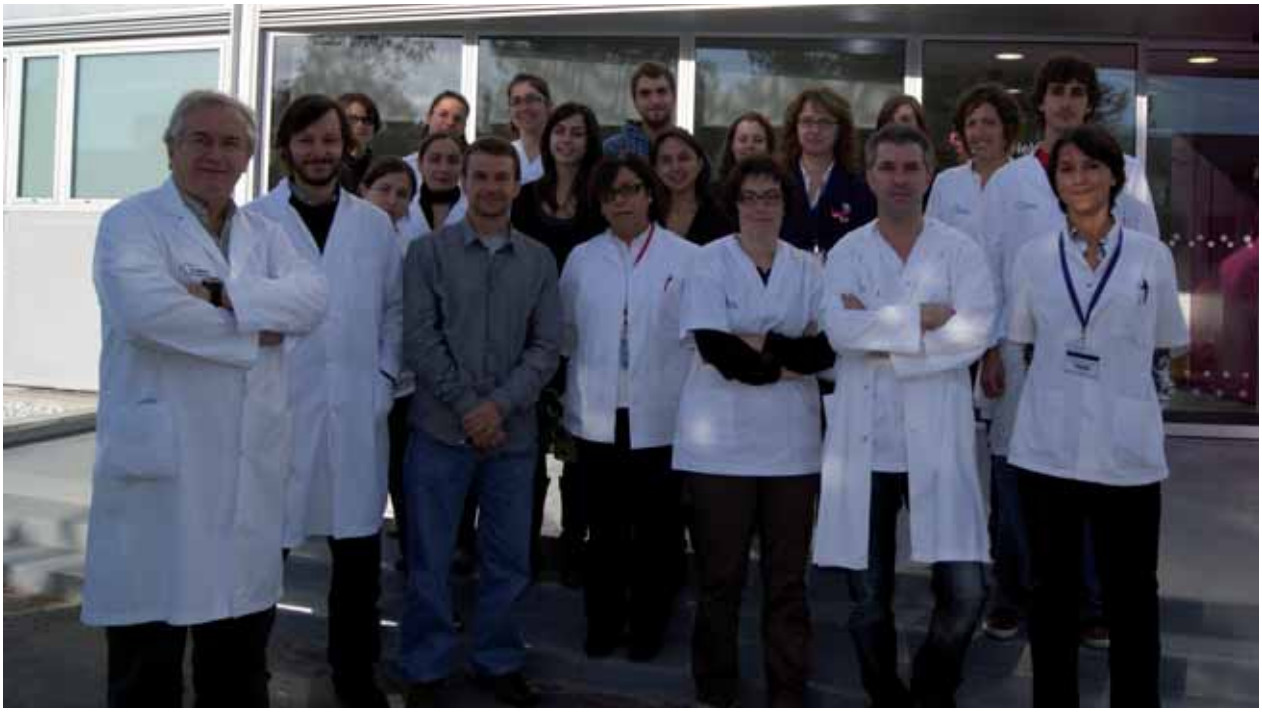
2.1 Area 1: Oncology and Genetics

Research Unit in Biomedicine and Translational and Pediatric Oncology



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Research Laboratories

A) Laboratory of Translational Urological Research

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 tumors. 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 the 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.

Group Leader
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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 determine 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 can help to circumvent the low specificity of the currently-used PSA serum measurements. We use liquid chromatography, mass spectrometry and triple quadruple 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 develop humanized animal models for metastatic prostate cancer able to mimic the human dissemination of PC cells to the 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*

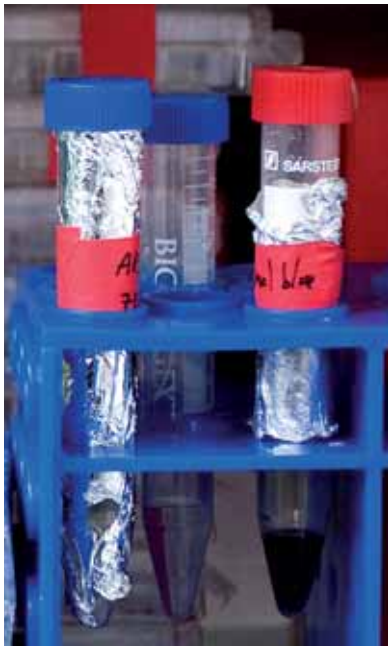
  By analyzing the changes in protein expression levels by proteomics in the metastases obtained from this animal model, we examine whether the reinjection of bone metastasis cells affects the specificity or phenotype, due to reprogramming. We attempt to identify the factors that attract human prostate 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. Less 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 microenvironmental 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: a) an invasive and migratory phenotype, b) expression of epithelial-mesenchymal transition genes and c) 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 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, 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: a) our data support the notion that PIA may be considered a premalignant lesion, and b) 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 on prostate cancer

Decrease of plasmatic levels of testosterone produced by androgen deprivation alters indirectly 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 on prostate cancer

The cardiovascular mortality is the leading cause of death in patients with prostate cancer and it is believed that the 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 the androgen deprivation on prostate cancer

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

High grade intraepithelial neoplasia and prostate cancer

High grade intraepithelial neoplasia is the preneoplasics prostate cancer damage. Nevertheless, it is unknown the molecular mechanisms who define his neoplasic transformation or his persistance as high grade intraepithelial neoplasia isolated. A high grade intraepithelial neoplasia detection in a prostatic biopsy entails a repeat biopsy strategy not clearly stablished. This research line integrates the analysis of molecular predictors of his 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

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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 determinant 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 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 I have shown the involvement of RUNX1 in distant metastasis in endometrial cancer. Using proteomics, I have also shown a series of promising proteins involved in myometrial invasion that are differently expressed between cancer and age-matched uterine tissue. My 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 in 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 presence or absence of ovarian cancer.

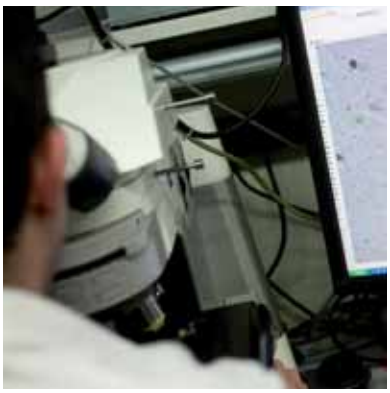
Mechanisms of cancer cell dissemination regulated by ETV5 in ovarian cancer

Previous research in our lab has identified ETV5 as a protein overexpressed in ovarian cancer. We have characterized its role in ovarian tumour progression. Actually, 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 the surgical vs laparoscopic staging and treatment in the primay endometrial cancer (clinical stage I)



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 intra-epithelial neoplasia.
- Results of neo-adjuvant concomitant chemo-radiotherapy in the treatment of locally advanced cervical cancer.
- Validation of robotic assisted and laparoscopic aortic extra-peritoneal 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.

C) Laboratory of Cell Signalling and Cancer Progression

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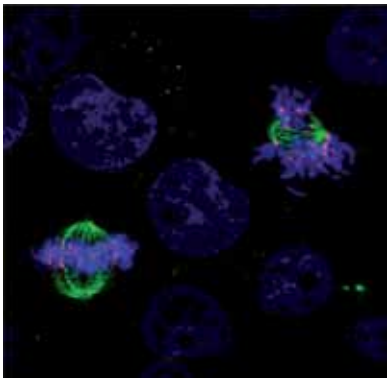
Technician
Raúl Morales

AIM: 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; 3) the relevant targets are further studied to understand their function and mechanisms of action on major cellular signaling pathways implicated in cancer progression.

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.

Figure 20
HeLa cells depleted of Flotillin-1 by specific siRNA were stained for tubulin (green), kinetochores (red) and DNA (blue) and images captured by confocal microscopy



- 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 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. To this aim, we follow 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 to oncogenesis and progression of carcinomas.

D) Laboratory of Translational Research in Paediatric Cancer

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Pablo Velasco

Research Focus

Malignant neoplasms in children and adolescents are rare diseases with different prognosis and biologic

behaviour. 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 neoplasms. Consequently, paediatric oncologists need new approaches to improve the efficacy of anticancer therapies. The molecular diagnosis, detection of microdisseminated disease and 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 tumours in children: neuroblastoma, Ewing's sarcoma, soft tissue sarcomas, nephroblastoma, brain tumours.
- 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 tumours. Our laboratory is the National Reference Centre for Biological Studies in soft tissue sarcomas, receiving tumour material of most of the cases included in the current therapeutic protocols in Spain.

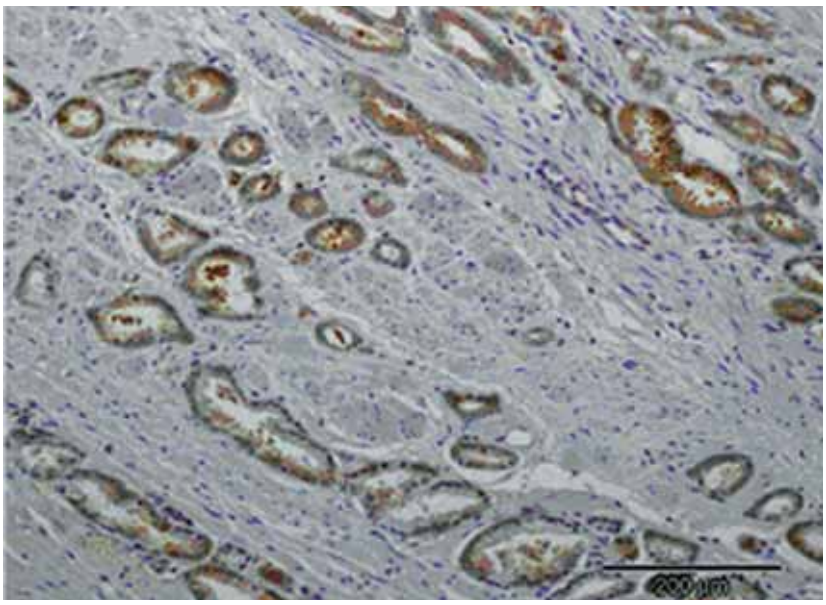


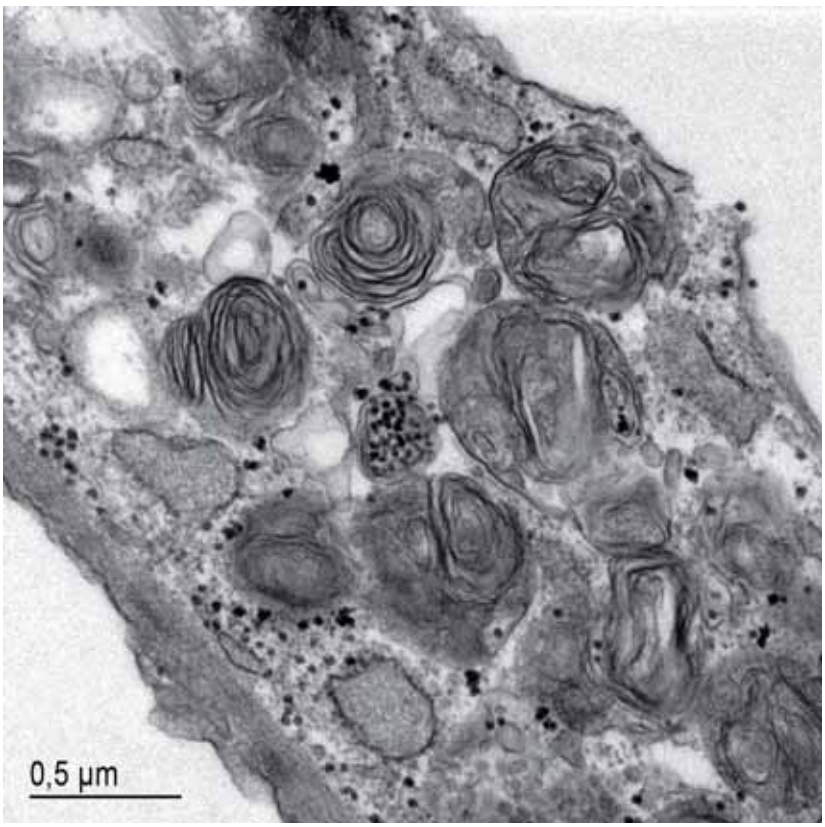
Figure 21
The image shows the expression of the protein PTOV1 in a prostate carcinoma

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 tumour-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 tumours from a single cell. The main objective of this line is to identify and separate tumour-initiating cells in rhabdomyosarcoma tumours and characterise the NOTCH pathway in this subpopulation as a possible candidate for the development of targeted therapies.

Figure 22
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.



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 tumours. 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

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María Teresa Quiles

Research Team
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Marta Rebull

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 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 more 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.

Clinical Research

Simulation and virtual reality

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

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

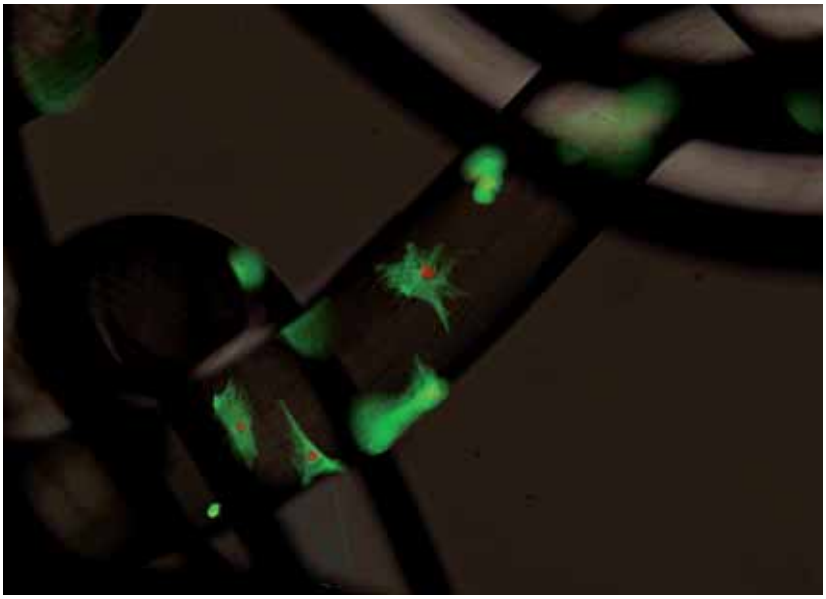

Figure 23
Representative vimentin-stained primary fibroblasts derived from the fascia of incisional hernia patients, grown on polypropylene meshes.

F) Laboratory of Stem Cells and Cancer

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Verónica Pons
Noelia Purroy

Research Focus

The focus of my laboratory is the basic mechanisms that regulate Side Population stem cells. Stem cells reside in most of 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 cells SP, as well as stem cell miRNAs and ABC transporters and the mechanisms by which regulate gene expression and resistance to chemotherapy.

We study the presence of SP cells in human solid tumors, orthotopically implanted in athymic mice as well as the 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 studies 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 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 that 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 the 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 Go 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 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: Miguel Abal Posada
Nuevas estrategias terapéuticas específicas de invasión tumoral y metástasis en cáncer de endometrio
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080797
Funding: 126,566 €
Duration: from 2009 to 2009

PI: 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: from 2008 to 2010

PI: Silvia Cabrera Díaz
Avaluació de teràpies experimentals contra el càncer d'endometri en models animals ortotòpics
Funding Agency: Mutual Mèdica de Catalunya i Balears
Reference: MMCB/02/2008
Funding: 3,000 €
Duration: from 2009 to 2009

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: from 2008 to 2010

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: from 2008 to 2010

PI: Joan Morote Robles
Identificación de marcadores proteómicos en orina para la detección precoz del cáncer de próstata
Funding Agency: Fundación Investigación Urología
Reference: FIU_01_2007
Funding: 18,150 €
Duration: from 2008 to 2010

PI: Francina Munell Casadesús
Mecanismos moleculares responsables del desarrollo de resistencia a los andrógenos en el cáncer de próstata. Identificación de marcadores predictivos de progresión y de respuesta al tratamiento
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI052684
Funding: 90,440 €
Duration: from 2006 to 2009

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: from 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: from 2009 to 2011

PI: Jordi Pétriz González
Caracterización de células madre de la Side Population de origen fetal y placentario
Funding Agency: Fundació Santiago Dexeus Font
Reference: FSDF_01_2007
Funding: 6,000 €
Duration: from 2007 to 2009

PI: Jordi Pétriz 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: from 2008 to 2010

PI: Jordi Pétriz 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: from 2009 to 2011

PI: Verónica Pons Escoll
Identificación y caracterización de células madre de la Side Population en leucemias agudas. Papel en la resistencia a la quimioterapia
Funding Agency: Mutual Mèdica de Catalunya i Balears
Reference: MMCB_04_2007
Funding: 3,000 €
Duration: from 2008 to 2009

PI: Jaume Reventós Puigjaner
Investigación y desarrollo de productos y tecnologías de diagnóstico-pronóstico y aplicaciones terapéuticas en la enfermedad neoplásica
Funding Agency: Ministerio de Industria Programa CENIT (CDTI), empresa farmacéuticas y de biotecnología
Reference: CENIT/01/2006
Funding: 249,550 €
Duration: from 2006 to 2009

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

Publications

Impact Factor: 65.481

Castellví J, García A, Ruiz-Marcellán C, Hernández-Losa J, Peg V, Salcedo M, Gil-Moreno A, Ramón y Cajal S. Cell signaling in endometrial carcinoma: phosphorylated 4E-binding protein-1 expression in endometrial cancer correlates with aggressive tumors and prognosis. *Hum Pathol* 2009 Oct; 40 (10): 1418-26. ⇨ IF: 3.322.

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Eixarch H, Gómez A, Kadar E, George M, Martínez N, Espejo C, Pétriz J, Gimeno R, Barquinero J. Transgene expression levels determine the immunogenicity of transduced hematopoietic grafts in partially myeloablated mice. *Mol Ther* 2009 Nov; 17 (11): 1904-9. ⇨ IF: 5.97.

Gallardo F, Lloreta J, Garcia F, Moll X, Baró T, González LA, Morote J, Reventós J, Mogas T. Immunolocalization of androgen receptors, estrogen alpha receptors, and estrogen beta receptors in experimentally induced canine prostatic hyperplasia. *J Androl* 2009 May-Jun; 30 (3): 240-7. ➪ IF: 2.396.

Guillén-Martí J, Díaz R, Quiles MT, López-Cano M, Vilallonga R, Huguet P, Ramón y Cajal S, Sánchez-Niubò A, Reventós J, Armengol M, Arbós MA. MMPs/TIMPs and inflammatory signalling deregulation in human incisional hernia tissues. *J Cell Mol Med* 2009 Nov-Dec; 13 (11-12): 4432-43. ➪ IF: 5.114.

Marotta M, Ruiz-Roig C, Sarria Y, Peiró JL, Núñez F, Cerón J, Munell F, Roig-Quilis M. Muscle genome-wide expression profiling during disease evolution in mdx mice. *Physiol Genomics* 2009 Apr 10; 37 (2): 119-32. ➪ IF: 3.436.

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Monge M, Colàs E, Doll A, Gil-Moreno A, Castellví J, Díaz B, González M, López-López R, Xercavins J, Carreras R, Alameda F, Canals F, Gabrielli F, Reventós J, Abal M. Proteomic approach to ETV5 during endometrial carcinoma invasion reveals a link to oxidative stress. *Carcinogenesis* 2009 Aug; 30 (8): 1288-97. ➪ IF: 4.93.

Monge M, Doll A, Colàs E, Gil-Moreno A, Castellví J, García A, Colomé N, Pérez-Benavente A, Pedrola N, López-López R, Dolcet X, Ramón y Cajal S, Xercavins J, Matias-Guiu X, Canals F, Reventós J, Abal M. Subtractive proteomic approach to the endometrial carcinoma invasion front. *J Proteome Res* 2009 Oct; 8 (10): 4676-84. ➪ IF: 5.684.

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Morote J, Planas J, Salvador C, Raventós CX, Catalán R, Reventós J. Individual variations of serum testosterone in patients with prostate cancer receiving androgen deprivation therapy. *BJU Int* 2009 Feb; 103 (3): 332-5; discussion 335. ➪ IF: 2.704.

Morote J, Ramírez C, Gómez E, Planas J, Raventós CX, Torres IM de, Catalán R. The relationship between total and free serum testosterone and the risk of prostate cancer and tumour aggressiveness. *BJU Int* 2009 Aug; 104 (4): 486-9. ➪ IF: 2.704.

Pinós T, Barbosa-Desongles A, Hurtado A, Santamaría-Martínez A, Torres I de, Morote J, Reventós J, Munell F. Identification, characterization and expression of novel Sex Hormone Binding Globulin alternative first exons in the human prostate. *BMC Mol Biol* 2009 Jun 17; 10: 59. ➪ IF: 2.81.

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Santamaría-Martínez A, Barquinero J, Barbosa-Desongles A, Hurtado A, Pinos T, Seoane J, Poupon MF, Morote J, Reventós J, Munell F. Identification of multipotent mesenchymal stromal cells in the reactive stroma of a prostate cancer xenograft by side population analysis. *Exp Cell Res* 2009 Oct 15; 315 (17): 3004-13. ➪ IF: 3.948.

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2.1 Area 1: Oncology and Genetics

Research Group: Paediatric Hemato-oncologic Diseases

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Anna Llort
Maria Milà
Teresa Olivé
Marta Pérez Campdepadrós
Sandra Pisa
Constantino Sabado

Objectives

This research group is devoted to translational clinical research in paediatric cancers. The main objectives are the molecular diagnosis, analysis of minimal disseminated disease, search for new molecular therapeutic targets, epidemiology of paediatric cancers in Catalonia, Spain and Europe and clinical haematology and stem cell transplantation.

Research Lines

A) Molecular Oncology

Malignant neoplasms in children and adolescents are rare diseases with different prognosis and biologic behaviour. 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 neoplasms. Consequently, paediatric oncologists need new approaches to improve the efficacy of anticancer therapies. The molecular diagnosis, detection of microdisseminated disease and search for new therapeutic strategies would help to improve the results of the current treatments of paediatric cancer.
Our research group is focused on:

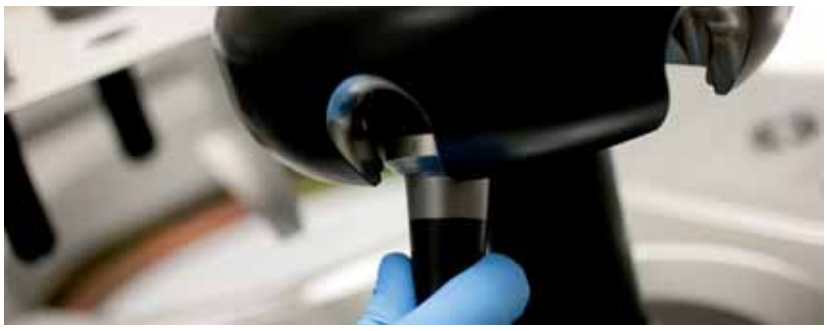
- Molecular diagnosis of malignant tumours in children: neuroblastoma, Ewing's sarcoma, soft tissue sarcomas, nephroblastoma, brain tumours.
- Analysis of the prognostic impact of minimal disseminated disease (MDD).
- Search for new molecular therapeutic targets in children with cancer.

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 tumours. Our laboratory is the National Reference Centre for Biological Studies in soft tissue sarcomas, receiving tumour material of 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 tumour-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 tumours from a single cell. The main objective of this line is to identify and separate tumour-initiating cells in rhabdomyosarcoma tumours 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 tumours. 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.

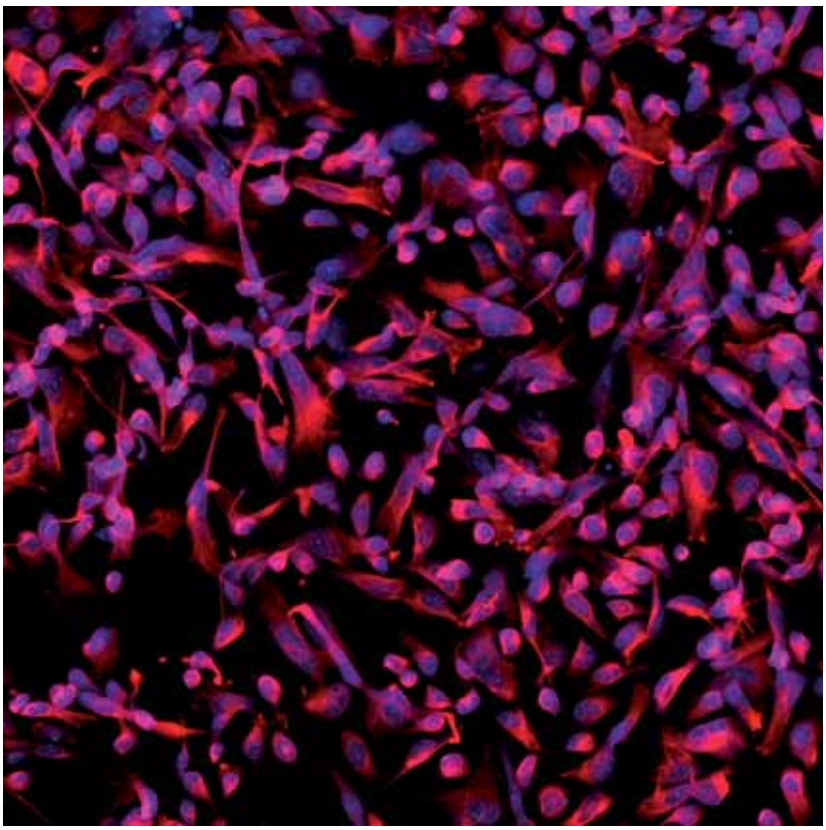


Figure 24
Rhabdomyosarcoma cell line treated with γ-secretase inhibitors, labeled with anti-desmin antibody and Topro-3 nuclear staining

Gene expression profiles in brain tumors
The expression profiles in brain tumors will be analyzed in order to identify new prognostic markers and novel therapies in high grade gliomas, ependimomas and medulloblastomas. This strategy will improve the risk-stratification of patients with these tumors and from this analysis we would find new therapeutic targets to be tested in cell cultures and animal models.

B) Epidemiology

Since 1980, our team has participated in the scientific development of the National Cancer Paediatric Registry. We have studied in depth the epidemiology of paediatric cancers in Catalonia, Spain and Europe.

C) Clinical Haematology and Stem Cell Transplantation (SCT)

Minimal residual disease in SCT
One objective of this line is to study the effect of MRD in children with leukaemia undergoing allogenic SCT.

Generation and differentiation of genetically-corrected induced pluripotent stem cells (iPS cells) in genetic diseases affecting the haematopoietic and immune system
Project involved in UK/Spanish Consortium (CIEMAT, CMRB, HUVH, HNJ, CH London). The objectives of the Project are:

- Generation of genetically-corrected iPS cells from animal models and patients suffering from genetic diseases (Fanconi anemia) of the immuno-hematopoietic system.
- Development of optimized conditions aiming the lympho-hematopoietic differentiation of genetically-corrected iPS cells.
- Development of iPS cell generation and differentiation protocols compatible with their application in the clinics.

Clinical studies in paediatric haematological diseases.

Current Research Projects

PI: Soledad Gallego
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: from 2008 to 2009

PI: Marta Pérez Campdepadrós
Calidad de vida en pacientes pediátricos afectos de tumores en el Sistema Nervioso Central. Papel modulador de las secuelas y de las estrategias de afrontamiento de los padres
Funding Agency: Asociación Española Contra el Cáncer
Reference: AECC 6/2008
Funding: 18,000 €
Duration: from 2009 to 2011

Publications

Impact Factor: 20.658

Arostegui JI, Toledo JS de, Pascal M, Garcia C, Yagüe J, Díaz de Heredia C. A novel G6PC3 homozygous 1-bp deletion as a cause of severe congenital neutropenia. *Blood* 2009 Aug 20; 114 (8): 1718-9. ⇨ IF: 10.432.

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Madero L, Sánchez de Toledo J, Castel V, Sevilla J, González-Esteban J, Sanz-Rodríguez C. Compassionate use study of caspofungin in children with proven or suspected invasive mycosis or persistent febrile neutropenia. *J Chemother* 2009 Apr; 21 (2): 229-31. ⇨ IF: 0.843.

Muñoz A, Díaz de Heredia C, Badell I, Bureo E, Gómez P, Martínez A, Verdeguer A, Pérez-Hurtado JM, Fernández-Delgado R, González-Vicent M, Maldonado MS. Allogeneic stem cell transplantation for myelodysplastic syndromes in children: a report from the Spanish Working Party for Blood and Marrow Transplantation in Children (GETMON). *Pediatr Hematol Oncol* 2009 Jul-Aug; 26 (5): 345-55. ⇨ IF: 0.897.

Negre Busó M, Simó Perdigo M, Roca Bielsa I, Aguadé Bruix S, Sánchez de Toledo J, Castell Conesa J. Differentiated thyroid carcinoma in children: study of 80 cases. *Med Clin* (Barc) 2009 Sep 12; 133 (9): 339-43. ⇨ IF: 1.258.

2.1 Area 1: Oncology and Genetics

Research Group: Molecular Pathology

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César Javier Sevillano Aguilera
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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.

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, are being characterized, at the molecular level, the factors involved in controlling the translation cap dependent and independent in malignant tumors.

Study of gene expression of senescence in human tumors

Santiago Ramón y Cajal Agüeras

The expression of mRNA 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. Also are characterizing the biochemical pathways where these genes may be involved.

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

Stefania Landolfi

Studying in 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 inestability.

Study of new genes involved in proliferation

Matilde Esther 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 a 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 process, 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 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 the biopsies from patients with different kinds of tumors collected at the Pathology Department of the Vall d'Hebron Hospital.

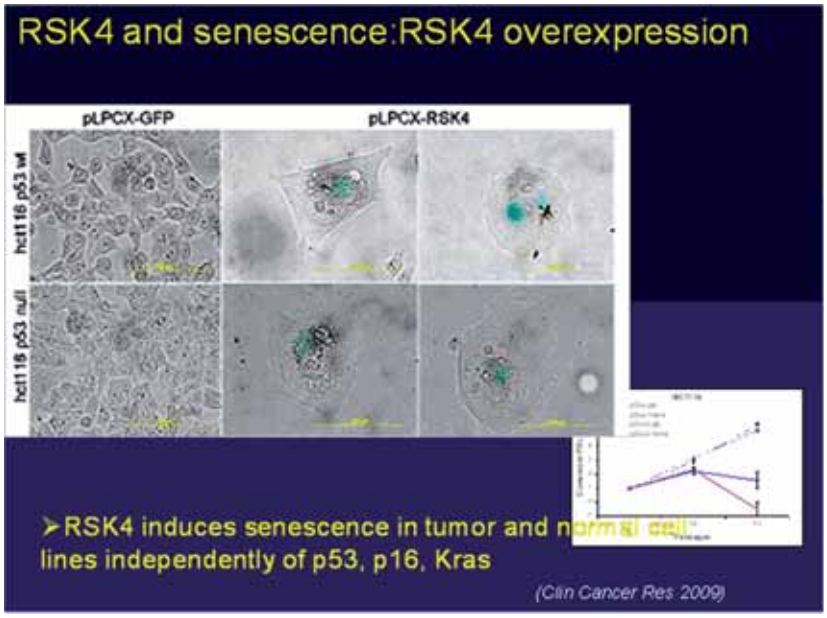


Figure 25
Overexpression of RSK4 induces mechanisms of cellular senescence including X-gal staining

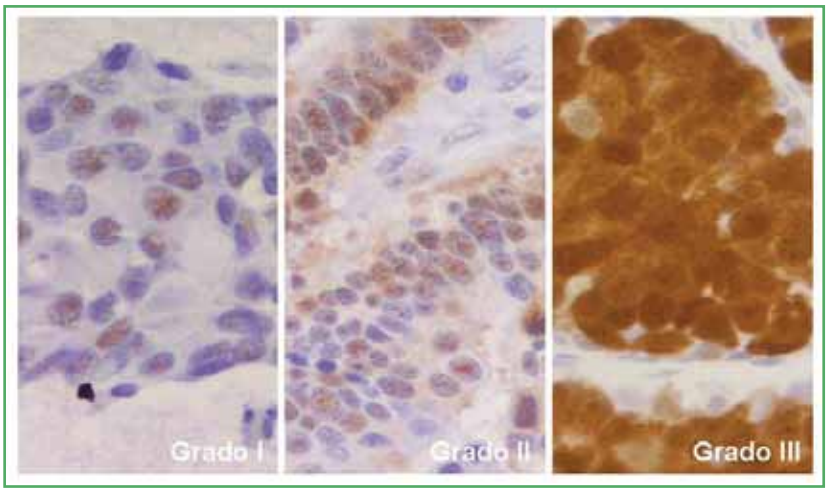


Figure 26
High p-4EBP1 expression correlate with tumoral grade. Immunohistochemistry in breast carcinomas

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 tumoral 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 on tumoral / non-tumoral and co-culture them with monocytes in order to study transcriptional profile changes.

From all the data obtained, overexpressed /underexpressed genes are being identified and validated. Stromal and inflammatory genes also will 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 microinflammation 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 the clinical response. Immunohistochemistry analysis of microinflammation (mast cells, intraepithelial lymphocytes and eosinophils) in Irritable Bowel Syndome (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 **od** 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 nodes 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 patients outcome and, ii) determine the function of hHAVcr-1, which remains elusive, in 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 on 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 Cancer Renal CIBBIM-IRHUVH)

Study of genes involved in genotoxic response in carcinomas

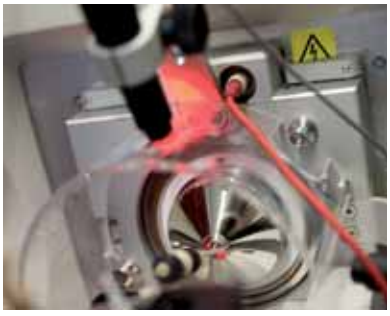
Carlos Parada Cobo

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. In this respect we have found some of this 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 to functions such as DNA damage response, gene expression regulation, 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 triggers in cellular transformation. Within this family receptors, HER1/EGFR and HER2/neu are the best known, being subject to interest other family members like HER3. The aim of the study is establish de 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 the implication of HER3 in the 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 types of skeletal muscle involvement in CF patients who present exercise intolerance and its 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 GSK3β/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 β-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 GSK3β) 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. Besides, 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. These studies will contribute to the development of new therapeutic strategies to prevent age-related neurodegeneratives diseases.

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

Josep Castellví

In previous works we studied several factors involved in cell signalling pathways that control cell growth. The 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 the aggressive tumors show activation of this factor. On the other hand, it has been shown that under hypoxia conditions 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-depdendent/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 tumours. *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 retroviral constructs recently generated. In cell lines expressing high levels of specific connexins, we knockdown 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 tumour 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 the malignancy, prognosis, chemoresistance and overall survival in a variety of cancers 2) Gain mechanistic insight and identify direct functional roles of connexins and pannexins during tumour progression.

Current Research Projects

PI: Javier Hernández Losa

Papel de HER3 en la carcinogénesis de tumores de mama y endometrio. Búsqueda de nuevos factores predictivios de respuesta a tratamientos anti-HER

Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMM2009/02
Funding: 49,200 €
Duration: from 2009 to 2011

PI: Matilde Lleonart Pajarín

Imiten les cèl·lules canceroses l'estratègia de les cèl·lules mare embrionàries per ser immortals?

Funding Agency: Fundació La Marató de TV3
Reference: TV3/052130
Funding: 221,100 €
Duration: from 2006 to 2009

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: from 1997 to 2009

PI: Santiago Ramón y Cajal Agüeras
Estudio e identificación de nuevos genes de senescencia y factores pivotales o comodines en señalización celular, angiogénesis e invasividad en carcinomas humanos: correlación clínico-patológica
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI050818
Funding: 102,340 €
Duration: from 2006 to 2009

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: from 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 deRSK4 en senescencia
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080143
Funding: 147,862 €
Duration: from 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: Ministerio de Ciencia e Innovación
Reference: CENIT2009/01
Funding: 356,298.75 €
Duration: from 2009 to 2012

PI: Cleofé Romagosa Pérez-Portabella
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: from 2008 to 2010

Publications

Impact Factor: 170.860

Artero-Castro A, Callejas FB, Castellví J, Kondoh H, Carnero A, Fernández-Marcos PJ, Serrano M, Ramón y Cajal S, Lleonart ME. Cold-inducible RNA-binding protein bypasses replicative senescence in primary cells through extracellular signal-regulated kinase 1 and 2 activation. *Mol Cell Biol* 2009 Apr; 29 (7): 1855-68. ⇨ IF: 5.942.

Artero-Castro A, Kondoh H, Fernández-Marcos PJ, Serrano M, Ramón y Cajal S, Lleonart ME. Rplp1 bypasses replicative senescence and contributes to transformation. *Exp Cell Res* 2009 May 1; 315 (8): 1372-83. ⇨ IF: 3.948.

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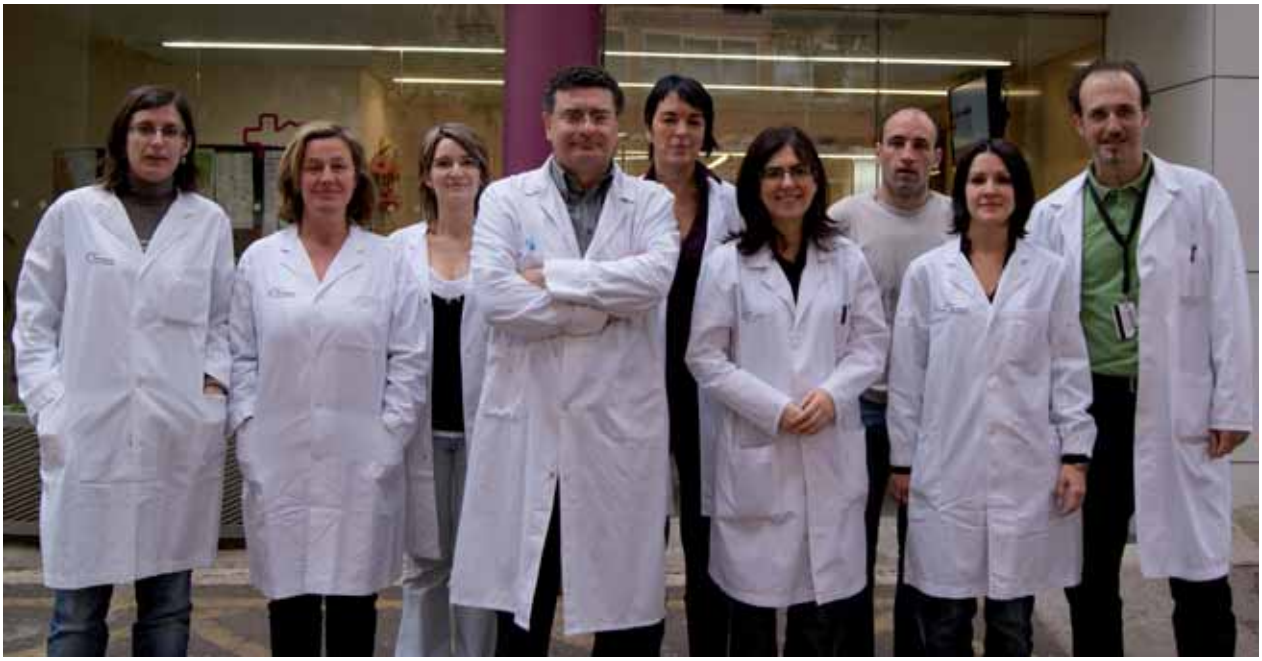
2.2 Area 2: Endocrinology, Growth, Metabolism and Diabetes

Research Group: Diabetes and Metabolism



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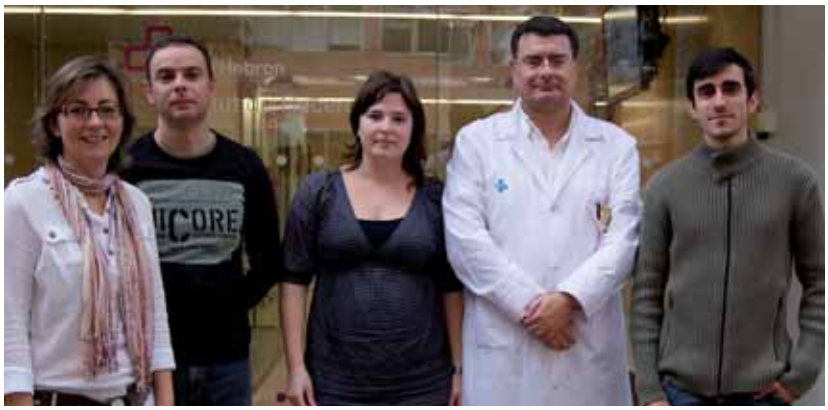
Josep A. Villena Delgado

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

Nursing, Technical and Administrative
Francesc Xavier Duran Sanmartí
Olga Mestres Soler
Rosario Pardo Díaz
Lorena Ramos Pérez

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 also 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 find out 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 new potential drugs for the treatment of diabetic macular edema.
- 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: Rafael Simó Canonge
Mediadores patogénicos del edema macular diabético: exploración de nuevos candidatos mediante análisis proteómico en humor vítrico y cultivos celulares
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2006-05284
Funding: 150,766 €
Duration: from 2006 to 2009

PI: Rafael Simó Canonge
Identification of neurodegenerative mechanisms that promote development of diabetic retinopathy: the role of insulin signalling and apoptosis
Funding Agency: ISCIII.CIBERDEM
Reference: NEURONET-DIAB
Funding: 32,000 €
Duration: from 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: ISCIII.CIBERDEM
Reference: GIDIPRED
Funding: 30,000 €
Duration: from 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: ISCIII.CIBERDEM
Reference: StemOb
Funding: 25,000 €
Duration: from 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: ISCIII.CIBERDEM
Reference: DIASOBS
Funding: 30,600 €
Duration: from 2009 to 2010

PI: Albert Lecube Torelló
Síndrome de apneas-hipoapneas del sueño en mujeres premenopáusicas con obesidad mórbida incluidas en un programa de cirugía bariátrica. Influencia sobre los factores de riesgo cardiovascular: activación simpática, inflamación y resistencia a la insulina
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060476
Funding: 25,410 €
Duration: from 2007 to 2009

PI: Albert Lecube Torelló
Mediadors patogènics de l'obesitat: Estudi comparatiu i exploració de nous candidats mitjançant l'anàlisi proteòmic del líquid cefalorraquidi
Funding Agency: Societat Catalana d'Endocrinologia i Nutrició
Reference: SCEN_01_2007
Funding: 6,000 €
Duration: from 2008 to 2009

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: from 2009 to 2011

PI: Josep A. Villena
Role of PGC-1b in white adipose tissue and its contribution to the development of obesity and type 2 diabetes
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-03644
Funding: 168,190 €
Duration: from 2009 to 2011

PI: Josep A. Villena
Implication of estrogen-related receptors in the ethiology of diabetic cardiomyopathy: role as potential targets for treatment of diabetic cardiomyopathy
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3/20/2008
Funding: 199,138 €
Duration: from 2009 to 2011

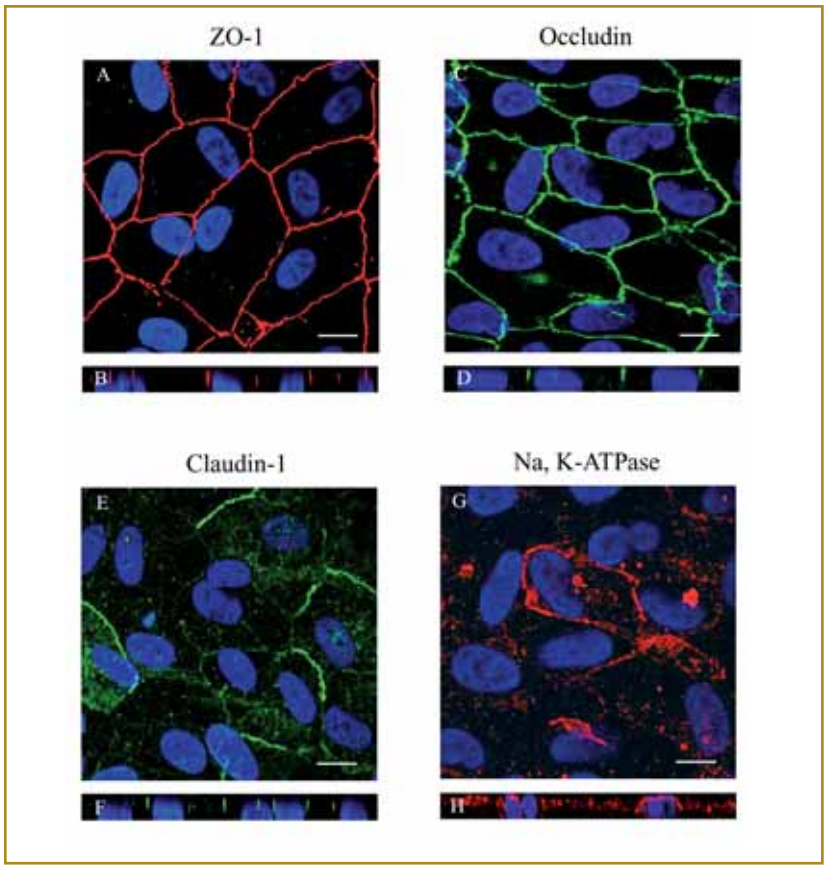
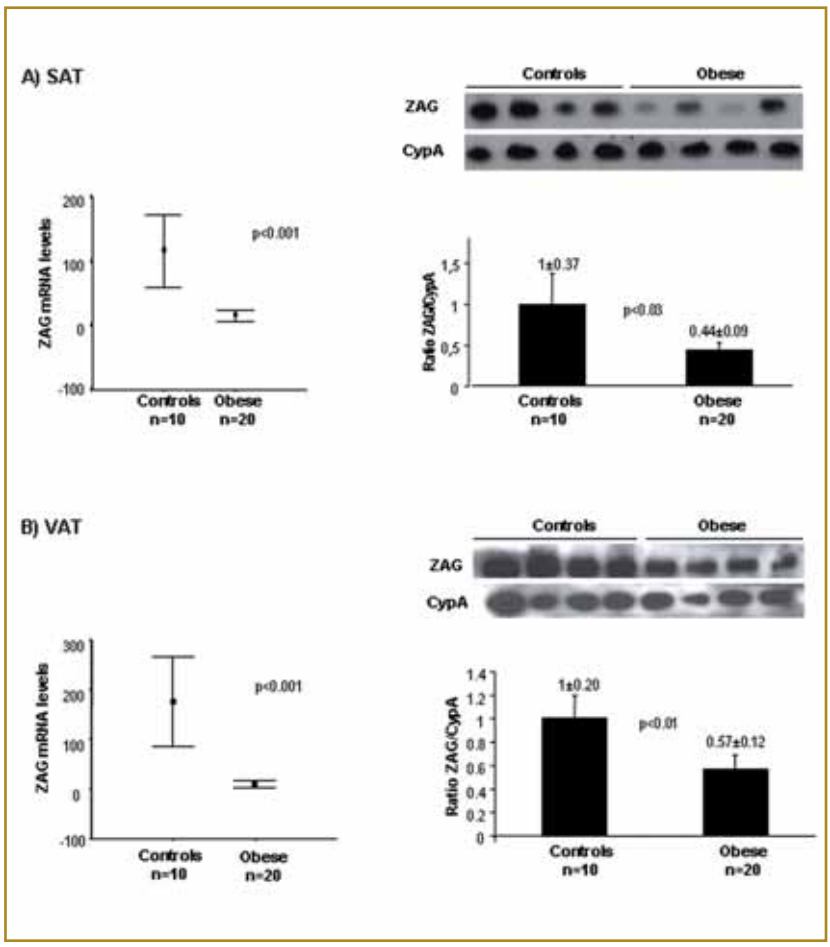


Figure 27
Evidence for tight junctions and polarity in ARPE-19 monolayers. (A) Expression of ZO-1 (C) occludin (E) claudin-1 and (G) Na+/K+ ATPase. Confocal vertical (X-Z) sections showing polarization of ARPE-19 cells. (H) Immunofluorescence of the apical marker enzyme Na+/K+ ATPase and (B) ZO-1 (D) occludin and (F) claudin-1 staining showing apical localization of tight junctions. Bar: 10µm (Published in *Exp Eye Res*)

Figure 28
ZAG levels (mRNA and protein) in subcutaneous (A) and visceral adipose tissue (B). ZAG mRNA levels are expressed as median and CI 25-75%. Protein concentration are expressed as mean ± SD (Published in *J Clin Endocrinol Metab*)



PI: Josep A. Villena
Function of PGC-1a and PGC-1b coactivators in adipose tissue. Implications in obesity and insulin resistance
Funding Agency: Ministerio de Ciencia e Innovación
Reference: RYC-2006-002429
Funding: 183,000 €
Duration: from 2007 to 2012

Publications

Impact Factor: 74.927

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Pardina E, Baena-Fustegueras JA, Llamas R, Catalán R, Galard R, Lecube A, Fort JM, Llobera M, Allende H, Vargas V, Peinado-Onsurbe J. Lipoprotein lipase expression in livers of morbidly obese patients could be responsible for liver steatosis. *Obes Surg* 2009 May; 19 (5): 608-16. ➪ IF: 2.913.

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2.2 Area 2: Endocrinology, Growth, Metabolism and Diabetes

Research Group: Paediatric Endocrinology

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Diego Yeste Fernández

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Laura Audí Parera
Núria Camats Tarruella
Mónica Fernández Cancio
Ester Vilaró Gordillo

Affiliations

- Department of Paediatrics, Hospital Vall d'Hebron.
- Institut de Recerca Hospital Vall d'Hebron (VHIR).
- Autonomous University of Barcelona.
- Grup de Recerca Consolidat by AGAUR (Patologia del creixement)
- Research Group within the Centre for Biomedical Research Network on Rare Diseases (CIBERER) of the Instituto de Salud Carlos III (Ministerio de Ciencia)

Objectives

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

Research Lines

Normal growth and development patterns in children

Antonio Carrascosa

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 autochtonous and immigrant populations. The cross-sectional autochnonous charts comprise those for: newborns from 26 to 42 weeks GA and normal children from birth to 22 years. The longitudinal autochtonous 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

Antonio Carrascosa

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 response 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)

Antonio Carrascosa and Laura Audí

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.

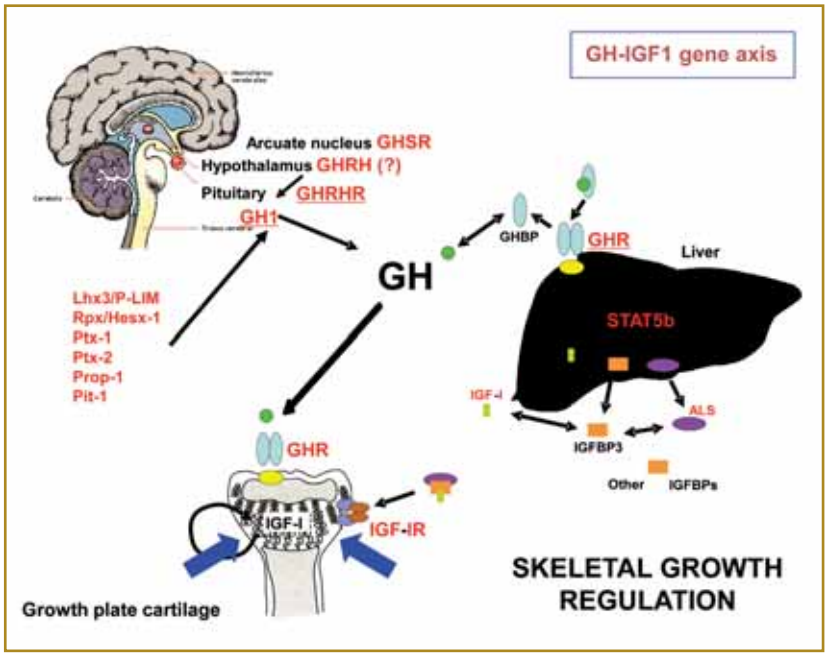
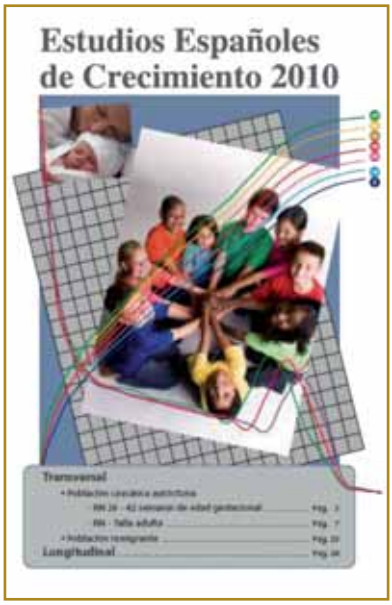


Figure 29
Postnatal skeletal growth regulating genes analysed

Figure 30
Cross-sectional autochnonous growth charts for newborns from 26 to 42 weeks of gestational age and normal children from birth to 22 years.
Growth charts at birth for the immigrant population (children of parents from Magreb, SubSaharan Africa and Central and South America).
Cross-sectional growth charts from birth to adult height for children from Magreb and SubSaharan Africa.
Longitudinal autochtonous growth charts according to age at onset of the pubertal growth spurt (very early, early, intermediate, late and very late)



Human epiphyseal growth cartilage chondrocyte proliferation and gene expression regulation

Antonio Carrascosa, Laura Audí and Mónica Fernández Cancio

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, and vitamin D (VitD) has been well described as a calcium homeostasis regulator and 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

Antonio Carrascosa, Miquel Gussinyé and Diego Yeste

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

Antonio Carrascosa, Diego Yeste and Laura Audí

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

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

Antonio Carrascosa and Marian Albisu

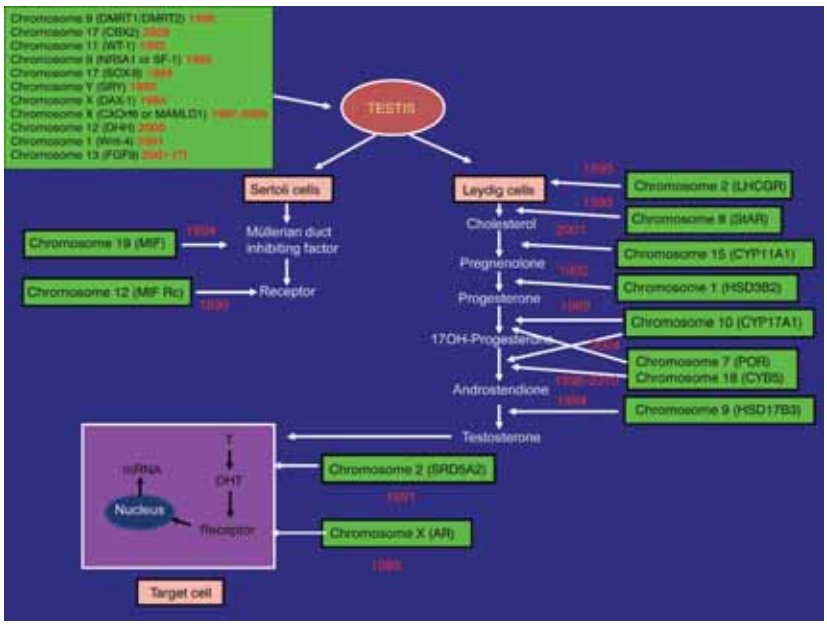
Our Group forms a reference centre for the diagnosis and treatment of congenital hypothyroidism in Catalonia. The approach is multidisciplinary with the collaboration of paediatric endocrinologists, psychologists and the research laboratory. The latter, localized in Hospital La Paz (Madrid) contributes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

Hypothyroxynaemia in extreme preterm infants

Antonio Carrascosa, Marian Albisu and Maria Clemente

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.

Figure 31
Main genes involved in 46,XY male sex development during foetal life with chromosomal location and cloning year



Disorders of sex development (DSD): clinical and molecular diagnosis (AR, SRD5A2, HSD17B3, CYP17A1, NR5A1, MAMLD1)

Laura Audí, Mónica Fernández, Núria Camats and Antonio Carrascosa

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.

Familial isolated glucocorticoid deficiency (FGD) (MC2R, MRAP, StAR genes)

Miquel Gussinyé, María Clemente, Laura Audí, Mónica Fernández Cancio and Núria Camats

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 University Children's Hospital of Berne.

Hyperinsulinism and hypoglycaemia

Miquel Gussinyé, María Clemente and Antonio Carrascosa

Our Group forms a reference centre for the diagnosis and treatment of infants and children with the 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)

María Clemente, Miquel Gussinyé and Antonio Carrascosa

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

Diego Yeste, Norma Irene García, Sandra Gussinyé and Antonio Carrascosa

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 to training medical professional 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

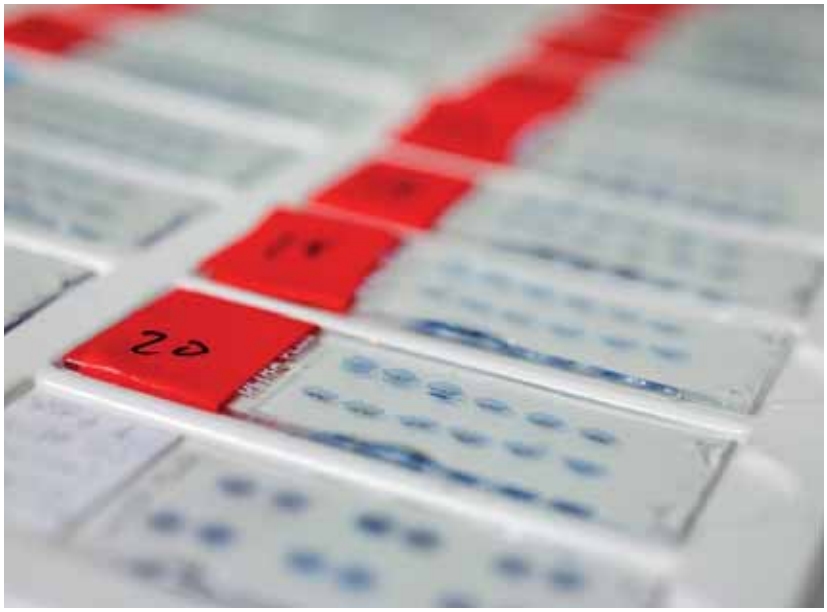
Marcadores moleculares de la acción de los andrógenos: aplicaciones básicas al conocimiento de la regulación de la diferenciación sexual y diagnósticas en el pseudohermafroditismo masculino

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060903
Funding: 125,840 €
Duration: from 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: from 2008 to 2010



Publications

Impact Factor: 9.091

Conway GS, Szarras-Czapnik M, Racz K, Keller A, Chanson P, Tauber M, Zacharin M, Carrascosa A. *et al.* Treatment for 24 months with recombinant human GH has a beneficial effect on bone mineral density in young adults with childhood-onset GH deficiency. *Eur J Endocrinol* 2009 Jun; 160 (6): 899-907. ➪ IF: 3.791.

Fernández-Cancio M, Audí L, Carrascosa A, Torán N, Andaluz P, Esteban C, Granada ML. Vitamin D and growth hormone regulate growth hormone/insulin-like growth factor (GH-IGF) axis gene expression in human fetal epiphyseal chondrocytes. *Growth Horm IGF Res* 2009 Jun; 19 (3): 232-7. ➪ IF: 2.008.

Ferrández A, Carrascosa A, Audí L, Baguer L, Rueda C, Bosch-Castañé J, Gussinyé M, Yeste D, Labarta JI, Mayayo E, Fernández-Cancio M, Albisu MA, Clemente M. Longitudinal pubertal growth according to age at pubertal growth spurt onset: data from a Spanish study including 458 children (223 boys and 235 girls). *J Pediatr Endocrinol Metab* 2009 Aug; 22 (8): 715-26. ➪ IF: 0.938.

Yeste D, Chacón P, Clemente M, Albisu MA, Gussinyé M, Carrascosa A. Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents. *J Pediatr Endocrinol Metab* 2009 Jun; 22 (6): 487-92. ➪ IF: 0.938.

Yeste D, González-Nino C, Pérez de Nanclares G, Audí L, Castaño L, Carrascosa A. ACTH-dependent precocious pseudopuberty in an infant with DAX1 gene mutation. *Eur J Pediatr* 2009 Jan; 168 (1): 65-9. ➪ IF: 1.416.

2.3 Area 3: Cardiovascular Diseases, Hemostasis and Hypertension

Research Group: Cardiovascular Diseases

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Jaume Casaldàliga
Joan Castell Conesa
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Laura Dos Subirà
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Irma Vila Pérez

Administrative Staff
Giuliana Ríos Quiñones

Objectives

The Mission of the Research Group on Cardiovascular (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 multidisciplinar, translational research program including molecular and cellular investigation, clinical studies, and epidemiological and outcome research studies. The group is 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

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:

- Mitochondrial changes and mitochondria-sarcoplasmic reticulum interaction during myocardial ischemia-reperfusion
- Role of Connein43, in particular in its mitochondrial localization in cell death and cardioprotection signalling during ischemia-reperfusion
- Cytoskeletal fragility and calpain activation as a mechanism of reperfusion injury.
- Microvascular injury in reperfused myocardium
- Prevention of LV remodelling by siRNA inhibition in reperfused myocardium
- Effect of ageing on myocardial tolerance to ischemia
- Coadjuvant cardioprotection in patients with STEMI undergoing primary percutaneous coronary intervention
- NMR-based metabolomics in ischemia-reperfusion
- Early resynchronization and cell therapy to prevent adverse remodelling after acute myocardial infarction

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:

- Platelet function in acute coronary syndromes
- Determinants of LV remodelling
- Tissiu factor as a predictor of final infarct size in patients with STEMI receiving primary PCI
- Antithrombotic treatment in patients with high thromboembolic risk receiving coronary stents.

Prognostic stratification of patients with ischemic heart disease by nuclear cardiology

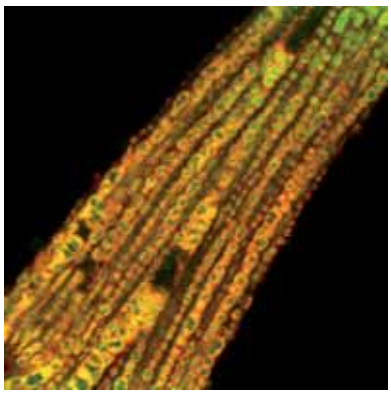
Jaume Candell Riera

This line aims to the development of new methodologies for the evaluation of the functional significance of coronary disease.

Sub-lines:

- Evaluation of non-significant coronary stenoes
- Assessment of myocardial viability
- Prognostic significance of silent ischemia
- Multimodal imaging and 3D image fusion.

Figure 32
Confocal microscopy of isolated cardiomyocytes showing the colocalization of mitochondria (green) and sarcoplasmic reticulum (red)



Myocardial diseases and heart failure

Enrique Galve

Molecular mechanisms of cardiomyopathies and determinants of heart failure.

Sub-lines:

- Genotype/phenotype relation in hyperthrophyc cardiomyopathy
- Analysis of myocardial fibrosis by NMR and new biomakers
- Mitochondrial function in heart failure.

Valvular heart disease

María 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:

- Epidemiology, pathophysiology and treatment of aortic stenosis, with emphasis on trans-catheter aortic valve implantation
- Determinants of the results of surgical treatment of cardiac valve diseases
- 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:

- Diagnostic work-up in syncope
- Pharmacological treatment of syncope
- Predictors of adequate ICD discharge
- Early resynchronization therapy after AMI
- 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:

- Pathophysiology of pericardial syndromes
- Prevention of recidives in patients with pericarditis
- Pericarditis in patients with cancer.

Diseases of the aorta

Artur Evangelista Masip

The general purpose of this line is to improve our understanding of the pathophysiology and natural history of the different forms of acute and chronic diseases of the aorta, including aneurism, ulcer, intramural haematoma 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:

- Diagnostic evaluation of aortic dissection
- Prognostic determinants in aortic dissection
- Intramural haematoma as a new form of aortic disease
- Molecular pathophysiology, pronostic evaluation and treatment of Marphan syndrome

Congenital heart disease

Jaume Casaldáliga and Josep Girona Comas

Studies on the pathophysiology and clinical management of congenital heart diseases from intra-utero life to adulthood.

Sub-lines:

- Pathophysiology and evolution of systemic right ventricle
- Pharmacological treatment in patients with systemic right ventricle
- Chronic volume overload of the right ventricle
- Predictors of arrhythmic events after surgical treatment of TOF
- Remodelling of the right ventricle after surgery
- Consequences of LV outflow obstruction in TGV treated with atrial switch
- Percutanous transcatheter pulmonary valve implantation.

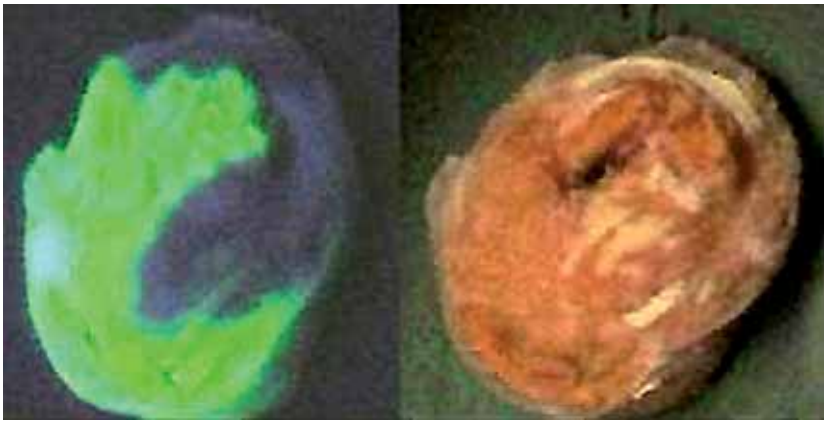


Figure 33
Images of a rat heart section showing the area of ischemia (dark zone, *left*), and the areas undergoing necrosis (pale areas, *right*)

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:

- Variability in clinical practice and long term results of drug eluting stent implantation in Spain
- Evaluation of resources and strategies for myocardial reperfusion in patients with acute myocardial infarction in Spain
- Evaluation of risk stratification algorithms and results in cardiac surgery coronary artery stenting with drug eluting stents
- Quality of life in very old patients with aortic valve stenosis receiving aortic valve prostheses
- Evaluation of Health-care delivery in relation to cerebrovascular disease in Catalonian hospitals
- Evaluation of the social impact of biomedical research in Catalonia.

Current Research Projects

PI: Santiago Aguadé Bruix
Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease. EVINCY-Study
Funding Agency: European Comission
Reference: EVINCY-222915
Funding: 56,266 €
Duration: from 2009 to 2011

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: from 2008 to 2011

PI: Laura Dos
Antagonistas aldosterónicos en el tratamiento de pacientes con ventrículo derecho sistémico: ensayo clínico aleatorizado
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90112
Funding: 195,205 euros
Duration: from 2007 to 2010

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: from 2007 to 2010

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 severa dilatación. Implicaciones terapéuticas
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080608
Funding: 50,578 €
Duration: from 2009 to 2011

PI: Arturo Evangelista
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 euros
Duration: 2009

PI: Ignacio Ferreira González
Interrupción de la doble antiagregación durante el primer año tras la implantación de stent liberador de fármacos: factores determinantes e impacto sanitario
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/90031
Funding: 71,995 €
Duration: from 2008 to 2010

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: from 2007 to 2010

PI: David García-Dorado
Protección miocárdica durante la reperfusión en pacientes con síndrome coronario agudo y 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: from 2007 to 2010

Figure 34
Two hearts with initially similar infarcts (clear zone) with adverse remodelling (dilation and wall thinning, *left*) or without it

PI: David García-Dorado
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: from 2009 to 2013

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: from 2009 to 2011

PI: Àngel Moya Mitjans
Safety, fesaibility 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: from 2008 to 2010

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: from 2007 to 2010

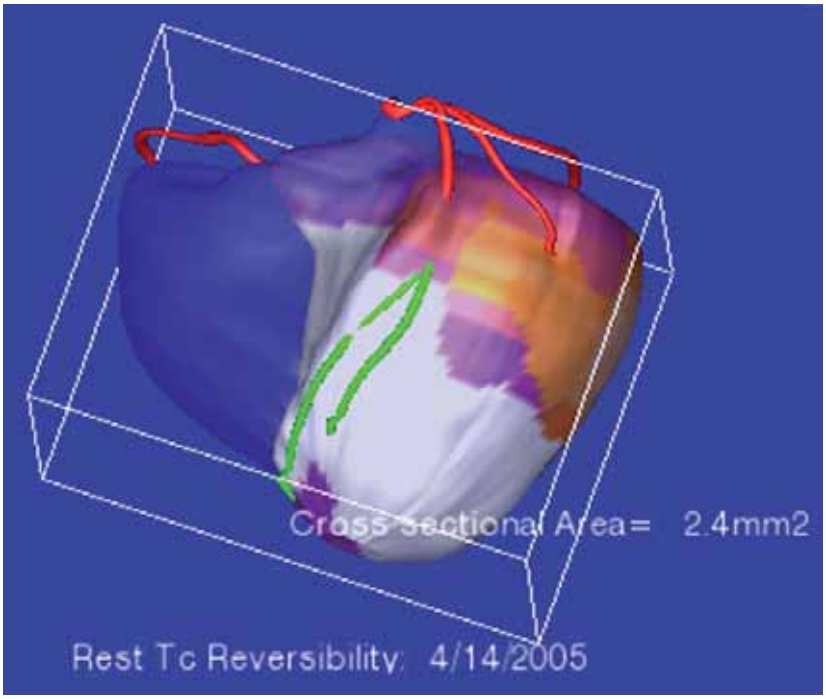


Figure 35
Off-line fusion cardiac imaging showing myocardial perfusion and coronary arteries

PI: Josep Pinar Sopena
Prevalence of degenerative aortic stenosis and aortic sclerosis in the Spanish population
Funding Agency: CNIC
Reference: CNIC-09-02
Funding: 301,530 €
Duration: from 2008 to 2010

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: from 2009 to 2010

PI: Marisol Ruiz Meana
Determinación del papel de la hipercontracción y la apertura del poro de transición mitocondrial como efectores de la muerte celular de cardiomiocitos durante la reperfusión miocárdica
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060996
Funding: 32,065 €
Duration: from 2007 to 2009

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: from 2009 to 2011

PI: Antonia Sambola Ayala
Papel predictor del factor tisular activo en la extensión del infarto agudo de miocardio tratado con angioplastia primaria
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061658
Funding: 22,385 €
Duration: from 2007 to 2009

PI: Pilar Tornos Mas
Degenerative-calcific aortic valve disease: from pathogenical to epidemiological characterization
Funding Agency: CNIC
Reference: CNIC-09
Funding: 415,955 €
Duration: from 2008 to 2012

Publications

Impact Factor: 331.301

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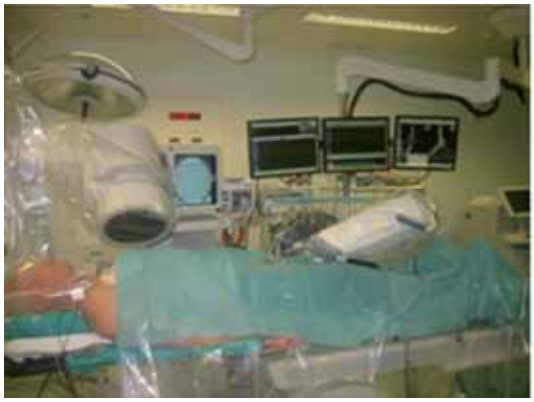
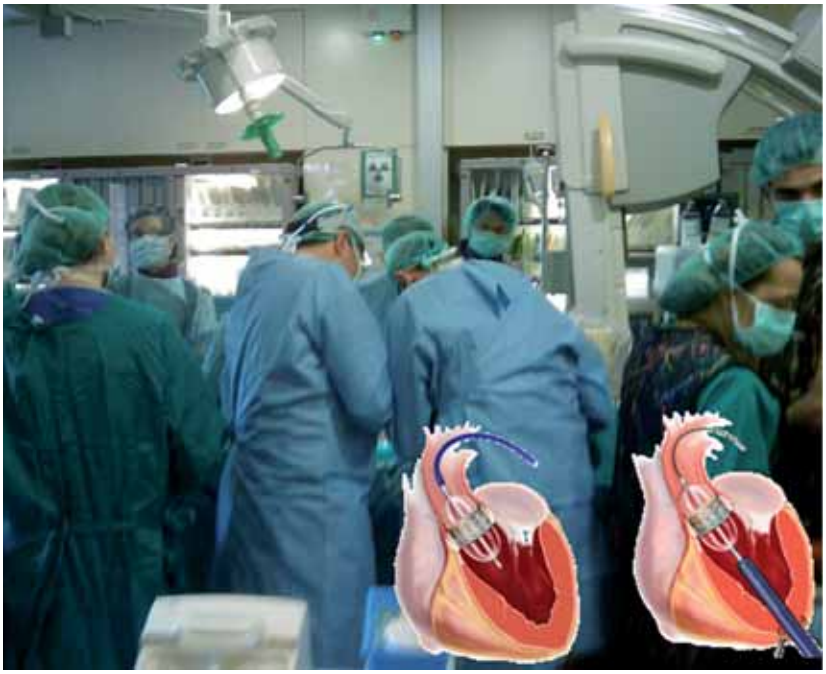


Figure 36
Treatment of atrial fibrillation with the aid of a robot

Figure 37
Confocal microscopy of isolated The cardiac team in the cath lab in a procedure of trans-catheter aortic valve implantation. This can be done through the femoral artery or through the left ventricular apex (bottom figures)



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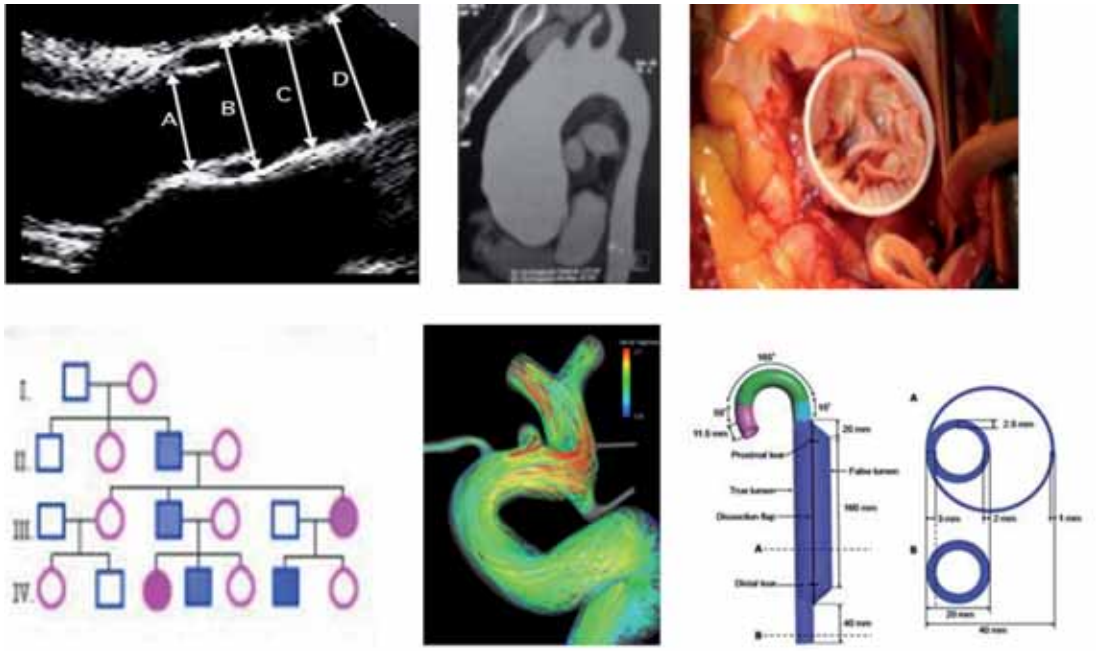

Figure 38
Different approaches to the study of Marfan syndrome: echocardiography and cardiac imaging, surgery, genetic evaluation, computer simulation

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2.4 Area 4: Neurosciences

Research Group: Alzheimer

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Technical, Nursing and Administrative
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Emma Rodríguez Noriega
Tejuca

Objectives

- To correlate the specific biomarkers in CSF (beta-amyloid 42 protein, total and phosphorilated Tau) in the extracerebral compartment (plasma).
- Determine, in a molecular level, a risk profile associated to other biomarkers to complete the basic range that gathers different Alzheimer's clinic phenotypes and therapeutic strategies on specific targets.
- To know 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 wide series of cases and controls.
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 the 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 identification of genetic factors linked to tau positive and granulin positive mutations in fronto-temporal lobar degenerations, understood as an orphan treatment disease.

Functional food
Mercè Boada Rovira
Functional food study in animal model as well as in humans focused on aging and neurodegenerative diseases. This research line will bring new concomitant and multimodal treatment designs in this population.

Clinical Research
Mercè Boada Rovira
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 DEM.

Current Research Projects

PI: Mercè Boada Rovira
Participación de sistemas proteolíticos en la progresión de la angiopatía amiloide cerebral
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI070737
Funding: 161,535 €
Duration: from 2008 to 2010

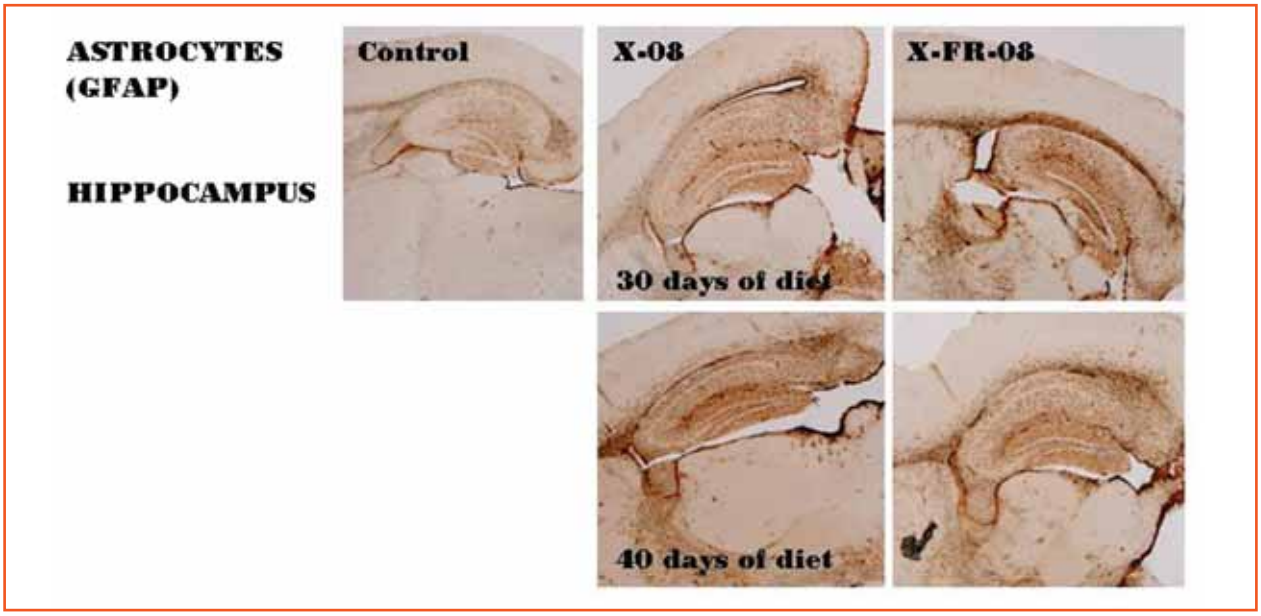

Figure 39
Neurogenic, neuroprotector and antioxidant effect of rich in polyphenols diets, administered in 129 SW mice (NUTS Study)

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Impact Factor: 42.716

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2.4 Area 4: Neurosciences

Research Group: Clinical Neuroimmunology

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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.

Research Lines

Therapeutic Research in multiple sclerosis

Carlos Nos

During 2009, the Clinical Neuroimmunology Research Group participated in fifteen international clinical trials, namely, six phase II, seven phase III, and two phase IV trials as well as eleven extension studies of previous trials, i.e. seven phase II and four phase III trials. Xavier Montalbán is involved, as member of the Steering Committee, in the conduct of seven of these trials. Dr. Nos 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 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) 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.

Anti-NMO IgG determination as a tool for multiple sclerosis differential diagnosis

Carme Costa

Anti-NMO IgG are detected through immunofluorescence staining in serum of patients with a first event of neuritis optica or myelitis or both, seeking to differentiate neuromyelitis optica from multiple sclerosis.

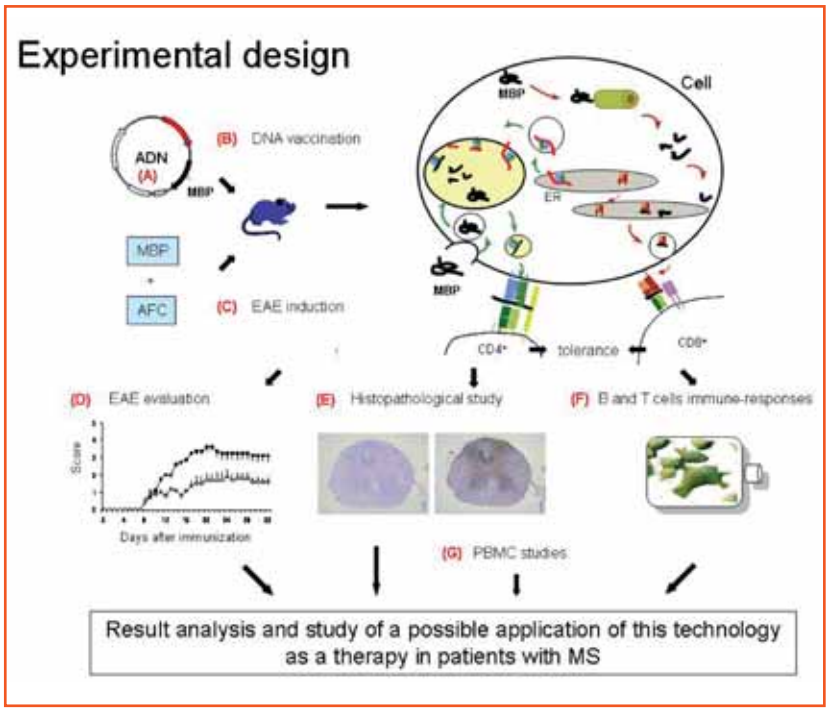

Figure 40
Understanding the protective mechanisms promoted by the use of DNA-based vaccines in EAE, precursor to the possible application of this technology as a new therapy in patients with MS

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-Garriga

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.

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 collaboration 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 to induce 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.

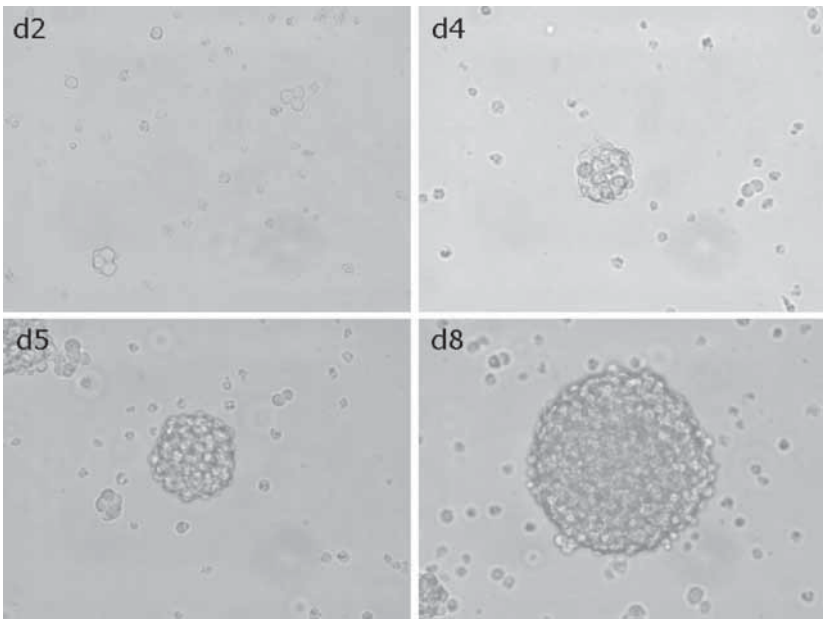

Figure 41
Neurosphere formation. From a single cell suspension (d2) mouse neural stem cells proliferate and form neurospheres (d4, d5 and d8)

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. At the present time, there are two research lines that are ongoing: (i) an incidence study in Catalonia using an official MS Registry of new cases and (ii) a prevalence study in the Osona region. The Registry as well as the results from previous studies will lead to collaborative studies on possible risk factors associated with the disease.

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: from 2007 to 2010

PI: Xavier Montalbán 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: from 2007 to 2010

PI: Carmen Espejo Ruiz
Función de las proteínas de choque térmico (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: from 2008 to 2010

PI: Manuel Comabella López
Search for biomarkers of IFN-beta bioactivity in MS patients
Funding Agency: European Comission.
Reference: FP7-PEOPLE-07-1-1-IT
Funding: 188,522 €
Duration: from 2008 to 2011

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: 73,250.00 €
Duration: from 2009 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: from 2009 to 2011

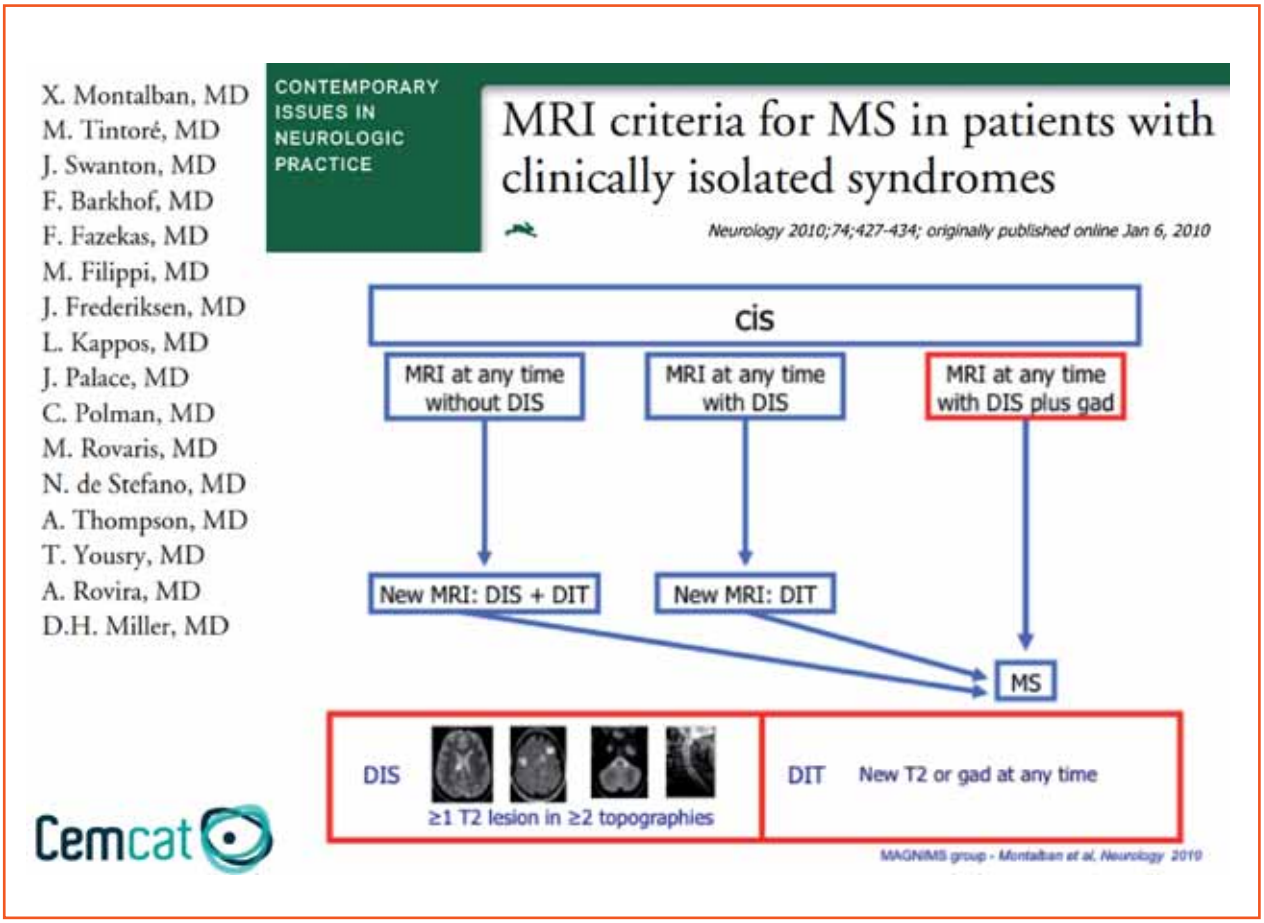

Figure 42
Algorithm proposal for the diagnosis of patients with clinically isolated syndromes. Adapted from Montalbán et al. (Neurology 2010)

CIS: clinically isolated syndromes; DIS: dissemination in space; DIT: dissemination in time; MRI: magnetic resonance imaging; Gd: presence of at least one gadolinium enhancing lesion

Publications

Impact Factor: 215.417

PI: Manuel Comabella López
Estudio con células madre para encontrar nuevos tratamientos en la esclerosis múltiple
Funding Agency: Fundación Caja Navarra
Reference: CAN2008-15271
Funding: 2863.83 €
Duration: from 2009 to 2009

PI: Carmen Espejo Ruiz
¿Participan las proteínas de choque térmico (heat shock protein) en el desarrollo de la esclerosis múltiple?
Funding Agency: Fundación Caja Navarra
Reference: CAN2008-15272
Funding: 760.50 €
Duration: from 2009 to 2009

PI: Nicolás Miguel Fissolo
Vacunas DNA para la esclerosis múltiple
Funding Agency: Fundació Institut de Recerca Hospital Universitari Vall d'Hebron
Reference: IR-HUVH-2/2008
Funding: 30,000 €
Duration: from 2009 to 2011

Bosma LV, Kragt JJ, Brieva L, Khaleeli Z, Montalbán X, Polman CH, Thompson AJ, Tintoré M, Uitdehaag BM. The search for responsive clinical endpoints in primary progressive multiple sclerosis. *Mult Scler* 2009 Jun; 15 (6): 715-20. ⇨ IF: 3.312.

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2.4 Area 4: Neurosciences

Research Group: Neuro Magnetic Resonance

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Silvana Isabel Sarria Estrada
Sahyly Siurana Montilva

Technicals
Juan Francisco Corral Gámez
Elena Huerga Núñez
Osvaldo Anibal Pino

Objectives

The multidisciplinary character of our group (neuroradiologists, physicist, biochemist, engineer, 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 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.

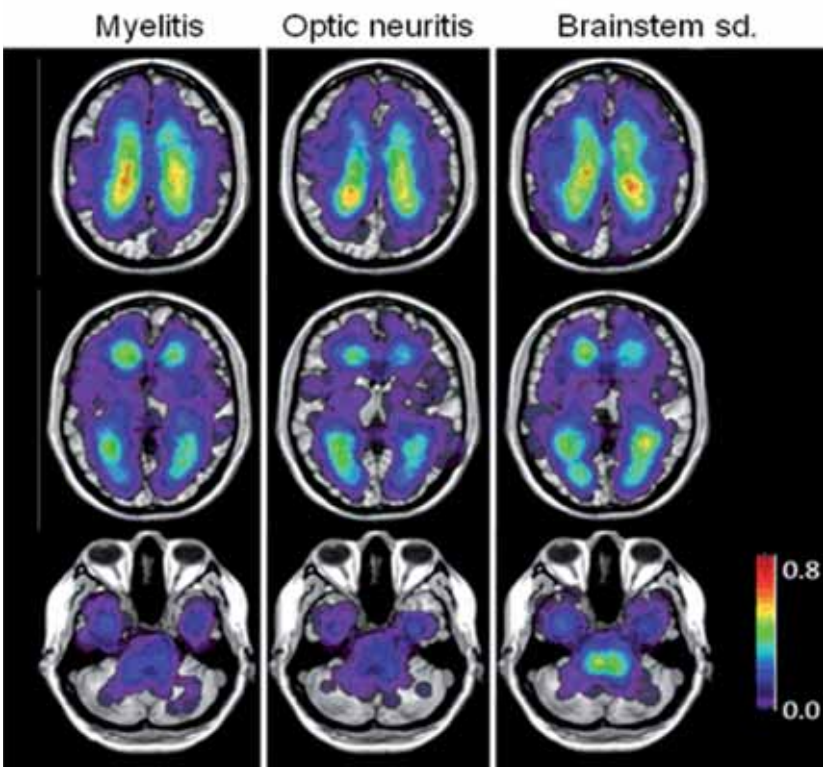

Figure 43
Lesion probability maps in patients with different types of clinically isolated syndromes

Research Lines

Application of MR imaging and spectroscopy techniques to the study of multiple sclerosis

Àlex Rovira

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

The objective of this line is to obtain information about the pathophysiologic mechanisms involved in the development of hepatic encephalopathy. It is mainly focused on cerebral edema: its characteristics, evolution, and relationship with clinical variables.

Functional MR imaging

Deborah Pareto

Over the last years we have dedicated considerable effort to 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

Xavier Aymerich

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.

Design of MR protocols and quantitative analysis of the images

Àlex Rovira

With the development of research projects centered on the lines described above we have acquired an important experience that allow 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: 67.432

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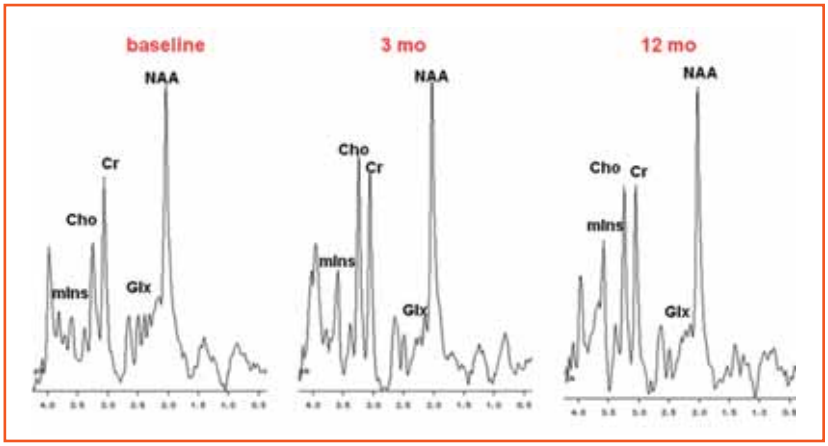
Figure 44
H-MR spectra obtained from normal appearing white matter in a cirrhotic patient before and 3 months and one year after liver transplantation. The initial spectrum shows an increase in the glutamic/glutamine region (Glx) and a decrease in the myo-Inositol (mIns) and choline (Cho) resonances. These abnormalities normalized after liver transplantation



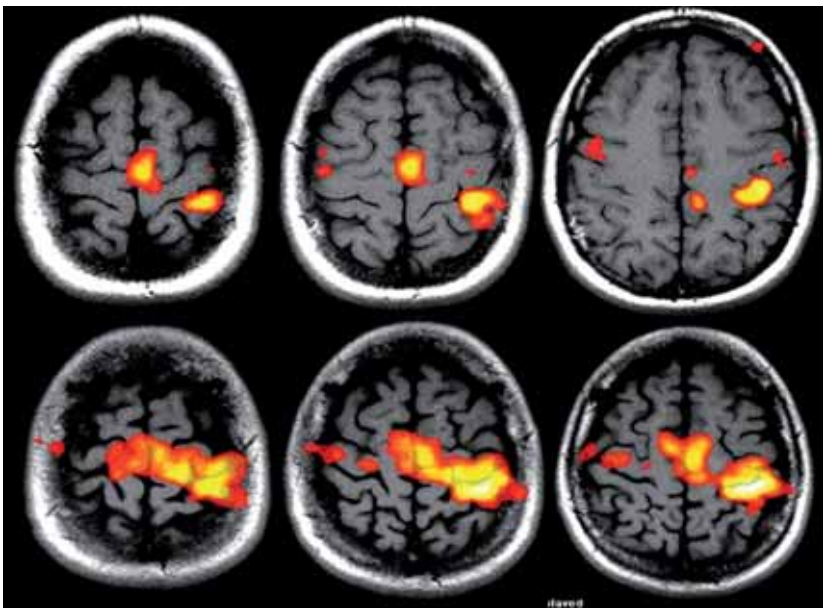


Figure 45
Functional MR imaging in a healthy subjectr (upper row) and in a patient with secondary progressive MS (lower row) after performing a movement with the right hand. Observe the greater task-related activation in both the primary and supplementary motor areas in the patient as compared to the healthy subject

Montalbán X, Sastre-Garriga J, Tintoré M, Brieva L, Aymerich FX, Río J, Porcel J, Borras C, Nos C, Rovira A. A single-centre, randomized, double-blind, placebo-controlled study of interferon beta-1b on primary progressive and transitional multiple sclerosis. *Mult Scler* 2009 Oct; 15 (10): 1195-205. ⇨ IF: 3.312.

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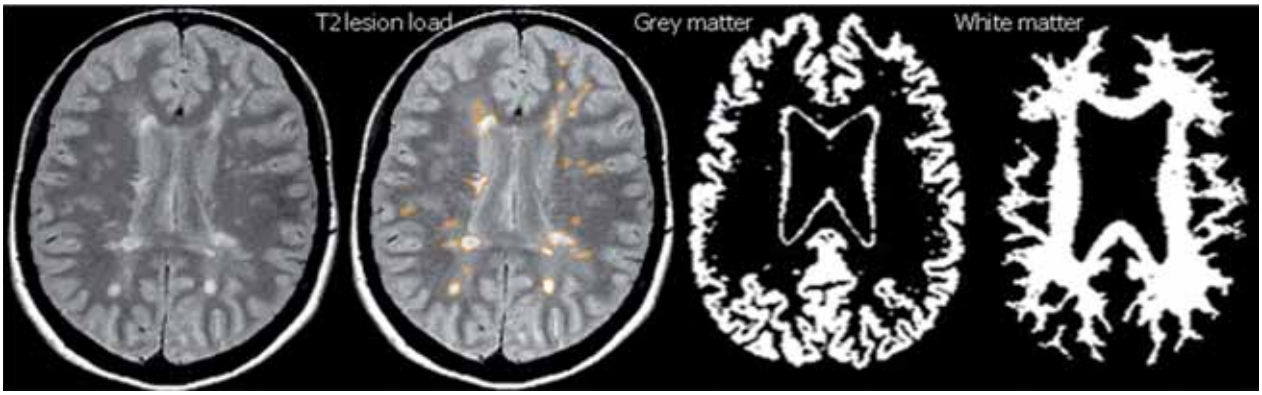

Figure 46
Different tissue based measures commonly used in multiple sclerosis research studies

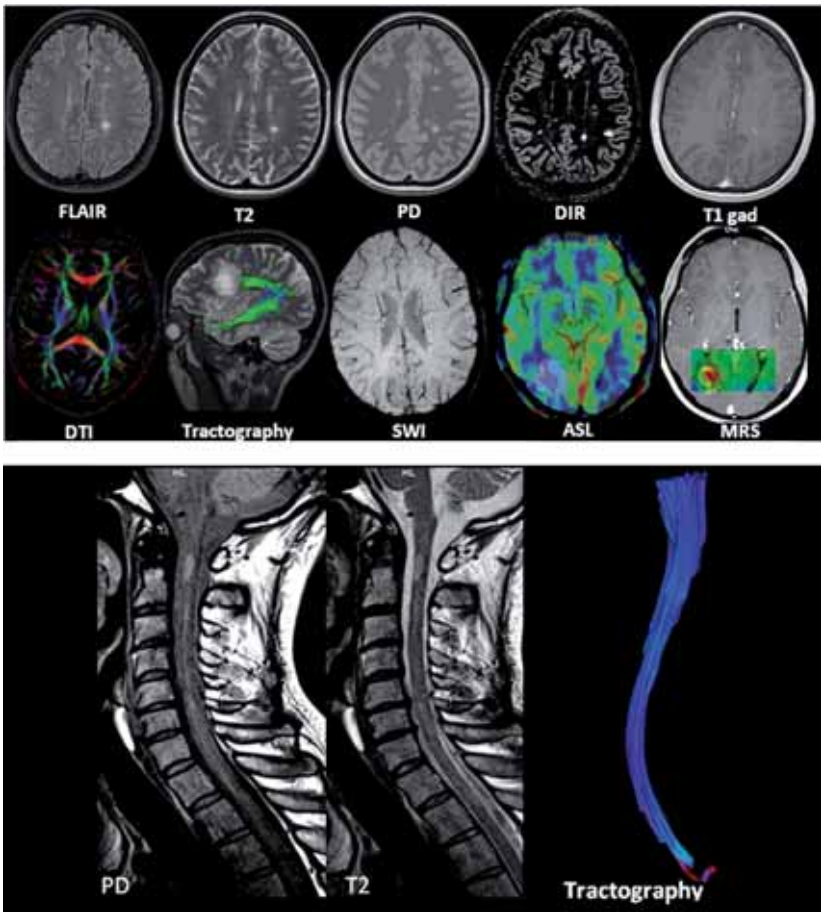

Figure 47
Different MR techniques used in clinical and research studies

Roussel BD, Macrez R, Jullienne A, Agin V, Maubert E, Dauphinot L, Potier MC, Plawinski L, Castel H, Hommet Y, Munuera J, Montaner J, Yepes M, Ali C, Vivien D. Age and albumin D site-binding protein control tissue plasminogen activator levels: neurotoxic impact. *Brain* 2009 Aug; 132 (Pt 8): 2219-30. ⇨ IF: 9.603.

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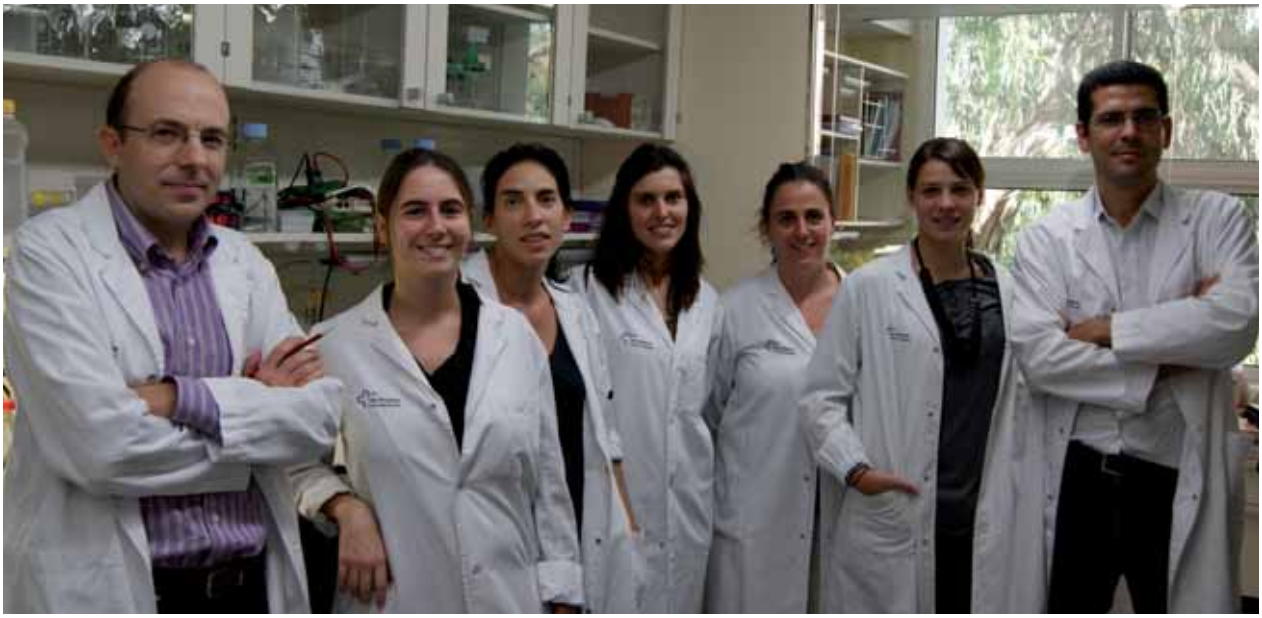
2.4 Area 4: Neurosciences

Research Group: Neurodegenerative Diseases



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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.

Research Lines

Mitochondrial dysfunction and Parkinson's disease

Miquel Vila

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.

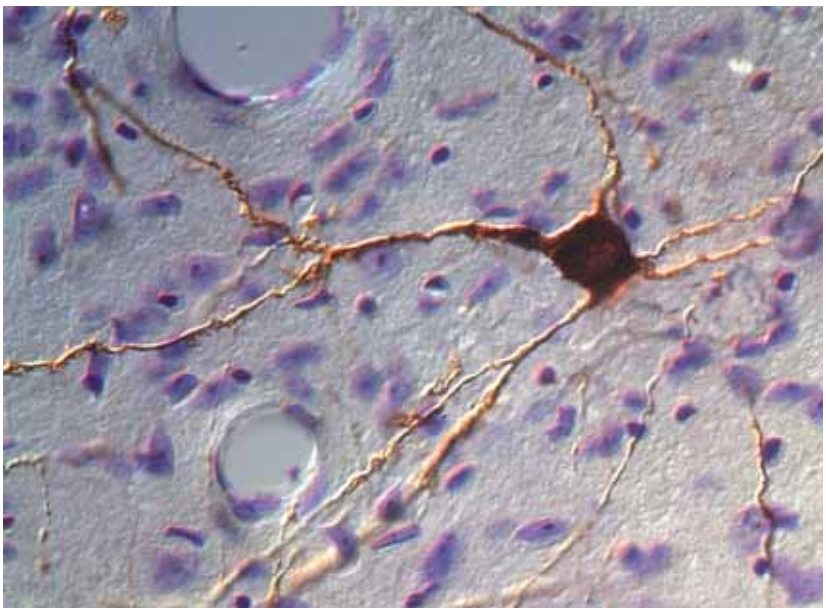
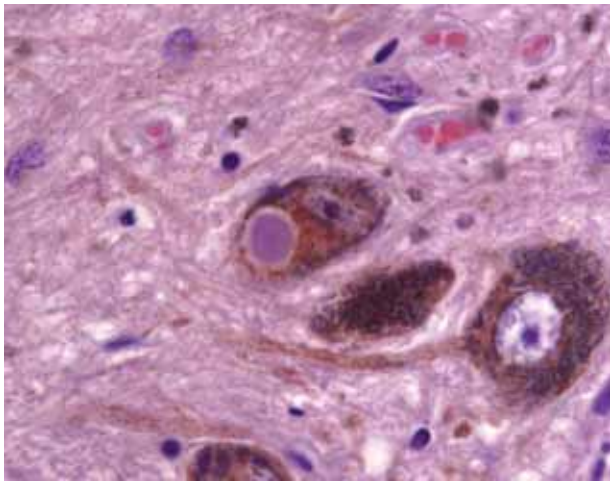
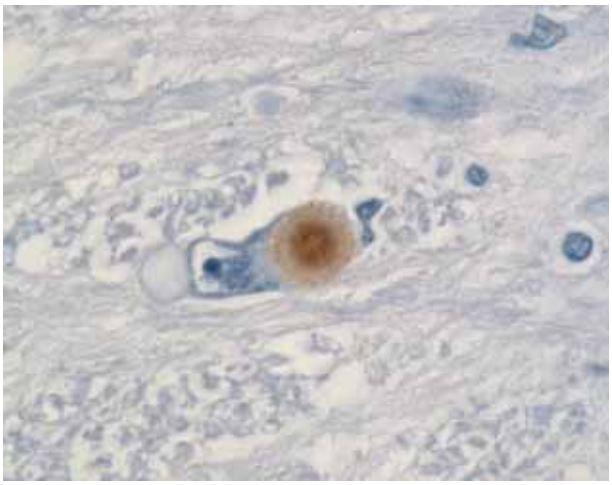


Figure 49
Dopaminergic neuron in the substantia nigra of a mouse ventral midbrain revealed by immunohistochemistry against tyrosine-hydroxilase (TH, brown color), the rate-limiting enzyme of dopamine synthesis

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 color) with a dense core surrounded by a halo





Figures 50
Lewy bodies contain a variety of proteins, of which alpha-synuclein, a mutation in which gene was the first to be identified in a familial form of PD, is a major component. In the Figure, an alpha-synuclein-containing Lewy body (brown color) in a dopaminergic neuron of the substantia nigra is shown in a post-mortem brain sample from a PD patient

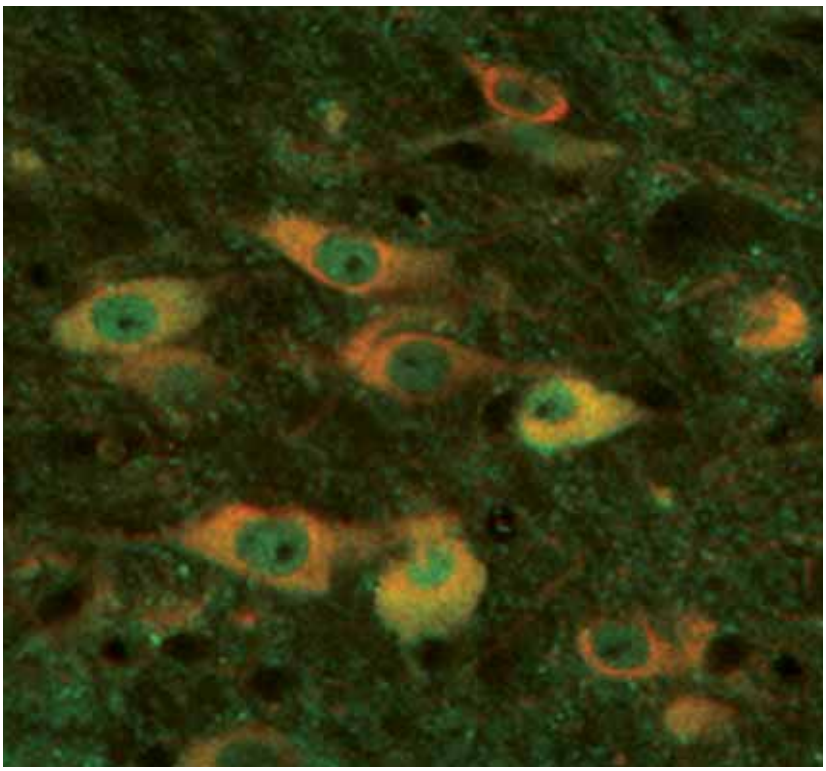


Figure 51
Alpha-synuclein abnormally accumulates in the cytoplasm of substantia nigra dopaminergic neurons after intoxication with parkinsonian neurotoxin MPTP in mice. The co-localization of alpha-synuclein (green color) with tyrosine hydroxilase (red color) results in a yellow immunofluorescent staining

Targeting programmed cell death in Parkinson's disease

Miquel Vila

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

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 region 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

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.

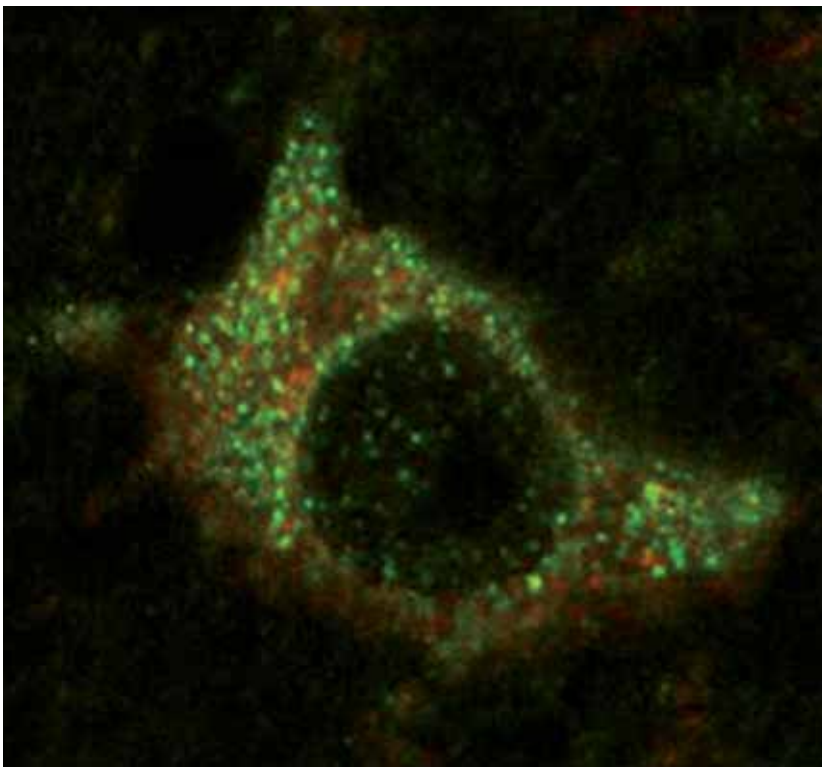


Figure 52
Pro-apoptotic protein Bax (green color) plays an instrumental role in mitochondria-dependent dopaminergic neurodegeneration induced by the parkinsonian neurotoxin MPTP in mice

Current Research Projects

PI: Miquel Vila Bover
Targetting programmed cell death in Parkinson's disease (Targeting PCD in PD)
Funding Agency: European Comission
Reference: PCD-IN-PD-24929
Funding: 1,151,774.03 €
Duration: from 2005 to 2009

PI: Miquel Vila Bover
Paper de la disfunció mitocondrial en la mort neuronal de la malaltia de Parkinson
Funding Agency: Obra Social "la Caixa"
Reference: BM06-153-0
Funding: 90,000 €
Duration: from 2007 to 2009

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: from 2008 to 2010

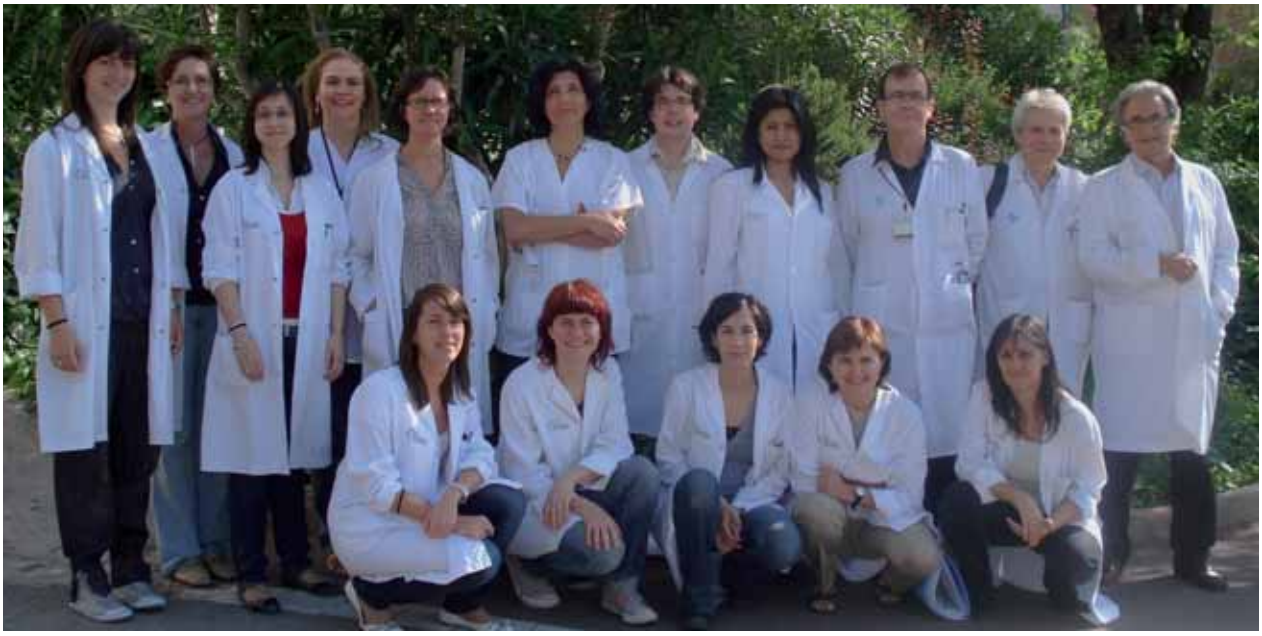
Publications

Impact Factor: 5.399

Hoang T, Choi DK, Nagai M, Wu DC, Nagata T, Prou D, Wilson GL, Vila M, Jackson-Lewis V, Dawson VL, Dawson TM, Chesselet MF, Przedborski S. Neuronal NOS and cyclooxygenase-2 contribute to DNA damage in a mouse model of Parkinson disease. *Free Radic Biol Med* 2009 Oct 1; 47 (7): 1049-56. ➪ FI: 5.399.

2.4 Area 4: Neurosciences

Research Group: Neurotraumatology and Neurosurgery



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Mercedes Arribas
Lourdes Expósito

The Neurotraumatology and Neurosurgery Research Unit (UNINN) was established in late 1990 and since 2007 it has been part of the Universitat Autónoma 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

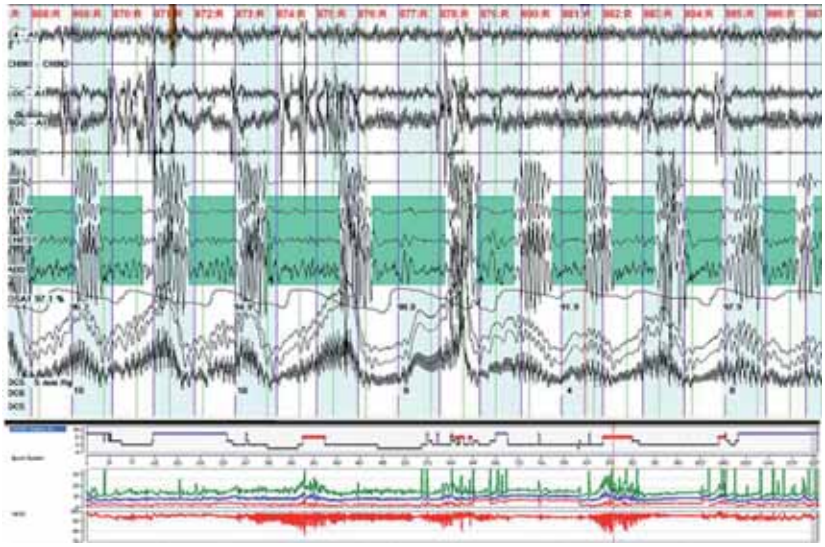


Figure 53
Hidrocephalus. Polisomnography and ICP recording in NPH patient during night

the European research community, acting as the coordinator of multicentre 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.

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 infaction, 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 54
Neurotraumatology. Diffusion Tension Imaging (DTI) of patient with Traumatic Brain Injury (TBI)

Research Lines

Consolidated Lines of Investigation

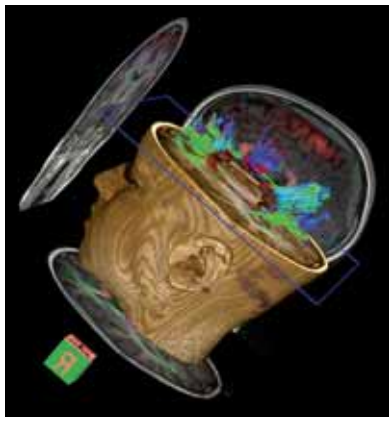
We consider a line of investigation to be consolidated when it has produced continuous publications, financial support and a doctoral thesis.

Neurotraumatology

Juan Sahuquillo Barris and Ángel Garnacho

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 optimize the treatment of severe head injury and MMCAI using new therapeutic techniques such as the combination of moderate hypothermia and decompressive craniotomy.



Emerging Lines of Investigation

Hydrocephalus and alterations in the dynamics of cerebrospinal fluid (CSF)

Maria Antònia Poca and Juan Sahuquillo

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. 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)

Juan Sahuquillo and José Álvarez Sabín

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 study and evaluate the quality of life of patients who survive a malignant middle cerebral artery infarction (MMCAI).

Congenital malformations of the cranio-vertebral junction

Maria Antònia Poca and Juan Sahuquillo

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. 4) 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

Juan Sahuquillo 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. 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: Maria Antònia 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: from 2008 to 2010

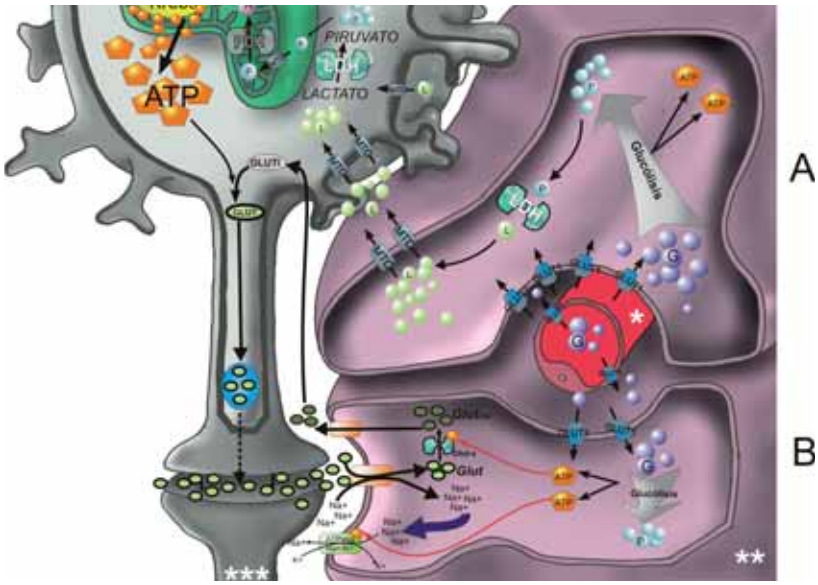
PI: Joan Sahuquillo Barris
Análisis del perfil temporal de los mediadores de respuesta neuroinflamatoria en el espacio extracelular cerebral mediante microdiálisis cerebral de alta resolución en pacientes con un traumatismo craneoencefálico grave
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI051092
Funding: 121,380 €
Duration: from 2006 to 2009

PI: Joan Sahuquillo Barris
Advanced Arterial Hypotension Adverse Event Prediction Through a Novel Bayesian Neural Network
Funding Agency: European Comission
Reference: AVERT-IT-217049
Funding: 129,304 €
Duration: from 2008 to 2010

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: from 2009 to 2011

PI: Joan Sahuquillo Barris
Análisis de la respuesta metabólica e inflamatoria inducida por los fenómenos de despolarización cortical propagada (CSD y CSD-like) en pacientes con lesiones cerebrales agudas
Funding Agency: Fundación Mapfre Medicina
Reference: MAPFRE/05/2008
Funding: 15,000 €
Duration: from 2009 to 2009

Figure 55
MMCAI. Schematic representation of energy metabolism in the brain



Publications

Impact Factor: 35.112

Benejam B, Sahuquillo J, Poca MA, Frascheri L, Solana E, Delgado P, Junque C. Quality of life and neurobehavioral changes in survivors of malignant middle cerebral artery infarction. *J Neurol* 2009 Jul; 256 (7): 1126-33. ⇨ IF: 2.536.

Peñuelas S, Anido J, Prieto-Sánchez RM, Folch G, Barba I, Cuartas I, García-Dorado D, Poca MA, Sahuquillo J, Baselga J, Seoane J. TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma. *Cancer Cell* 2009 Apr 7; 15 (4): 315-27. ⇨ IF: 24.962.

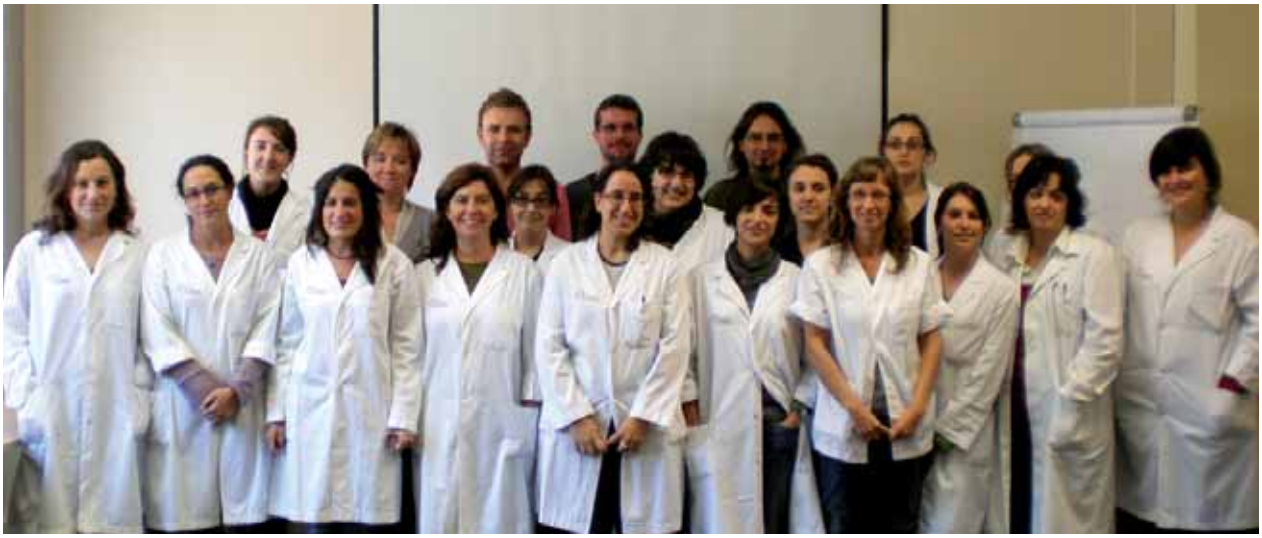
Ríos JA de los, Sahuquillo J, Merino MA, Poca MA, Expósito L. High Resolution Microdialysis. Methodological issues and application to the study of inflammatory brain response. *Neurocirugia* (Astur) 2009 Oct; 20 (5): 433-448. ⇨ IF: 0.277.

Sahuquillo J, Pérez-Bárcena J, Biestro A, Zavala E, Merino MA, Vilalta A, Poca MA, Garnacho A, Adalia R, Homar J, LLompart-Pou JA. Intravascular cooling for rapid induction of moderate hypothermia in severely head-injured patients: results of a multicenter study (IntraCool). *Intensive Care Med* 2009 May; 35 (5): 890-8. ⇨ IF: 5.055.

Stell A, Sinnott R, Jiang J, Donald R, Chambers I, Citerio G, Enblad P, Gregson B, Howells T, Kiening K, Nilsson P, Ragauskas A, Sahuquillo J, Piper I. Federating distributed clinical data for the prediction of adverse hypotensive events. *Philos Transact A Math Phys Eng Sci* 2009 Jul 13; 367 (1898): 2679-90. ⇨ IF: 2.282.

2.4 Area 4: Neurosciences

Research Group: Neurovascular



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Gonzalo Pablo Mazuela Águila
Laura Ortega Torres
Anna Penalba Morenilla
Jorge Pagola Pérez Blanca
David Rodríguez Luna

Objectives

One in six persons in the world will suffer a stroke during their life-time; in fact neurovascular disease is the number one killer among Spanish women. To change these dramatic figures, the Neurovascular research group is focused in 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 those 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.

Research Lines

Biomarkers

Joan Montaner Villalonga

The use of plasma biomarkers is becoming increasingly popular in several fields of medicine. In fact, decision-making processes using biomarkers is 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 really believe that biochemical markers of stroke, 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 diagnosis
- 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 articles like this (Circulation 2003) have been cited more than 180 times since its publication.

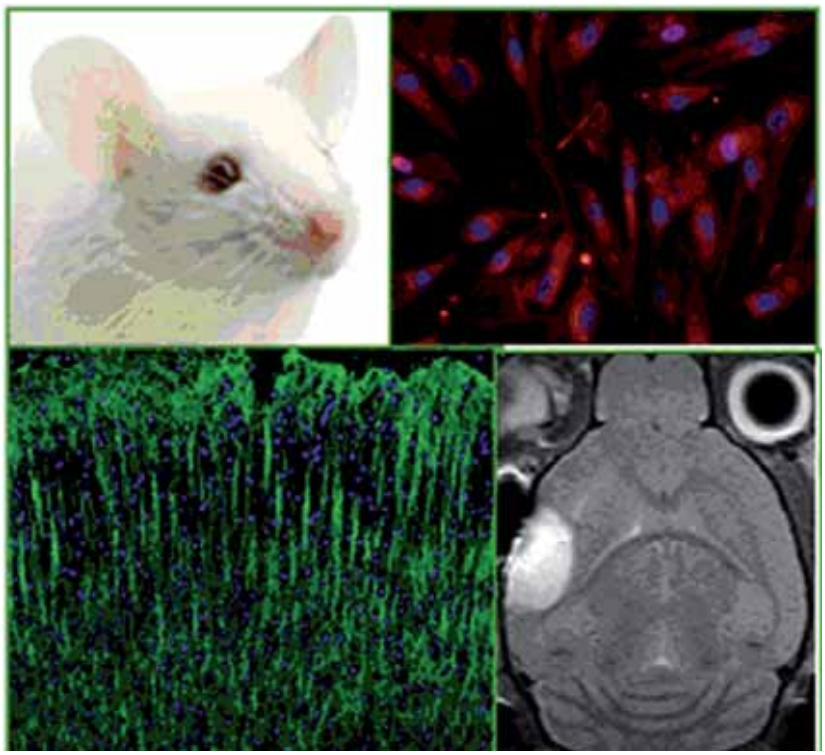
The study of these molecules will also have diagnostic implications because we have proposed the biochemical diagnostic of stroke by means of the identification of a biomarkers panel that distinguish between a stroke and other stroke-mimicking conditions. This might contribute to refer only to real stroke patients to the stroke centres, saving huge resources to the system.

These two examples, identification of biomarkers to predict tPA related bleedings and a stroke diagnostic 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 the clinical practice. That might close the circle of applied research.

We are involved in several projects with public or private funding supporting our research on stroke biomarkers. One of such exciting projects is FIS PI 08/361 "Identificación y uso de biomarcadores pronósticos en el ictus isquémico", aiming to identify biomarkers that predict main causes of stroke worsening (Infarct growth, cardiac complications, hemorrhagic transformation, infections, recurrence or new vascular events) to guide Stroke Unit allocation and stay of our patients.

We are using a combination of discovery techniques and biological human and animal samples to identify new stroke-related biomarkers: All these results have been possible since 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.

Figure 56
Stroke experimental models are used in our lab to test new neuroprotectant drugs and also cell therapy, such as endothelial progenitor cells as shown in the Figure



Genetics

Israel Fernández Cadenas

Neurovascular Genetics is an important part of the research in our Laboratory.

We are participating in the first pharmacogenomic study in patients treated with t-PA, 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 been studied already and more than 6 articles have been published in international journals, showing for example for the first time the risk of suffering hemorrhagic complications and the 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 which primary's objective is to identify of the genetic markers that determine the risk to suffer 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 from 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 pretends to determine the genetic risk factors associated to stroke. Two different group 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 of persons, the "cases" will be composed by patients from the Geno-tPA study and are patients who suffered an ischemic stroke. The second group, the "controls" will be formed by 540 persons healthy of vascular diseases. 200 polymorphisms have been analyzed and differences between the groups of cases and controls have been studied. This will lead to the identification of genes and genetic variants (polymorphisms but also haplotypes or copy number variants) implicated in the stroke dis-

ease. Moreover, functional studies will be performed to determine the exact contribution of each variant described at the biological level. Four we are performing the first Genome Wide Analysis in Spanish stroke samples identifying up to 1 million of SNPs in 240 patients. The project called project GRECAS is in the genotyping process and we will have this results next year. In addition a new GWAs has been funded by Spanish government called GWAs Geno t-PA.

Apart from these studies, our group offers a service of Neurovacular Genetic Consult by a neurologist. This consult aims to diagnose specifically patients (and their families) with cerebrovascular diseases of genetic origin. A 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 consult, we recently published the first case of CARASIL syndrome in a Caucasian population demonstrating that this disease is common and no restricted to Asian population (figure 1). To obtain more information on the Neurovascular Genetic Consult, you can send us an email though the "contact" section of this website.

The Neurovascular Research Laboratory actively collaborates in two consorcia: The IGSC (International Genetic Stroke Consortium), a consortium that joint 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 the collaboration among different centers and to perform genome-Wide Analysis in spanish population.

Acute Theraphy

Lidia García Bonilla

The only approved stroke treatment so far is the acute thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) when administered within 3-4.5 hours after symptoms onset. However, a reduced number of patients (5-8%) profit by this treatment, primarily because of the narrow therapeutic time-window and the risk of brain bleedings beyond thromrbolytic therapy to achieve the recanalization of the occluded artery. Moreover, the inflammatory response that accompanied necrotic brain injury contributes to aggravate acutely 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.

Thereby, it would be desirable to improve the efficacy and safety for thrombolytic therapy of 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 out 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 attempt to obtain the most therapeutic benefice in the acute phase of ischemic stroke.

For these purposes we are using the Intra-arterial Suture Occlusion Model of Focal Cerebral Ischemia, and the Embolic Model of Focal Cerebral Ischemia, coupled with several neuroimaging techniques. Further details are given in www.lin-bcn.com.

Neurorepair

Anna Rosell

New therapies beyond the hyperacute phase of stroke are needed to be able to treat much more patients in delayed phases of this devastating disease. The idea that neurovascular plasticity contributes to stroke recovery can be 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 the 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 used for those purposes are mainly:

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 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).

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.

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: angiovasculogenic 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.

Amyloid

María del Mar Hernández Guillamón

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 mollecular 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.

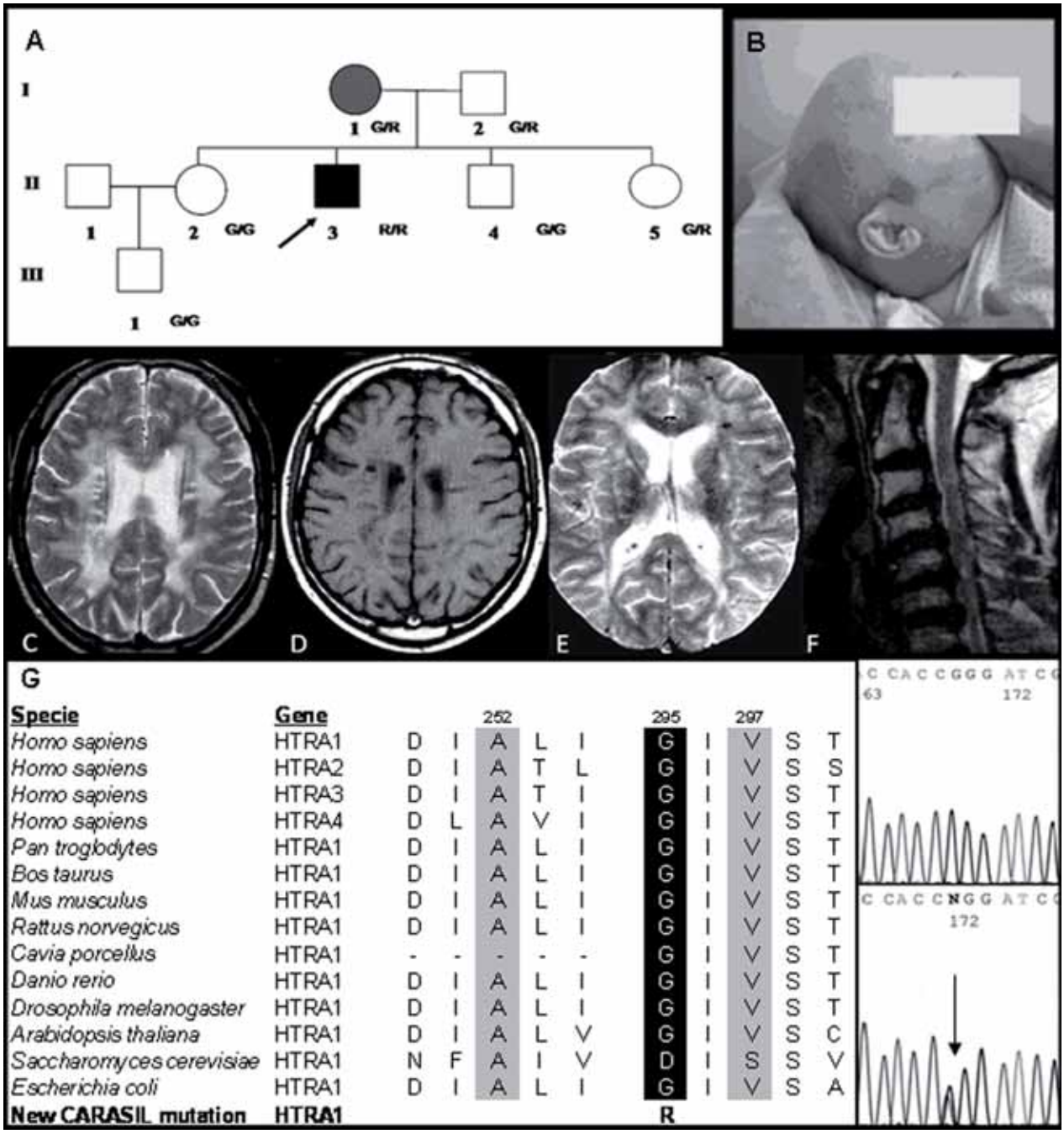


Figure 57
Our lab identified CARASIL patients in western countries for the first time.
A. HTRA1 mutation distribution in the pedigree, the black symbol indicates complete CARASIL phenotype and the grey symbol only leukoencephalopathy. Aminoacids in position 295 are noted as glycine (G) or arginine (R). **B.** The proband showed severe alopecia. **C-E.** Brain transverse MRI revealed an extensive leukoencephalopathy involving anterior temporal lobes, external capsules and semiovale centers (T2-weighted) (C); ancient lacunar infarctions (T1-weighted) (D); subcortical microbleeds (T2*GE) (E). **F.** Cervical spine sagital T2-weighted MRI showed multilevel degenerative disease producing moderate-to-severe stenosis of the central canal. **G.** Sequence analysis of HTRA1 revealed a transition in exon 4 (c.883 G>A), leading to the replacement of an evolutionary conserved glycine to arginine at position 295. Mutated glycine residue is shown in black; pathogenic mutations reported by Hara *et al.* are shown in grey

Our study includes:

- The identification of both tissue and plasma biomarkers for the diagnosis and prognosis of CAA-related hemorrhages.

- The search of 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).

- The study of MMPs role 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.

Prevention

María Pilar Delgado Martínez

Since cerebrovascular diseases and dementia are responsible for a huge economic burden, the early detection of patients at high risk for them, and the implementation of preventive measures as soon as possible, might be of great interest and profit. The purposes of our research are:

- To promote awareness and knowledge of stroke in the general population and enhance collaboration between primary care services and hospital departments.

- To accurately predict those patients at high-risk for 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 or not widely applied by means of cost-efficiency studies.

- To study quantitative predictors of preventive treatment compliance.

Our main project in this area:

"Silent cerebral infarction detection and biomarkers associated with the risk of stroke in hypertensive spanish population".

Silent cerebral infarctions (SCI) detected with neuroimaging techniques, particularly with brain MRI, are common in aged healthy 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 adequate and cost-efficient tool, to avoid further strokes and dementia.

Our current project will include a estimated sample size of 1000 hypertensive patients, without 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 prevalence of silent cerebral infarctions in our setting, which is largely unknown.

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 therefore, the improvement of the link between Primary Care Systems and the remaining hospitalary services, will favor in the future the preventive treatment and care of the patients.

Current Research Projects

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: from 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 t-PA
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/04/2005
Funding: 25,000 €
Duration: from 2006 to 2009

PI: Joan Montaner Villalonga
Identificación de biomarcadores de isquemia cerebral mediante análisis de expresión génica y proteica de diferentes poblaciones celulares obtenidas por microscopia-catapultaje en core y penumbra tras el ictus en humanos
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI050322
Funding: 221,935 €
Duration: from 2006 to 2009

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: from 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 t-PA
Funding Agency: Fundación Ramón Areces
Reference: ARECES/1/2006
Funding: 110,000 €
Duration: from 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: from 2007 to 2010

PI: Joan Montaner Villalonga
European Stroke Research Network (EUSTROKE)
Funding Agency: European Comission
Reference: EUSTROKE-202213
Funding: 463,200 €
Duration: from 2008 to 2013

PI: Joan Montaner Villalonga
Estudio sobre las causas que originan diferencias de género en la enfermedad neurovascular ¿Es el ictus una patología machista?
Funding Agency: Fondo de Investigación Sanitaria
Reference: MD07/00209
Funding: 41,910 €
Duration: from 2008 to 2009

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: from 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: from 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: from 2009 to 2012

PI: Patricia Pozo Rosich
CHROMIG: genotipatge del risc de desenvolupar migranya crònica
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3_072310
Funding: 199,413.75 €
Duration: from 2008 to 2011

PI: Marc Ribó Jacobi
Búsqueda de patrones genéticos predictivos de la evolución del paciente con ictus isquémico después del tratamiento con t-PA
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060586
Funding: 211,145 €
Duration: from 2007 to 2010

Publications

Impact Factor: 128.422

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Fernández-Cadenas I, Mendioroz M, Munuera J, Álvarez-Sabín J, Rovira A, Quiroga A, Corbeto N, Rubiera M, Delgado P, Rosell A, Ribó M, Molina CA, Montaner J. Lower concentrations of thrombin-antithrombin complex (TAT) correlate to higher recanalisation rates among ischaemic stroke patients treated with t-PA. *Thromb Haemost* 2009 Oct; 102 (4): 759-64. ➪ IF: 3.803.

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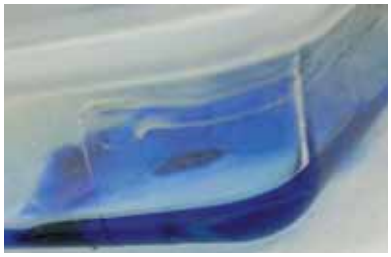

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Saqqur M, Tsivgoulis G, Molina CA, Demchuk AM, Shuaib A, Alexandrov AV. Residual flow at the site of intracranial occlusion on transcranial Doppler predicts response to intravenous thrombolysis: a multicenter study. *Cerebrovasc Dis* 2009; 27 (1): 5-12. ➪ IF: 3.041.

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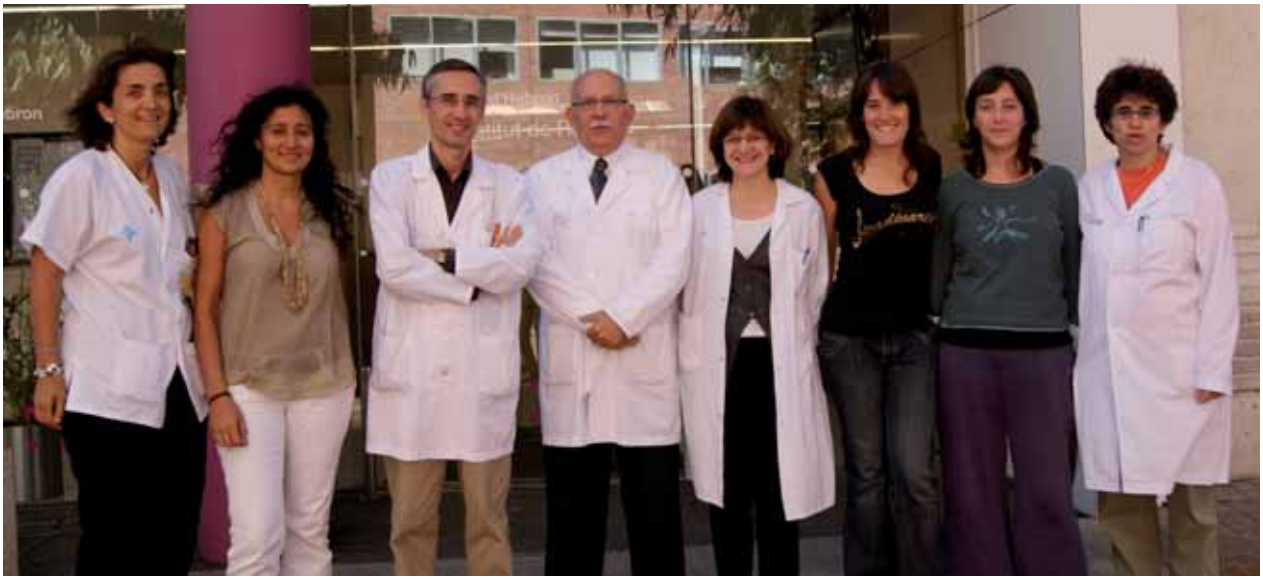
2.4 Area 4: Neurosciences

Research Group: Pediatric Neurology



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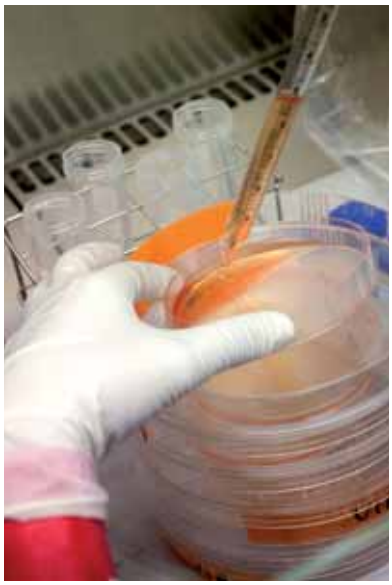
Susana Boronat Guerrero
Daniel Carranza Rojo
Marina Flotats Bastardes
Miquel Raspall Chaure
Mireia del Toro Riera

PhD Students
Aintzane Urbizu Serrano
Marta Vila Pueyo

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.



Research Lines

The interests of the research group are mainly focused on two areas:

Pediatric neurogenetics

Alfons Macaya

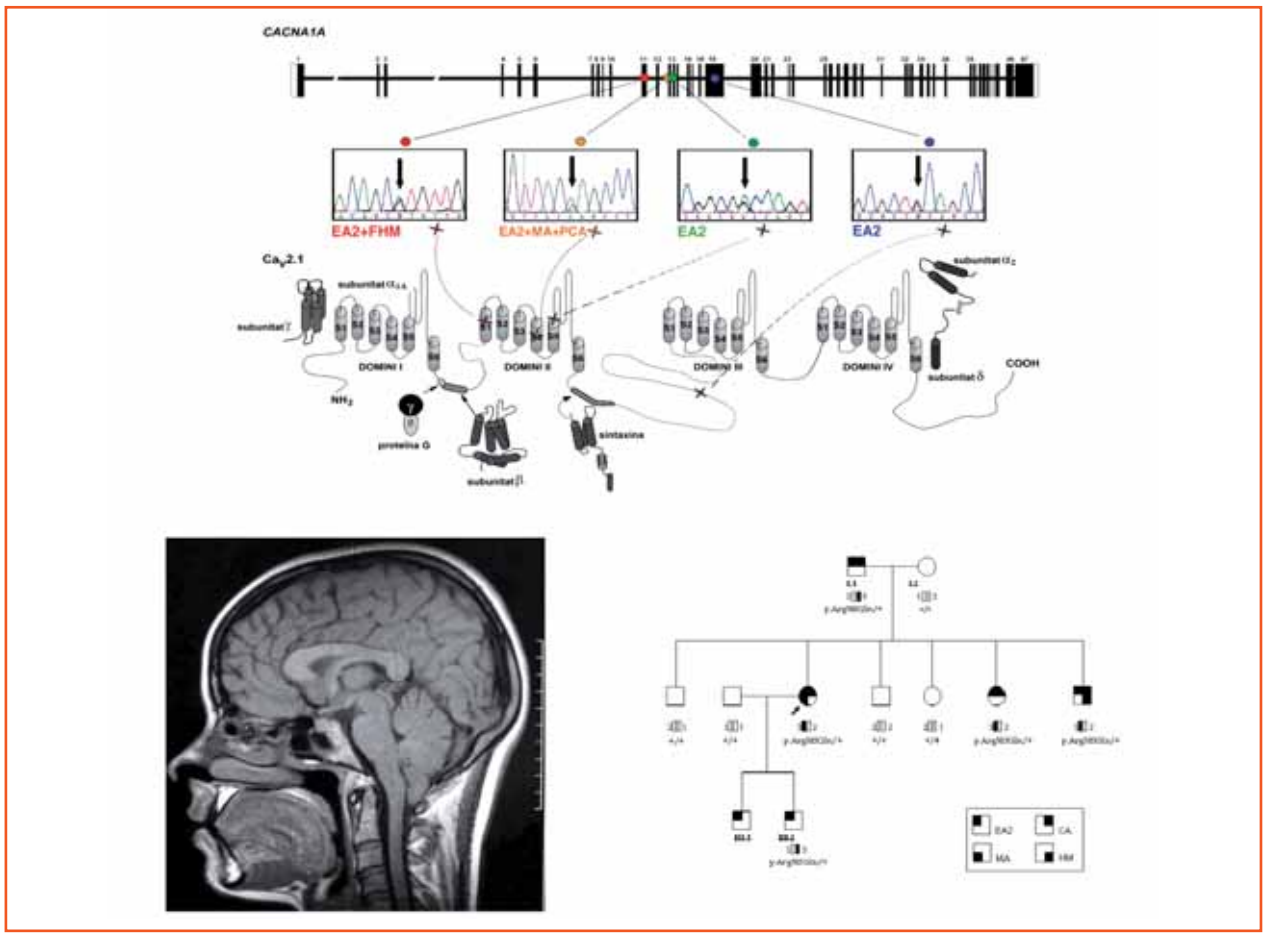
Neurogenetics of paroxysmal neurological disorders (neuronal channelopathies.

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 in epigenetic modification of susceptibility genes.

Figure 58
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 and Manuel Roig

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: TV3/062710
Funding: 194,125 €
Duration: from 2007 to 2010

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: from 2007 to 2010

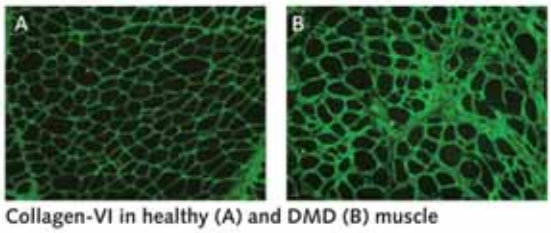
PI: Alfons Macaya Ruiz

Bases genéticas de la malformación de Chiari tipo I

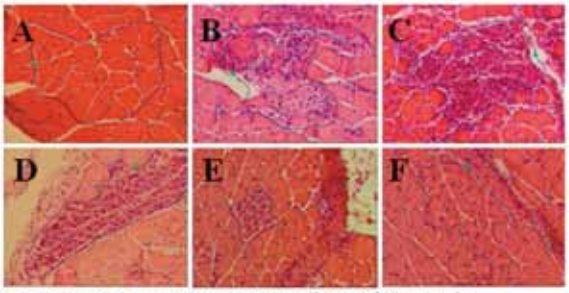
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061606
Funding: 84,216 €
Duration: from 2007 to 2010

Figure 59
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

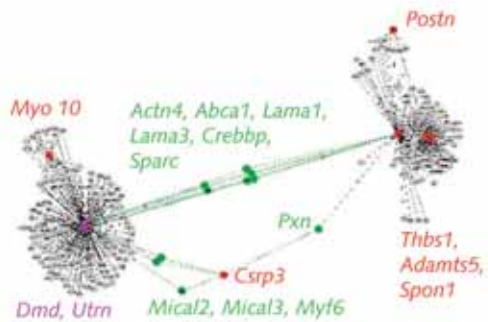
DMA animal mode



Collagen-VI in healthy (A) and DMD (B) muscle



Necrosis-regeneration process in dystrophic muscle



Functional gene relationship in mdx mice skeletal muscle

PI: Manuel Roig Quilis

Defining targets for therapeutics in Spinal Muscular Atrophy. GENAME Project

Funding Agency: Fundación Genoma España
Reference: GENAME
Funding: 155,968.63 €
Duration: from 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 Pompe y controles sanos

Funding Agency: FEEL (Federación Española de Enfermedades Lisosomales)
Reference: FEEL2008/01
Funding: 10,000 €
Duration: from 2009 to 2010

Publications

Impact Factor: 33.108

Corominas R, Ribases M, Camina M, Cuenca-León E, Pardo J, Boronat S, Sobrido MJ, Cormand B, Macaya A. Two-stage case-control association study of dopamine-related genes and migraine. *BMC Med Genet* 2009 Sep 21; 10 (1): 95. ⇨ IF: 2.762.

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Santamaría-Martínez A, Barquinero J, Barbosa-Desongles A, Hurtado A, Pinos T, Seoane J, Poupon MF, Morote J, Reventós J, Munell F. Identification of multipotent mesenchymal stromal cells in the reactive stroma of a prostate cancer xenograft by side population analysis. *Exp Cell Res* 2009 Oct 15; 315 (17): 3004-13. ⇨ IF: 3.948.

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Velasco-Puyo P, Boronat-Guerrero S, Toro-Riera M del, Vázquez-Méndez E, Roig-Quilis M. Intracranial hypertension associated with cerebral venous sinus thrombosis and mastoiditis. Two paediatric case reports. *Rev Neurol* 2009 Nov 16-30; 49 (10): 529-32. ⇨ IF: 1.083.

2.4 Area 4: Neurosciences

Research Group: Psychiatry and Mental Health

Group Leader
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Eugeni Bruguera Cortada
Natalia Calvo Piñero
Francisco Collazos Sánchez
Marina Comín Zafón
Margarita Corominas Roso
Montserrat Corrales de la Cruz
Joan Creixell Sureda
Constanza Daigre Blanco
Francisco Javier Eiroa Orosa
Marc Ferrer Vinardel
Sara Guila Fidel Kinori
Beatriz Gancedo Villegas
Javier Agustín Gastaminza Pérez
Andrea di Genova
Begoña P Gonzalvo Cirac
Carlos Jacas Escarcellé
Pilar Lusilla Palacios
Nieves Gu Martínez Luna
José Eduardo Montejo Celis
Mariana Morais Nogueira
José Antonio Navarro Sanchís
Gemma Nieva Rifa
Gemma Parramón Puig
Marta Quesada Franco
Adil Qureshi Burckhardt
José Antonio Ramos Quiroga
Marta Ribases Haro
Vanesa Richarte Fernández
Amanda Rodríguez Urrutia
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Anna Giannoni Pastor
Cristina Sánchez Mora
Yolanda Santaella Andrés
Ruth Tasqué Cebrián
Yemima Villegas Urbina

Objectives

Consolidating Clinical Research Programs already started, emphasizing interaction of various diseases and research of genetic-based common etiopathogenic mechanisms.

Research Lines

Trimorbility: TDAH, TLP and Addictions
Miquel Casas

Obsessive - compulsive disorders
Miquel Casas

Disorder and Attention Deficit Hyperactivity Disorder in adults (ADHD)
Josep Antoni Ramos-Quiroga

Borderline Personality Disorders (BPD)
Marc Ferrer

Tabagism
Eugeni Bruguera

Dual Pathology
Carlos Roncero

Transcultural Psychiatry
Francisco Collazos

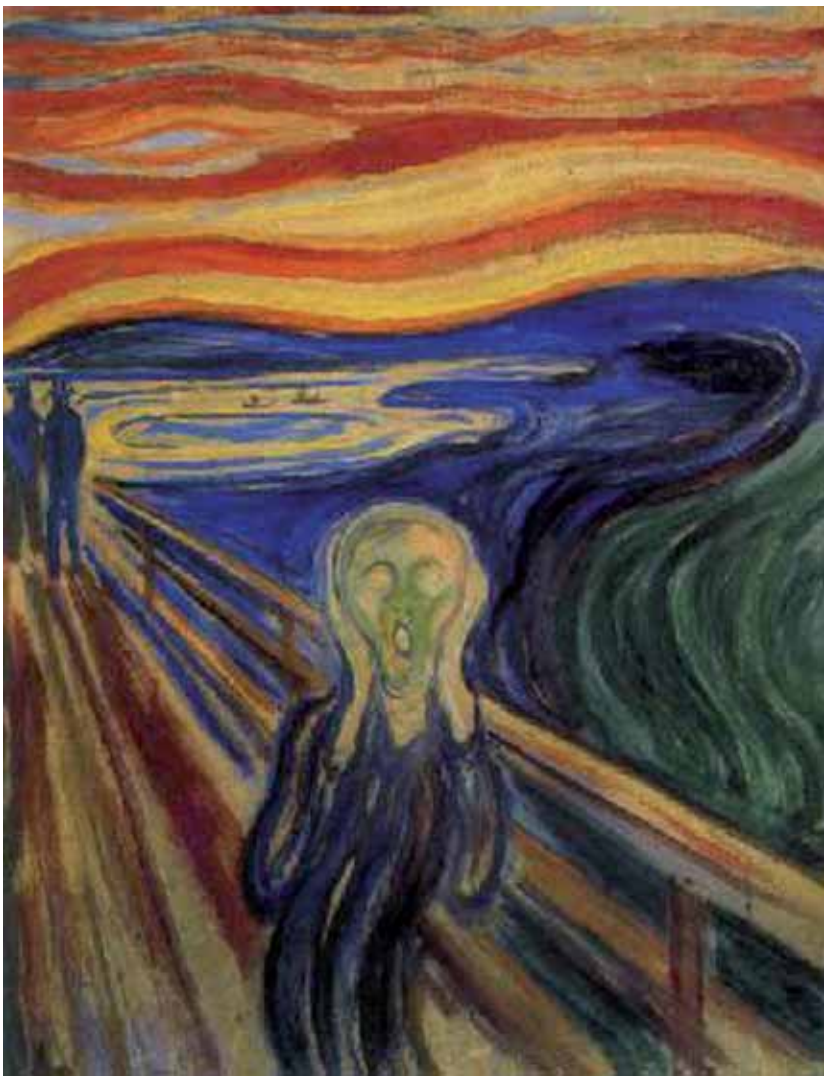

Figure 60
"The Scream", by Edvard Munch, one of the best expressions of feeling fear

Interconsultation Psychiatric in general Hospitals and Liaison Psychiatry
Gemma Parramón

Interconsultation Psychiatric in children's Hospitals and Liaison Psychiatry
Javier Gastaminza

Sexual Dysfunctions
José Antonio Navarro

Chronic Fatigue
Naia Saez

Suicide
Marta Quesada

Post-Traumatic Stress Disorder
José María Argüello

Gender Abuse
Joan Creixell

Psychiatric Genetics
Marta Ribases

Developmental Disorders
Anna Bielsa

Obsessive-compulsive disorder in Children and Youth
Núria Bassas

Current Research Projects

PI: Miquel Casas Brugué
El test de apomorfina como marcador biológico de recaídas en pacientes dependientes de cocaína
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI051982
Funding: 124,355 €
Duration: from 2006 to 2009

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: from 2007 to 2010

PI: Marta Ribases
Genetic susceptibility factors in Attention-Deficit/Hiperactivity Disorder (ADHD)
Funding Agency: Fondo de Investigación Sanitaria
Reference: CP09/00119
Funding: 44,800 €
Duration: from 2009 to 2012

PI: Marta Ribases
Genetic susceptibility factors in Attention-Deficit/Hiperactivity Disorder (ADHD): a two stage genome-wide association study
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3/2009/01
Funding: 144,712.50 €
Duration: from 2009 to 2012

Publications

Impact Factor: 56.910

Alegret M, Boada-Rovira M, Vinyes-Junqué G, Valero S, Espinosa A, Hernández I, Modinos G, Rosende-Roca M, Mauleon A, Becker JT, Tarraga L. Detection of visuoperceptual deficits in preclinical and mild Alzheimer's disease. *J Clin Exp Neuropsychol* 2009 Oct; 31 (7): 860-7. ⇨ IF: 2.184.

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Corominas R, Ribases M, Cuenca-León E, Cormand B, Macaya A. Lack of association of hormone receptor polymorphisms with migraine. *Eur J Neurol* 2009 Mar; 16 (3): 413-5. ⇨ IF: 2.732.

Corominas R, Ribases M, Cuenca-León E, Narberhaus B, Serra SA, Toro M del, Roig M, Fernández-Fernández, Macaya A, Cormand B. Contribution of syntaxin 1A to the genetic susceptibility to migraine: a case-control association study in the Spanish population. *Neurosci Lett* 2009 May 15; 455 (2): 105-9. ➪ IF: 2.200.

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Pailhez G, Rodríguez A, Ariza J, Palomo A, Bulbena A. Somatotype and schizophrenia. A case-control study. *Actas Esp Psiquiatr* 2009 Sep-Oct; 37 (5): 258-66. ➪ IF: 0.446.

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Ribases M, Bosch R, Hervas A, Ramos-Quiroga JA, Sánchez-Mora C, Bielsa A, Gastaminza X, Guijarro-Domingo S, Nogueira M, Gómez-Barros N, Kreiker S, Gross-Lesch S, Jacob CP, Lesch KP, Reif A, Johansson S, Plessen KJ, Knappskog PM, Haavik J, Estivill X, Casas M, *et al.* Case-control study of six genes asymmetrically expressed in the two cerebral hemispheres: association of BAIAP2 with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2009 Nov 15; 66 (10): 926-34. ➪ IF: 8.672.

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Roncero C, Rodríguez-Urrutia A, Grau-López L, Casas M. Antiepilectic drugs in the control of the impulses disorders. *Actas Esp Psiquiatr* 2009 Jul-Aug; 37 (4): 205-12. ➪ IF: 0.446.

Santamarina Pérez P, Corral M. Influence of cognitive reserve on neuropsychological performance in epileptic patients. *Med Clin* (Barc) 2009 Apr 4;132 (12): 459-62. ➪ IF: 1.258.

2.5 Area 5: Digestive Physiopathology and Hepatology

Research Group: Digestive Transplants

Group Leader
Ramón Charco Torra
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Itxarone Izaskun Bilbao Aguirre
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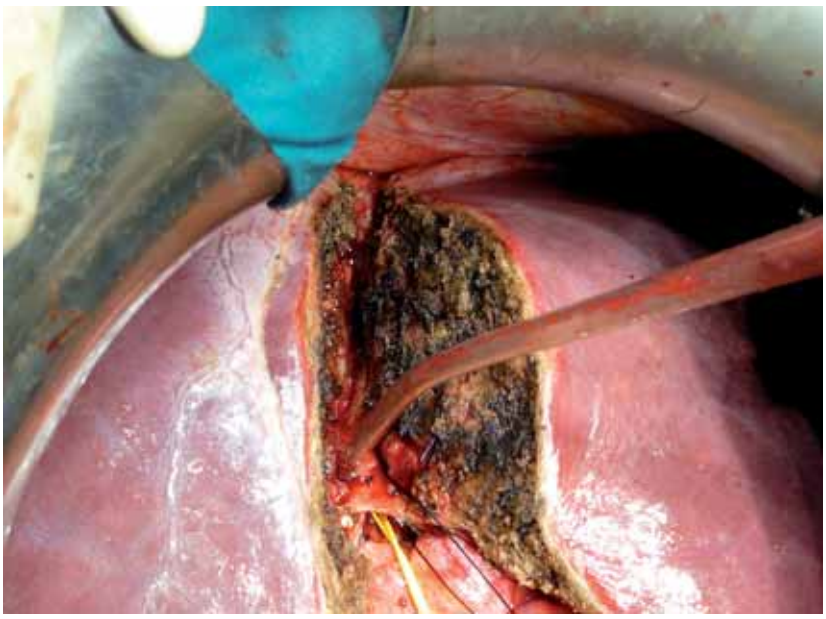
Javier Bueno Recio
Mieria Caralt Barba
Ramon Charco Torra
Cristina Dopazo Taboada
Francisco Espín
Jose Luis Lázaro Fernández
Javier Naval Álvaro
Roberto Rodríguez Revuelto
Gonzalo Sapisochin

Objectives

- Clinical studies on immunosuppression in human liver transplantation.
- Experimental research in minimally invasive surgery through orifices Naturals 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).

Figure 61
Right hepatectomy due to colorectal liver metastasis



Research Lines

Morbidity and quality of life after liver transplantation

Itxarone Bilbao Aguirre, Javier Bueno Recio and Cristina Dopazo Taboada

Risk factors of early and late morbid-mortality after liver transplantation in adults and children.

Treatment of hepatocellular carcinoma

Ramón Charco, Gonzalo Sapisochin, Joaquín Balsells Valls, Lluís Castells Fusté

Management of different treatments for hepatocarcinoma using resection, transplantation, percutaneous methods, chemoembolization and chemotherapy.

Treatment of liver metastases of colorectal cancer

Ramón Charco, José Luis Lázaro Fernández, Cristina Dopazo, Mireia Caralt, Gonzalo Sapisochin and Josep Maria Tabernero Caturla

New surgical techniques and chemotherapy treatments.

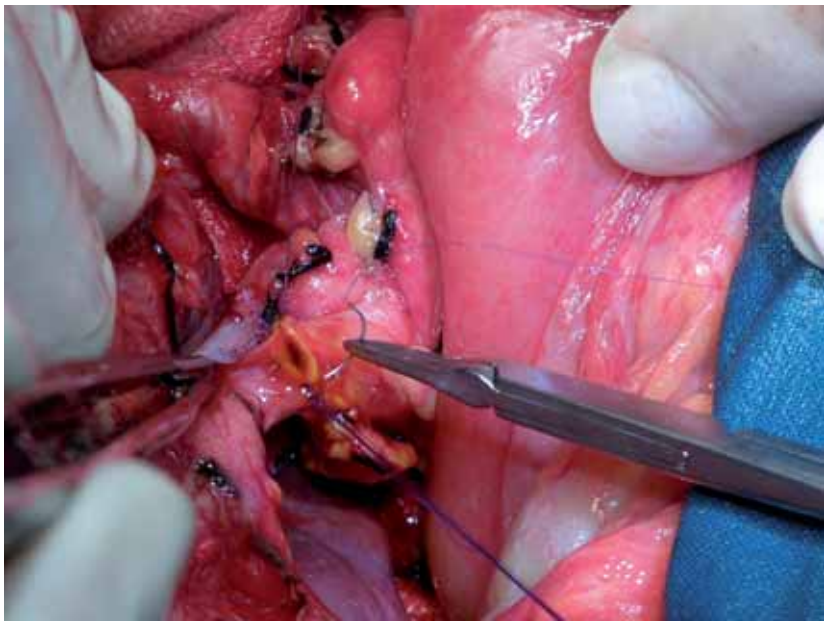
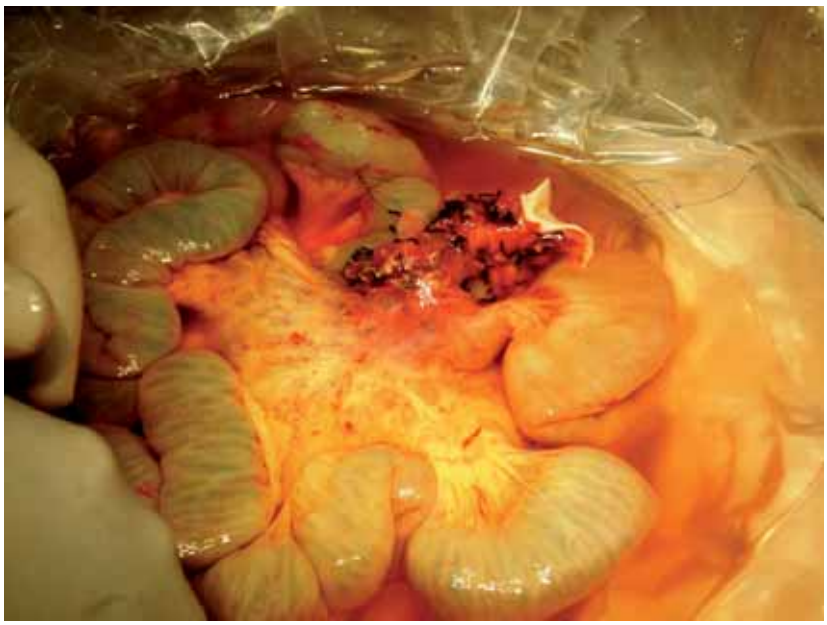


Figure 62
Liver transplantation. Biliary anastomosis

Figure 63
Intestinal graft



Technical advances in hepatobiliopancreatic surgery and transplants
Joaquim Balsells Valls, José Luis Lázaro and Ramón Charco
Evaluating new technologies: laparoscopy, robotics and image processing.

Pancreatic function after pancreatectomy
Joaquim Balsells, Laia Blanco and Javier Naval
Evaluating antibiotics elimination by pancreatic liquid.

Advances in staging of pancreatic cancer
Joaquim Balsells, Laia Blanco and Javier Naval
Studying sentinel ganglion.

Treatment of plaquetopenia after liver transplantation
Itxarone Bilbao, José Luis Lázaro, Roberto Rodríguez, Lluis Castells and Ramón Charco
Evaluating splenic flow occlusion.

Post-transplant monitoring in paediatric liver transplantation
Jesus Quintero, Maria Legarda, Javier Bueno and Ramón Charco
Advances in vascular thrombosis prevention.

Publications

Impact Factor: 6.509

Bilbao I, Sapisochin G, Dopazo C, Lázaro JL, Pou L, Castells L, Caralt M, Blanco L, Gantxegi A, Margarit C, Charco R. Indications and management of everolimus after liver transplantation. *Transplant Proc* 2009 Jul-Aug; 41 (6): 2172-6. ⇨ IF: 1.055.

Charco R, Malagelada C, Llopart L, Bueno J, Bilbao I, Caralt M, Vilallonga R, Gavalda J, Dot J, Abu-Suboh M, Planas M, Accarino A, Armengol-Miró JR, Azpiroz F. Non-anatomical intestinal transplantation. *Rev Esp Enferm Dig* 2009 Feb; 101 (2): 139-41, 141-3. ⇨ IF: 1.263.

Dopazo C, Bilbao I, Lázaro JL, Sapisochin G, Caralt M, Blanco L, Castells L, Charco R. Severe rhabdomyolysis and acute renal failure secondary to concomitant use of simvastatin with rapamycin plus tacrolimus in liver transplant patient. *Transplant Proc* 2009 Apr; 41 (3): 1021-4. ⇨ IF: 1.055.

Martí J, Modolo MM, Fuster J, Comas J, Cosa R, Ferrer J, Molina V, Romero J, Fondevila C, Charco R, García-Valdecasas JC. Prognostic factors and time-related changes influence results of colorectal liver metastases surgical treatment: a single-center analysis. *World J Gastroenterol* 2009 Jun 7; 15 (21): 2587-94. ⇨ IF: 2.081.

Venturi C, Bueno J, Gavaldà J, Tórtola T, Pou L, Medina A, Codina G, Charco R, Pahissa A. Impact of valganciclovir on Epstein-Barr Virus polymerase chain reaction in pediatric liver transplantation: preliminary report. *Transplant Proc* 2009 Apr; 41 (3): 1038-40. ⇨ IF: 1.055.

2.5 Area 5: Digestive Physiopathology and Hepatology

Research Group: Liver Diseases

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Juan Ignacio Esteban Mur
Rafael Esteban Mur
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Antonio González Fernández
Rossend Jardí Margalef
María Martell Pérez Alcalde
Beatriz Mínguez Rosique
Luis Palenzuela Díaz
Josep Quer Sibila
Francisco Rodríguez Frías
Silvia Sauleda Oliveras
Melanie Schaper
Víctor Vargas Blasco
Lluìs Viladomiu

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Laia Chavarria Vilarasau
Mar Coll Loperena
María Cubero León
Rita García Martínez
Maria Homs Riba
Marc Oria Alonso
David Tabernero Caellas

Nursing and Technicians
Judit Carbonell Segura
Damir García Cehic
Imma Raurell Saborit
Jordi Romero Giménez

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 and Rossend Jardí

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 and Juan Ignacio Esteban

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

Physiopatholy of splanhnic arterial vasodilation. Treatment of variceal bleeding.

Liver failure and metabolic encephalopaties

Juan Córdoba Cardona

Physiopathology and treatment of cerebral edema amd liver failure. Mechanisms implicated in metabolic encephalopaties.

Liver transplantation and hepatocarcinoma

Víctor Vargas Blasco, Lluís Castells Fusté and Beatriz Mínguez

Hepatitis C postransplantation. New inmmunosuppressors. Prognostic factors and new therapies for hepatocarcinoma.

Current Research Projects

PI: Lluís Castells Fusté

Trasplante hepático en pacientes infectados por el VIH en España (2005-2007)

Funding Agency: Fundación invest. y prevención SIDA - FIPSE
Reference: FIPSE/TOH/VIH-05
Funding: 4,950 €
Duration: from 2006 to 2012

PI: Juan Córdoba Cardona

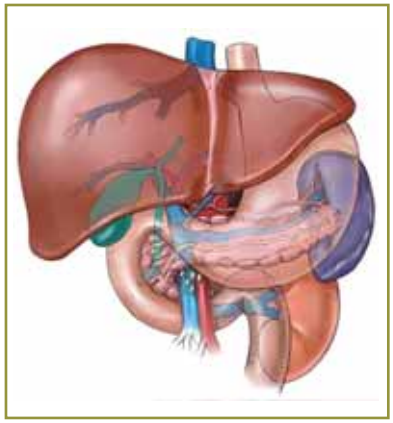
Alteración de la barrera hematoencefálica y edema cerebral en la insuficiencia hepática experimental

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080698
Funding: 258,940 €
Duration: from 2009 to 2011

PI: Juan Ignacio Esteban Mur

Estudi de tolerància perifèrica a la proteïna no estructural NS3 del virus de l'hepatitis C (VHC) per desenvolupar immunoteràpia contra la infecció per VHC per a la prevenció de l'hepatocarcinoma

Funding Agency: Fundació La Marató de TV3
Reference: TV3/052310
Funding: 165,000 €
Duration: from 2006 to 2009



PI: Juan Ignacio Esteban Mur

Selección y expansión de linfocitos T CD4+NS3-específicos de pacientes coinfectados por VIH y VHC. Caracterización del estado de anergia en la infección crónica y restauración funcional para su empleo en inmunoterapia adaptativa para la prevención y/o tratamiento de la recurrencia postransplante

Funding Agency: Fundación invest. y prevención SIDA - FIPSE
Reference: FIPSE/36623/06
Funding: 85,800 €
Duration: from 2006 to 2009

PI: Joan Genescà Ferrer

Estudio longitudinal de la expresión génica diferencial de la alteración vascular esplácnica en el modelo experimental de hipertensión portal de rata. Papel de los mecanismos de angiogénesis

Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2006-03714
Funding: 83,490 €
Duration: from 2006 to 2009

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: 123,420 €
Duration: from 2009 to 2011

Figure 64
The liver and its arterial and venous vasculature

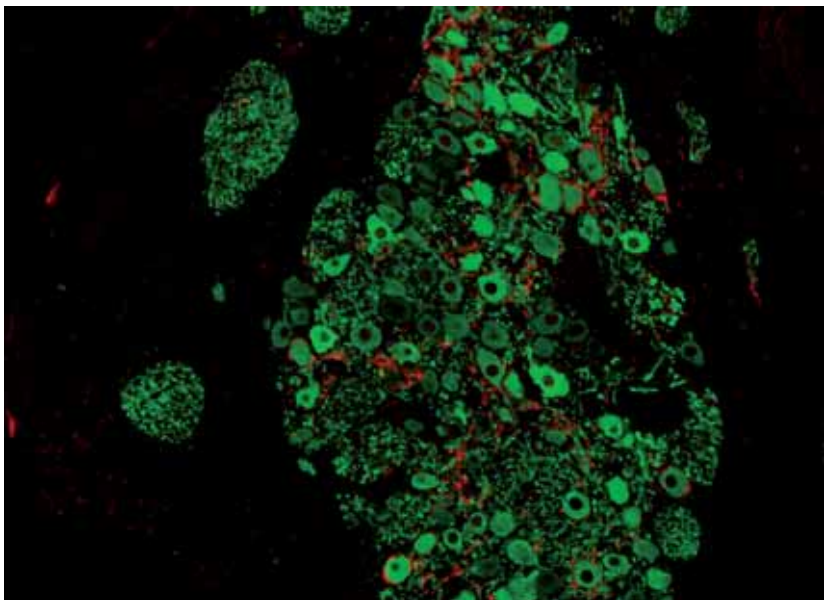


Figure 65
Immunofluorescence of superior mesenteric ganglion of rat: adrenergic neuronal bodies stained with tyrosine hydroxilase (in green) surrounded by nitrergic axons stained by neuronal nitric oxide synthase (in red)

PI: Jaume Guardia Massó
Selección y expansión de linfocitos T CD4+ NS3-específicos de pacientes infectados por Virus de la hepatitis C (VHC). Caracterización del estado de anergia de la infección crónica
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2006-03681
Funding: 90,750 €
Duration: from 2006 to 2009

PI: Josep Quer Sivila
Selección y expansión de linfocitos CD4+NS3-específicos de pacientes VHC. Caracterización del estado de anergia en cronicidad y restauración funcional para empleo en inmunoterapia adaptativa para prevención y tratamiento de la recurrencia postrasplante
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061244
Funding: 113,740 €
Duration: from 2007 to 2009

PI: Francisco Rodríguez Frías
Variabilidad de la región codificante de la proteína de la cápsida viral del virus de la hepatitis B y su relación con el curso de la infección y la respuesta a tratamientos antivirales
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI061512
Funding: 56,265 €
Duration: from 2007 to 2009

PI: Silvia Sauleda Oliveras
Collection and storage of blood samples
Funding Agency: European Comission
Reference: BOTIA-6487
Funding: 277,040 €
Duration: from 2006 to 2009

PI: Silvia Sauleda Oliveras
Caracterización serológica, inmunologica 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: from 2008 to 2010

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: from 2008 to 2010

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: from 2007 to 2010

Publications

Impact Factor: 116.266

Augustin S, Muntaner L, Altamirano JT, González A, Saperas E, Dot J, Abu-Suboh M, Armengol JR, Malagelada JR, Esteban R, Guardia J, Genescà J. Predicting Early Mortality After Acute Variceal Hemorrhage Based on Classification and Regression Tree Analysis. *Clin Gastroenterol Hepatol* 2009 Dec; 7 (12): 1347-54. ➪ IF: 6.068.

Avidan NU, Goldstein D, Rozenberg L, McLaughlin M, Ferenci P, Masur H, Buti M, Fauci AS, Polis MA, Kottilil S. Hepatitis C viral kinetics during treatment with peg IFN-alpha-2b in HIV/HCV coinfected patients as a function of baseline CD4+ T-cell counts. *J Acquir Immune Defic Syndr* 2009 Dec 1; 52 (4): 452-8. ➪ IF: 4.57.

Barba I, Chavarria L, Ruiz-Meana M, Mirabet M, Agulló E, García-Dorado D. Effect of intracellular lipid droplets on cytosolic Ca2+ and cell death during ischaemia-reperfusion injury in cardiomyocytes. *J Physiol* 2009 Mar 15; 587 (Pt 6): 1331-41. ➪ IF: 4.605.

Bes M, Esteban JI, Casamitjana N, Pirón M, Quer J, Cubero M, Puig L, Guardia J, Sauleda S. Hepatitis C virus (HCV)-specific T-cell responses among recombinant immunoblot assay-3-indeterminate blood donors: a confirmatory evidence of HCV exposure. *Transfusion* 2009 Jul; 49 (7): 1296-305. ➪ IF: 3.475.

Bilbao I, Sapisochin G, Dopazo C, Lázaro JL, Pou L, Castells L, Caralt M, Blanco L, Gantxegi A, Margarit C, Charco R. Indications and management of everolimus after liver transplantation. *Transplant Proc* 2009 Jul-Aug; 41 (6): 2172-6. ➪ IF: 1.055.

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2.5 Area 5: Digestive Physiopathology and Hepatology

Research Group: Phisiology and Pathophisiology of the Digestive Tract

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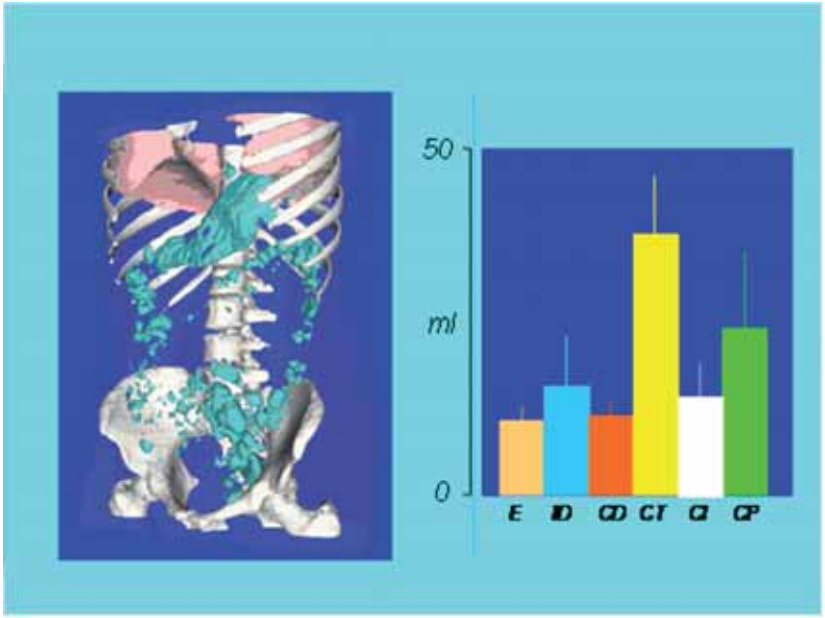
Sara Mendez Soriano
Antonio Torrejón Herrera

Objective

To investigate the integrated function of the intestinal tract including secretion, motility and absorption in health and disease, prioriticing the transmission of knowledge to clinical practice. The research on a digestive motility interacts with the disorders of visceral sensitivity, brain-gut axis and intestinal alergia. The research line on intestinal inflammation has also interactions with some aspects of enteric flora in inflammatory bowel disease.

Figure 66
Left pannel shows volume of gas in stomach, small bowel, right transverse, left and pelvic colon healthy subjects



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 neuro-myopathic disorders of the digestive tract. Specifically, an overload test has been developed that increases the sensitivity of intestinal manometry to the detect small bowel motor dysfunction. Non-invasive evaluation of intestinal motility has been approached using an original program of endoluminal image analysis using 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 distention has been identified by means of morpho-volumetric analysis of the abdominal cavity and electromyography of the abdominal walls.

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 programme 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

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 trandiferentiation, stellate cell activation, epithelial-to-mesenchymal transition and cancer development. In human pancreatitis we investigate environmental and genetic determinants (with special focus at CFTR dysfunction) and new treatment modalities for acute and chronic pancreatitis.

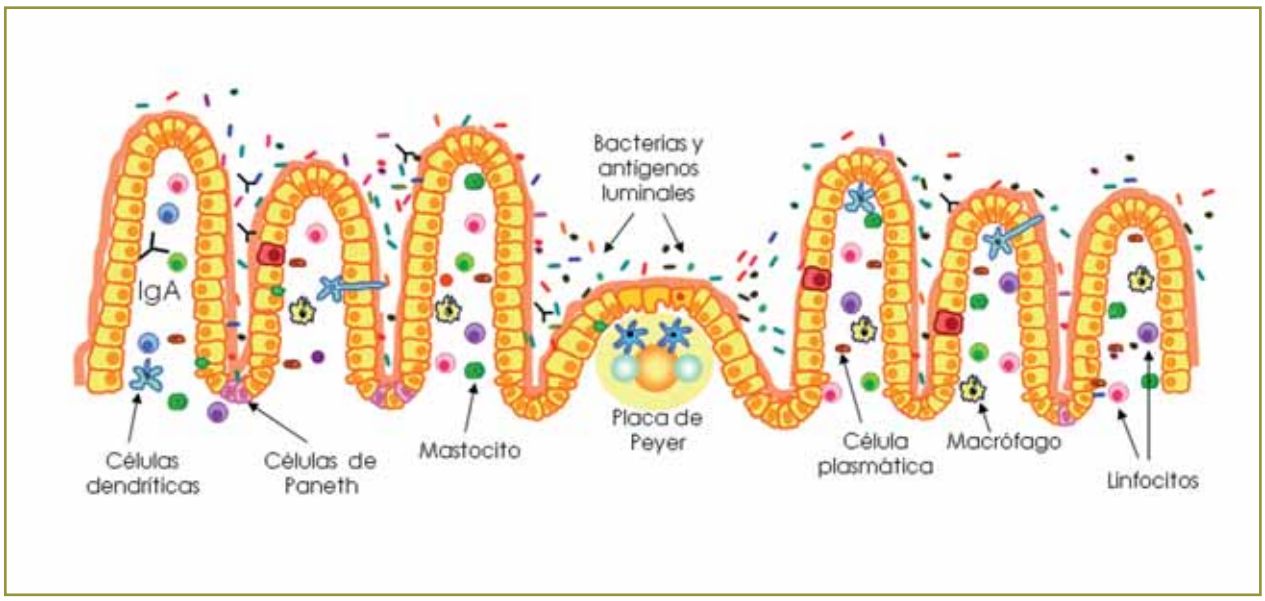


Figure 67
Components of intestinal barrier at that prevent passage of an antigens and luminal bacteria within the organism

Neuro-Immuno-Gastroenterology

Javier Santos Vicente

The 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. Clinical course is chronic and recurrent. However, sensitive and specific diagnostic biological markers are lacking and clinical management is suboptimal as well. 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 search for better targets helpful for the diagnosis, prevention and treatment of IBS and related disorders. In addition, preclinical and clinical assays are also being carried out.

Current Research Projects

PI: Fernando Azpiroz Vidaur
Neurofisiología y neurofisiopatología digestiva
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2006-03907
Funding: 133,100 €
Duration: from 2006 to 2009

PI: Fernando Azpiroz Vidaur
Dolor abdominal idiopàtic crònic: mecanismes fisiopatològics
Funding Agency: Fundació La Marató de TV3
Reference: MARATV3_072010
Funding: 177,425 €
Duration: from 2008 to 2011

PI: Francisco Guarner Aguilar
Señales antiinflamatorias del ecosistema microbiano intestinal
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2007-64411
Funding: 169,400 €
Duration: from 2007 to 2010

PI: Francisco Guarner Aguilar
Metagenomics of the Human Intestinal Tract (MetaHIT)
Funding Agency: European Comission
Reference: METAHIT-201052
Funding: 580,800 €
Duration: from 2008 to 2011

PI: Francesc Xavier Molero Richard
Evaluation of the antifibrogenic-antiinflamatory properties of the COX-2 inhibitor celecoxib in chronic pancreatitis
Funding Agency: Fundación Pfizer
Reference: PFIZER_01_2007
Funding: 63,952 €
Duration: from 2007 to 2009

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: from 2009 to 2011

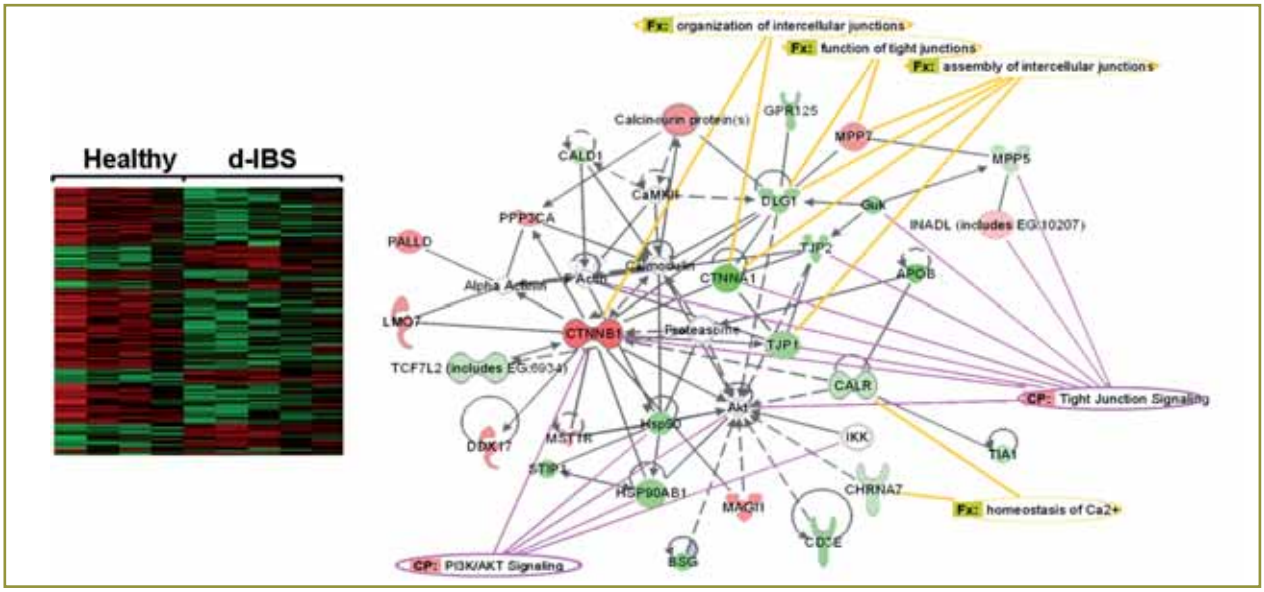
PI: Francisco Javier Santos Vicente
Efecto de la estabilización prolongada del mastocito intestinal con cromoglicato disódico en la evolución clínica y la microinflamación de la mucosa intestinal en los pacientes con síndrome de intestino irritable tipo diarrea
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90148
Funding: 168,190 €
Duration: from 2007 to 2010

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: from 2009 to 2011

PI: Francisco Javier Santos Vicente
Role of Eosinophil activation on mucosal inflammation in diarrhoea-IBS patients
Funding Agency: IFFGD International Founda for Functi Gastro
Reference: IFFGD_01_2008
Funding: 33,898.31 €
Duration: from 2008 to 2009

PI:Esteban Saperas Franch
Ensayo clínico, aleatorizado, controlado con placebo, paralelo, doble ciego, para evaluar el efecto de Talidomida en la prevención de la recidiva de la hemorragia en pacientes con angiodisplasia gastrointestinal
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00282
Funding: 173,030 €
Duration: from 2009 to 2011

Figure 68
Both figures show differences in gene expression in the jejunal mucosa of d-IBS patients compared to healthy volunteers. Moreover, signalling pathways linked to the transcriptomic profile of d-IBS highlight the epithelial barrier function and mast cell biology as differentially active in these patients



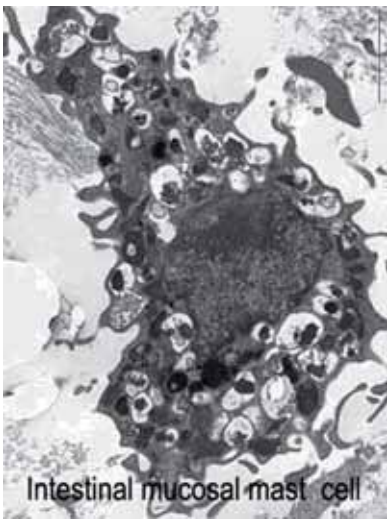


Figure 69
Intestinal mucosal mast cell

Publications

Impact Factor: 86.982

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Guarner L, Navalpotro B, Molero X, Giralt J, Malagelada JR Management of painful chronic pancreatitis with single-dose radiotherapy. *Am J Gastroenterol* 2009 Feb; 104 (2): 349-55. ⇨ IF: 6.444.

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2.6 Area 6: Infectious Diseases and AIDS

Research Group: Infectious Diseases

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Eva van den Eynde Otero
Sara Villar del Saz Cano

Technicians
Xavier Gomis Rodríguez

Objective

The Infectious Diseases Service, created in 1996, has since its origin a vocation for teaching and research, both related to their main task which is health care. Most of the research that develops in the Service is clinical, with the intention of trying to provide answers or at least to increase knowledge of the problems we see in our day to day as doctors at a hospital of infectious diseases where the complexity is very important.

All the different lines of research created, have responsible physicians belonging to the stable staff of the Service and working directly on individual problems.

The Service develops most of its investigation within the environment 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 is considered a Consolidated Research Group in Catalonia.

Research Lines

Coinfection HIV / HCV

Manuel Crespo

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.

Opportunistic infections in HIV + patients

Esteve Ribera Pascuet and Vicenç 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 the 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 line is divided into pharmacokinetics and toxicity lines. The main objective of the pharmacokinetic research line is studying drug plasma levels of those drugs susceptible of presenting interactions, knowing whether drug levels are inside the therapeutic range, evaluating potential interactions and evaluating the impact of some co-infections in plasma concentrations (chronic HCV infection, tuberculosis,...) and whether if its necessary to modify doses in these cases. The main objective of the toxicity line is to evaluate the side effects that can occur with antiretroviral therapy, especially mitochondrial toxicity, lypodystrophy and metabolic complications, looking for factors that contribute to their apparition and looking for potential solutions.

Orthopaedic bone and joint infection

Carlos Pigrau Serrallach and Dolors Rodríguez Pardo

The aim of the research are 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

Vicenç 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. In this way we are studying changes in incidence, clinical presentation of pneumococcal infection in adults, serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae*. In the next future novel antipneumococcal vaccines will be implemented and a continuous monitoring of these infections is needed.

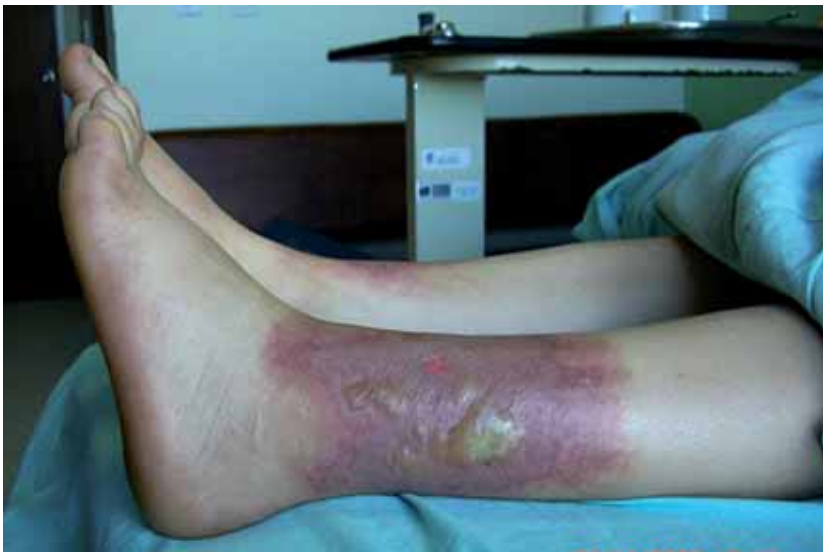

Figure 70
This kind of infections are studied in this group

Infection in the oncohematologic patients

Isabel Ruiz

To establish the risk and type of infection in different populations receiving chemotherapy according to the 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 immigrant population under chemotherapy.

Invasive fungal infections (IFI)

Joan Gavaldà and Isabel Ruiz

Surveillance studies of invasive candidiasis in our country. PK/PD antifungal studies in animal model. To study voriconazole and posaconazole plasma levels and its applications in clinical management of IFI. To establish the risks, incidence, types and natural history of IFI in different setting to applicate a more rational and successful preventative strategies.

Infections in solid organ transplant

Joan Gavaldà and Oscar Len

The research of 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*

Dolors Rodríguez and Benito Almirante

Due to the increasing number of cases of *Clostidium difficile* associated diarrhoea (CDAD) reported worldwide, our research line attempt to know the epidemiology of CDAD in 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

Israel Molina

The main lines of research are focused at 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.

Also devote 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

We study the most relevant epidemiological, clinical, and therapeutic features of infections caused by multidrug-resistant pathogens, specially methicillin-resistant *S. aureus* and multidrug-resistant gramnegative bacilli.

Central catheter infection

Benito Almirante and Nuria Fernández Hidalgo

An in vivo experimental model of *Staphylococci* and *Candida* central-venous catheter-related infections has been developed. We evaluate several courses of antimicrobials alone or in combination with anticoagulants.

Infective endocarditis

Benito Almirante and Nuria Fernández Hidalgo

We prospectively study the epidemiological changes of infective endocarditis at the beginning of the XXI century and, especially, their consequences on outcome. Research is focused on modifiable risk factors for mortality.

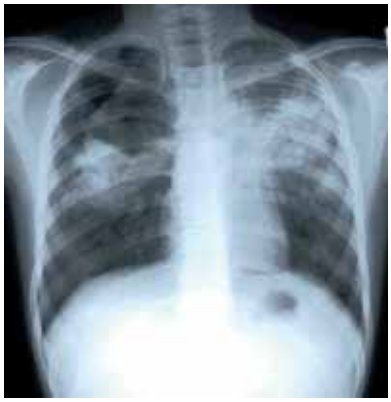

Figure 71
Pneumonia infection

Infections secondary to cytomegalovirus and Epstein Barr virus

Joan Gavaldà

Infections by virus of the family *Herpesviridae* and specifically cytomegalovirus (CMV) and Eppstein Barr virus (EBV) are common in recipients of solid allograft. Besides the direct effects related to disease caused by the infection itself, indirect effects caused by its appearance are very important as well. 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 Posttransplant Lymphoproliferative Disease. In this research line, several projects that tried and still try to find answers to the questions previously asked are included.

Animal models of infection

Joan Gavaldà

The aim of the Research Line using Animal Models of Infection carried out in the Research Lab on Infectious Diseases is try to find answers to questions asked in the Clinical 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.

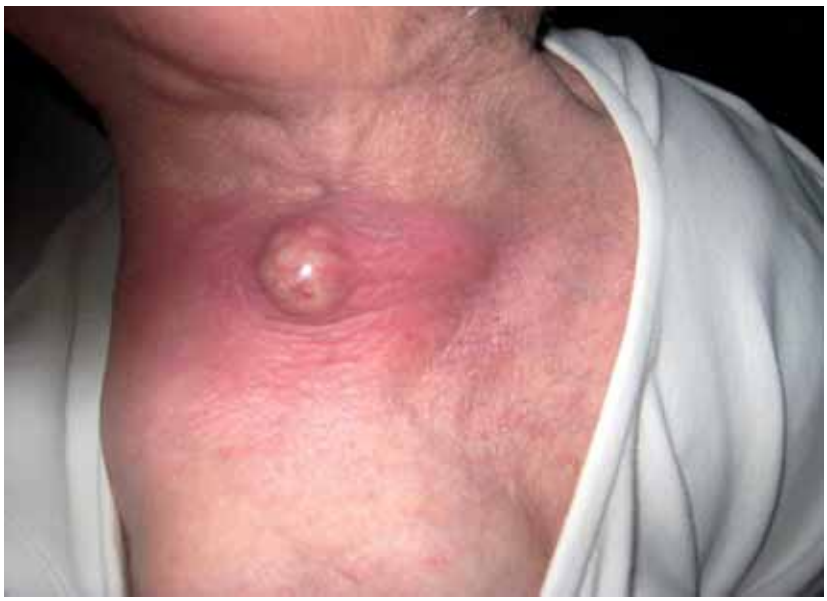

Figure 72
Tuberculoses disseminated with ganglionic affectation

Current Research Projects

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: from 2007 to 2010

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: from 2008 to 2011

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: from 2008 to 2010

PI: Israel Molina Romero
INTER Support Action (International Network of Teleconsultation Excellecence & Referral
Funding Agency: European Commission
Reference: INTER-23610
Funding: 33,590 €
Duration: from 2009 to 2010

Publications

Impact Factor

162.029

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: 201,465 €
Duration: from 2009 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 postquirúrgica precoz y hematógena de prótesis articular

Funding Agency: Fondo de Investigación Sanitaria
Reference: EC08/00223
Funding: 9,680€
Duration: from 2009 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: from 2007 to 2010

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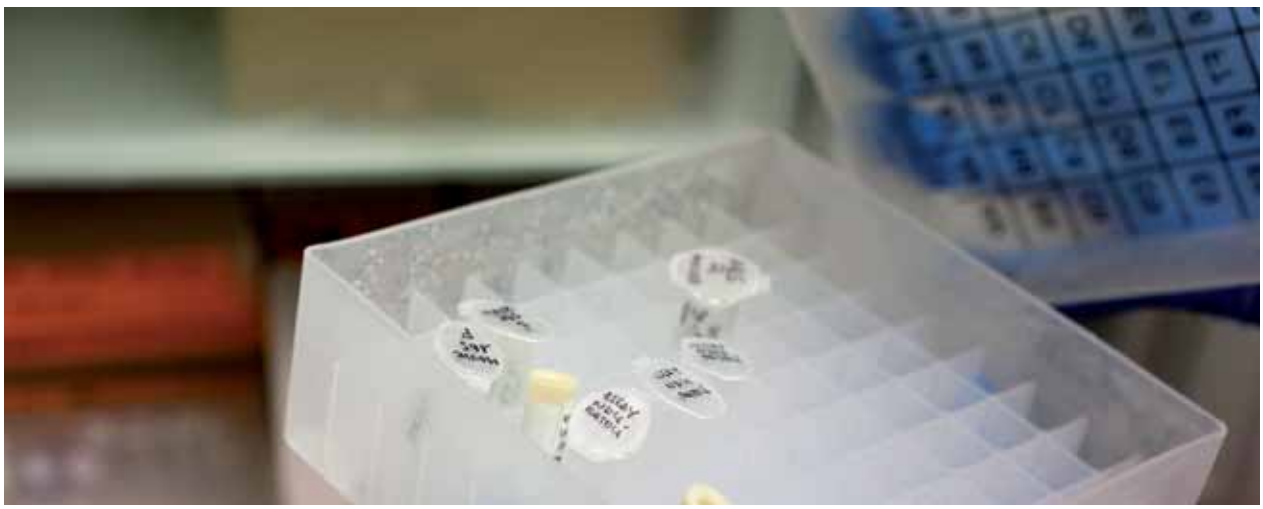

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2.6 Area 6: Infectious Diseases and AIDS

Research Group: Infection, Sepsis and Organic Failure and Critical Patient Disease

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José Luis Bóveda Treviño
Jesús Caballero López
Laura Campos García
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Lluis Llopart Corsà
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Mercedes Palomar Martínez
Marcos Pérez Carrasco
Águeda Pérez García
Lourdes Pérez Rodríguez
Isabel Porta Pampalona
Oriol Roca Gas
Juan Carlos Ruiz Rodríguez
Judith Sacanell Lacasa
Joaquim Serra Vich
Luis Tenorio López

Technical
Paquita Cornet Ciurana

Objective

The objective of this group is to carry out an investigation with critically ill patients, especially regarding physiopathological alterations and their relation with the clinical evolution of patients. There are areas of particular interest such as infectious diseases, acute respiratory failure and its treatment and acute hemorrhagic neurovascular disease, including experimental research on animals.

Research Lines

Studying respiratory failure in lung transplantation postoperative
Lluís Tenorio López

Disorder of haemostasis in critically ill patients
José Luis Bóveda Treviño

Sedation and psychological distress in patients undergoing mechanical ventilation
Jesús Caballero López

Acute respiratory failure
Judith Sacanell Lacasa

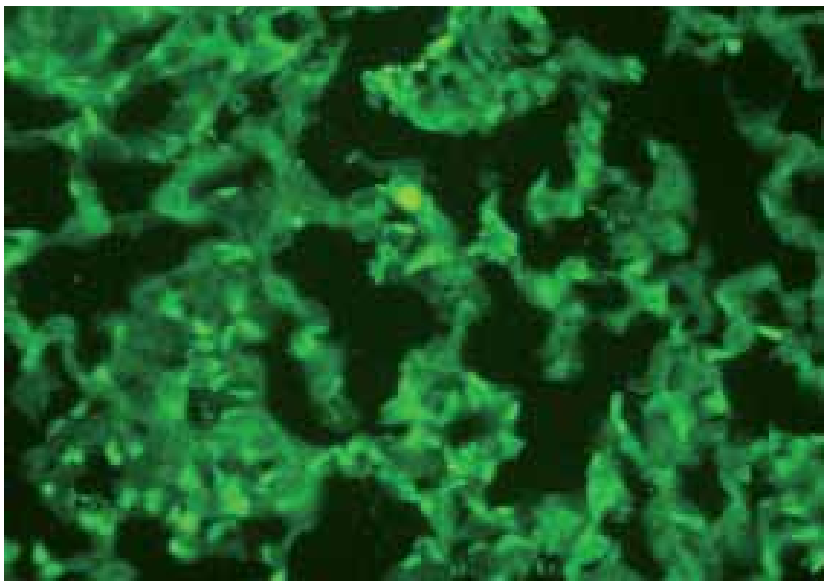

Figure 73
Alveolar apoptosis analysis, through TUNEL method, of a lung with acute lung injury produced by LPS instillation in animal-experimentation model. This investigation has been carried out in collaboration with the Servei d'Anatomia Patològica de l'Hospital

Publications

Impact Factor: 19.741

Infectious disease in critically ill patients
Mercedes Palomar Martínez

Systemic inflammatory response syndrome
Juan Carlos Ruiz Rodríguez

Cardiopulmonary resuscitation
Xavier Nuvials Casals

Neurocritically ill patient
Isabel Porta Pampalona

Experimental studies on acute lung injury in animal model
Joan Ramon Masclans

Charco R, Malagelada C, Llopart L, Bueno J, Bilbao I, Caralt M, Vilallonga R, Gavaldà J, Dot J, Abu-Suboh M, Planas M, Accarino A, Armengol-Miró JR, Azpiroz F. Non-anatomical intestinal transplantation. *Rev Esp Enferm Dig* 2009 Feb; 101 (2): 139-41, 141-3. ⇨ IF: 1.263.

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Hansen S, Schwab F, Behnke M, Carsauw H, Heczko P, Klavs I, Lyytikainen O, Palomar M, Riesenfeld Orn I, Savey A, Szilagyi E, Valinteliene R, Fabry J, Gastmeier P. National influences on catheter-associated bloodstream infection rates: practices among national surveillance networks participating in the European HELICS project. *J Hosp Infect* 2009 Jan; 71 (1):66-73. ⇨ IF: 2.956.

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Palomar M, Álvarez-Lerma F. To Ithaca Without Odysseus.]*Enferm Infecc Microbiol Clin* 2009 Dec; 27 (10): 559-60. ⇨ IF: 1.432.

2.6 Area 6: Infectious Diseases and AIDS

Research Group: Microbiology

Group Leader
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Researchers
Antònia Andreu Domingo
Rosa M. Bartolomé Comas
Núria Martín Casabona
Gema Codina Grau
Juan José González López
Anna M. Planes Reig
M. Teresa Tórtola Fernández

Researchers in Training
Alicia Coelho
J. Natalia Quintero Zárate
Nieves Larrosa Escartín
Eva Roselló Mayans
Elena Sulleiro Igual

Technicians
Thais Cornejo Sánchez
Cristina Mellado Claros

Objectives

- Working on its main basic lines of activity: mechanisms of resistance to antimicrobials, pathogenicity, taxonomy and epidemiology, and infectious diseases diagnostics.
- Promoting a more clinic research resulting of welfare work.
- Taking part actively in RETIC net of the *Instituto de Salud Carlos III: Red Española de Investigación en Patología Infecciosa (REIPI).*
- Continuing its labor as *Laboratori de Suport a la Direcció General de Salut Pública de la Generalitat de Catalunya.*

Research Lines

Mechanism of Antimicrobials Resistance

Klebsiella pneumoniae *and* Escherichia coli *which carry* β*-lactamases* $bla_{CTX\text{-}M\text{-}15}$*:*

Alicia Coelho

Epidemiological and molecular study of *K. pneumoniae* clones and multiresistant *E. coli* which produce this enzyme. Its main goal is to define the epidemic expansion of these strains and to compare the vectors that carry these genes.

Plasmid mediated bla_{oxy}

Juan José González López

Description of the first plasmid carrying bla_{oxy} β-lactamase; and study of its diffusion capacity.

Study the antimicrobial activity of new antimicrobials

Rosa M. Bartolomé

The progressive increase of resistances 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

Nuria Martín Casabona

Standardization's techniques to study the sensitivity of *M. tuberculosis* and *M. avium*. Participating in the international net of WHO and IUATLD. Acting as Supranational Reference Laboratory of WHO to control the quality of the susceptibility tests of *M. tuberculosis*. Standardization's susceptibility tests of *M. tuberculosis* to second-line drugs.

Pathogenicity

Escherichia coli: *Extraintestinal infection, population drifts and virulence factors*

Antonia Andreu

Study of virulence factors, phylogenic groups and pathogenicity islands of *E. coli* which cause extraintestinal infections through molecular techniques. Evaluating the pathogenic capacity of strains of various phylogenic groups with a variable number of virulence factors through 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 of 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) at outpatient environment*

Nieves Larrosa Escartín

Multicentric work between our group and other state centers that study the relation among epidemiology of colonization and the pathological processes that cause MRSA strains and their relation with virulence factors.

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 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 know their incidence in lung transplantation in our country and evaluating the role played by respiratory viruses in the evolution to the 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: from 01/01/2008 to 30/12/2010

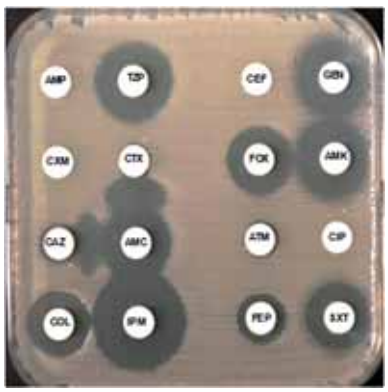

Figure 74
Antibiogram of *K. pneumoniae* that carries β-lactamasa CTX-M-15

Publications

Impact Factor: 106.993

Álvarez-Uria G, Falcó V, Martín-Casabona N, Crespo M, Villar del Saz S, Curran A, Ocaña I, Ribera E, Pahissa A. Non-tuberculous mycobacteria in the sputum of HIV-infected patients: infection or colonization? *Int J STD AIDS* 2009 Mar; 20 (3): 193-5. ⇨ IF: 1.075.

Ángel Diaz M, Ramon Hernández J, Martínez-Martínez L, Rodríguez-Baño J, Pascual A, Martínez Peinado C, Ordas JF, Garduño E, Domínguez M A, Navarro F, Prats G, *et al.* Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in Spanish hospitals: 2nd multicenter study (GEIH-BLEE project, 2006). *Enferm Infecc Microbiol Clin* 2009 Nov; 27 (9): 503-10. ⇨ IF: 1.432.

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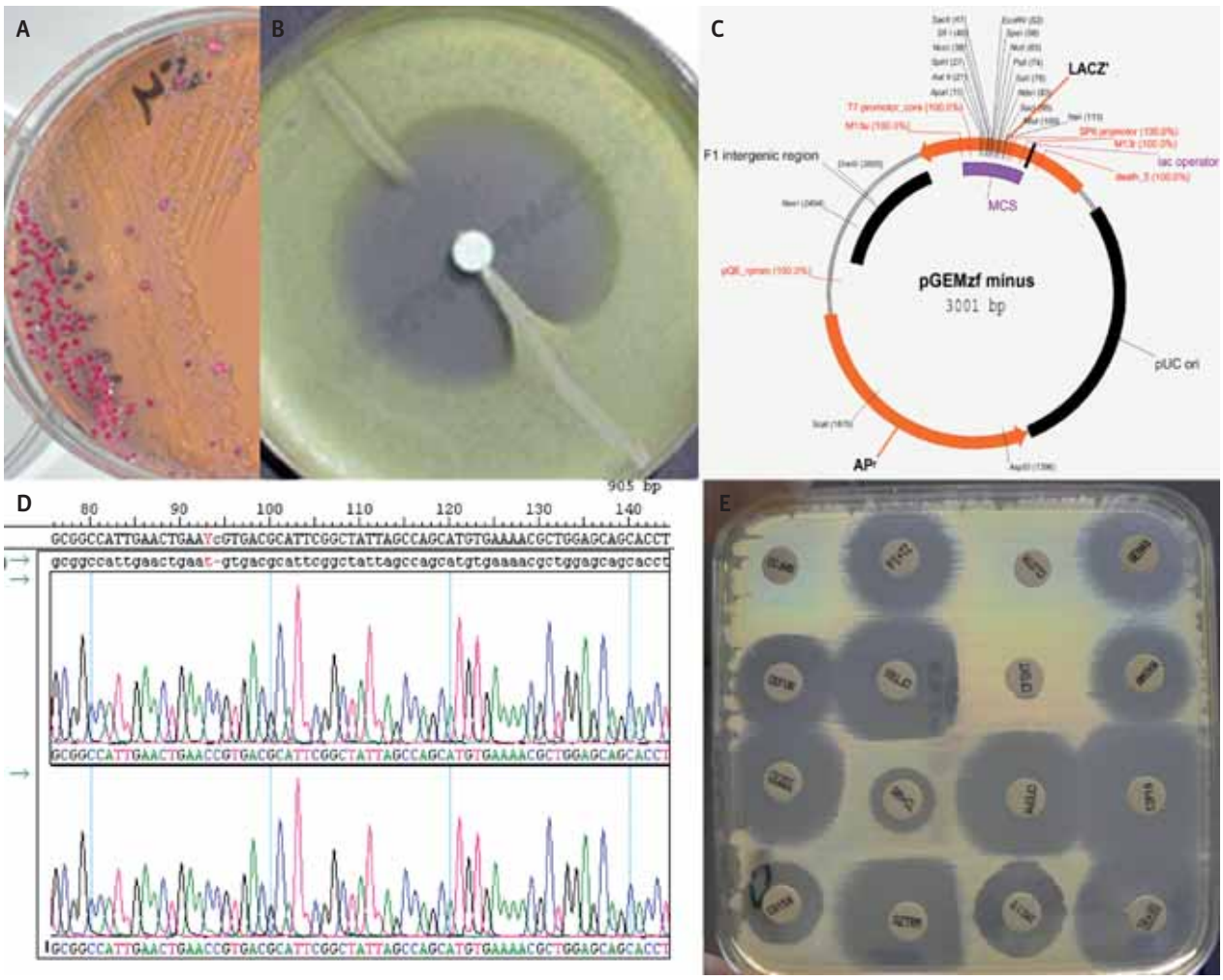

Figure 75
β-lactamase characterization
A. Bacterial isolation. **B.** Got's test. **C.** Cloning. **D.** Sequencing. **E.** Antibiogram

Coelho A, Mirelis B, Alonso-Tarrés C, Nieves Larrosa M, Miró E, Clivillé Abad R, Bartolomé RM, Castañer M, Prats G, Johnson JR, Navarro F, González-López JJ. Detection of three stable genetic clones of CTX-M-15-producing *Klebsiella pneumoniae* in the Barcelona metropolitan area, Spain. *J Antimicrob Chemother* 2009 Oct; 64 (4): 862-4. ⇨ IF: 4.328.

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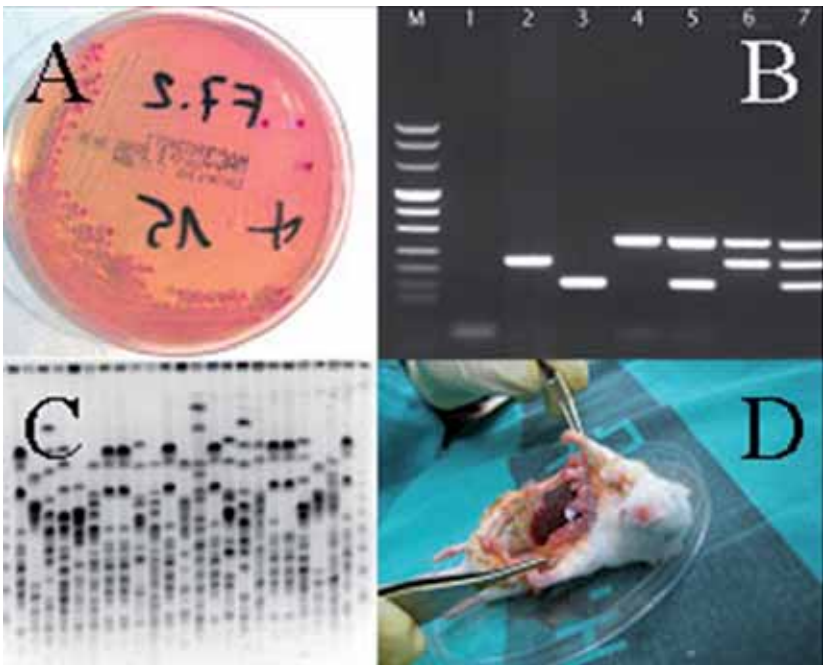

Figure 76
A. Selecting the microorganisms to be studied
B. Establishing the phylogenic group
C. Clonality relation among related microorganisms
D. Studying the correlation, in animal testing, among the potential pathogen of the microorganism and its phylogenic drift

García-Aljaro C, Moreno E, Andreu A, Prats G, Blanch AR. Phylogroups, virulence determinants and antimicrobial resistance in stx(2) gene-carrying *Escherichia coli* isolated from aquatic environments. *Res Microbiol* 2009 Oct; 160 (8): 585-91. ⇨ IF: 2.055.

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Planes AM. Usefulness of anaerobic vial in the diagnosis of bacteremia or fungemia. *Med Clin* (Barc) 2009 May 23; 132 (19): 743-5. ➪ IF: 1.258.

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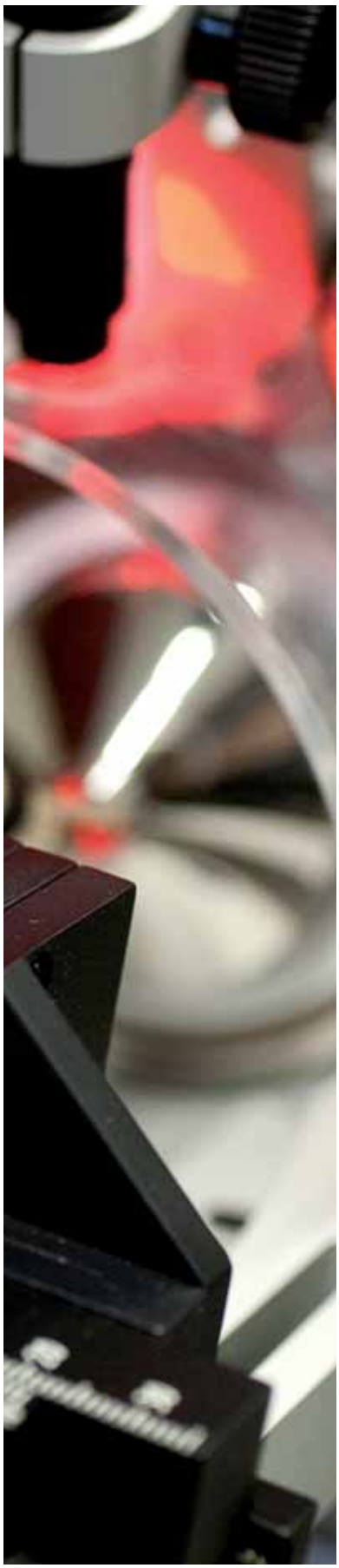

2.7 Area 7: Immunology: Respiratory, Systemic and Genetic Disorders

Research Group: Immunology

Group Leader
Teresa Español Borén
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Researchers
Drahomira Detkova
Isabel Caragol

Objectives

- We are interested in the physiopathogenic mechanisms (immunologic factors, infections, etc.) involved in the evolution and prognosis of patients with Primary Immunodeficiencies (PID).
- And 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 and Drahomira Detkova

Immunological studies of relatives of patients with Common variable immunodeficiency and IgA deficiency to know the real incidence of these defects in family clusters, that will facilitate further genetic studies
Teresa Español, Isabel Caragol and Drahomira Detkova

Publications

Impact Factor: 34.403

Gathmann B, Grimbacher B, Beaute J, Dudoit Y, Mahlaoui N, Fischer A, Knerr V, Kindle G, Caragol I, *et al.* The European internet-based patient and research database for primary immunodeficiencies: results 2006-2008. *Clin Exp Immunol* 2009 Sep; 157 Suppl 1: 3-11. ⇨ IF: 2.853.

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Locci M, Draghici E, Marangoni F, Bosticardo M, Catucci M, Aiuti A, Cancrini C, Marodi L, Español T, Bredius RG, Thrasher AJ, Schulz A, Litzman J, Roncarolo MG, Casorati G, Dellabona P, Villa A. The Wiskott-Aldrich syndrome protein is required for iNKT cell maturation and function. *J Exp Med* 2009 Apr 13; 206 (4): 735-42. ⇨ IF: 15.219.

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Martínez-Pomar N, Detkova D, Arostegui JI, Álvarez A, Soler-Palacín P, Vidaller A, Español T, Sampalo A, Gracia J de, Hernández M, Yagüe J, Matamoros N. Role of TNFRSF13B variants in patients with common variable immunodeficiency. *Blood* 2009 Sep 24; 114 (13): 2846-8. ⇨ IF: 10.432.

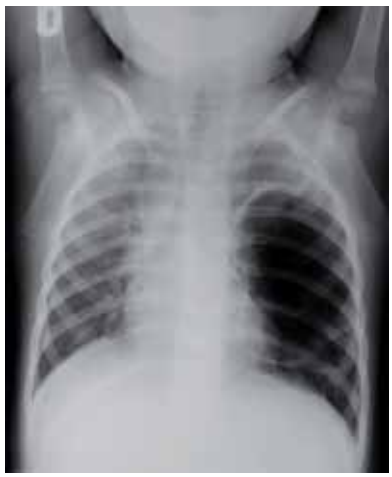
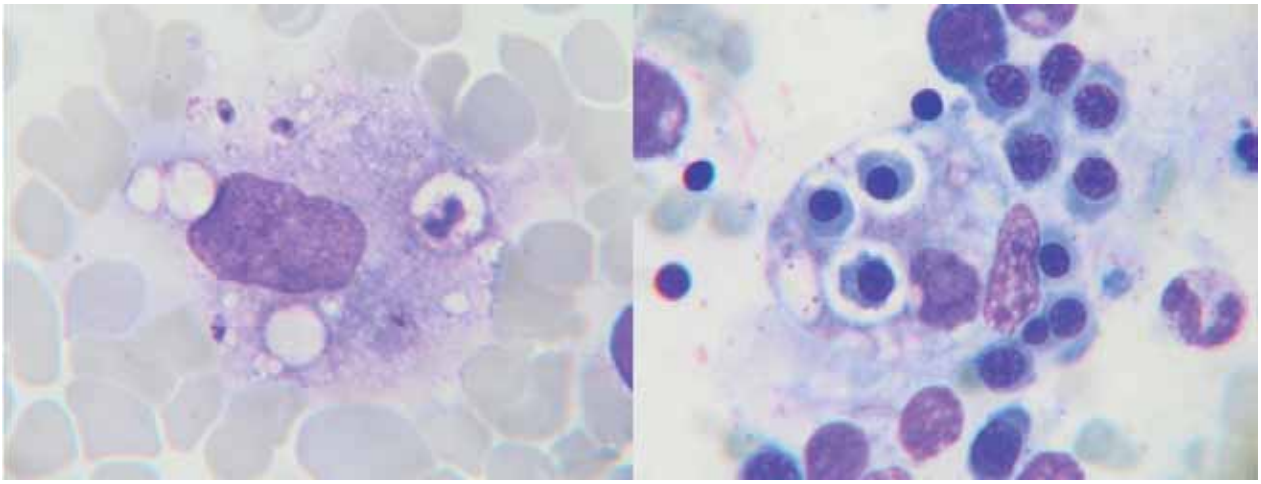


Figure 77
Lung cyst in a patient with Hyper IgE syndrome and a mutation in STAT3

Figure 78
Visceral leishmaniasis in a patient with XL-CGD who developed a macrophage activation syndrome



2.7 Area 7: Immunology: Respiratory, Systemic and Genetic Disorders

Research Group: Ear, Nose and Throat Disorders

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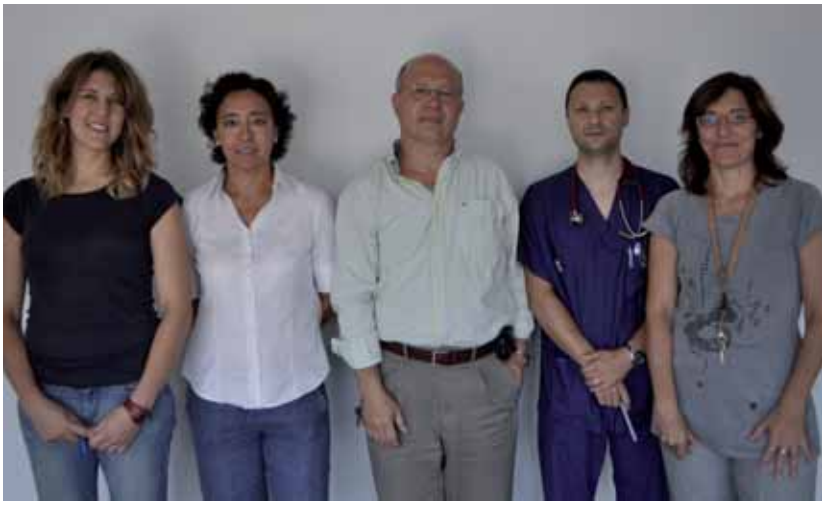
Manuel García Lopez
Pere Huguet Redecilla
Mª José Jurado
Santiago Lavín González
Marta Planellas Bachs
Isabel Roca Bielsa
Roser Velarde Nieto



Objectives

- Defining similarities and differences between human patients and animals regarding this disease in order to use, if that were the case, brachiocephalic dogs as animal model in treatment options of human disease.
- Validating diagnostic accuracy of sentinel ganglion in pharyngeal-laryngeal carcinoma T1-2 No as stadiage tool, through a lymphogammagraphy 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 effectiveness of symptom quest in gastroesophageal reflux diagnosis in these patients.

Research Lines

Obstructive sleep apnea syndrome (osas)

Juan Lorente Guerrero

Research group in obstructive sleep apnea syndrome (OSAS), using as animal model the brachiocephalic breed, Boxer (English and French) is constituted by 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 that were the case, use brachiocephalic breed as animal models in the options of treatment for the human disease.

The specific objectives of this research line are the following ones:

- Defining histopathological and immunohistochemical changes regarding myosin fiber distribution of type I and II, that produce soft palate in brachiocephalic dogs affected by upper airway obstruction syndrome, regarding dogs without this pathology which have been euthanize for different reasons.
- Establishing existing similarities and differences between soft palates in brachiocephalic dogs affected by upper airway obstruction syndrome and uvula of human patients with OSAS.
- Determining correlation between degree of injuries observed at histopathological and immunohistochemical level and the clinics presented in each patient, firstly in each specie alone and afterwards comparing them.
- 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 dogs that are not affected by this pathology.
- Evaluating surgical treatment efficacy as therapeutic alternative, in dogs affected by upper airway obstruction syndromes, through a clinical monitoring, supported by complementary diagnostic tests.

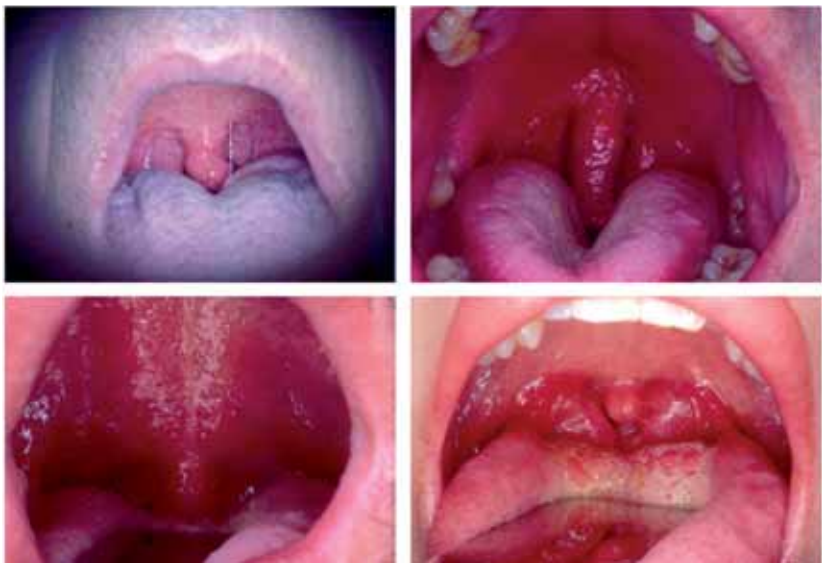


Figure 79
Palates of OSAS patients

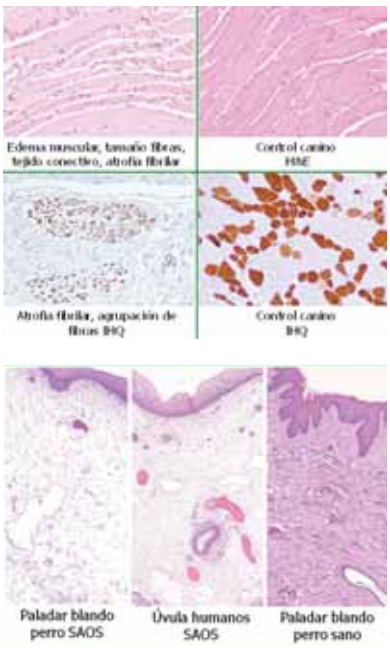


Figure 80
Technique of partial resection veil palate (RPP)

Sentinel ganglion in pharynx and larynx carcinoma

Juan Lorente Guerrero

In this project, we are working on the patients collection phase. Currently we have 5 patients.
Objectives of this study are:

- Validating sentinel ganglion diagnostic accuracy in carcinoma pharyngolaryngeal T1-2 No as staging tool, through a SPECT-CT lymphoscintigraphy the day before surgery and surgical location of sentinel ganglion using a probe during surgery.
- Studying and identifying lymphatic drainage of these tumors.
- Comparing its usefulness versus conventional staging in clinics and CT.
- Avoiding overtreatment of patients, eliminating VCG in No when Sentinel Ganglion is negative (once validated this technique).

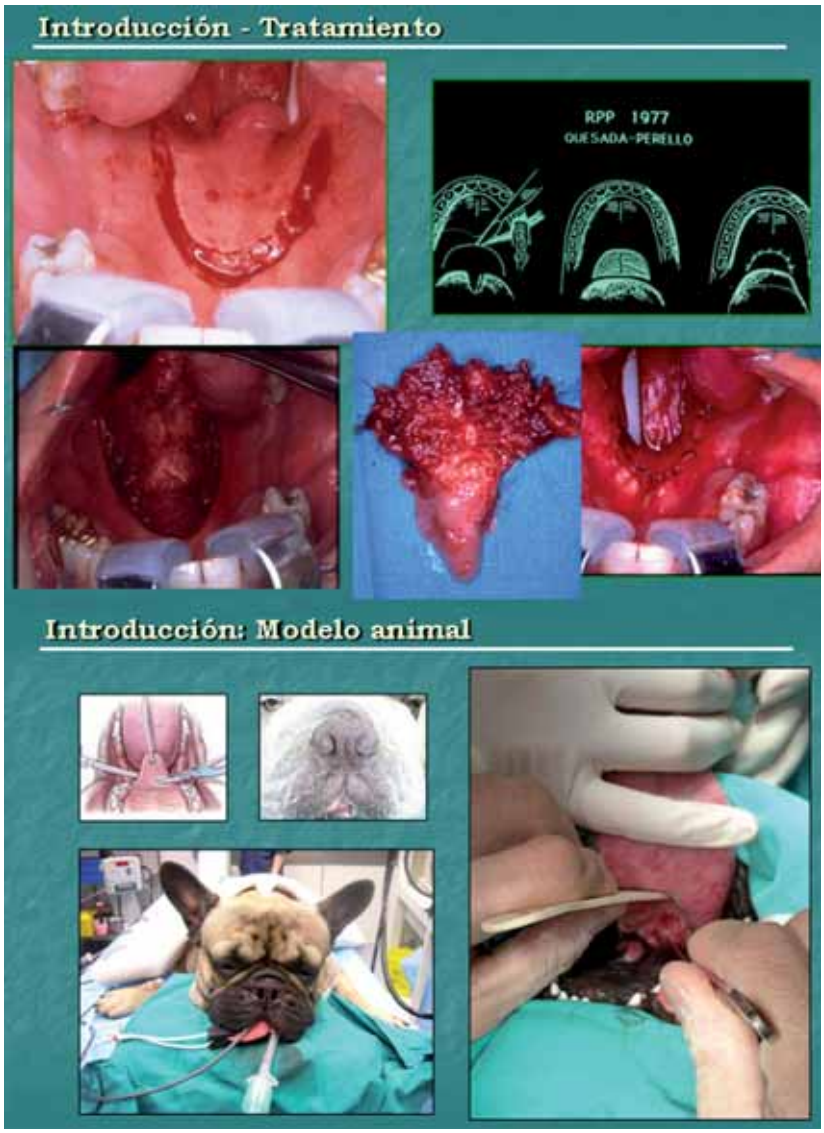


Figure 81
Animal model: Resection of the soft palate

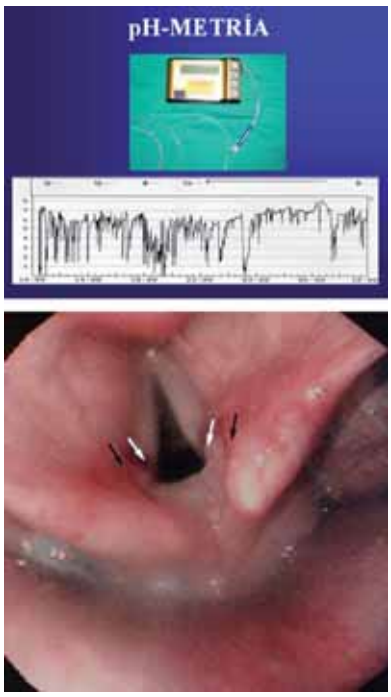


Figure 82
Reflux laryngitis

Gastroesophageal reflux prevalence in patients with obstructive sleep apnea syndrome

Juan Lorente Guerrero, Juan Luis Quesada Martínez, Mª Jose 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 influence of OSAS upon GERD are not known yet.

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.

Identifying patients with gastroesophageal reflux among patients affected by obstructive sleep apnea, in order to establish therapeutic measures to prevent GERD complications.

Figure 83
Endolaringea Microsurgery: Injection of radiate tracer in the tumor

Publications

Impact Factor: 4.454

Ensenat J, Quesada JL, Aparicio J, Pamies C, Barber X, Topczewski T, Ferrer E. Prospective comparative study on 50 patients between microsurgical sublabial transsphenoidal approach and endoscopic endonasal transsphenoidal approach. *Neurocirugia* (Astur) 2009 Aug; 20 (4): 335-44; discussion 344-5. ⇨ IF: 0.277.

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Morales J, García M, Pérez C, Valverde JV, López-Sánchez C, García-Martínez V, Quesada JL. Low frequency electromagnetic radiation and hearing. *J Laryngol Otol* 2009 Nov; 123 (11): 1204-11. ⇨ IF: 0.796.

Selva-O'Callaghan A, Sampol G, Romero O, Lloberes P, Trallero-Araguas E, Vilardell-Tarrés M. Obstructive sleep apnea in patients with inflammatory myopathies. *Muscle Nerve* 2009 Feb; 39 (2): 144-9. ⇨ IF: 2.594.

2.7 Area 7: Immunology: Respiratory, Systemic and Genetic Disorders

Research Group: Pulmonology

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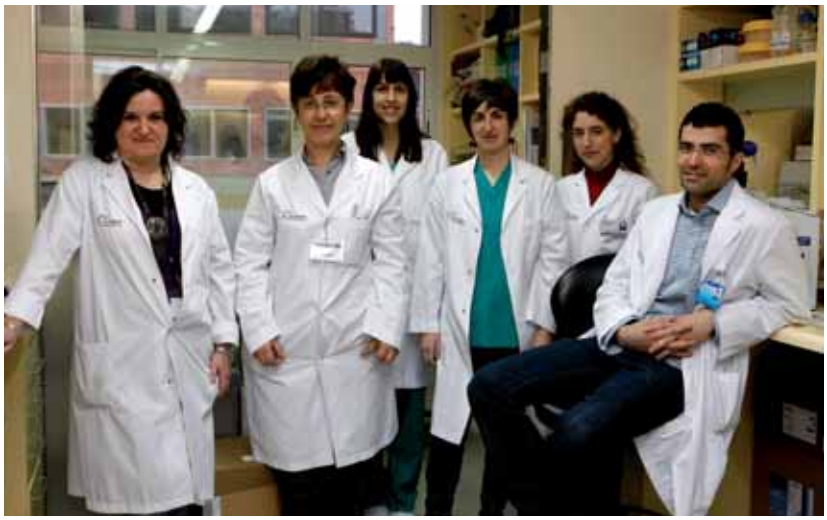
Objectives

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.

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

The Group is considered a referral team for the diagnosis and treatment of "work-related lung diseases" in Catalonia, centring 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 results 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 been 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 Gracias

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 a1-antitrypsin deficit. Moreover, the team is considered to be expert in the control of tuberculous disease.

COPD and pleural diseases

Jaume Ferrer

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 a-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

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

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: PI060256
Funding: 26,837.80 €
Duration: from 2007 to 2010

Figure 84
Whole body plethysmograph to measure the ventilatory function in mice

PI: María Jesús Cruz Carmona
Utilidad de la medida del pH en el condensado de aire exhalado en el diagnóstico de asma ocupacional
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/90086
Funding: 15,125 €
Duration: from 2008 to 2009

PI: Jaume Ferrer Sancho
Validación de metodología de determinación del contenido de amianto en población urbana española a partir de tejido pulmonar y lavado broncoalveolar
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/90478
Funding: 22,385 €
Duration: from 2008 to: 2009

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: from 2007 to 2010

PI: Sergi Martí Beltran
Eficacia de dos sistemas de ahorro de oxígeno líquido en deambulación
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/90074
Funding: 11,616 €
Duration: from 2008 to 2009

PI: Sergi Martí Beltran
¿Existe una correlación entre la actividad inflamatoria y la gravedad de la EPOC?
Funding Agency: Sociedad Española de Patología Torácica (SEPAR)
Reference: SEPAR/06
Funding: 9,000 €
Duration: from 2006 to 2009

PI: Víctor Monforte
Estudio del surfactante en pacientes con trasplantados pulmonares que reciben profilaxis con anfotericina B liposomal (ambisome) nebulizada como profilaxis de la infección por aspergillus *spp.*
Funding Agency: Sociedad Española de Patología Torácica (SEPAR)
Reference: SEPAR/06
Funding: 18,000 €
Duration: from 2006 to 2009

PI: Fco. 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: from 2007 to 2010

PI: Fco. 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: from 2009 to 2011

PI: Fco. Javier Muñoz Gall
Papel de la ocupación en la gravedad del asma
Funding Agency: Fundació Catalana de Pneumologia (FUCAP)
Reference: FUCAP/09
Funding: 12,000 €
Duration: from 2009 to 2010

PI: Antonio Román
Estudio de la utilidad clínica de la medición del gasto cardíaco en reposo y ejercicio de forma no invasiva mediante un método de inhalación de gases inertes (Innocor) en pacientes con hipertensión arterial pulmonar
Funding Agency: Fundació Catalana de Pneumologia (FUCAP)
Reference: FUCAP/08
Funding: 12,000 €
Duration: from 2008 to 2010

Publications

Impact Factor: 116.153

Antón E, Casanova A, Xaubet A, Román A, Villena V, Montero MC, Molina-Molina M, Pérez-Sánchez E, Sueiro A, Morell F, Girón RM, Ancochea J. Lymphangioleiomyomatosis: a study of 72 patients from the Spanish registry. *Sarcoidosis Vasc Diffuse Lung Dis* 2009 Jul; 26 (2): 85-91. ➪ IF: 1.267.

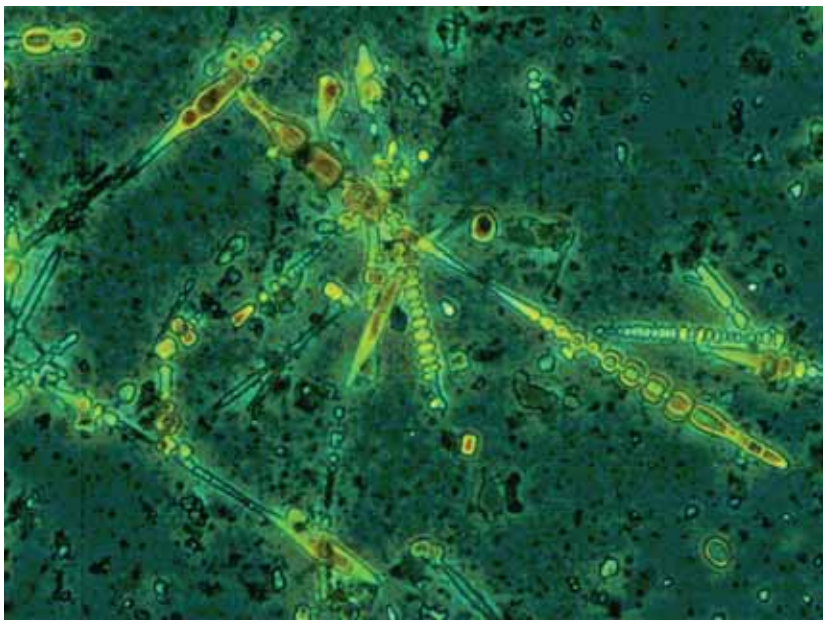


Figure 85
Asbestos bodies in lung

Balcells E, Anto JM, Gea J, Gómez FP, Rodríguez E, Marín A, Ferrer A, Batlle J de, Farrero E, Benet M, Orozco-Levi M, Ferrer J, Agustí AG, Galdiz JB, Belda J, Garcia-Aymerich J, *et al.* Characteristics of patients admitted for the first time for COPD exacerbation. *Respir Med* 2009 Sep; 103 (9): 1293-302. ⇨ IF: 2.338.

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2.7 Area 7: Immunology: Respiratory, Systemic and Genetic Disorders

Research Group: Systemic Autoimmune Diseases

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Objectives

Systemic autoimmune diseases are illnesses of unknown aetiology which present an autoantibody-mediated pathogenicity with a heterogeneous clinical behaviour characterized by different clinical manifestations. Our research is aimed at studying: 1) their aetiology (both at the genetic and the immunologic regulation levels); 2) their biologic and clinical expression (detection of new markers that can help us to characterize each single systemic autoimmune disease); 3) their morbi-mortality (by performing epidemiologic studies), and 4) their response towards the drugs given to the patients. With these objectives in mind, we seek to improve the diagnosis, the clinical follow-up, and the prognosis of our patients.

The Grup de Recerca de Reumatologia (GRR) is a biomedical research group specialized in the genomic research of chronic inflammatory diseases, principally of those affecting the musculoskeletal system like Rheumatoid Arthritis. Its main objective is the achievement of Personalized Medicine in this group of prevalent diseases through the generation of knowledge that helps to develop better therapeutical approaches. The GRR hosts the IMID-Biobank, a biobank specialized in the collection and preservation of samples and the associated clinical data from patients with chronic inflammatory diseases. By the end of 2009, the IMID-Biobank will already be storing 78,000 samples of this group of diseases. IMID-Biobank was originally created as part of the Singular and Strategic Project "IMID-Kit" funded by the Spanish Science and Innovation Minister and coordinated by the GRR. It is the first Spanish hospital biobank to have obtained the International Organization for Standardization (ISO 9001:2000) quality certification.

With regards to the clinical research area, the GRR also is performing studies on fibromyalgia and juvenile idiopathic arthritis. In the latter, the main objectives have been the consolidation of the collaboration with European research groups (PRINTO) for the study of the clinical and genetic heterogeneity of this rheumatic disease. The Pediatric Rheumatology Unit is actually a national reference in the study and treatment of the chronic inflammatory diseases of the musculoskeletal system in the infancy.

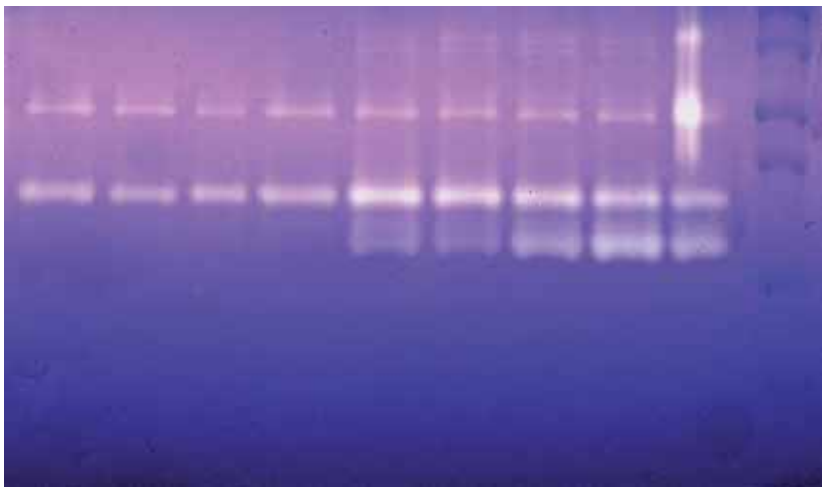

Figure 86
Pharmacologic mechanisms in cutaneous lupus. Induction of metalloproteinases (MMP2 i MMP9) in human skin fibroblasts after being treated with thalidomide

Research Lines

Study of IFN-gamma/STAT and TGF-beta/SMAD pathways in lupus patients with skin involvement. Role in the evolution to fibrosis

Josep Ordi Ros

With this project we aim at studying 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. Clinic and therapeutic implications.

Jesús Castro Marrero

The main goal of this research line consists on studying the effect that thalidomide may have in the 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 the 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. It 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 the responsible for triggering anti-DNA antibodies. To find out the reason why this DNA hypomethylation is taking place, we have evaluated the expression level 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 overexpression 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 for 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 being currently studied in our lab in patients with SLE. This virus has been detected in blood samples of patients suffering from chronic fatigue syndrome (CFS). Interestingly, many patients with lupus also suffer from CFS. Based on these facts, with 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 nowadays setting up the already described XMRV-specific PCR and RT-PCR assays. We will also study the immunologic response of these patients against particular XMRV proteins.

Urinary biomarkers detection in lupus nephritis

Josep 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/some biomarker/s (MCP-1, TWEAK, NGAL, APRIL, RANTES,...) that allow us to establish particular diagnosis and prognosis criteria equally effective or even more accurate than those obtained with the renal biopsy.

Immunologic lesional mechanisms in late adverse reactions against 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 the adverse effects.

Predictive kit to detect the possible establishment of late adverse effects related to bioimplants used in clinical practice

Jaume Alijotas Reig

A high variability in the prevalence of adverse effects with an immunologic basis seems to be related with any implant used in clinical practice. We have managed to find a particular association of HLA haplotypes that increase the risk for developing these effects up to 600 times. We are nowadays working on setting up a safe and reliable biochip or kit which predicts this risk easily in a routine test.

Characterization of mastocyte mediators released at intestinal level in patients with food allergy and irritable bowel syndrome. Relation with stress and intestinal permeability

Javier Santos and Mar Guilarte Clavero

This study establishes the importance of intestinal mastocytes on the regulation of the intestinal permeability in two inflammatory diseases such as food allergy and irritable bowel syndrome. It includes both experimental animal models and human studies.

Serological markers 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 on detecting anaphylaxis patients at 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 at detecting the prevalence of specific IgE in "polisensitized" patients towards pollen in Barcelona by means of the "component resolved diagnosis" technique from ISAC® (IgE specific microarray).

Cancer and myositis. Relevance of the anti-p155 antibodies and importance of the 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 diagnosis 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, the 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 from Europe and United States participate in this study. We contribute to add 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 diagnosis criteria for muscular inflammatory diseases. Although criteria given by Bohan and Peter are still used in clinical practice, some inflammatory diseases such as inclusion body myositis are not included. The hytopathological classification performed by Dalakas includes the latter entity but it does not take into account neither the paraneoplastic myositis nor those associated to systemic diseases.

Lung involvement in inflammatory myopathies

Albert Selva O'Callaghan

With this study we want to study the natural history of this syndrome mediated by anti-synthetase antibodies, the characterization of new antibodies that may be used as markers for lung involvement, as well as we aim at understanding better the etiopathogenicity and the treatment of this organic illness in patients with myositis.

Canine-myositis study

Albert Selva O'Callaghan

In this study we collaborate with the Faculty of Veterinary located at the Barcelona Autonomous University (Dr. Santiago Lavin) along with the Department of Pathology of the University of California (Prof G. Diane Shelton).

The only myositis spontaneous animal model is found in dogs, especially in Collies, and when it accompanies cancer, in Boxers. Several antibodies have been described in dogs but it is not known if they are also found in humans. Alternatively, myositis specific antibodies may be positive or negative in dogs. If human beings and dogs share a common autoimmune response, a new door can be opened to deepen in the etiopathogenia and the species-specificity of these illnesses.

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.

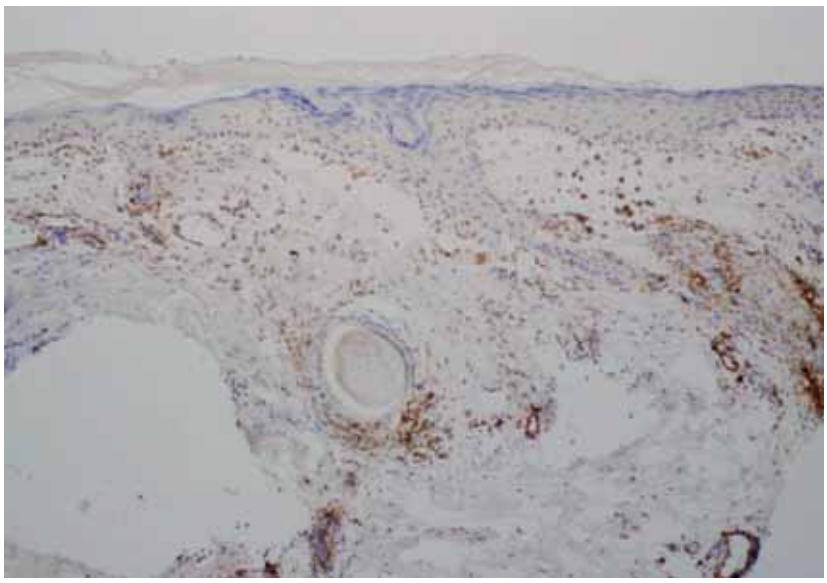

Figure 87
Dendritic cell infiltration ($CD123^+$) in the skin of a patient with discoid lupus

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.

Immunobiology and immunopathology of recurrent pregnancy loses and spontaneous loses

Jaume Alijotas Reig

Around 2-3% of reproductive-age couples suffer recurrent pregnancy loses. 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 at studying which isolated, and specially associated, anomalies can be identified as risk markers to be able to evaluate possible treatments.

Cellular microparticles study in women with and without antiphospholipid antibodies with recurrent pregnancy loses 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 loses and preeclampsia. It is thought that their thrombophilic capacity may be higher in those patients with antiphospholipid 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 loses, 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 throphoblastic).

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 to 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 the microparticles analysis, we could end up by finding several elements that might act as risk markers; in turn, it might even help us to fine-tune the currently used therapeutic approaches.

Development of the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS/EUROMAP)

Jaume Alijotas Reig and Immaculada Farran Codina

The so-called obstetric antiphospholipid syndrome seems to have pathogenic, biologic, therapeutic, and evolution features somehow different from the ones observed in those patients who suffer from 'classic' antiphospholipid syndrome. Although experience and scientific evidence seem to support this idea, there is a lack of information that allows us to suggest changes in the classification and/or therapeutic criteria. The European Forum on Antiphospholipid Antibody Syndrome has decided to carry on this project and it has chosen the Vall d'Hebron Hospital as the European Coordinating Centre. Many important 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-κB. 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 at detecting the intracellular signal pathways (STAT). We are also working on the characterization of the genes involved in these abnormal biologic responses.

Specific Antinuclear antibodies of scleroderma as markers for different clinical patterns

Carmen Pilar Simeón and Vicenç Fonollosa

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) with the different demographic and clinical features as well as with the disease prognosis.

Genetic basis of scleroderma

Carmen Pilar Simeón and Vicenç Fonollosa

With this study we aim at studying the genetic background of the disease to deepen in its pathogenesis to be able to establish links between genetic variations and different clinic-biologic patterns. This research is based on a multicentric study and it is led by Prof. Javier Martín from 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 and Vicenç Fonollosa

This multicentric study includes 14 hospitals with a cohort of 916 scleroderma patients. Its main goal consists in determining both the prognosis factors and the survival of these patients.

Significance of Capillaroscopy in Raynaud's phenomenon and scleroderma

Carmen Pilar Simeón and Vicenç Fonollosa

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

Vicenç Fonollosa and Carmen Pilar Simeón

This study, carried out along with researchers from the Hospital del Mar and from the "Institut Municipal d'Investigació Mèdica", aims at correlating 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.

Current Research Projects

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: from 2009 to 2011

PI: Albert Selva O'Callaghan

Aticuerpos antitransglutaminasa en biopsias musculares de pacientes con miopatía inflamatoria

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI080450
Funding: 33,880 €
Duration: from 2009 to 2011

PI: J. Martin, V. Fonollosa and CP. Simeón

Estudio de los factores genéticos asociados con susceptibilidad a esclerodemia mediante un rastreo sistemático del genoma

Funding Agency: Fundación Española de Reumatología (FER/SER)
Reference: FER/SER
Funding: 182,742 €
Duration: from 2008 to 2010

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

Efectivitat, seguretat i adecuació dels medicaments biotecnològics en el tractament dels pacients amb artritis reumatoide

Funding Agency: Agència Avaluació Tecnologia i Recerca Mèdica
Reference: 053/02/2006
Funding: 46,560 €
Duration: from 2007 to 2010

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-new-IMID"

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

PI: Sara Marsal Barril
Diagnóstico precoz de artritis reumatoide, psoriasis y enfermedad inflamatoria intestinal
Funding Agency: Fundación Caja Navarra
Reference: CAN2009-15450
Funding: 6,002.41 €
Duration: from 2009 to 2011

PI: Jaume Alijotas Reig
Estudio clínico e inmunológico de las reacciones inflamatorias tardías secundarias a los bioimplantes de uso médico
Funding Agency: SEMCC
Reference: SEMCC/01/07
Funding: 200,000 €
Duration: from 2007 to 2009

PI: Jaume Alijotas Reig
Citocinas, inflamación crónica y envejecimiento prematuro
Funding Agency: SEMCC
Reference: SEMCC/02/07
Funding: 100,000 €
Duration: from 2007 to 2009

PI: F Miró and J. Alijotas Reig
Envejecimiento endotelial y sus efectos pleiotrópicos sobre procesos inflamatorios, de la respuesta inmune y angiogénesis
Funding Agency: Fundacion Investigación Mutua Madrileña
Reference: FMM/05/2007
Funding: 60,000 €
Duration: from 2007 to 2010

PI: Jaume Alijotas Reig
Envejecimiento endotelial y procesos inflamatorios crónicos
Funding Agency: Fundació Agrupació Mutua
Reference: PFAM/2008
Funding: 15,000 €
Duration: from 2009 to 2010

PI: Jaume Alijotas Reig
Autoinmunidad, inflamación y complicaciones obstétricas
Funding Agency: GrupHotel
Reference: PM/21/2009
Funding: 90,000 €
Duration: from 2009 to 2012

Publications

Impact Factor: 132.773

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2.8 Area 8: Pathology, Cellular and Gene Therapy

Molecular Biology and Biochemistry Research Center for Nanomedicine (CIBBIM-Nanomedicine)

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The CIBBIM was created in 1995 as a joint effort of several scientist 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 in two main fields, the nanodiagnosis and the nanotherapy. The final mission of the CIBBIM-Nanomedicine is to foster basic research on biomarker discovery and new therapeutics 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 the 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 are a must to achieve success in "nanodiagnostics", as well as in "targeted delivery". There is an increasingly growing request of 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
- Aging Basic Research

Area 2
Experimental Chemistry and Applied Nanotechnology

This is a newly started area, which is currently focused 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-toxical in *in vivo* approaches.

On the other hand, this area also collaborates with external groups for 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 science research on biomarker discovery and new therapeutic targets, one additional aim of CIBBIM-Nanomedicine is to provide the Industry and other research groups wit an optimal in vitro and in vivo validation platforms for "proof of concept" demonstrations and initial preclinical studies of new nanotechnological based approaches. With this purpose, this area is formed by two technological platforms, one for *in vitro* analyses (*In vitro Experimental Platform*), and another one for those studies requiring animal experimentation (*In vivo Experimental Platform*).

Molecular Biology and Biochemistry Research Center for Nanomedicine (CIBBIM-Nanomedicine)

Impact Factor:

242.730

2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: Drug Delivery and Targeting

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Hanna Parkkola
Helena Pla Solans

Nursing and Technical Staff
Isabel Mougan Albela
Laura Garcia Latorre
Fina Argandoña

Objectives

The group on Drug Delivery and Targeting seeks two main goals; on the one hand, the identification of new disease biomarkers and therapeutic targets, with special focus on cancer molecular pathways; and on the other hand, the development of new delivery strategies in applied nanomedicine, with a particular interest into new delivery and targeting approaches for clinical applications.

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 relation 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 into 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

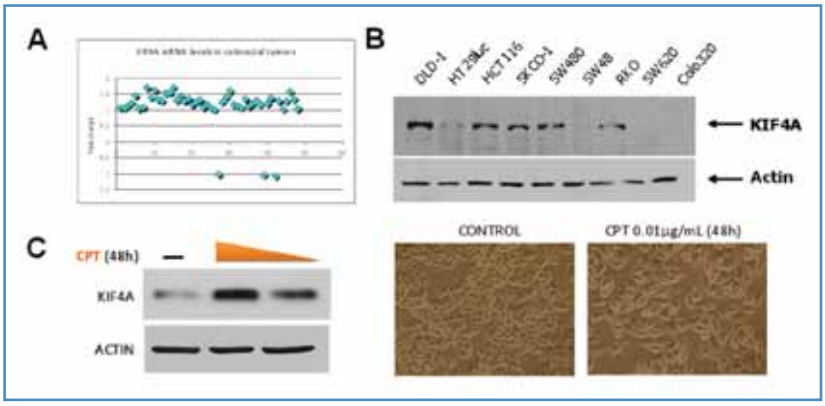
Simó Schwartz Navarro

This research line is focused into 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 into 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 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.

Figure 88
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



Enzyme replacement therapy for storage diseases: new therapeutic strategies

Simó Schwartz Navarro

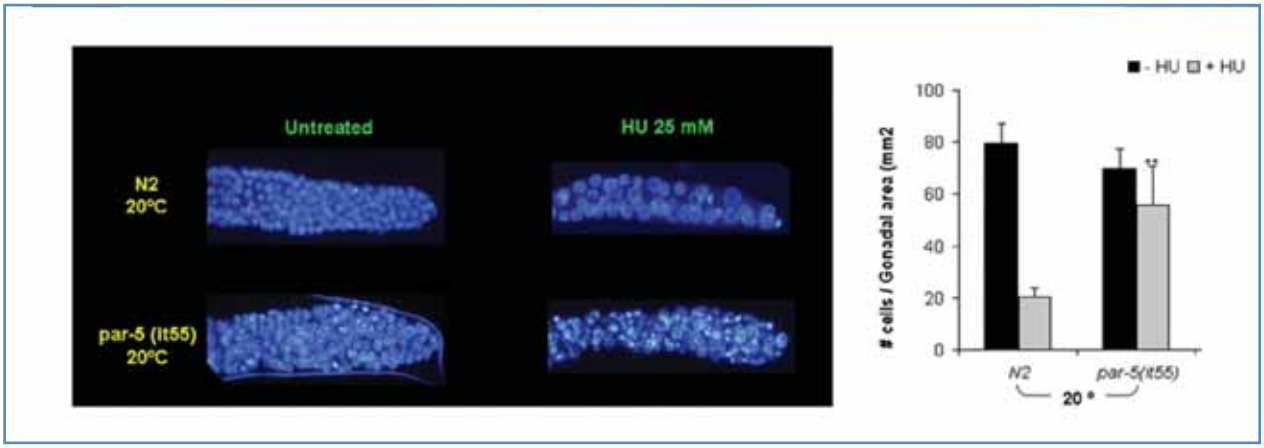
Fabry disease is an X-linked recessive disorder caused by a deficiency of lysosomal hydrolase α-galactosidase A (GLA). This enzymatic defect causes the progressive cellular accumulation of neutral glycosphingolipids, giving rise to a multisystemic clinical symptomatology. Current enzyme replacement therapy (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, multihost 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 the 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 into the design of specific vehicles for the simultaneous deliver of chemotherapeutic drugs and/or shRNAs with known antitumor activity to breast CSC. To this end, different types of nanoparticles will be directed to the CSC compartment by using the CD44 receptor as a target. Such systems will allow specific CSC-targeting, and together with the enhanced retention an permeability effect (EPR) will improve accumulation of drugs into the tumor area and should yield 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.

Figure 89
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 th germline. The images in 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



ONCONANOTARGET: Advancing the field of drug delivery - combined targeted treatments against human breast cancer and human leukemia

Simó Schwartz Navarro

The idea in the ONCONANOTARGET Network is to selectively abrogate tumour-protective functions aiming at either improving sensitivity of tumour 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: (i) To design and characterise ligand-targeted nanosystems for nucleic acid (siRNA) and drug delivery; (ii) 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; (iii) To evaluate the cytotoxic activity of individual treatments with either 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 (iv) 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 medicaments, specifically adjuvant combinations of 5-fluorouracil and Irinotecan, which bring many adverse effects to the affected patient. This project proposes a program centred on the development of new nanomedicines, based on polymers of multifunctional character that brought 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 will favour the liberation of the drug and its activity in MMP rich environments, so to say primary tumors and metastatic sites. The project includes the processes of synthesis, chemical characterization and optimization of the nanomedicines, as well as their *in vitro* and *in vivo* validation.

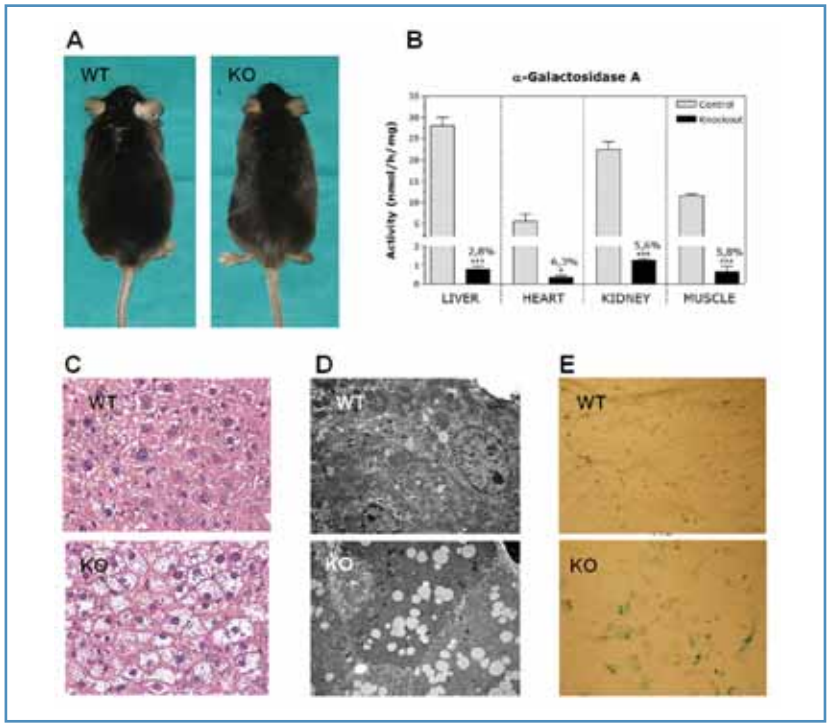


Figure 90
Characterization of the Fabry KO mice. **A.** Overall phenotype, **B.** GLA activity, **C.** Liver histology, **D.** Lysosomal deposits shown by electronic microscopy, and **E.** Senescence (b-Gal staining) in primary endothelial cultures

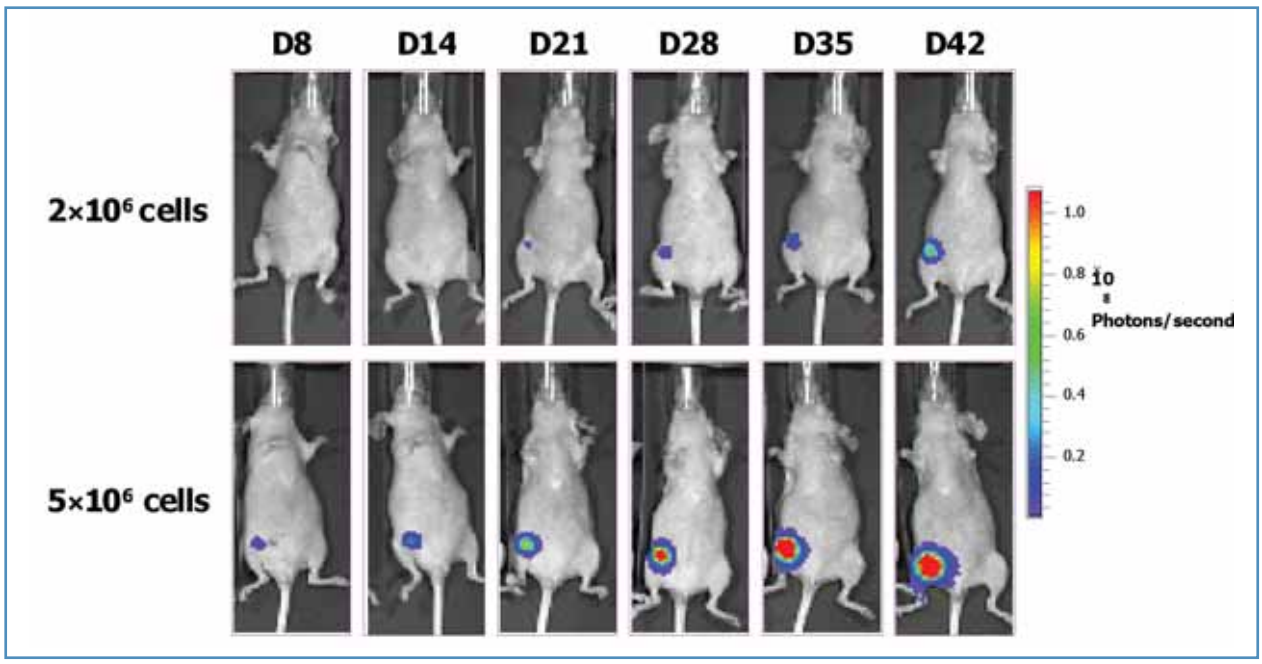


Figure 91
Orthotopic mammary fat pad tumor growth and spontaneous metastases of breast cancer cells with luciferase overexpression. Female mice received a orthotopic injection of 2 or 5x106 MDA-MB-231 cells and bioluminescence tumor growth was monitored over time using the IVIS® Spectrum This same model will be used for the therapeutic evaluation of the nanosystems developed within the ONCONANOTARGET Network

Current Research Projects

IP: Simó Schwartz Navarro
Bioingeniería, biomateriales y nanomedicina
Funding Agency: CIBER Bioing., Biomateriales y Nanomedicina, BBN
Reference: CB06/01/0012
Funding: 480,000 €
Duration: from 2007 to 2010

IP: Simó Schwartz Navarro
Sistemas diagnósticos y tratamiento en modelos in vivo mediante nanopartículas magnéticas (Grup participant)
Funding Agency: CIBER Bioing., Biomateriales y Nanomedicina, BBN
Reference: CB06/01/0012-NANOMAG
Funding: 259,200 €
Duration: from 2008 to 2010

IP: Simó Schwartz Navarro
Terapia enzimática sustitutiva en la enfermedad de Fabry: nuevos nanoconjugados con actividad terapéutica (Grup participant)
Funding Agency: CIBER Bioing., Biomateriales y Nanomedicina, BBN
Reference: CB06/01/0012-NANOFABRY
Funding: 365,014 €
Duration: from 2008 to 2010

IP: Simó Schwartz Navarro
Desarrollo de estrategias de imagen molecular y de fenotipo in vivo de modelos animales de la patología humana. Extensión translacional a pacientes (Grup participant)
Funding Agency: CIBER Bioing., Biomateriales y Nanomedicina, BBN
Reference: CB06/01/0012-IMAFEN
Funding: 340,280 €
Duration: from 2007 to 2010

IP: Simó Schwartz Navarro
Obtención de biosensores para la identificación de microorganismos patógenos con usos diagnósticos (Grup participant)
Funding Agency: CIBER Bioing., Biomateriales y Nanomedicina, BBN
Reference: CB06/01/0012-MICROPLEX
Funding: 316,400 €
Duration: from 2007 to 2010

IP: Simó Schwartz Navarro
Financiación plataforma tecnológica de experimentación «in vivo»
Funding Agency: CIBER Bioing., Biomateriales y Nanomedicina, BBN
Reference: CB06/01/0012-Plataforma *in vivo*
Funding: 450,000 €
Duration: from 2008 to 2009

IP: Simó Schwartz Navarro
Investigación y desarrollo de productos y tecnologías de diagnóstico-pronóstico y aplicaciones terapéuticas en la enfermedad neoplásica
Funding Agency: Oncnosis Pharma, AIE
Reference: CENIT/02/2006
Funding: 249,000 €
Duration: from 2006 to 2009

IP: 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: from 2009 to 2012

IP: Simó Schwartz Navarro
Activación de vías oncogénicas alternativas por KRAS y BRAF en la tumorogénesis del cáncer colorectal en modelos in vivo
Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2008-04702-C02-02
Funding: 35,000 €
Duration: from 2008 to 2009

IP: 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: from 2009 to 2011

IP: 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: from 2009 to 2011

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: from 2008 to 2010

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Impact Factor: 92.470

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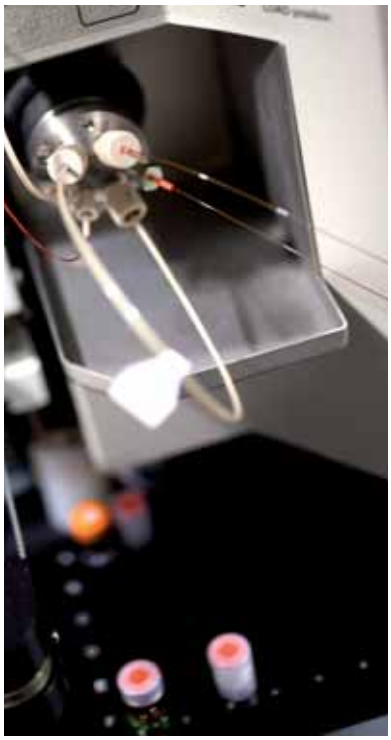
2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: Molecular Oncology



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Predoctoral Researchers
Jose Higinio Dopeso
Rocco Mazzolini
Paulo Rodrigues
Laura Lagares Tena
Antón Ameneiro Álvarez

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 dead 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 markers of prognosis, 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.

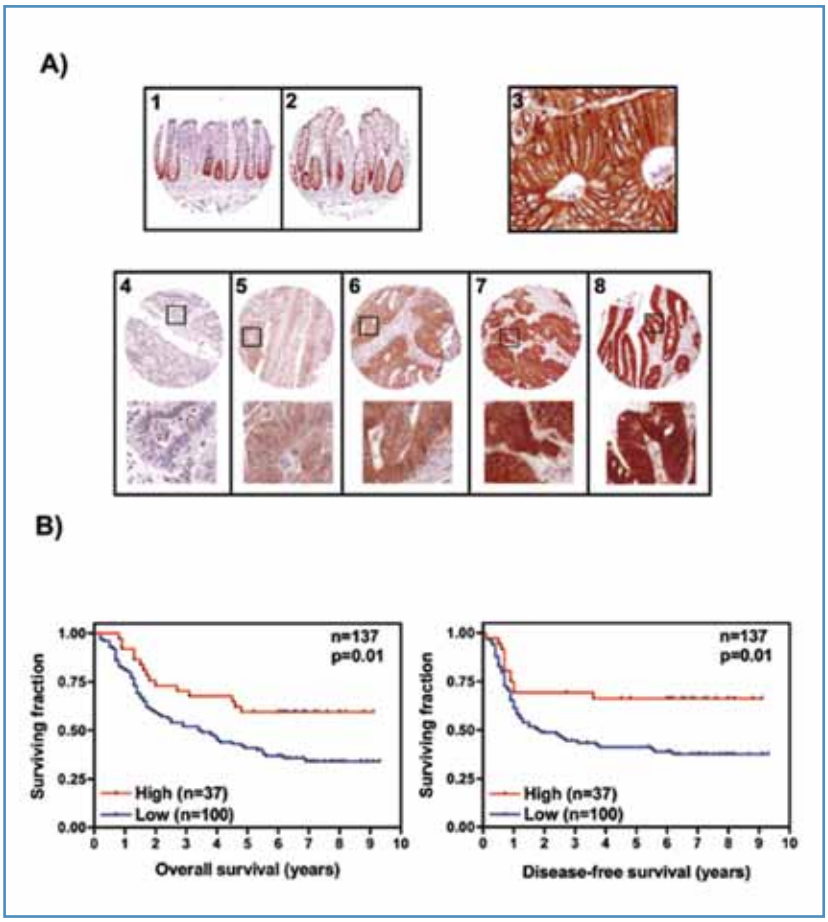

Figure 92
EPHB4 expression and survival of colorectal cancer patients

Research Lines

Identification of new markers of prognosis and response to treatment for colorectal cancer patients

Diego Arango

Colorectal cancer is the second leading cause of cancer related dead in the western world and represents a serious health concern. To put in perspective the magnitude of the problem posed by colorectal cancer 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 life. Patients diagnosed with early stage (I and II) tumors have good prognosis (5-year survival greater than 80%). However, the majority of patients 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 makers, they 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

EPH receptors are the largest family of receptor tyrosine kinases (RTKs), proteins that play a crucial role in many biological processes such as embryonic development, cell proliferation and differentiation. EPH signalling plays an important role in the regulation of proliferation and cell migration in the intestinal epithelium. Defects in EPH signalling have been reported in multiple tumor types and at least EPHB2 and EPHB4 have been shown to be important tumor suppressor genes in colorectal cancer. Our group is currently investigating the role of several additional members of the EPH family in gastrointestinal tumorigenesis.

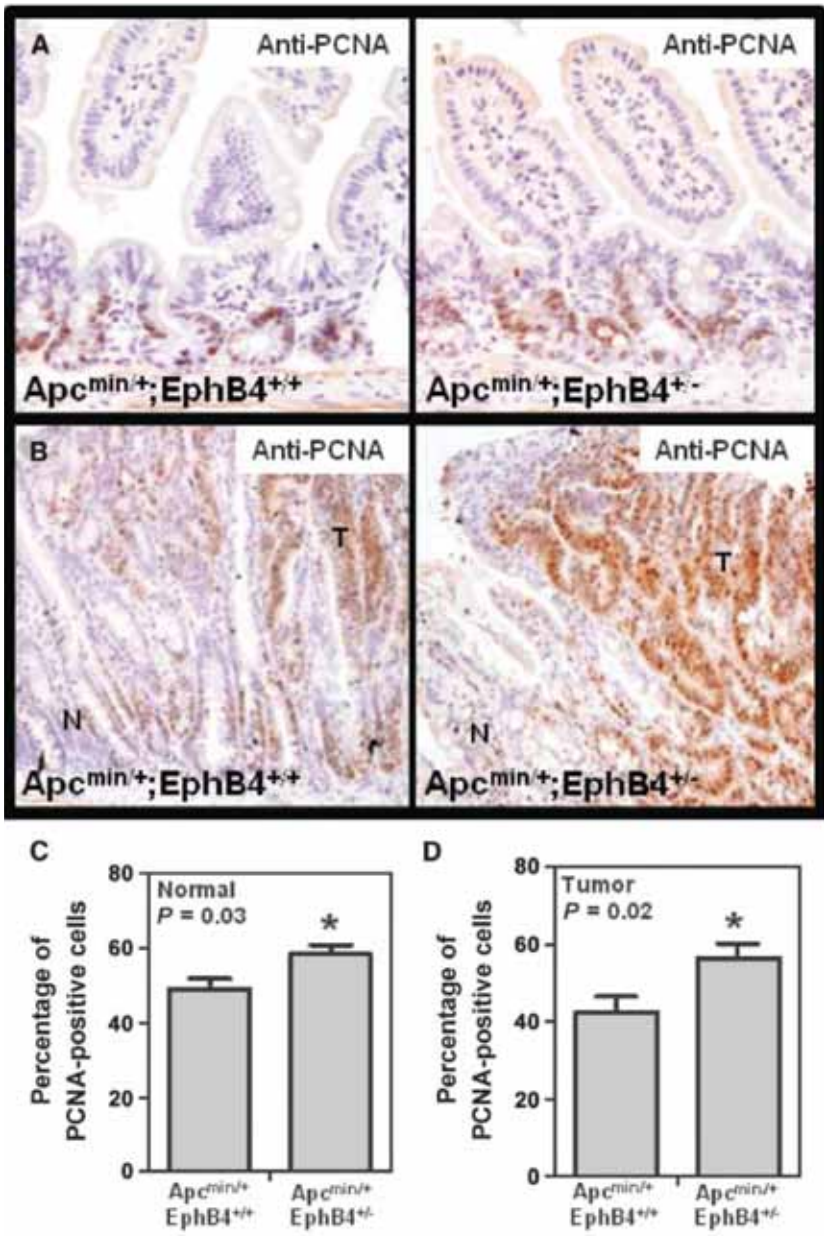

Figure 93
Effects of EPHB4 on intestinal proliferation

Role of small GTPAses in colorectal cancer

Diego Arango

RhoA is a member of the small GTPase family that regulates cytoskeletal remodelling, protein and lipid trafficking, transcriptional activation and cell growth. We have recently demonstrated that patients whose tumors have low levels of RhoA have significantly worse prognosis than patients with high RhoA tumor levels (Arango 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 achieved materials from human tumor samples.

Current Research Projects

PI: Diego Arango Corro
Estudio de EPHB4 en cáncer colorrectal
Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/07/2005
Funding: 45,000 €
Duration: from 2006 to 2009

PI: Diego Arango Corro
Papel funcional de los receptores con actividad quinasa EPH y sus ligandos en el cáncer colorrectal
Funding Agency: Fondo de Investigación Sanitaria
Reference: FIS 05-1394
Funding: 124,950 €
Duration: from 2006 to 2009

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: from 2008 to 2011

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: from 2009 to 2011

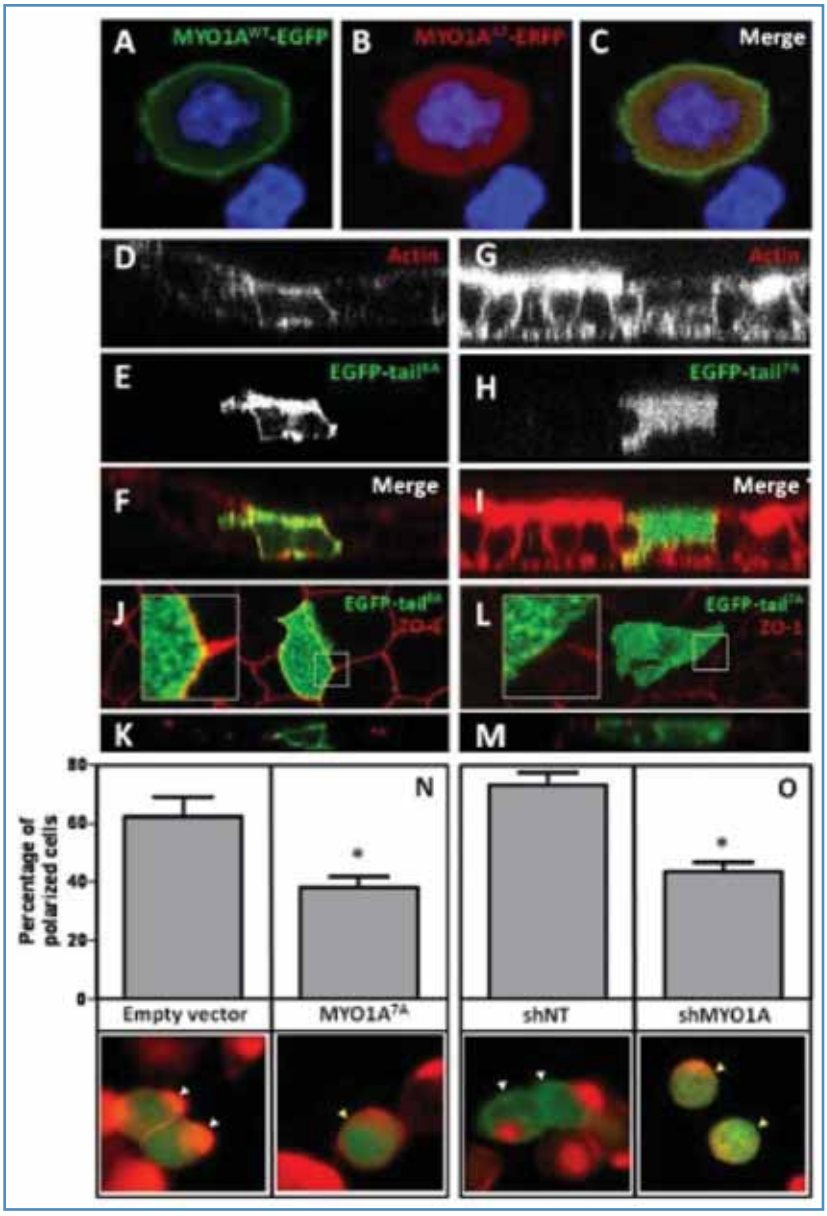

Figure 94
Subcellular localization of MYO1A

Publications

Impact Factor: 21.516

Dopeso H, Mateo-Lozano S, Mazzolini R, Rodrigues P, Lagares-Tena L, Cerón J, Romero J, Esteves M, Landolfi S, Hernández-Losa J, Castaño J, Wilson AJ, Ramón y Cajal S, Mariadason JM, Schwartz S Jr, Arango D. The receptor tyrosine kinase EPHB4 has tumor suppressor activities in intestinal tumorigenesis. *Cancer Res* 2009 Sep 15; 69 (18): 7430-8. ⇨ IF: 7.514.

Jorissen RN, Gibbs P, Christie M, Prakash S, Lipton L, Desai J, Kerr D, Aaltonen LA, Arango D, Kruhoffer M, Orntoft TF, Andersen CL, Gruidl M, Kamath VP, Eschrich S, Yeatman TJ, Sieber OM. Metastasis-Associated Gene Expression Changes Predict Poor Outcomes in Patients with Dukes Stage B and C Colorectal Cancer. *Clin Cancer Res* 2009 Dec 15; 15 (24): 7642-7651. ⇨ IF: 6.488.

Yuan Z, Shin J, Wilson A, Goel S, Ling YH, Ahmed N, Dopeso H, Jhawer M, Nasser S, Montagna C, Fordyce K, Augenlicht LH, Aaltonen LA, Arango D, Weber TK, Mariadason JM. An A13 Repeat within the 3'-Untranslated Region of Epidermal Growth Factor Receptor (EGFR) Is Frequently Mutated in Microsatellite Instability Colon Cancers and Is Associated with Increased EGFR Expression. *Cancer Res* 2009 Oct 1; 69 (19): 7811-8. ⇨ IF: 7.514.

2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: Immunobiology

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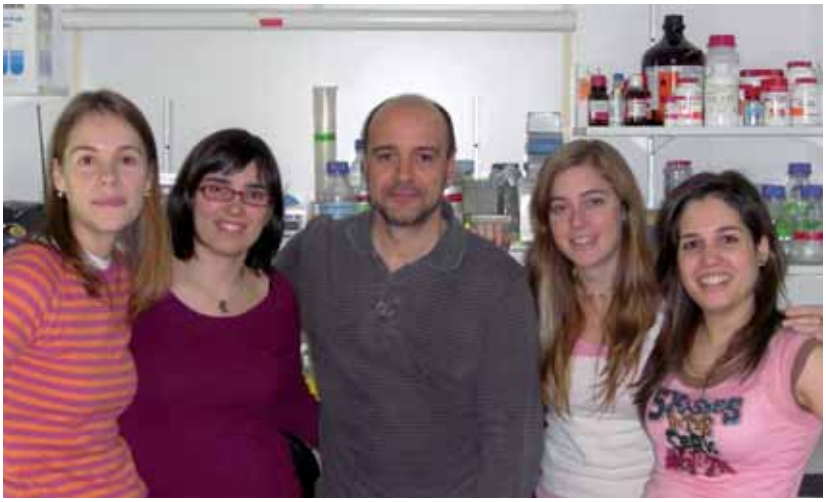

Objectives

The CD300 family of immunoreceptors is composed by 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 a novel family (IREM) of immune receptors encoded in a region of human chromosome 17q25

Joan Sayós

In the last years it has been shown the existence of a number of multigenic families of activating and inhibitory immune receptors belonging to the immunoglobulin superfamily. The physiologic ligand of some of these receptors has been identified, though the ligand of most of them still remains unknown. The importance of these receptors for the immune system regulation was revealed by showing that the dysfunction of some of them increases the 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 map 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 understand the mechanisms involved in the development of autoimmune disorders.

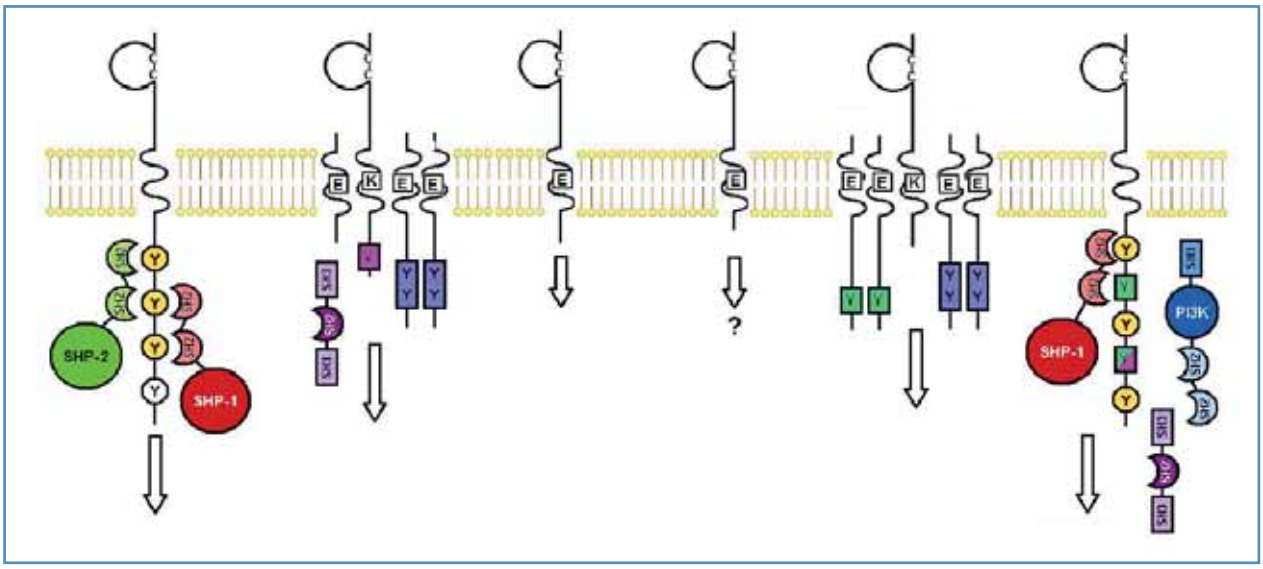

Figure 95
Schematic representation of the CD300 family of Immunoreceptors

Analysis of the functional role of the CD300 immunoreceptors in the tumour associated macrophages in colorectal cancer

Joan Sayós

Tumour-associated macrophages (TAM) are a prominent component of solid tumours. Over the years it has become increasingly that TAM not only does not have the potential to kill tumour cells, but they are active players in the process of tumour progression and invasion. In the tumour site those macrophages find factors that polarise them toward M2 type macrophages. The main objective of this project will be the characterization of the role of the IREM/CD300 family of immunoreceptors in the function of TAM. We expect that that our studies would allow the identification of molecular mechanism that might be amenable to therapeutic intervention.

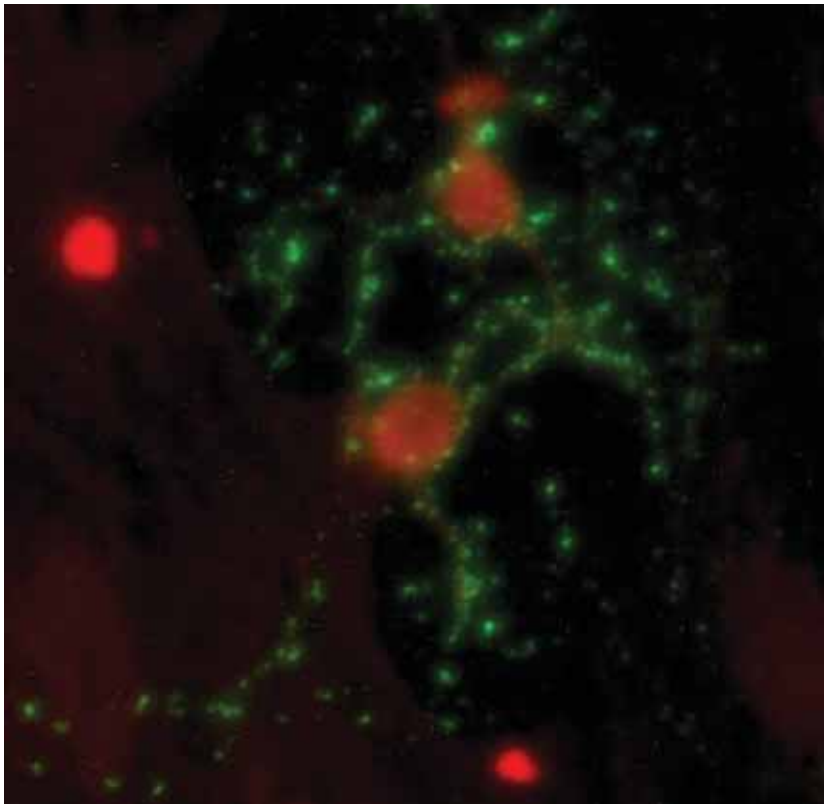

Figure 96
CD300f natural ligand is expressed on the surface of oligodendrocytes obtained from rat brain

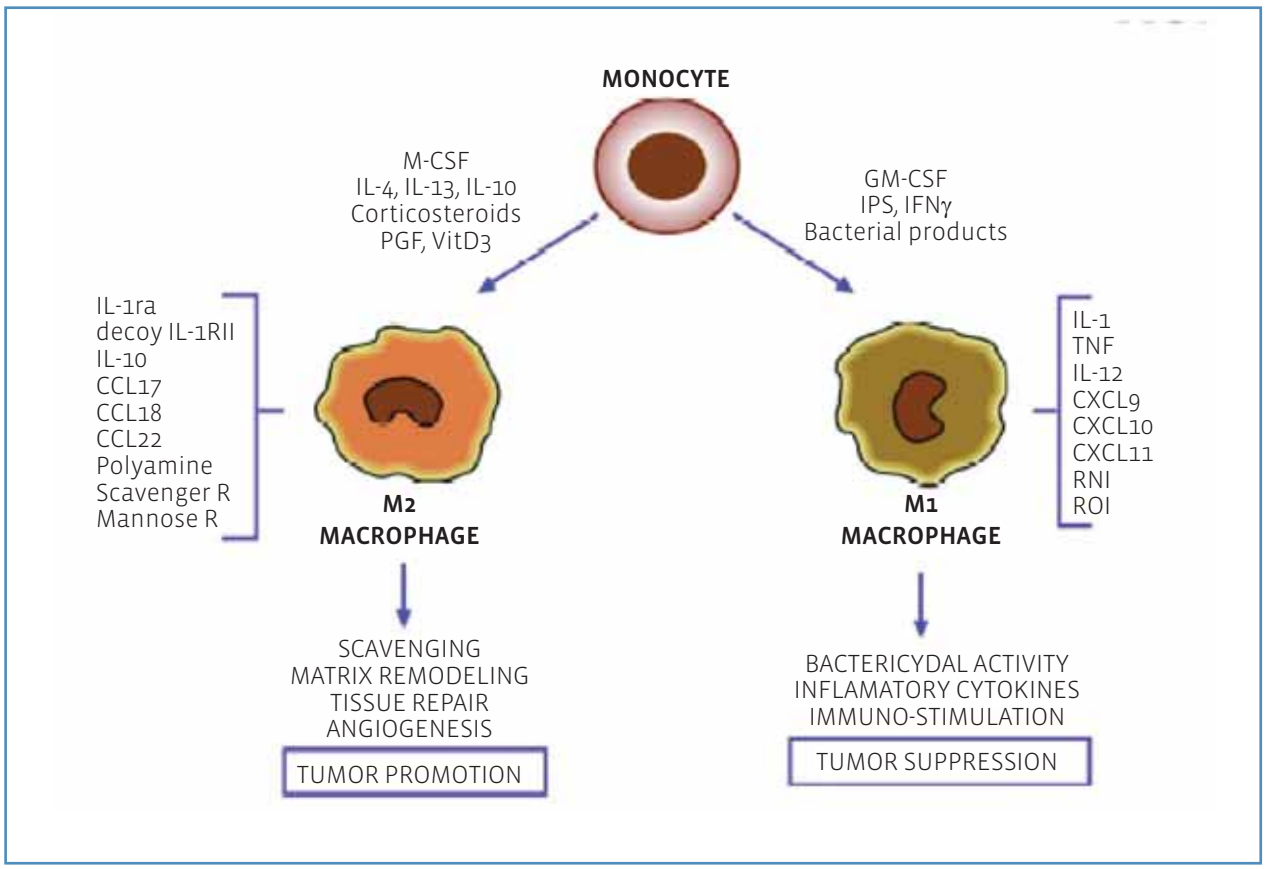

Figure 97
Schematic representation of Macrophage maturation process from pheripheral monocytes

The role of the CD300 family of inmunoreceptors in the function of microglial cells

Joan Sayós

In the last years we have been working in the identification and functional characterization of the CD300 family of immunoreceptors. We have described that these molecules are expressed by cells of myeloid lineage and that some of them are activating receptors while others acted as a negative regulators. We want to analyze the expression and possible role of the 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.

Current Research Projects

PI: Joan Sayós Ortega
Análisis del papel funcional de los inmunorreceptores CD300 en los macrófagos infiltrados en tumores colorrectales
Funding Agency: Fondo de Investigación Sanitaria
Referente: CP06/00058
Funding: 42,000 €
Duration: from 2007 to 2009

PI: Joan 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: 221,430 €
Duration: from 2009 to 2011

2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: Lysosomal Storage Diseases and Cell Pathophysiology

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Víctor Rodríguez Sureda (CIBER-ER)
Olga Sánchez García

Researchers in Training
Ángel Vilches García

Nursing and Technical Staff
Olga Gibernet Gómez
Anna Pedrosa Pujol
Silvina Vellosillo Almajano

The activity of this group is health care (50%) and biomedical research (50%)

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

Carmen Domínguez Luengo, Elisa Llurba Olivé, Olga Sánchez García and María Goya

Diagnostic and disease progression biomarkers in lysosomal storage diseases, ischaemic stroke and multiple sclerosis

Mª Carmen Domínguez Luengo, Víctor 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 Rodríguez Sureda, Olga Sánchez García and Pilar Martín Gallán

Current Research Projects

PI: Carmen Domínguez

Immune response and oxidative stress evaluation in Gaucher disease patients treated with the three new therapeutic options

Funding Agency: CIBERER
Reference: INTRA/09/752,2
Funding: 28,000 €
Duration: from 2008 to 2010

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 arteriosclerótica en madres y fetos con preeclampsia y/o retraso de crecimiento

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI071095
Funding: 61,226 €
Duration: from 2008 to 2010

Publications

Impact Factor: 4.730

Comabella M, Domínguez C, Río J, Martín-Gallán P, Vilches A, Vilarrasa N, Espejo C, Montalbán X. Plasma chitotriosidase activity in multiple sclerosis. *Clin Immunol* 2009 May; 131 (2): 216-22. ➪ IF: 3.606.

Soler-Palacín P, Clemente S, Martín A, Cabañas MJ, Hidalgo E, Figueras C. Severely immunocompromised HIV-infected paediatric patient with drug-resistant cytomegalovirus infection treated with subcutaneous interleukin-2. *J Paediatr Child Health* 2009 Apr; 45 (4): 234-5. ➪ IF: 1.124.

2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: Renal Pathophysiology

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Joan López Hellín
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Thais Cuadros Arasa
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Guillermo Suñé Rodríguez

Nursing and Technical
María Fernández Escobar

Research Associates
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Clinical Colaborators
Albert Blanco Grau
M. Carmen Cantarell Aixendri
Sonia Caparrós Molina
Lluís Capdevila Plaza
Sara Chocrón
Enrique Lara Moctezuma
Álvaro Madrid Aris
Carme Mir Maresma
Mª Ángeles Montero Fernández
Joan Morote
Jose L. Nieto Rey
Santiago Ramón y Cajal
Mª Teresa Salcedo Allende
Inés de Torres Ramírez
Jose Luis Tovar Méndez
Enric Trilla Herrera
Ramon Vilalta Casas

Objectives

A major focus 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 ischemia-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 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 to 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 immunossuppressant 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.

Anna Meseguer

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 nephrotoxic-induced renal tubular injury. Overexpression of this protein in kidney injury has been described. However, whether its involvement is associated with processes enabling to recover tubular epithelium 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.

Figure 98
Chimeric knock-out KAP mice

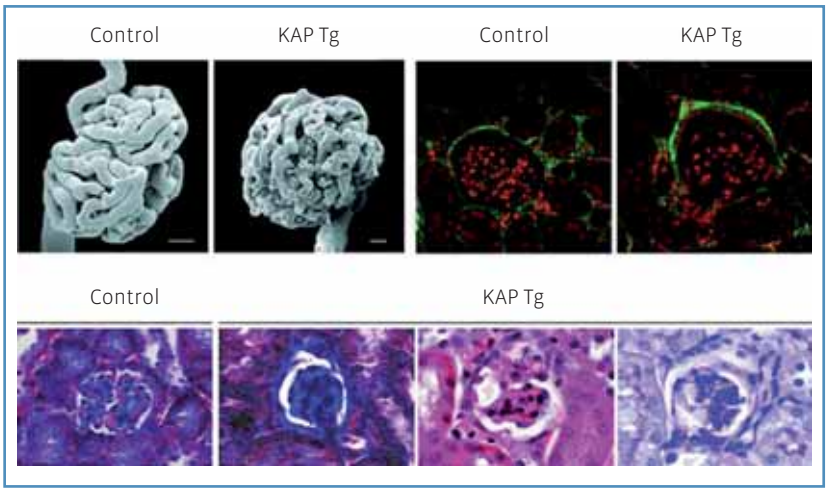


Figure 99
Histological and pathological assessment of KAP transgenic kidneys

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

Anna Meseguer

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 in kidney. 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.

Pathologic mechanisms leading to chronic allograft disease and its potential mediators. Detection of early markers of the chronic kidney disease of the graft

Anna Meseguer

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 other reasons. We want to determine the proteomic and genomic changes occurring in tubular cells after different noxious agents (cyclosporin, 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 starges. Those putative markers will be clinically validated in collaboration with the Nephrology and the Pathology services of Vall d'Hebron Hospital.

Focal segmental glomerulosclerosis

Joan López Hellín

Idiopathic nonfamilial focal segmental glomerulosclerosis (FSG) is a disease with no treatment, whose usual outcome is end-stage renal disease frequently relapsing after transplantation. In close cooperation with the Nephrology and Paediatric Nephrology services of Vall d'Hebron hospital together with hospitals throughout the country that provide a significant number of patients, we intend to identify the hypothetical blood factor that causes the proteinuria observed in this disease. Identification of such 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 relapse and the consequent loss of the graft following renal transplantation to FSG patients.

Current Research Projects

PI: Anna Meseguer Navarro

Las ciclofilinas en el fracaso renal agudo tóxico. Identificación de biomarcadores pronósticos y de posibles dianas terapéuticas

Funding Agency: Fundación Invest. Médica Mutua Madrileña
Reference: FMMA/01/2005
Funding: 38,200 €
Duration: from 2006 to 2009

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: from 2006 to 2010

PI: Anna Meseguer Navarro
Implicación de la ciclofilina B (CYBP) y de las proteínas que con ella interaccionan en el daño renal agudo
Funding Agency: Fundación Renal Iñigo Álvarez de Toledo
Reference: FRIAT_01_2007
Funding: 18,000 €
Duration: from 2008 to 2009

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: from 2008 to 2011

PI: Anna Meseguer Navarro
Acción andrógénica 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: from 2009 to 2011

Publications

Impact Factor: 36.919

Hellín JL, Bech-Serra JJ, Moctezuma EL, Chocrón S, Santín S, Madrid A, Vilalta R, Canals F, Torra R, Meseguer A, Nieto JL. Very Low-Molecular-Mass Fragments of Albumin in the Plasma of Patients With Focal Segmental Glomerulosclerosis. *Am J Kidney Dis* 2009 Nov; 54 (5): 871-80. ⇨ IF: 4.822.

Puigmulé M, López-Hellín J, Suñé G, Tornavaca O, Camano S, Tejedor A, Meseguer A. Differential proteomic analysis of cyclosporine A-induced toxicity in renal proximal tubule cells. *Nephrol Dial Transplant* 2009 Sep; 24 (9): 2672-86. ⇨ IF: 3.568.

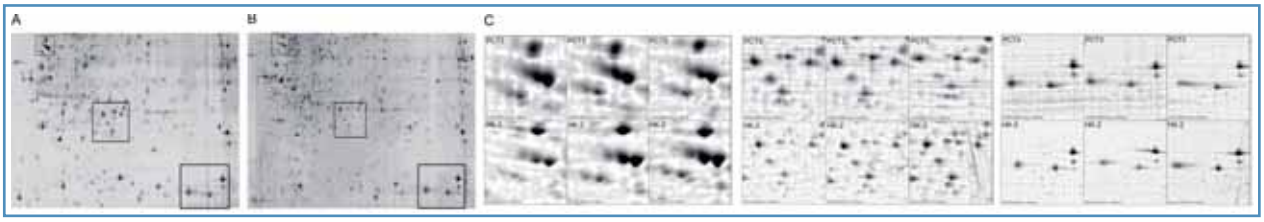
Santín S, Ars E, Rossetti S, Salido E, Silva I, García-Maset R, Giménez I, Ruíz P, Mendizábal S, Luciano Nieto J, Peña A, Camacho JA, Fraga G, Cobo MA, Bernis C, Ortiz A, Pablos AL de, Sánchez-Moreno A, Pintos G, Mirapeix E, Fernández-Llama P, Ballarín J, Torra R, López-Hellín J, Madrid A, Ventura C, Vilalta R, *et al.* TRPC6 mutational analysis in a large cohort of patients with focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2009 Oct; 24 (10): 3089-96. ⇨ IF: 3.568.

Santín S, García-Maset R, Ruiz P, Giménez I, Zamora I, Peña A, Madrid A, Camacho JA, Fraga G, Sánchez-Moreno A, Cobo MA, Bernis C, Ortiz A, Pablos AL de, Pintos G, Justa ML, Hidalgo-Barquero E, Fernández-Llama P, Ballarín J, Ars E, Torra R, López-Hellín J, *et al.* Nephrin mutations cause childhood- and adult-onset focal segmental glomerulosclerosis. *Kidney Int* 2009 Dec; 76 (12): 1268-76. ⇨ IF: 6.418.

Tornavaca O, Pascual G, Barreiro ML, Grande MT, Carretero A, Riera M, García-Arumí E, Bardají B, González-Nuñez M, Montero MA, López-Novoa JM, Meseguer A. Kidney androgen-regulated protein transgenic mice show hypertension and renal alterations mediated by oxidative stress. *Circulation* 2009 Apr 14; 119 (14): 1908-17. (Recommended by the Faculty of 1000 Biology.) ⇨ IF: 14.595.

Villarroya J, Bolos C de, Meseguer A, Hirano M, Vila MR . Altered gene transcription profiles in fibroblasts harboring either TK2 or DGUOK mutations indicate compensatory mechanisms. *Exp Cell Res* 2009 May 1; 315 (8): 1429-38. ⇨ IF: 3.948.

Figure 100
Differential proteomic analyses of CsA-treated proximal tubule cells



2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: Neuromuscular and Mitochondrial Diseases

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Gisela Nogales Gadea
Tomàs Pinós Figueras

Researchs in Training
Marc Cuadros Arasa
Javier Torres Torronteras

Nursing and Technical Staff
Ramiro Martínez Estéfano
Mª Jesús Melià Grimal

Objectives

The group focuses on the study of pathogenic mechanisms of mitochondrial DNA mutations (mtDNA) associated with diverse neuromuscular syndromes. It is specially interested in understanding the pathogenic mechanisms involved in mutations of structural genes of mtDNA, as well as the adaptative mechanisms of the cell in the 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 transmitochondrial hybrids. Actually we are 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.

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

Ramon 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

Ramon 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: from 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: from 2009 to 2010

PI: Antonio Luis Andreu Périz

Base fisiopatológica de la toxicidad mitocondrial y neuropática causada por el antibiótico linezolid

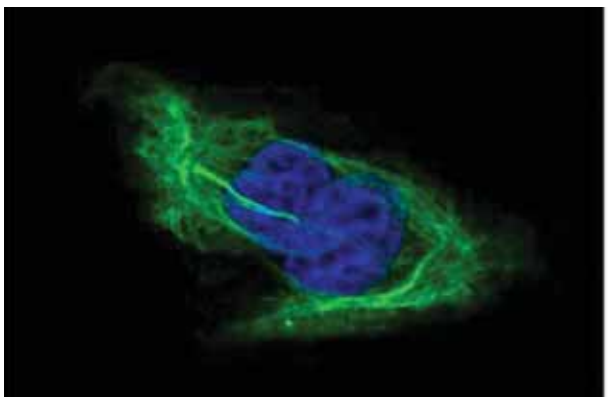
Funding Agency: CIBER de Enfermedades raras
Reference: INTRA /09/722,1
Funding: 14,000 €
Duration: 2009

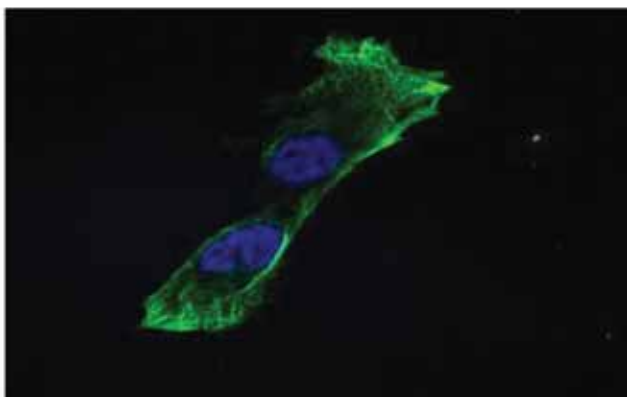
PI: Antonio Luis Andreu Périz

Evaluación de la función mitocondrial en adrenoleucodistrofia con ligamento al X

Funding Agency: CIBER de Enfermedades raras
Reference: INTRA/08/759,2
Funding: 26,000 €
Duration: 2009

Figure 101
Confocal microscopy images of transmitochondrial cybrids showing the nuclei (DAPI staining) and the mitochondrial network (anti-ATP5a antibody)





PI: Ramon Martí Seves
Terapia génica para el tratamiento del MNGIE (Mitochondrial Neurogastrointestinal Encephalomyopathy). Introducción del gen timidina fosforilasa en líneas celulares humanas y en un doble knock-out *murino como modelos experimentales*
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060735
Funding: 180,895 €
Duration: from 2007 to 2009

PI: Elena García Arumí
Efecto de las mutaciones en el DNA mitocondrial sobre la expresión de genes involucrados en la función mitocondrial. Relación con su patogenicidad y fenotipo
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI060848
Funding: 70,059 €
Duration: from 2007 to 2009

Publications

Impact Factor: 61.917

Andreu AL, Martínez R, Martí R, García-Arumí E. Quantification of mitochondrial DNA copy number: pre-analytical factors. *Mitochondrion* 2009 Jul; 9 (4): 242-6. ⇨ IF: 4.262.

Frangini M, Rampazzo C, Franzolin E, Lara MC, Vila MR, Martí R, Bianchi V. Unchanged thymidine triphosphate pools and thymidine metabolism in two lines of thymidine kinase 2-mutated fibroblasts. *FEBS J* 2009 Feb; 276 (4): 1104-13. ⇨ IF: 3.139.

García-Consuegra I, Rubió JC, Nogales-Gadea G, Bautista J, Jiménez S, Cabello A, Lucia A, Andreu AL, Arenas J, Martín MA. Novel mutations in patients with McArdle disease by analysis of skeletal muscle mRNA. *J Med Genet* 2009 Mar; 46 (3): 198-202. ⇨ IF: 5.713.

García-Consuegra I, Rubió JC, Nogales-Gadea G, Bautista J, Jiménez S, Cabello A, Lucia A, Andreu AL, Arenas J, Martín MA. Novel human pathological mutations. Gene symbol: PYGM. Disease: McArdle disease. *Hum Genet* 2009 Apr; 125 (3): 341, 342, 343. ⇨ IF: 12.126.

Guitart M, Andreu AL, García-Arumí E, Briones P, Quintana E, Gómez-Foix AM, García-Martínez C. FATP1 localizes to mitochondria and enhances pyruvate dehydrogenase activity in skeletal myotubes. *Mitochondrion* 2009 Jul; 9 (4): 266-72. ⇨ IF: 4.262.

López LC, Akman HO, García-Cazorla A, Dorado B, Martí R, Nishino I, Tadesse S, Pizzorno G, Shungu D, Bonilla E, Tanji K, Hirano M. Unbalanced deoxynucleotide pools cause mitochondrial DNA instability in thymidine phosphorylase-deficient mice. *Hum Mol Genet* 2009 Feb 15; 18 (4): 714-22. ⇨ IF: 7.249.

López-Gallardo E, Solano A, Herrero-Martín MD, Martínez-Romero I, Castaño-Pérez MD, Andreu AL, Herrera A, López-Pérez MJ, Ruiz-Pesini E, Montoya J. NARP syndrome in a patient harbouring an insertion in the MT-ATP6 gene that results in a truncated protein. *J Med Genet* 2009 Jan; 46 (1): 64-7. ⇨ IF: 5.713.

Montero R, Sánchez-Alcazar JA, Briones P, Navarro-Sastre A, Gallardo E, Bornstein B, Herrero-Martín D, Rivera H, Martín MA, Martí R, García-Cazorla A, Montoya J, Navas P, Artuch R. Coenzyme Q10 deficiency associated with a mitochondrial DNA depletion syndrome: a case report. *Clin Biochem* 2009 May; 42 (7-8): 742-5. ⇨ IF: 1.926.

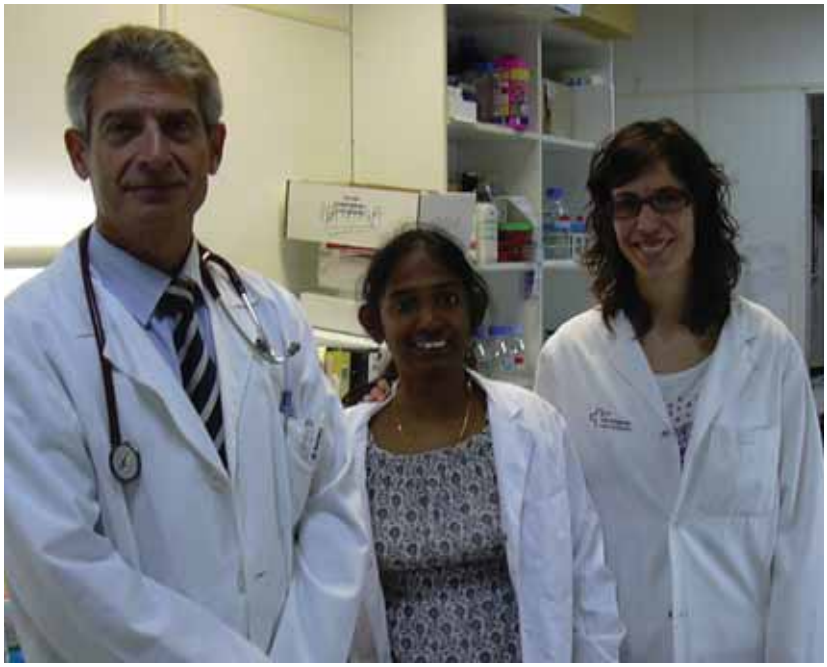
Pérez M, Ruiz JR, Fernández del Valle M, Nogales-Gadea G, Andreu AL, Arenas J, Lucia A. The second wind phenomenon in very young McArdle's patients. *Neuromuscul Disord* 2009 Jun; 19 (6): 403-5. ⇨ IF: 2.932.

Tornavaca O, Pascual G, Barreiro ML, Grande MT, Carretero A, Riera M, García-Arumí E, Bardají B, González-Nuñez M, Montero MA, López-Novoa JM, Meseguer A. Kidney androgen-regulated protein transgenic mice show hypertension and renal alterations mediated by oxidative stress. *Circulation* 2009 Apr 14; 119 (14): 1908-17. ⇨ IF: 14.595.

2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: Aging Basic Research



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Researchs in Training
Renuka Kandhaya

Nursing and Technical Staff
Natalia García Aranda

Objectives

Our goal is the study of the molecular and immunological alterations associated to the aging process. In particular, the association and correlation of cellular aging and endothelial cell senescence with epigenetic and telomeric alterations, taking the inmunological alterations as the basis of cellular inmunosenescence. Identification of such alterations might provide us with new candidates for therapeutic intervention.

Research Lines

Immunological alterations as basis of inmunosenescence in pathological aging

Jaume Alijotas Reig

This research line is centred into the study of the role of cross-reactivity among oxidized lipoproteins (oxLDL), antiB2-GP1 and membrane phospholipids, as well as between these complexes and heat shock proteins. We also focus into the role of pro-inflammatory (IL2 / IL6 / TNFalpha) and anti-inflammatory (IL4 / IL-10) cytokines, as well as with the different activation profiles of TCR and/or CD14 (TLR4) and the role of hormones such as melatonin and the growth hormone.

Endothelial senescence and their pleiotropic effects onto 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.

Current Research Projects

PI: Jaume Alijotas Reig
Recerca bàsica en envelliment
Funding Agency: Societat Espanyola de Medicina i Cirurgia Cosmètica
Reference: SEMCC
Funding: 300,000 €
Duration: from 2007 to 2010

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: 36,000.00 €
Duration: from 2008 to 2011

PI: Jaume Alijotas Reig
Envejecimiento endotelial y procesos inflamatorios crónicos
Funding Agency: Fundació Agrupació Mutua
Reference: FAM
Funding: 15,000 €
Duration: from 2008 to 2010

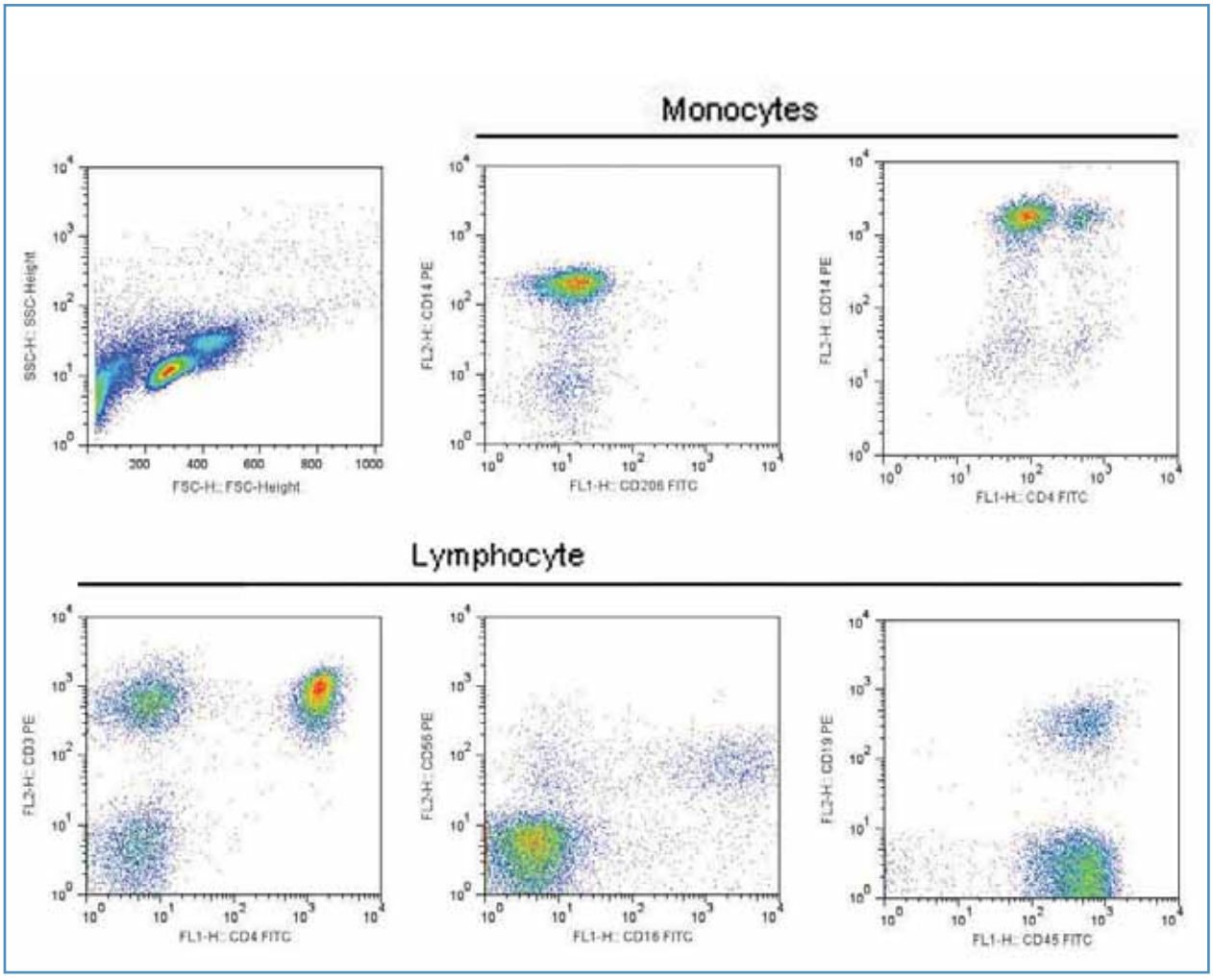
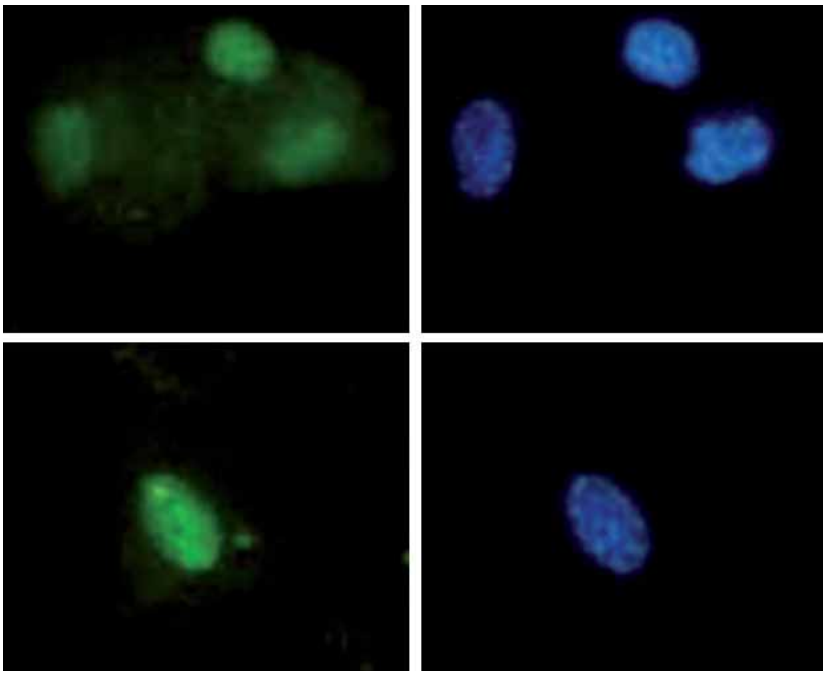


Figure 102
Characterization of monocytic and lymphocytic population in healthy and pathological donors

Figure 103
Accumulation of p21 and p53 within senescent endothelial cell nucleis



Publications

Impact Factor: 10.026

Alijotas-Reig J. Recurrent urticarial vasculitis related to nonanimal hyaluronic acid skin filler injection. *Dermatol Surg* 2009 Feb; 35 Suppl 1: 395-7; discussion 397-8. ⇨ IF: 2.102.

Alijotas-Reig J, García-Giménez V, Miró-Mur F, Vilardell-Tarrés M. Delayed immune-mediated adverse effects related to polyacrylamide dermal fillers: clinical findings, management, and follow-up. *Dermatol Surg* 2009 Feb; 35 Suppl 1: 360-6. ⇨ IF: 2.102.

Alijotas-Reig J, García-Giménez V, Vilardell-Tarrés M. Late-Onset Immune-Mediated Adverse Effects after Poly-L-Lactic Acid Injection in Non-HIV Patients: Clinical Findings and Long-Term Follow-Up. *Dermatology* 2009; 219 (4): 303-8. ⇨ IF: 2.227.

Alijotas-Reig J, Palacio-García C, Vilardell-Tarrés M. Circulating microparticles, lupus anticoagulant and recurrent miscarriages. *Eur J Obstet Gynecol Reprod Biol* 2009 Jul; 145 (1): 22-6. ⇨ IF: 1.565.

Miró-Mur F, Hindie M, Kandhaya-Pillai R, Tobajas V, Schwartz S Jr, Alijotas-Reig J. Medical-grade silicone induces release of proinflammatory cytokines in peripheral blood mononuclear cells without activating T cells. *J Biomed Mater Res B Appl Biomater* 2009 Aug; 90 (2): 510-20. ⇨ IF: 2.03.

2.8 Area 8: Pathology, Cellular and Gene Therapy

CIBBIM-Nanomedicine

Research Group: *In Vitro* and *In Vivo* Experimental Platform

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Researchers
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Technicians
Sonia Miranda Blázquez
Mª Eugènia López Sánchez

Objectives

The Area of Functional Validation and Preclinical Research aims to validate the activity and function of candidate genes, target molecules and therapeutic compounds identified or developed by other groups at the CIBBIM, by using appropriate cellular and animal models. The area also intends to provide the industry and other research groups with an optimum technical platform for testing new biomedical applications based on nanotechnology such us antitumoral treatments, new applications in diagnosis and imaging, nanotargeting of solid tumors, etc. Likewise, the efficacy and toxicity of the therapeutic nanoconjugates developed in collaboration with other research groups are being currently evaluated, with the objective of favouring the entry of those compounds into clinical trials.

The area is formed by two technological platforms, one for *in vitro* analyses (*In vitro Experimental Platform*), and another one for those studies requiring animal experimentation *(In vivo Experimental Platform)*. Both platforms are partially financed by the CIBER-BBN (Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine) and belong to the research infrastructure program of CIBER-BBN.

In Vitro Experimental Platform

This platform offers standard *in vitro* experimentation procedures for the functional validation of candidate genes and biomarkers, and for the efficacy and toxicological evaluation of new drugs, biomaterials and nanomedicines. Experiments performed in this platform will lead to more efficient candidate selection and yield valuable information for the design of future *in vivo* studies.

Assays performed within this platform are designed specifically for each gene, biomaterial or drug in process of validation. Basically, there are four different types of assays:

- *Loss or gain of function assays.* The role of a specific genes or molecules is studied by selectively increasing or reducing their expression.

- *Toxicity assays.* The toxicity of new drugs, nanoparticles or biomaterials is exhaustively evaluated by standard cell viability/toxicity assays, hemocompatibility analysis and production of reactive oxygen species (ROS), among others.

- *Efficacy of therapeutic agents.* Different assays are conducted to evaluate the efficacy, internalization and mechanism of action of new drugs and nanotherapies for the treatment of cancer and certain rare diseases (i.e. Fabry disease).

- *Generation of reporter cell lines for bioluminescence and fluorescence imaging.* Cancer cells of different origins have been modified to overexpress specific reporter genes. These cells will be later used by the In vivo *Experimental Platform* for the non-invasive monitoring of tumor growth and progression.

In vivo Experimental Platform

At the moment, the platform offers standard *in vivo* experimentation procedures for the evaluation of new therapeutic targets, nanotherapies and biomarkers in the field of oncology and rare diseases. Basic preclinical studies including toxicology, histopathology and efficacy treatments are complemented with non-invasive optical imaging technologies, which help to accelerate the development process of new therapeutic agents.
The platform offers different types of services:

- *Oncology models.* The *in vivo* platform has available a panel of tumor cell lines that overexpress bioluminescent and fluorescent proteins that allow the tracking of

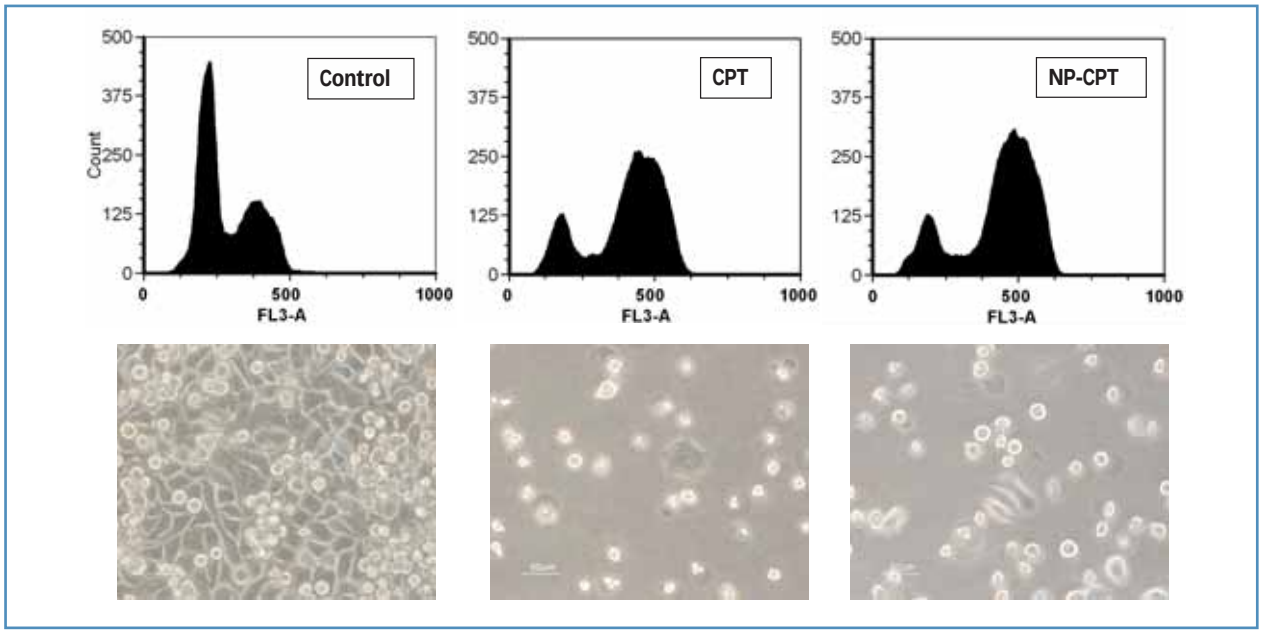


Figure 104
Drug-loaded nanoparticles (NP-CPT) have a similar effect (in cell cycle and cell morphology) as the "naked" drug (CPT)

tumor progression *in vivo* by non-invasive optical imaging. As for the experimental animal models, tumor progression and spontaneous and experimental metastasis models are offered (see Table 26). In a special manner, some of these models allow the monitoring of disease progression, the treatment efficacy and/or the compound biodistribution by means of non-invasive optical imaging techniques (see Figure 105 and 106).

- Non-invasive optical imaging (bioluminescence and fluorescence). The equipment for non-invasive imaging is run through the recently created Molecular Imaging Platform (PIM) located within the Animal Facility of the IR-HUVH. The platform is equipped with a Xenogen IVIS® Spectrum and a Leica MacroFluo that were bought by the CIBER-BBN, and transferred to the IR-HUVH.

- *Preclinical histology.* The platform counts with conventional histology equipments exclusively devoted to preclinical tissue processing. In this unit, all the biological material collected during the experimental phase is processed rapidly and accurately. In addition, when required, histopathological assessments carried out by specialized veterinary personnel are provided.

The key applications of platform are focused on:

– *In vivo* validation of new biomarkers and therapeutic targets.

– Efficacy of new therapies under development using specific animal models.

– *In vivo* monitoring using optical imaging of:

  - Gene expression
  - Tumor growth and metastasis dissemination
  - Biodistribution of labelled compounds
  - Induction of apoptosis (DEVD-luciferin)
  - Activity of matrix metalloproteinases (MMPs), and similar enzymes, using enzyme-specific probes

Tumor Models

Subcutaneous models
Orthotopic models:
Intraprostatic
Intramammary (i.m.f.p.)
Stereotactic
Ceccum
Experimental metastases:
Intracardiac (bone metastases)
Intravenous (lung metastases)
Intraportal (liver metastases)
Spontaneous metastases

Table 26
Oncology Tumor Models

Figure 105
Biodistribution of Cy5,5-llabelled nanopartides by means of *in vivo* fluorescence imaging in a tumor-bearing mouse

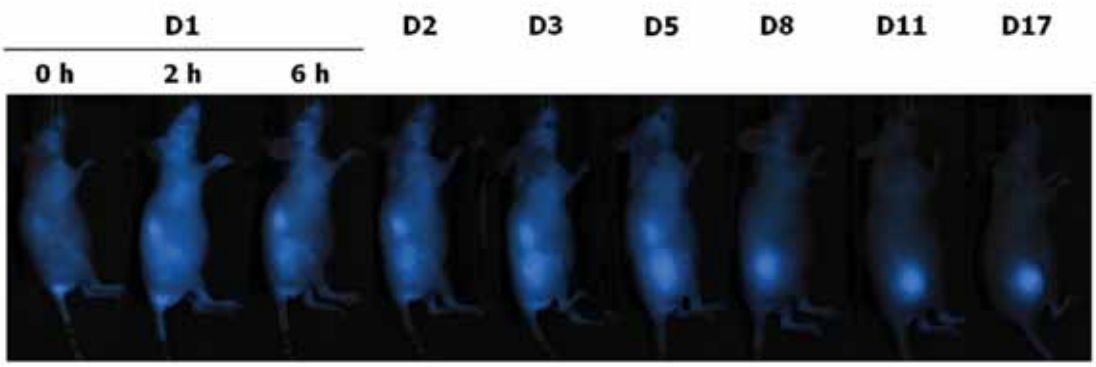
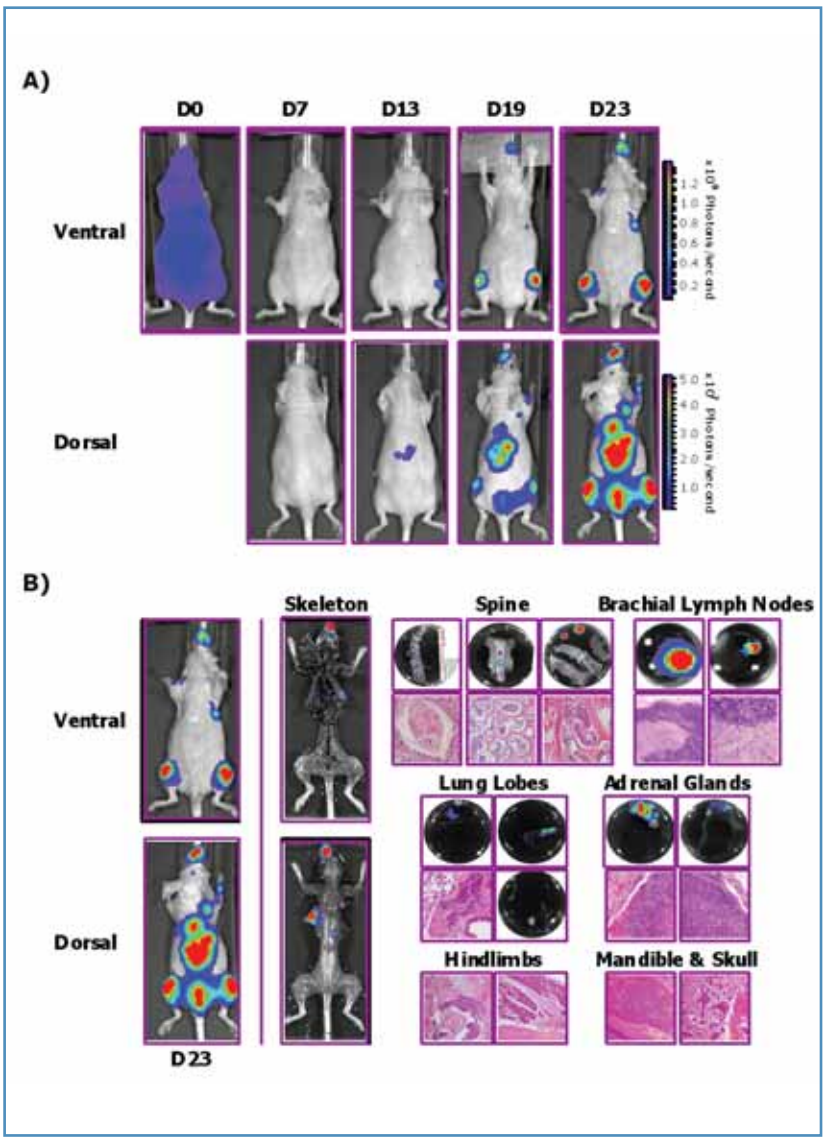


Figure 106
Intracardiac experimental bone metastasis model of colon cancer cells injected into the left ventricle of mice heart. **A.** *In vivo* images of metastatic lesions of a representative mouse over time are shown. **B.** *Ex vivo* imaging and hitopathology confirmed metastases in various tissues including jaw, cervical lymph nodes, tibia or femur and thorax



Publications

Impact Factor: 15.152

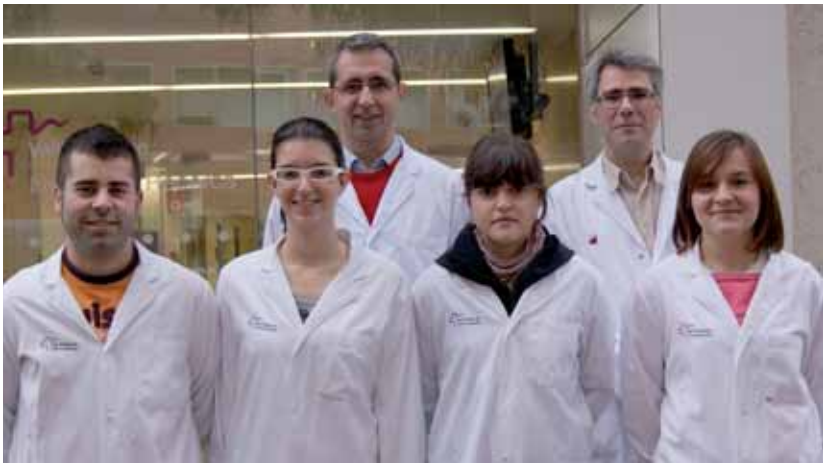
Abasolo I, Pujal J, Rabanal RM, Serafín A, Navarro P, Millán O, Real FX. FDG PET imaging of Ela1-myc mice reveals major biological differences between pancreatic acinar and ductal tumours. *Eur J Nucl Med Mol Imaging* 2009 Jul; 36 (7): 1156-66. ➪ IF: 4.532.

Martín A, Rojas S, Pareto D, Santalucía T, Millán O, Abasolo I, Gómez V, Llop J, Gispert JD, Falcón C, Bargalló N, Planas AM. Depressed glucose consumption at reperfusion following brain ischemia does not correlate with mitochondrial dysfunction and development of infarction: an in vivo positron emission tomography study. *Curr Neurovasc Res* 2009 May; 6 (2): 82-8. ➪ IF: 3.571.

Pujal J, Huch M, José A, Abasolo I, Rodolosse A, Duch A, Sánchez-Palazón L, Smith FJ, McLean WH, Fillat C, Real FX. Keratin 7 promoter selectively targets transgene expression to normal and neoplastic pancreatic ductal cells *in vitro* and *in vivo*. *FASEB J* 2009 May; 23 (5): 1366-75. ➪ IF: 7.049.

2.8 Area 8: Pathology, Cellular and Gene Therapy

Research Group: Cell and Gene Therapy



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Researcher
Ramón Gimeno Martínez

Researchers in Training
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Nursing and Technical and Administrative staff
Sergio López Estévez

Objectives

- Investigating the mechanisms by which transplantation of hematopoietic cells expressing an autoantigen induces tolerance in murine models of autoimmune disease.
- Optimizing hematopoietic differentiation from human induced pluripotent stem cells (iPSC).
- *Ex vivo expansion strategies* of human hematopoietic progenitors.

Research Lines

Immune tolerance induction by expressing autoantigens in hematopoietic cells

Jordi Barquinero Máñez

In collaboration with the Clinical neuroimmunology group we are developing novel cell therapies based on hematopoietic cells transduced with autoantigens to induce tolerance to the transgene product in a murine model of multiple sclerosis.

Developing the human immunological system

Ramón Gimeno Martínez

Investigating the mechanisms involved mechanisms in hematopoietic's progenitor expansion and its differentiation towards lymphoid precursors. Soluble factors and signals derived from the contact with the stroma that controls these processes. Combining techniques from cellular, molecular biology and an experimental model of hematopoietic reconstruction, we are trying to establish an interrelation between these signals.

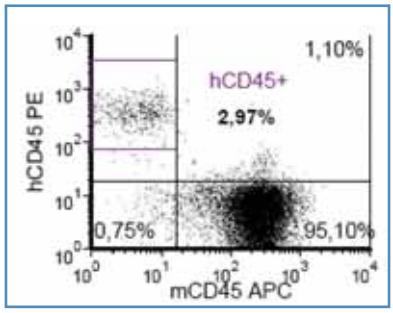


Figure 107
Reconstructing human hematopoiesis in an immunodeficient mouse. 8 weeks after the transplantation of 100 hematopoietic cells from umbilical cord, it is possible to detect graft (human CD45+ cells) in the peripheral blood of the recipient mice

Preclinical development of a gene therapy in hematopoietic cells for the mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

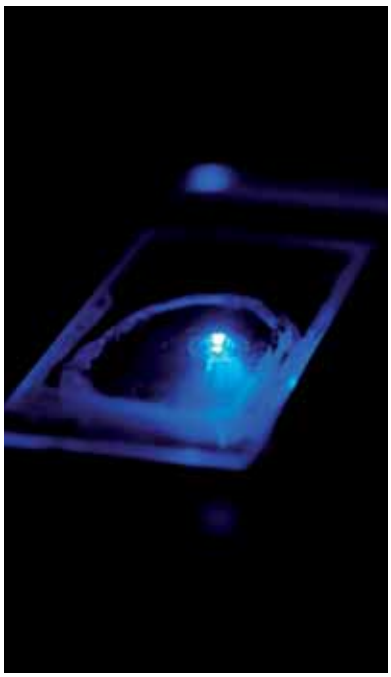
Ramon Martí Seves

In collaboration with mitochondrial and neuromuscular pathology group, we carry out preclinical studies of a gene therapy for MNGIE based on the correction of the molecular defect (thymidine phosphorylase) in hematopoietic cells.

Cellular immunotherapy in the treatment of infectious and tumoral diseases

Ramón Gimeno Martínez

There already are several ongoing clinical trials in which T lymphocytes with reactivity against viral or tumor antigens are injected to the patients. In collaboration with the Servei de Malalties Infeccioses, we are looking for new methods to generate, expand and increase the effector activity of these lymphocytes, specially those that have not had previous contact with the antigen of interest.



Current Research Projects

PI: Jordi Barquinero Máñez

Concerted safety and efficiency evaluation of retroviral transgenesis in gene therapy of inherited diseases

Funding Agency: European Comission
Reference: CONSERT-5242
Funding: 386,384 €
Duration: from 2005 to 2009

PI:Jordi Barquinero Máñez

Quimerismo molecular como inductor de tolerancia en la encefalomielitis autoinmune experimental: mecanismos y optimización

Funding Agency: Fondo de Investigación Sanitaria
Reference: PI051441
Funding: 177,310 €
Duration: from 2006 to 2009

PI: Jordi Barquinero Máñez

Generación y diferenciación de células madre pluripotentes inducidas (IPS) de pacientes con enfermedades genéticas del sistema inmunohematopoyético

Funding Agency: Ministerio de Ciencia e Innovación
Reference: PLE2009-0100
Funding: 302,540 €
Duration: from 2009 to 2012

PI: Ramón Gimeno Martínez

Expansión de progenitores hematopoyéticos humanos mediante manipulación de la vía de Notch

Funding Agency: Ministerio de Ciencia e Innovación
Reference: SAF2006-09230
Funding: 114,708 €
Duration: from 2006 to 2009

Publications

Impact Factor: 17.481

Eixarch H, Espejo C, Gómez A, Mansilla MJ, Castillo M, Mildner A, Vidal F, Gimeno R, Prinz M, Montalbán X, Barquinero J. Tolerance induction in experimental autoimmune encephalomyelitis using non-myeloablative hematopoietic gene therapy with autoantigen. *Mol Ther* 2009 May; 17 (5): 897-905. ⇨ IF: 6.239.

Eixarch H, Gómez A, Kadar E, George M, Martínez N, Espejo C, Petriz J, Gimeno R, Barquinero J. Transgene expression levels determine the immunogenicity of transduced hematopoietic grafts in partially myeloablated mice. *Mol Ther* 2009 Nov; 17 (11): 1904-9. ⇨ IF: 6.239.

Flaquer M, Franquesa M, Barquinero J, Lloberas N, Gutiérrez C, Torras J, Grinyo JM, Cruzado JM. Bone marrow transplantation induces normoglycemia in a type 2 diabetes mellitus murine model. *Transplant Proc* 2009 Jul-Aug; 41 (6): 2282-5. ⇨ IF: 1.055.

Santamaría-Martínez A, Barquinero J, Barbosa-Desongles A, Hurtado A, Pinos T, Seoane J, Poupon MF, Morote J, Reventós J, Munell F. Identification of multipotent mesenchymal stromal cells in the reactive stroma of a prostate cancer xenograft by side population analysis. *Exp Cell Res* 2009 Oct 15; 315 (17): 3004-13. ⇨ IF: 3.948.

2.8 Area 8: Pathology, Cellular and Gene Therapy

Research Group: Molecular Diagnosis and Therapy (UDTM)

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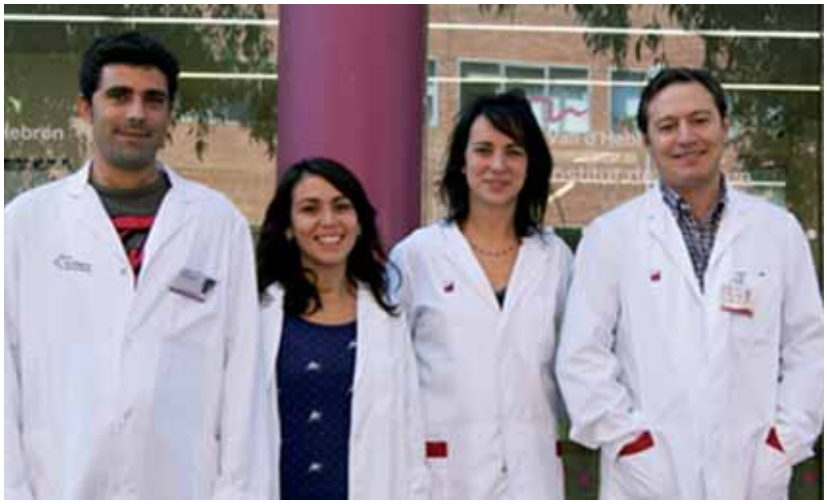
Researcher
Lluis Martorell Cedrés

Researcher in Training
Irene Corrales Insa

Nursing and Technical
Lorena Ramírez Orihuela



Objectives

The Molecular Diagnosis and Therapy Unit (UDTM) of the Blood and Tissue Bank, has a dual character since their foundation in 1998: diagnostic support in congenital coagulation disorders as well as other hereditary diseases; research and development of new approaches in the field of medical diagnostics and therapeutics. Also an important part of the current objectives are the innovation in technological tools and their transfer to the routine laboratory. The research activity of the UDTM is linked to the commitment with 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 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

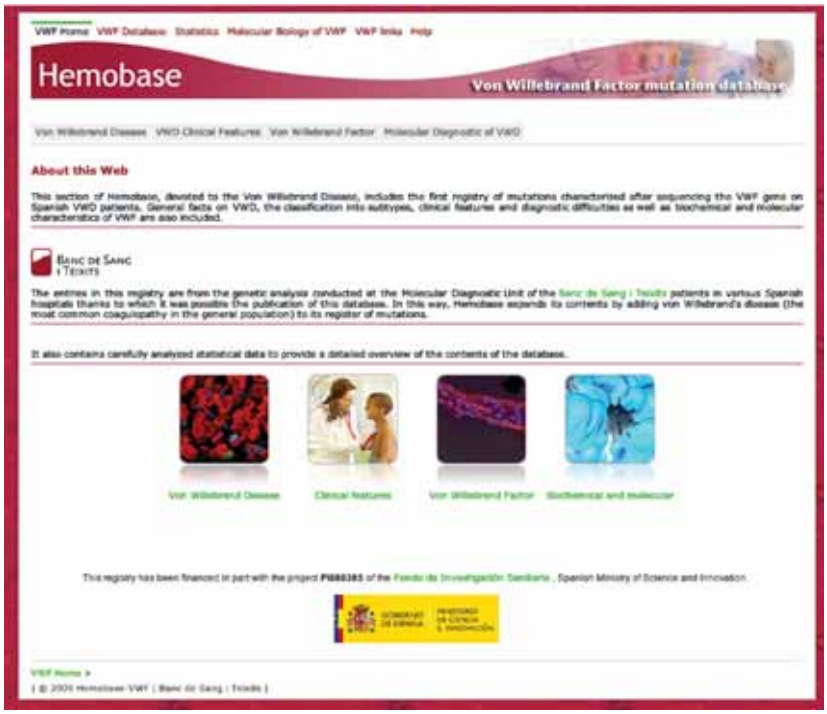


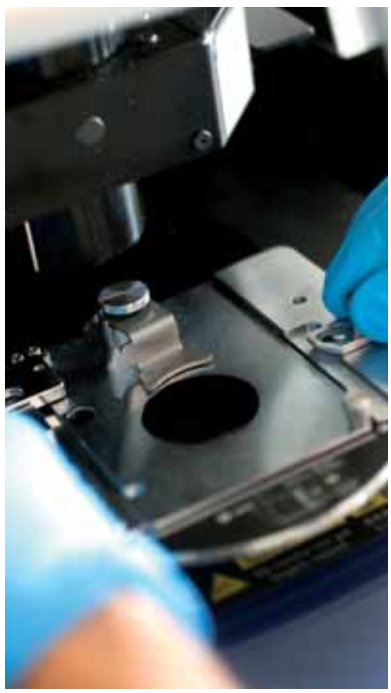
Figure 108
Screen capture of the website Hemobase (http://www.hemobase.com). Devoted to Hemophila and von Willebrand disease (VWD), it includes the first registry of mutations characterized from patients in the Spanish population. Comprises a dynamic registry with permanent updates. General facts on such 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 directly performed 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

Publications

Impact Factor: 9.773

Corrales I, Ramírez L, Altisent C, Parra R, Vidal F. Rapid molecular diagnosis of von Willebrand disease by direct sequencing. Detection of 12 novel putative mutations in VWF gene. *Thromb Haemost* 2009 Mar; 101 (3): 570-6. ➪ IF: 3.803.

Eixarch H, Espejo C, Gómez A, Mansilla MJ, Castillo M, Mildner A, Vidal F, Gimeno R, Prinz M, Montalbán X, Barquinero J. Tolerance induction in experimental autoimmune encephalomyelitis using non-myeloablative hematopoietic gene therapy with autoantigen. *Mol Ther* 2009 May; 17 (5): 897-905. ➪ IF: 5.97.



Current Research Projects

Exploring alternatives for the recombinant human factor VIII production by means of novel yeast expression systems
Francisco Vidal Pérez

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: from 2009 to 2011

2.9 Area T1: Epidemiology, Public Health and Health-Care Technology

Research Group: Epidemiology and Public Health (EPIDEM)

Group Leader
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Researchers in Training
Susana Otero Romero

Nursing, Technical and Administrative Staff
Eduard Hermosilla Pérez
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 evolution, features, host and healthcare-associated factors and impact of these infections.

Preventive vaccines
Magda Campins Martí
Developing studies on effectiveness and characteristics of use of preventive vaccines in hospital and community context.

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: from 2008 to 2010

PI: Josep Vaqué Rafart
Establecimiento de un modelo para mejorar la comparabilidad de los resultados del Estudio de Prevalencia de las Infecciones Nosocomiales en España (EPINE)
Funding Agency: Fondo de Investigación Sanitaria
Reference: PI07/90255
Funding: 45,375 €
Duration: from 2008 to: 2009

Publications

Impact Factor: 27.852

Benavente S, Vergés R, Hermosilla E, Fumanal V, Casanova N, Garcia A, Ramón y Cajal S, Giralt J. Overexpression of Phosphorylated 4E-BP1 Predicts for Tumor Recurrence and Reduced Survival in Cervical Carcinoma Treated with Postoperative Radiotherapy. *Int J Radiat Oncol Biol Phys* 2009 Dec 1; 75 (5): 1316-22. ⇨ IF: 4.639.

Campins M, Torres M, Varela P, López Clemente V, Gascó A, Prada M de la, Espuga M, Tapias G, Peña P, Hermosilla E, Otero S, Bastida T, Sanz P, Maria Bayas J, Serra C. Needlestick injuries in health care workers: analysis of non preventable risk factors through standard precautions. *Med Clin* (Barc) 2009 Feb 28; 132 (7): 251-8. ➪ IF: 1.258.

Imaz A, Falcó V, Peñaranda M, Jordano Q, Martínez X, Nadal C, Curran A, Planes AM, Dalmau D, Ribera E, Riera M, Ruiz de Gopegui E, Pahissa A. Impact of prior pneumococcal vaccination on clinical outcomes in HIV-infected adult patients hospitalized with invasive pneumococcal disease. *HIV Med* 2009 Jul; 10 (6): 356-63. ➪ IF: 3.103.

Labrador-Horrillo M, Martínez MA, Selva-O'Callaghan A, Delgado JF, Martínez-Gómez X, Trallero-Araguas E, Rodríguez-Sánchez JL, Vilardell-Tarrés M. Anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with idiopathic inflammatory myopathy. *Rheumatology* (Oxford) 2009 Jun; 48 (6): 676-9. ➪ IF: 4.136.

Peñalva A, San Martín A, Rosselló J, Pérez-Portabella C, Palacios A, Julia A, Planas M. Oral nutritional supplementation in hematologic patients. *Nutr Hosp* 2009 Jan-Feb; 24 (1): 10-6. ➪ IF: 1.096.

Simeón CP, Fonollosa V, Tolosa C, Palou E, Selva A, Solans R, Armadans L, Moreno E, Marsal S, Vilardell M. Association of HLA Class II Genes with Systemic Sclerosis in Spanish Patients. *J Rheumatol* 2009 Dec; 36 (12): 2733-6. ➪ IF: 3.282.

Urquizu-Padilla M, Balada E, Chacón P, Pérez EH, Vilardell-Tarrés M, Ordi-Ros J. Changes in lipid profile between flare and remission of patients with systemic lupus erythematosus: a prospective study. *J Rheumatol* 2009 Aug; 36 (8): 1639-45. ➪ IF: 3.282.

Urquizu-Padilla M, Balada E, Cortés F, Pérez EH, Vilardell-Tarrés M, Ordi-Ros J. Serum levels of soluble CD40 ligand at flare and at remission in patients with systemic lupus erythematosus. *J Rheumatol* 2009 May; 36 (5): 953-60. ➪ IF: 3.282.

Vaqué Rafart J. Influenza caused by A (H1N1) 2009 virus: low virulence but typical pandemic characteristics. *Med Clin* (Barc) 2009 Oct 17; 133 (14): 542-4. ➪ IF: 1.258.

Vaqué Rafart J, Gil Cuesta J, Brotons Agulló M. Main features of the new influenza virus a pandemic (H1N1). *Med Clin* (Barc) 2009 Oct 10; 133 (13): 513-21. ➪ IF: 1.258.

Vargas-Leguas H, Campins Martí M, Juste Sánchez C, Martínez Gómez X, Hermosilla Pérez E, Cabero Roura L. Rubella susceptibility of immigrant pregnant women in Catalonia. *Med Clin* (Barc) 2009 Mar 14; 132 (9): 344-7. ➪ IF: 1.258.

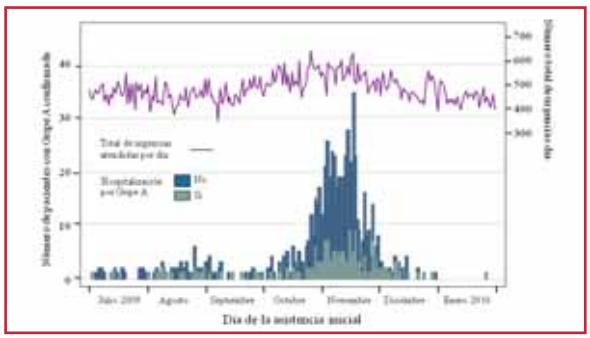

Figure 109
Distribution of confirmed cases of influenzavirus A (H1N1) 2009 which have been seen at Hospital Universitari Vall d'Hebron, from 2nd July, 2009 until 22nd January, 2010

Figure 110
Evolution of prevalence of patients with nosocomial infection in Spain, EPINE Study 1990-2009

2.10 Area T2: Pharmacology

Research Group: Clinical Pharmacology

(Catalan Institute of Pharmacology Foundation)

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Immaculada Danés Carreras
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Immaculada Fuentes Camps
Núria García Dolade
Luisa Ibáñez Mora
Eva María López Guerrero
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Nursing, Technical and Administrative Staff
Maria Elena Ballarín Alins
José J. Barroso García
Eulàlia Pérez Esquirol
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 medicines utilization and medicines adverse effects 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.

Research Lines

Risk of agranulocytosis associated with medicines use

Joan-Ramon Laporte

In collaboration with all the services of Haematology 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 and Mònica Sabaté

In collaboration with 12 Units of Hepatology 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 to identify 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

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 the severity, to describe the clinic characteristics and clinical course, the drugs involved, other associated risk factors, the length of the hospital stay, and the economical impact.

PROTECT (Pharmacoepidemiological Research on Outcome of Therapeutics by a European ConsorTium

Joan-Ramon Laporte and Luisa Ibáñez

The goal of this project is to strengthen the monitoring of benefit-risk 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.

Figure 111
In 2009 our group has celebrated the 25th anniversary of its foundation

Figure 112
Design and follow up of studies in collaboration with clinical investigators. Added value on design of questionnaires and reporting forms, platforms for data sharing and data analysis, and other tools for clinical research

Current Research Projects

PI: Joan-Ramon Laporte
Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium PROTECT
Funding Agency: Innovatives Medicines Initiative Joint Undertaking
Reference: IMI/115004
Funding: 594,900 €
Duration: from 2009 to 2014

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: from 2009 to 2012

PI: Maria Antònia Agustí Escasany and Alfons Segarra
Incidència de la insuficiència renal aguda produïda per fàrmacs en pacients hospitalitzats, factors de risc associats, morbiditat, mortalitat i cost econòmic
Funding Agency: Agència d'Avaluació de Tecnologies i Recerca Mèdica
Reference: 374/09/2008
Funding: 34,149 €
Duration: from 2009 to 2011

PI: Immaculada Danés Carreras
Estudio de utilización de antifúngicos sistémicos en los hospitales españoles
Funding Agency: Fondo de Investigación Sanitaria
Reference: EC07/90336
Funding: 18,755 €
Duration: from 2007 to 2009

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: from 2009 to 2012

Publications

Impact Factor: 26.877

Aguilera C, Mesas A, Muñoz C, Salicru S. Therapeutic alternatives to epidural analgesia in labor pain of childbirth. *Med Clin* (Barc) 2009 Oct 24; 133 (15): 599-601. ➪ IF: 1.258.

Balbuena FR, Aranda AB, Figueras A. Self-medication in older urban Mexicans: an observational, descriptive, cross-sectional study. *Drugs Aging* 2009; 26 (1): 51-60. ➪ IF: 2.11.

Braga Ceccato MG, Acurcio Fde A, Vallano A, Comini Cesar C, Crosland Guimaraes M. Assessment of factors associated with patients' comprehension of treatment at the start of antiretroviral therapy. *Enferm Infecc Microbiol Clin* 2009 Jan; 27 (1): 7-13. ➪ IF: 1.432.

Brotons C, Falces C, Alegre J, Ballarín E, Casanovas J, Cata T, Martínez M, Moral I, Ortiz J, Pérez E, Rayo E, Recio J, Roig E, Vidal X. Randomized clinical trial of the effectiveness of a home-based intervention in patients with heart failure: the IC-DOM study. *Rev Esp Cardiol* 2009 Apr; 62 (4): 400-8. ➪ IF: 2.88.

Colomina MJ, Bagó J, Fuentes I. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. *Spine* 2008; 33: 2577-80. *Spine (Phila Pa 1976).* 2009 Jul 15; 34 (16): 1740-1; author reply 141. ➪ IF: 2.793.

Colomina MJ, Bagó J, Vidal X, Mora L, Pellisé F. Antifibrinolytic therapy in complex spine surgery: a case-control study comparing aprotinin and tranexamic acid. *Orthopedics* 2009 Feb; 32 (2): 91. ➪ IF: 0.588.

Mitja O, Pigrau C, Ruiz I, Vidal X, Almirante B, Planes AM, Molina I, Rodríguez D, Pahissa A. Predictors of mortality and impact of aminoglycosides on outcome in listeriosis in a retrospective cohort study. *J Antimicrob Chemother* 2009 Aug; 64 (2): 416-23. ➪ IF: 4.328.

Pedrós C, Vallano A, Cereza G, Mendoza-Arán G, Agustí A, Aguilera C, Danés I, Vidal X, Arnau JM. An intervention to improve spontaneous adverse drug reaction reporting by hospital physicians: a time series analysis in Spain. *Drug Saf* 2009; 32 (1): 77-83. ➪ IF: 3.537.

Pérez C, Agustí MA, Tornos P. Late-onset anthracycline-induced cardiotoxicity. *Med Clin* (Barc) 2009 Sep 5; 133 (8): 311-3. ➪ IF: 1.258.

Remesar Navarro G, Danés Carreras I. Treatment of toxoplasmosis during pregnancy. *Med Clin* (Barc) 2009 Nov 21; 133 (19): 763-5. ➪ IF: 1.258.

Sánchez-Díaz P, Estany-Gestal A, Aguirre C, Blanco A, Carracedo A, Ibáñez L, Passiu M, Provezza L, Ramos-Ruiz R, Ruiz B, Salado-Valdivieso I, Velasco EA, Figueiras A. Prevalence of CYP2C9 polymorphisms in the south of Europe. *Pharmacogenomics J* 2009 Oct; 9 (5): 306-10. ➪ IF: 5.435.

2.11 Area T3: R+D, New Technologies and Experimental Surgery

Research Group: Fetal Surgery, Congenital Malformations and Orthopedical Anomalies

Group Leaders
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Ana Andaluz Martínez
Xavier Conesa Muñoz
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Félix García Arnás
César Galo García Fontecha
Carles Giné Pradas
Maria Gabriella Guillén Burrieza
Santiago Guindos Rúa
Alberto Hernández Fernández
Aamer Malik
Mario Marotta
Xavier Moll
José Orellana
Juan José Sevilla Tirado
Francisco Soldado Carrera
Núria Torán Fuentes
Roberto Vélez Villa

Objectives

In the beginnings, at late nineties, our group started experimental studies of fetal surgery for congenital diaphragmatic hernia and fetoscopic techniques in animal models, that promote its application to human clinics within the Fetal Surgery Program that currently offers the Hospital Vall d'Hebron. Then, we opened several lines of experimental research on prenatal congenital malformations amenable to be treated, such as cleft lip-palate, amniotic band syndrome and spina bifida. Orthopedic abnormalities and malformations are also focus of interest to our research group. Our goal is to study congenital malformations from different points of view, etiopathogenesis, natural history, pathophysiology, and diagnosis and treatment in the pre-and postnatal periods. The ultimate goal of the group is to perform translational research, applying the findings or therapeutic strategies that are discovered in laboratory experiments to the human clinical setting.

Research Lines

Fetal Surgery

Prenatal treatment of Congenital Diaphragmatic Hernia
José Luis Peiró Ibáñez and Vicenç Martínez Ibáñez

Fetal Surgery of Myelomeningocele
César Galo García Fontecha

Non-surgical antenatal treatment of myelomeningocele
César Galo García Fontecha

Intrauterine repair of fetal cleft lip-palate
José Luis Peiró Ibáñez

Study of local action tocolytics on myometrium in a rabbit model
Carles Giné Prades and José Luis Peiró Ibáñez

Fetal surgery of amniotic bands
Francisco Soldado Carrera and Màrius Aguirre Canyadell

Sonographic predictive findings of limb amputation by amniotic bands in fetal sheep
Francisco Soldado Carrera and Juan Carlos Bello

Prenatal treatment of intrauterine gangrene
Francisco Soldado Carrera

Neonatal Congenital Malformations

Study of intestinal motility and treatment strategies in gastroschisis
José Luis Peiró Ibáñez and Carles Giné Prades

Esophageal elongation techniques in long-gap esophageal atresia
José Luis Peiró Ibáñez and Alex Urbistondo

Orthopedical Anomalies

Experimental treatment of peripheral nerve injuries
Francisco Soldado Carrera

Experimental treatment of striated muscle lesions
Francisco Soldado Carrera

Experimental study of bone consolidation
Màrius Aguirre Canyadell

Experimental treatment of bone osteonecrosis
Màrius Aguirre Canyadell

Study of multimodal anaesthesia and bone consolidation
Màrius Aguirre Canyadell

Current Research Projects

PI: Màrius 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: from 2008 to 2010

Figure 113
Induction of cleft lip in fetal sheep

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: from 2008 to 2011

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: PI070503
Funding: 41,745 €
Duration: from 2008 to 2010

Figure 115
Congenital model of myelomeningocele in fetal mice

Figure 114
Fetoscopic treatment of myelomeningocele in fetal sheep

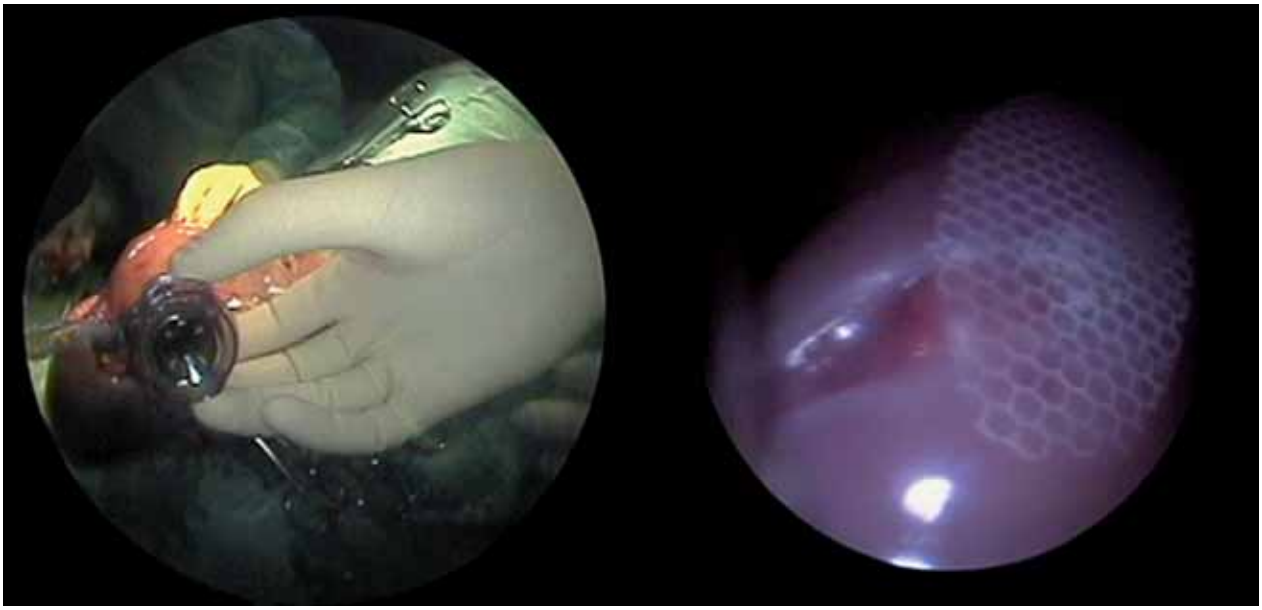

Figure 116
Sonography of extremities amniotic bands in fetal sheep

Publications

Impact Factor: 17.247

Fontecha CG, Peiró JL, Aguirre M, Soldado F, Anor S, Fresno L, Martínez-Ibáñez V. Inert patch with bioadhesive for gentle foetal surgery of myelomeningocele in a sheep model. *Eur J Obstet Gynecol Reprod Biol* 2009 Oct; 146 (2): 174-9. ➪ IF: 1.565.

Marotta M, Ruiz-Roig C, Sarria Y, Peiroó JL, Nuñez F, Cerón J, Munell F, Roig-Quilis M. Muscle genome-wide expression profiling during disease evolution in mdx mice. *Physiol Genomics* 2009 Apr 10; 37 (2): 119-32. ➪ IF: 3.436.

Peiró JL, Carreras E, Guillén G, Arévalo S, Sánchez-Durán MA, Higueras T, Castillo F, Marhuenda C, Lloret J, Martínez-Ibáñez V. Therapeutic indications of fetoscopy: a 5-year institutional experience. *J Laparoendosc Adv Surg Tech A* 2009 Apr; 19 (2): 229-36. ➪ IF: 0.912.

Peiró JL, Carreras E, Soldado F, Sánchez-Durán MA, Aguirre M, Barber I, Martínez-Ibáñez V. Fetoscopic release of umbilical cord amniotic band in a human fetus. *Ultrasound Obstet Gynecol* 2009 Feb; 33 (2): 232-4. ➪ IF: 2.69.

Pellisé F, Balagué F, Rajmil L, Cedraschi C, Aguirre M, Fontecha CG, Pasarín M, Ferrer M. Prevalence of low back pain and its effect on health-related quality of life in adolescents. *Arch Pediatr Adolesc Med* 2009 Jan; 163 (1): 65-71. ➪ IF: 4.32.

Soldado F, Aguirre M, Peiró JL, Carreras E, Arévalo S, Fontecha CG, Vélez R, Barber I, Martínez-Ibáñez V. Fetoscopic release of extremity amniotic bands with risk of amputation. *J Pediatr Orthop* 2009 Apr-May; 29 (3): 290-3. ➪ IF: 1.569.

Soldado F, Aguirre M, Peiró JL, Fontecha CG, Esteves M, Vélez R, Martínez-Ibáñez V. Fetal surgery of extremity amniotic bands: an experimental model of in utero limb salvage in fetal lamb. *J Pediatr Orthop* 2009 Jan-Feb; 29 (1): 98-102. ➪ IF: 1.569.

Vázquez E, Castellote A, Mayolas N, Carreras E, Peiró JL, Enriquez G. Congenital tumours involving the head, neck and central nervous system. *Pediatr Radiol* 2009 Nov; 39 (11): 1158-72. Epub 2009 Sep 23. ➪ IF: 1.186.

2.11 Area T3: R+D, New Technologies and Experimental Surgery

Research Group: Spinal Pathology Study

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Patricia Garcia Guarch
Ferran Pellisé Urquiza

Clinical director
Enric Càceres Palou

Objectives

International multicentric data base of adult scoliosis. Identification of peri-operative factors related with postoperative infection in spinal surgery. Data base of metastatic tumors of the spine. Scoliosis outcome after surgical deformity correction.

Research Lines

Perioperative anaesthesia management
Mª José Colomina Soler

Degenerative lumbar spine problems
Ferran Pellisé Urquiza

Scoliosis and other spinal deformities
Joan Bagó Graell

Thoracolumbar fractures
Carlos Villanueva Leal

Publications

Impact Factor: 12.493

Cervical spine
Josep M. 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 and Antonia Matamalas Adrover

Bagó J, Pérez-Grueso FJ, Les E, Hernández P, Pellisé F. Minimal important differences of the SRS-22 Patient Questionnaire following surgical treatment of idiopathic scoliosis. *Eur Spine J* 2009 Dec; 18 (12): 1898-904. ⇨ IF: 2.396.

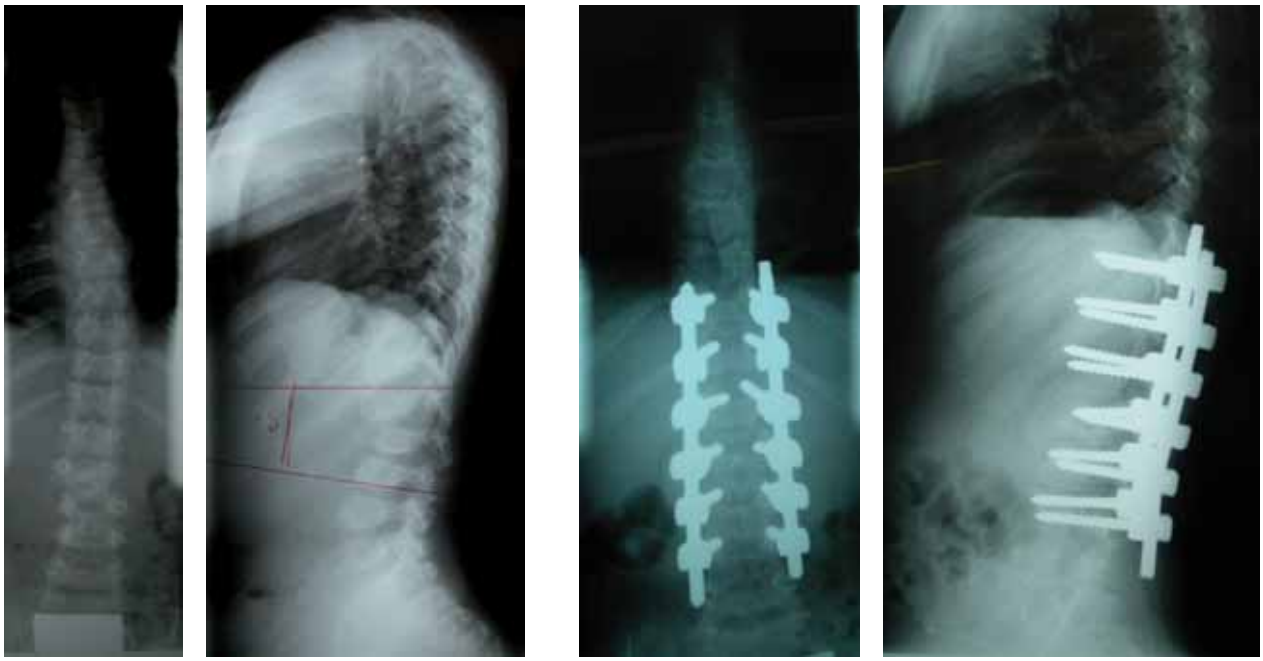
Colomina MJ, Bagó J, Fuentes I. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. Spine 2008; 33: 2577-80. *Spine* (Phila Pa 1976). 2009 Jul 15; 34 (16): 1740-1; author reply 141. ⇨ IF: 2.793.

Colomina MJ, Bagó J, Vidal X, Mora L, Pellisé F. Antifibrinolytic therapy in complex spine surgery: a case-control study comparing aprotinin and tranexamic acid. *Orthopedics* 2009 Feb; 32 (2): 91. ⇨ IF: 0.588.

Pellisé F, Balagué F, Rajmil L, Cedraschi C, Aguirre M, Fontecha CG, Pasarin M, Ferrer M. Prevalence of low back pain and its effect on health-related quality of life in adolescents. *Arch Pediatr Adolesc Med* 2009 Jan; 163 (1): 65-71. ⇨ IF: 4.32.

Pellisé F, Sell P. Patient information and education with modern media: the Spine Society of Europe Patient Line. *Eur Spine J* 2009 Aug; 18 Suppl 3: 395-401. ⇨ IF: 2.396.

Figure 117
Surgical treatment of thoracolumbar kyphosis in Hurler's syndrome



2.11 Area T3: R+D, New Technologies and Experimental Surgery

Research Group: Ophthalmology

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Carme Macià Badia
Vicente Martínez Castillo
Andrea Rodrigues Carvalho
Anna Salas Torras
Miguel Ángel Zapata Victori

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, upon which we are interested on the development of a new surgical technique for its treatment and the physiopathology of vitreoretinal proliferation; age-related macular degeneration (ADM), inside which we are studying genetic risk factors and the role played by inflammation in its pathogeny of uveitis, concretely the pathogeny of uveitic macular edema and the role played by antiangiogenic drugs in the treatment of this disorder.

Research Lines

Research group of Diabetic retinopathy
J García Arumí, MA Zapata Victori, A Rodrigues Carvalho, A Salas Torras and C Macià Badia
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 on 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.

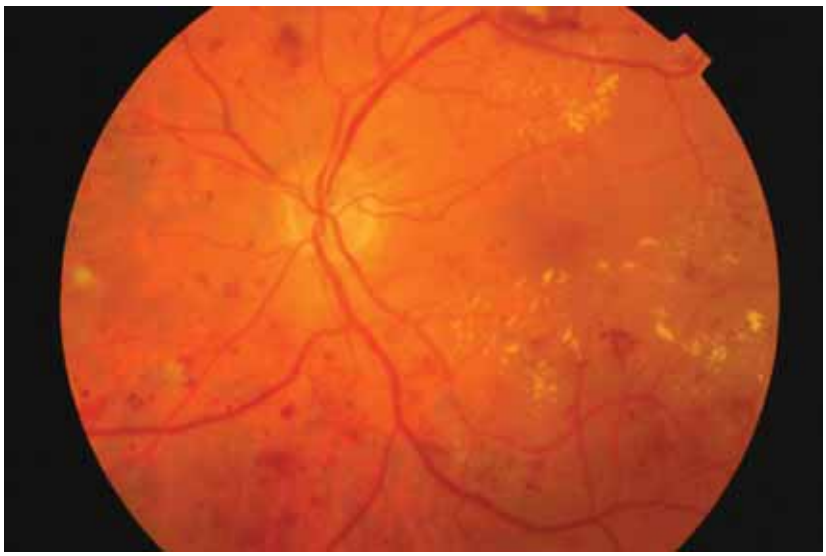


Figure 118
Diabetic retinopathy with diabetic macular edema

– Development of an anti-angiogenic gene therapy using non-viral vectors in attempt to improve DR treatment and patient's quality of life.

Research group of retinal artery occlusion

J García Arumí, MA Zapata Victori, A Rodrigues Carvalho, A Salas Torras and C Macià Badia

Our research group investigates physiopathology as well as novel surgical approaches of retinal artery occlusion.

Our research focus 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.

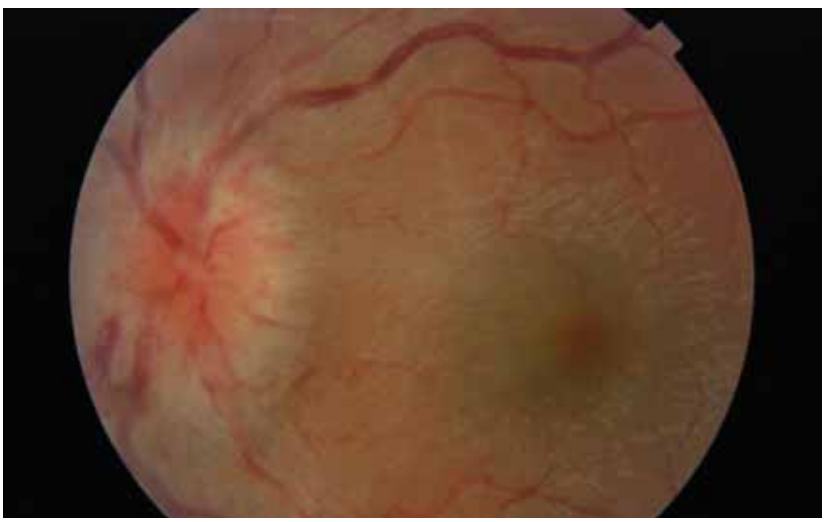
– Research on erythropoietin (EPO) and EPOr, VEGF and PEDF in ischemic retina.

Retinal vascular diseases

José García Arumí and Anna Boixadera

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 therapeutica 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 the foveal photoreceptors´ survival time after a branch retinal artery occlusion. For this purpose we are using an animal model (pig).

Figure 119
Optic disc edema and macular serous retinal detachment seen in neuroretinitis



Age related macular degeneration

Miguel Ángel Zapata

Our research group investigates one of the most prevalent and invalidated diseases present in the population older than 50 years old. Our research focus on clinic and basic science:

- Collaboration on multicentre clinical trials for new exudative age related macular degeneration therapies, with both industry and public funds.
- Collaboration on multicentre Studies of macular degeneration genotype.
- Collaboration on multicentre Studies in the progression of the atrophic macular degeneration.
- Independent clinical trial research with new medicaments to treat exudative macular degeneration.
- Research of biomarkers and risk factors in the intermediary macular degeneration.
- In vitro research of antiangiogenic and neuroprotective factors using primary and cell line of retinal pigmentary epithelium cultures.

Uveitis

Carme Macià

We are mainly investigating macular edema, which is an 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.

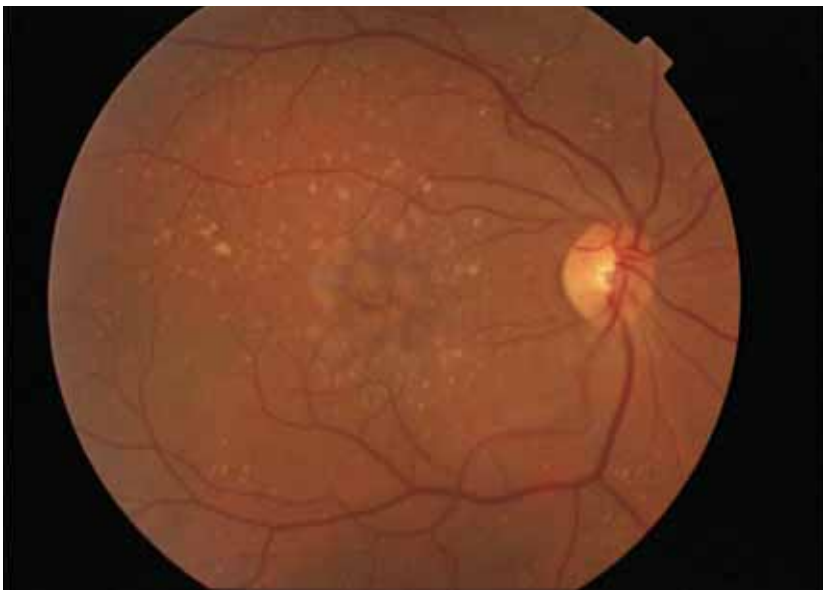


Figure 120
Soft, confluent drusen in Age-Related Macular Degeneration

Current Research Projects

PI: Àlex 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: from 2009 to 2011

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: PI060803
Funding: 58,080 €
Duration: from 2007 to 2010

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: from 2008 to 2010

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: from 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: from 2009 to 2011

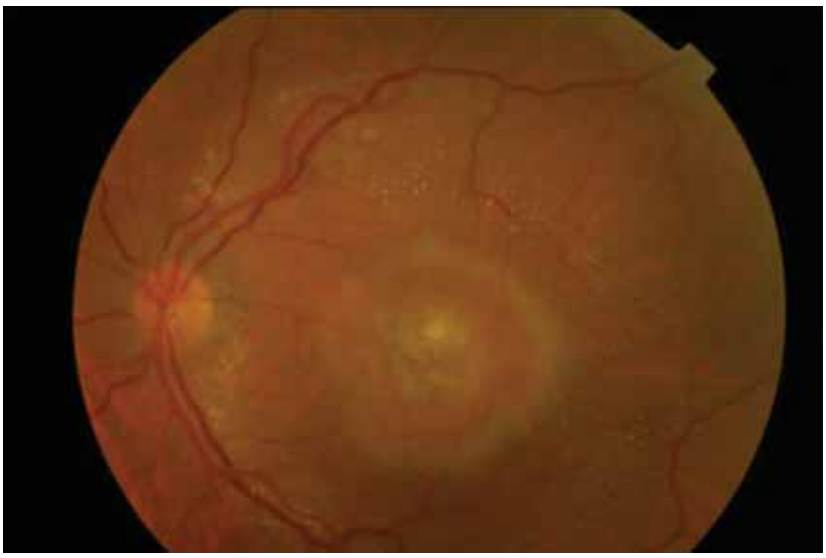


Figure 121
Neovascular Age-Related Macular Degeneration

Publications

Impact Factor: 22.862

Arias L, Armada F, Donate J, García-Arumí J, Giralt J, Pazos B, Piñero A, Martínez F, Mondéjar JJ, Ortega I, Zlateva G, Buggage R. Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. *Eye* (Lond) 2009 Feb; 23 (2): 326-33. ⇨ IF: 2.064.

Boixadera A, García-Arumí J, Martínez-Castillo V, Encinas JL, Elizalde J, Blanco-Mateos G, Caminal J, Capeans C, Armada F, Navea A, Olea JL. Prospective clinical trial evaluating the efficacy of photodynamic therapy for symptomatic circumscribed choroidal hemangioma. *Ophthalmology* 2009 Jan; 116 (1): 100-105.e1. ⇨ IF: 5.296.

Fonollosa A, Giralt J, Pelegrín L, Sánchez-Dalmau B, Segura A, García-Arumí J, Adan A. Ocular syphilis-back again: understanding recent increases in the incidence of ocular syphilitic disease. *Ocul Immunol Inflamm* 2009 May-Jun; 17 (3): 207-12. ⇨ IF: 0.919.

García-Ramírez M, Hernández C, Villarroel M, Canals F, Alonso MA, Fortuny R, Masmiquel L, Navarro A, García-Arumí J, Simó R. Interphotoreceptor retinoid-binding protein (IRBP) is downregulated at early stages of diabetic retinopathy. *Diabetologia* 2009 Dec; 52 (12): 2633-41. ⇨ IF: 6.418.

García-Arumí J, Fonollosa A, Macià C, Hernández C, Martínez-Castillo V, Boixadera A, Zapata MA, Simó R. Vitreous levels of erythropoietin in patients with macular oedema secondary to retinal vein occlusions: a comparative study with diabetic macular oedema. *Eye* (Lond) 2009 May; 23 (5): 1066-71. ⇨ IF: 2.064.

Martínez-Castillo V, Boixadera A, García-Arumí J. Pars plana vitrectomy alone with diffuse illumination and vitreous dissection to manage primary retinal detachment with unseen breaks. *Arch Ophthalmol* 2009 Oct; 127 (10): 1297-304. ⇨ IF: 3.242.

Medel R, Alonso T, Vela JI, Calatayud M, Bisbe L, García-Arumí J. Conjunctival cytology in floppy eyelid syndrome: objective assessment of the outcome of surgery. *Br J Ophthalmol* 2009 Apr; 93 (4): 513-7. ⇨ IF: 2.859.

2.11 Area T3: R+D, New Technologies and Experimental Surgery

Research Group: Robotic and Craniofacial Surgery

Group Leaders
Guillem Raspall Martin
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
Jorge Pamias Romero
Josep Rubió Palau
Manuel Sáez Barba

Objectives

Research and development of applications of robotics and information and image technologies in craniofacial surgery

Research Lines

Robotics
Juan Antonio Hueto,[1] Alícia Casals,[2] Josep Amat[2] and Javier Gutiérrez[1]

Imaging technology and virtual reality
Juan Antonio Hueto,[1] Isabel Navazo,[3] Pere Brunet[3] and Josep Rubió[1]

Microsurgery
Coro Bescós,[1] Jorge Pamias[1] and Manuel Sáez[1]

[1] Hospital General Universitario Vall d'Hebron
[2] Departament d'Enginyeria de Sistemes, Automàtica i Informàtica Industrial (ESAII), Universitat Politècnica de Catalunya (UPC)
[3] Departament de Llenguatges i Sistemes Informatics (LSI), Universitat Politècnica de Catalunya (UPC)

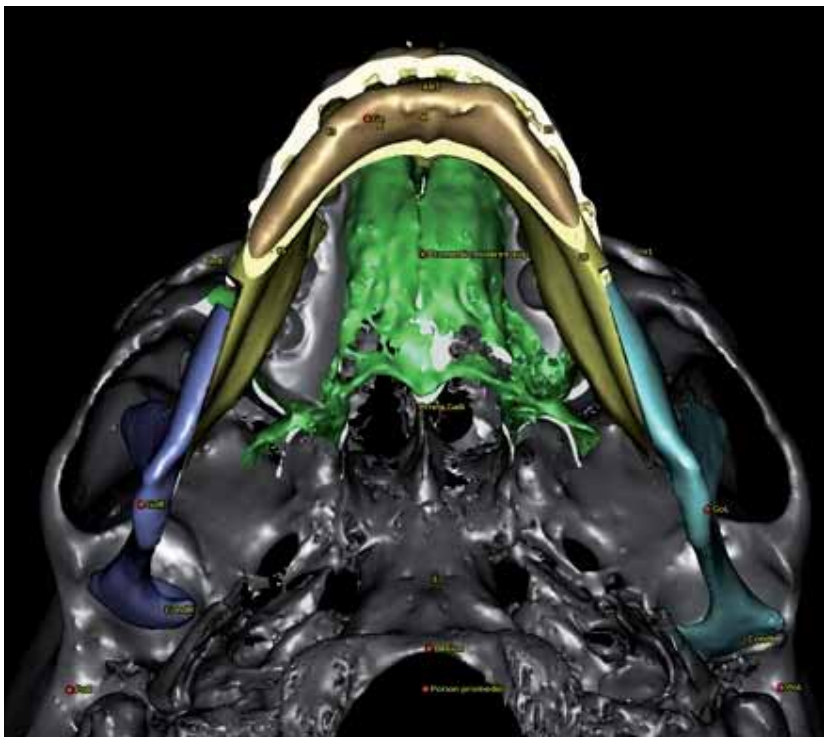


Figure 122
Imaging technology and virtual reality

Publications

Impact Factor: 2.866

Pigrau C, Almirante B, Rodríguez D, Larrosa N, Bescós S, Raspall G, Pahissa A. Osteomyelitis of the jaw: resistance to clindamycin in patients with prior antibiotics exposure. *Eur J Clin Microbiol Infect Dis* 2009 Apr; 28 (4): 317-23. ➪ IF: 2.866.

Current Research Projects

PI: Isabel Navazo Álvaro
Modelado, visualización, animación y análisis de entornos 3D altamente complejos en sistemas interactivos de realidad virtual
Funding Agency: Ministerio de Educación y Ciencia.
Reference: TIN2007-67982-C02-01
Funding: 352,110 €
Duration: from 2007 to 2010

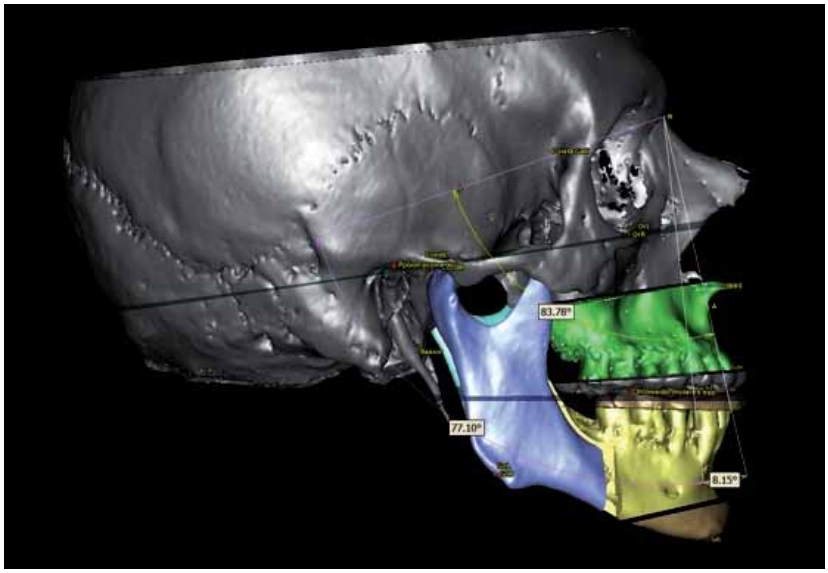
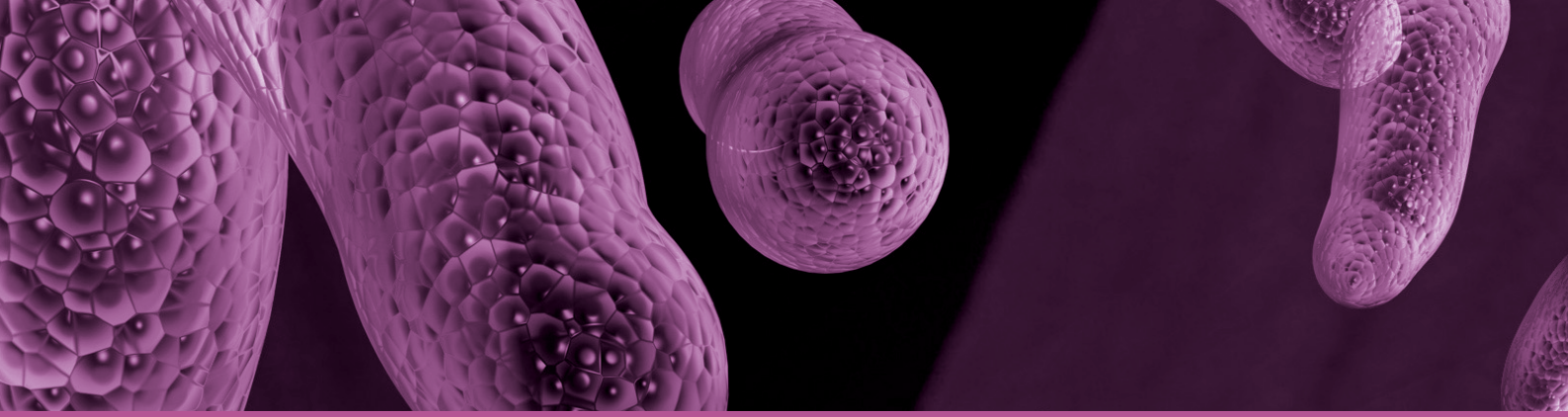
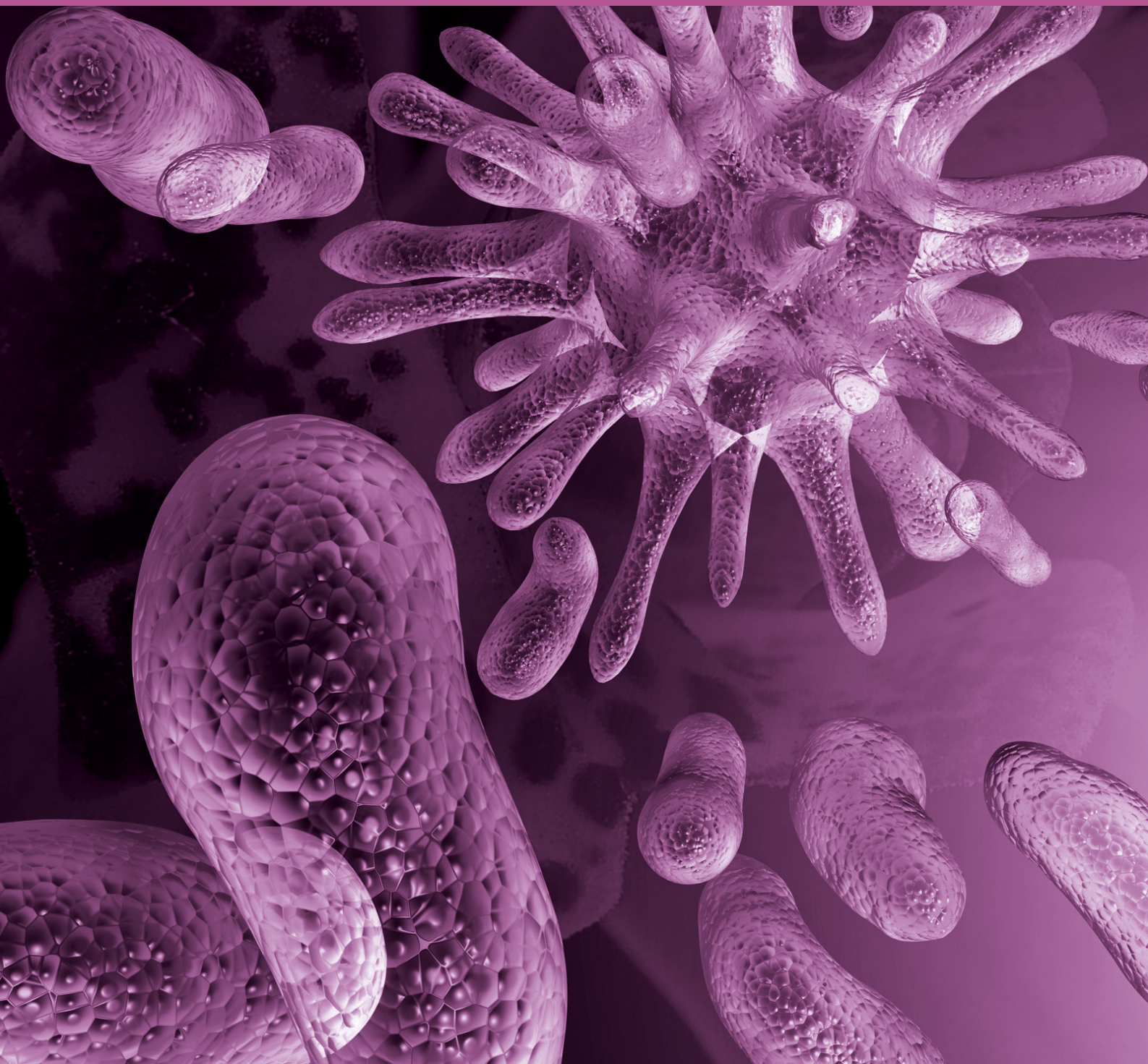


Figure 123
Example of craniofacial surgery

Vall d'Hebron
Institut de Recerca



3 Memòria Anual 2009 / Memoria Anual 2009



Memòria Anual 2009

OBJECTIUS

El propòsit general del Vall d'Hebron Institut de Recerca (VHIR) és donar suport, promoure i acollir recerca, coneixement científic i tecnològic, ensenyar, i formar en l'entorn de l'Hospital Universitari Vall d'Hebron (HUVH), de la Universitat Autònoma de Barcelona (UAB), i les seves àrees d'influència. La missió bàsica del VHIR és el desenvolupament de la recerca biomèdica i la promoció de la seva aplicació per millorar la salut dels ciutadans. El VHIR és un centre líder en la recerca biomèdica a nivell nacional i europeu. Degut a l'avantatge que li proporciona la seva relació privilegiada amb l'hospital de tercer nivell, aconsegueix una posició altament competitiva. L'Institut aprofundeix en les relacions de col·laboració amb parcs científics, universitats i altres instituts de recerca.

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 els òrgans de direcció següents: el Patronat, la Junta de Govern, la Direcció, i els Comitès Científics Interns i Externs.

Memoria Anual 2009

OBJETIVOS

El objetivo general del *Vall d'Hebron Institut de Recerca* (VHIR) es apoyar, promover y fomentar la investigación, el conocimiento científico y tecnológico, la enseñanza y la formación en el ámbito del *Hospital Universitari Vall d'Hebron* (HUVH), de la *Universitat Autònoma de Barcelona* (UAB) y sus áreas de influencia. La misión básica del VHIR es el desarrollo de la investigación biomédica y la promoción de su aplicación para mejorar la salud de los ciudadanos. El VHIR es un centro líder en investigación biomédica en el ámbito nacional y europeo. Debido a la ventaja de su relación privilegiada con un hospital de tercer nivel, consigue una posición altamente competitiva. El Instituto profundiza en las relaciones de colaboración con los parques científicos, universidades y otros institutos de investigación.

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 los órganos de dirección siguientes: el Patronato, la Junta de Gobierno, la Dirección, y los Comités Científicos Internos y Externos.

Direcció

El director de la Fundació té com a funcions, entre altres, assumir la direcció científica i docent de la Fundació, executar i fer complir les decisions dels òrgans de govern, definir la contractació i funcions del personal, impulsar les relacions amb altres organismes de recerca, coordinar les relacions de la Fundació amb l'Hospital Universitari Vall d'Hebron, la Universitat Autònoma de Barcelona i altres entitats que formen el Patronat de la Fundació.
El director de la Fundació és el Dr. Joan X. Comella.

Patronat

El govern i la representació de la Fundació corresponen al Patronat, que té totes les facultats necessàries per a la realització de les seves finalitats, sense prejudici de les facultats de delegació que li atorguen les lleis i els estatuts.
Està format d'un mínim de vuit persones i un màxim de 25, i és presidit per la Hble. Sra. Marina Geli Fàbrega, Consellera del Departament de Salut.

Junta de Govern

La Junta de Govern està formada per un mínim de cinc persones designades pel Patronat, havent d'estar representats l'Hospital Universitari Vall d'Hebron i la Universitat Autònoma de Barcelona. La Junta de Govern és presidida pel gerent de l'Hospital Universitari Vall d'Hebron, el Dr. José Luis de Sancho Martín.

Dirección

El director de la Fundación tiene entre otras funciones, asumir la dirección científica y docente de la Fundación, ejecutar y hacer cumplir las decisiones de los órganos de gobierno, definir la contratación y funciones del personal, impulsar las relaciones con otros organismos de investigación y coordinar las relaciones de la Fundación con el Hospital Universitari Vall d'Hebron, la Universitat Autònoma de Barcelona y otras entidades que forman el Patronato de la Fundación.
El director de la Fundación es el Dr. Joan X. Comella.

Patronato

El gobierno y la representación de la Fundación corresponden al Patronato, que tiene todas las facultades necesarias para la realización de sus finalidades, sin prejuicio de las facultades de delegación que le otorgan las leyes y los estatutos.
Está formado por un mínimo de ocho personas y un máximo de 25, y es presidido por la Hble. Sra. Marina Geli Fàbrega, Consellera del Departament de Salut.

Junta de Gobierno

La Junta de Gobierno está formada por un mínimo de cinco personas designadas por el Patronato, teniendo que estar representados el Hospital Universitari Vall d'Hebron y la Universitat Autònoma de Barcelona.
La Junta de Gobierno está presidida por el Gerente del Hospital Universitari Vall d'Hebron, el Dr. José Luis de Sancho Martín.

Comitè Científic Intern

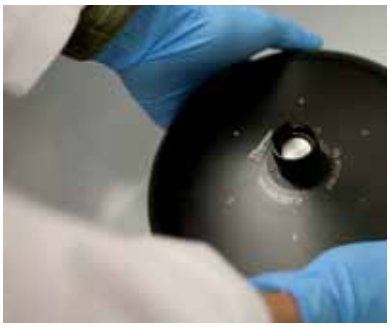
Designat pel Patronat, el Comitè Científic Intern està integrat per un nombre d'investigadors no inferior a tres membres. És un comitè assessor de la Direcció i les seves decisions no són vinculants; pot actuar en comissions.

Comitè Científic Extern

Està format per un mínim de quatre membres designats pel Patronat a proposta de la Junta de Govern. Són persones de reconegut prestigi científic i professional, a escala nacional i internacional, en l'àmbit de la recerca biomèdica, ciències de la salut i de la vida.

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.

Comité Científico Interno

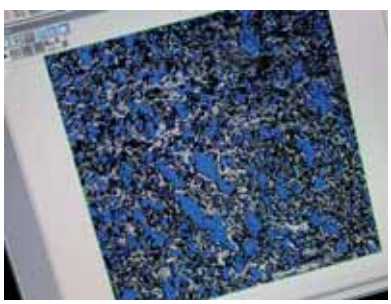
Designado por el Patronato, el Comité Científico Interno está integrado por un número de investigadores no inferior a tres miembros. Se trata de un comité asesor de la Dirección y sus decisiones no son vinculantes; puede actuar en comisiones.

Comité Científico Externo

Está formado por un mínimo de cuatro miembros designados por el Patronato a propuesta de la Junta de Gobierno. Son personas de reconocido prestigio científico y profesional, a escala nacional e internacional, en el ámbito de la investigación biomédica, ciencias de la salud y de la vida.

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.

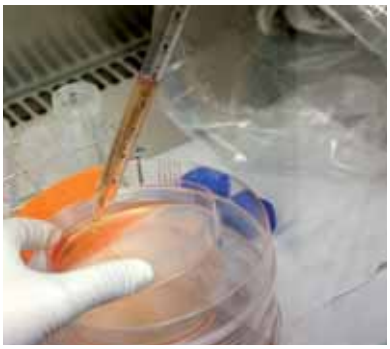


1. Innovación

El Hospital Universitari Vall d'Hebron, mediante l'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

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.

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 aquéllos 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.

Unitat de Comunicació i Imatge

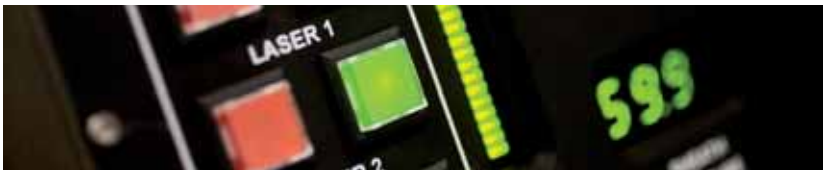
Vincula la recerca científica i la resta d'activitats de l'Institut i la societat a través dels mitjans de comunicació. Dóna a conèixer les activitats de l'Institut i els seus investigadors mitjançant notes i rodes de premsa, entrevistes, vídeos divulgatius i campanyes de comunicació concretes, desenvolupa 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·laboradors.

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.



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.

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.

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. 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 (UCTS)

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).

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 Bioinformàtica (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 (UCTS)

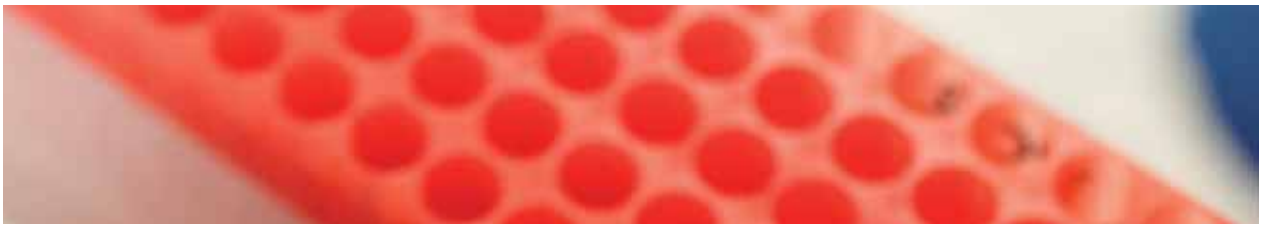
La Unidad Científico-Técnica de Soporte (UCTS) es un conjunto de servicios de tecnología puntera que dan soporte a las actividades docentes y de investigación del ámbito biomédico.

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 microscopía a un coste reducido, con una actualización constante y con el asesoramiento de personal especializado.

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.



La UCTS ofrece las siguientes plataformas: Citómica, Diagnóstico Molecular, Genómica, Microscopía, 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.

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 m² i una superfície útil de 683 m² 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.

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 m² y una superficie útil de 683 m² 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 inmunodeficien-

Unitat Central d'Investigació Clínica i Assaigs Clínics (UCICAC)

La UCICAC, constituïda per un equip de professionals multidisciplinaris, 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).

tes, 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 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 dóna recolzament a la realització d'assaigs clínics i estudis post-autorització 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.

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 post-autorización 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.

COMITÈS ÈTICS

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.

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.

COMITÉS ÉTICOS

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.

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.

RESUM DE L'ACTIVITAT INVESTIGADORA

Les activitats de recerca del VHIR que es presenten en aquesta *Memòria* de l'any 2009 queden reflectides de forma resumida en els següents apartats:

Personal investigador i tècnic

El 2009 el VHIR tenia un total de 46 grups de recerca amb 405 investigadors (metges, biòlegs, psicòlegs, bioquímics, farmacèutics, químics, veterinaris, i altres) amb 68 investigadors postdoctorals, 173 investigadors en formació i 328 personal de suport a la recerca (infermers, tècnics de laboratori, administratius i altres).

Dades financeres

El finançament total de recerca ha estat de 38,5 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 540 publicacions han estat realitzades per investigadors del VHIR, i s'han publicat en revistes científiques el 2009, amb un factor d'impacte total de 2474,709. El factor d'impacte mig per publicació ha estat de 4,58.

La distribució d'aquestes publicacions queda de la manera següent: 413 articles en revistes internacionals, 56 articles en revistes nacionals, 49 revisions o editorials en revistes internacionals i 22 revisions o editorials en revistes nacionals.

El factor d'impacte del 2009 es calcula utilitzant el "Journal Citation Reports" (JCR) del 2009, amb el càlcul basat en articles originals, revisions i editorials. Les cartes i abstracts s'exclouen del càlcul.

RESUMEN DE LA ACTIVIDAD INVESTIGADORA

Las actividades de investigación del VHIR que se presentan en esta Memoria del 2009 quedan reflejadas de forma resumida en los siguientes apartados:

Personal investigador y técnico

En 2009 el VHIR tenía un total de 46 grupos de investigación con 405 investigadores (médicos, biólogos, psicólogos, bioquímicos, farmacéuticos, químicos, veterinarios, y otros) con 68 investigadores postdoctorales, 173 investigadores en formación y 328 personal de apoyo a la investigación (enfermeros, técnicos de laboratorio, administrativos y otros).

Datos financieros

La financiación total de investigación ha sido de 38,5 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 540 publicaciones han sido realizadas por investigadores del VHIR, y se han publicado en revistas científicas en el 2009, con un factor de impacto total de 2474,709. El factor de impacto medio por publicación ha sido de 4,58.

La distribución de estas publicaciones es la siguiente: 413 artículos en revistas internacionales, 56 artículos en revistas nacionales, 49 revisiones o editoriales en revistas internacionales y 22 revisiones o editoriales en revistas nacionales.

El factor de impacto del 2009 se calcula utilizando el "Journal Citation Reports" (JCR) del 2009, con el cálculo basado en artículos originales, revisiones y editoriales. Las cartas y abstracts se excluyen del cálculo.

Projectes de recerca

El 2009, hi havia 230 projectes de recerca en curs, completament finançats per agències oficials i institucions privades.

Estudis clínics

Un total de 203 assaigs clínics se sotmetien al Comitè Ètic d'Investigació Clínica per a la seva aprovació, dels quals 173 (un 85 %) eren estudis multicentre i el resta 30 (15 %) eren estudis unicentre. Dels 203 assaigs presentats, 171 (84 %) eren patrocinats per la indústria farmacèutica, 14 (7 %) per investigadors del VHIR, i la resta, 18 (9 %), eren patrocinats per uns altres hospitals.

Nous contractes a investigadors i tècnics finançats per diferents organismes i programes

Al 2009, se signaven 9 contractes d'investigadors sèniors, 14 contractes d'investigadors postdoctorals, 12 contractes d'investigadors predoctorals i 8 contractes de tècnics de suport, finançats 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.

Proyectos de investigación

En el 2009, habían 230 proyectos de investigación en curso, completamente financiados por agencias oficiales e instituciones privadas.

Estudios clínicos

Un total de 203 ensayos clínicos se sometieron al Comité Ético de Investigación Clínica para su aprobación, de los cuales 173 (85 %) eran estudios multicéntricos y el resto 30 (15 %) eran estudios unicéntricos. De los 203 ensayos presentados, 171 (84 %) fueron patrocinados por la industria farmacéutica, 14 (7 %) por investigadores del VHIR, y el resto, 18 (9 %), fueron patrocinados por otros hospitales.

Nuevos contratos a investigadores y técnicos financiados por diferentes organismos y programas

En el 2009, se firmaron 9 contratos de investigadores seniors, 14 contratos de investigadores postdoctorales, 12 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.

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 catorze 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.

Tesis doctorals

Un total de 34 tesis doctorals supervisades i dirigides per personal del VHIR es llegeixen al 2009. D'aquestes, 30 a la Universitat Autònoma de Barcelona (UAB), 3 a la Universitat de Barcelona (UB), i 1 a la Universitat Pompeu Fabra (UPF).

Redes Temáticas de Investigación Cooperativa de l'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 catorce de proyectos.

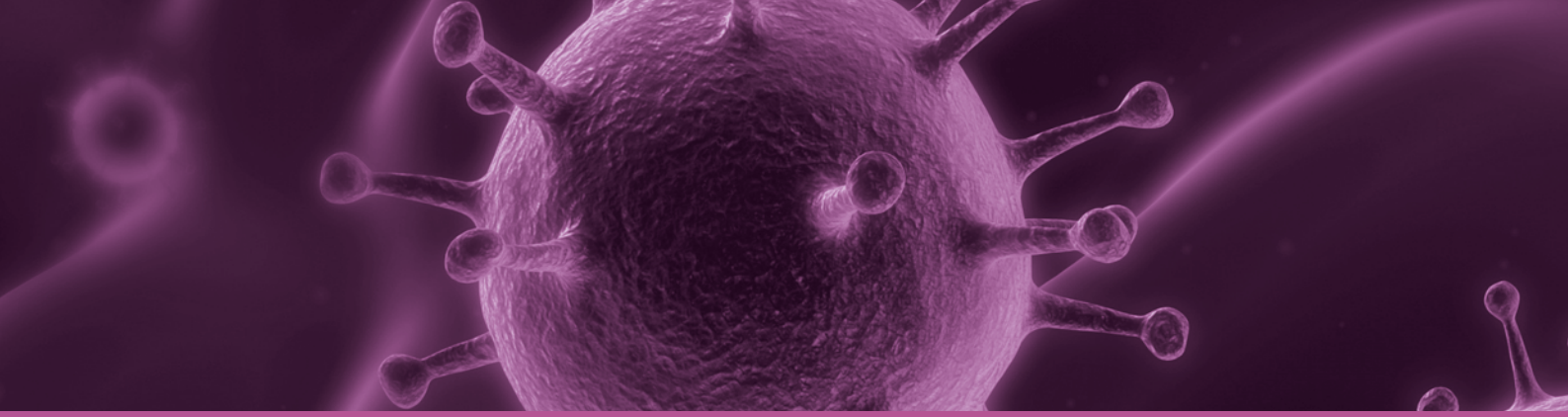
Grupos de Investigación reconocidos por la Generalitat de Catalunya

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.

Tesis doctorales

Un total de 34 tesis doctorales supervisadas y dirigidas por personal del VHIR se leen en 2009. De éstas, 30 en la Universidad Autónoma de Barcelona (UAB), 3 en la Universidad de Barcelona (UB), y 1 en la Universidad Pompeu Fabra (UPF).



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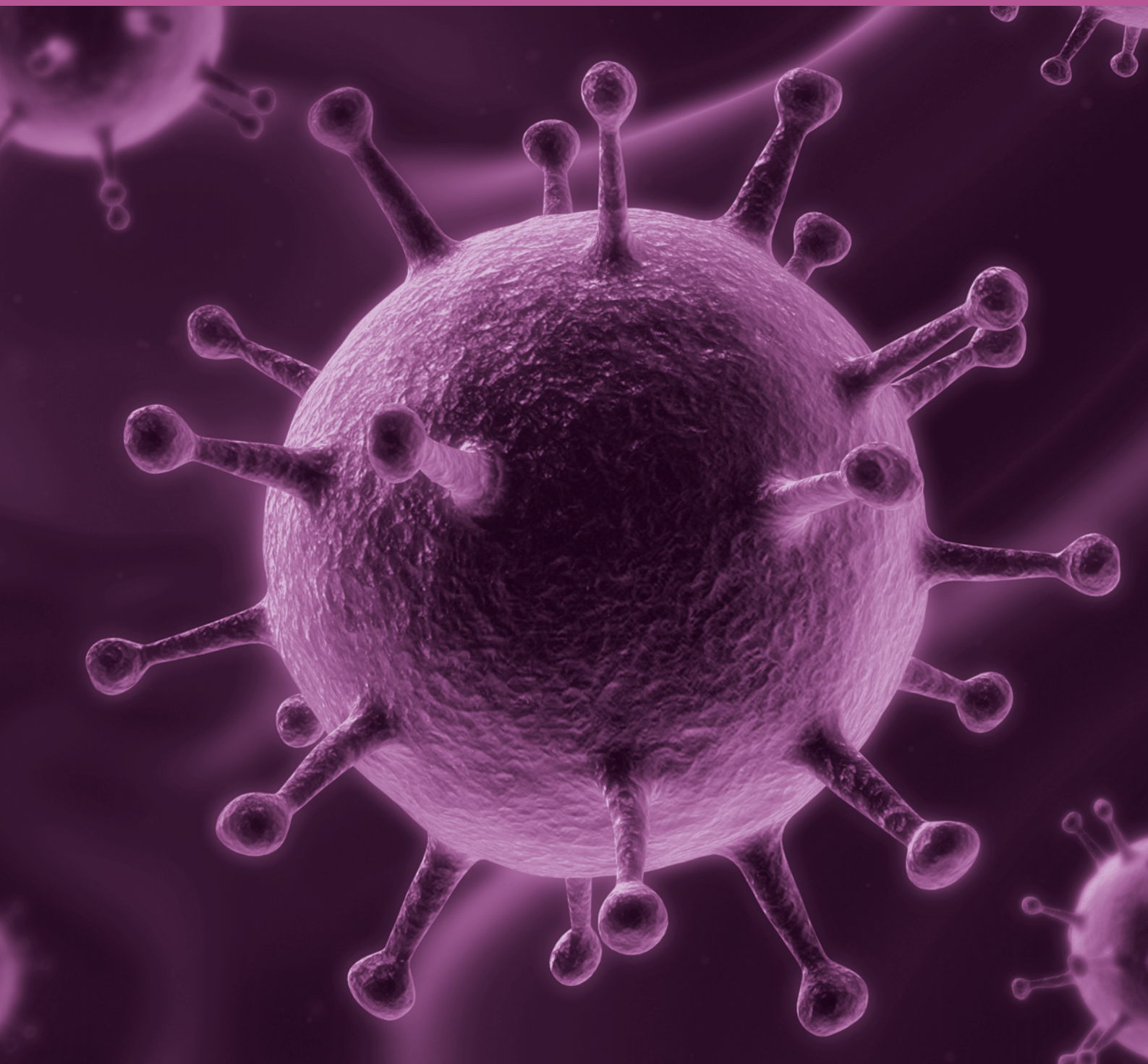

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MINISTERIO
DE CIENCIA
E INNOVACIÓN

Instituto
de Salud
Carlos III

LA MINISTRA DE CIENCIA E INNOVACIÓN

A PROPUESTA DEL INSTITUTO DE SALUD CARLOS III Y EL
DEPARTAMENT DE SALUT DE LA GENERALITAT DE CATALUNYA

Concede el presente Diploma de Acreditación como

INSTITUTO DE INVESTIGACIÓN SANITARIA AL

INSTITUT DE RECERCA HOSPITAL UNIVERSITARI VALL D'HEBRON

En Madrid, 5 de marzo de 2009

La Ministra de Ciencia e Innovación

Cristina Garmendia Mendizábal

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

Generalitat de Catalunya
Departament de Salut

Institut Català
de la Salut

UAB
Universitat Autònoma de Barcelona

ISC
Instituto
de Salud
Carlos III