Report 2012-2013

Department of Experimental and Health Sciences, UPF

Universitat Pompeu Fabra Barcelona

Department of Experimental and Health Sciences

Index

Foreword of the Director

"Somewhere, something incredible is waiting to be known"

Carl Sagan, Scientist, Teacher and Science Advocate

There are few jobs more rewarding than doing scientific research, communicating its questions and results to society and transmitting the knowledge and passion required to be both a scientist and a teacher to new generations of students. At the DCEXS, every day brings new opportunities of achieving these goals, and it is quite natural that we should feel delighted at the privilege. Somewhere, something incredible is waiting to be known and many times it is right here.

Admittedly, we have undergone hard times that have made more challenging to fulfil our mission. These are problems we have shared with the rest of the scientific community and indeed with society at large. However, we have managed to keep up with our work and, in doing so, we have learned valuable lessons. As Vivian Greene said, Life isn't about waiting for the storm to pass...It's about learning to dance in the rain. And how have we been dancing! Over the last two years the productivity of the DCEXS has increased in 1014 papers. Our external, competitive funding has been as solid as ever, with grants from an impressive range of bodies, including ERC, FP7, NIH and many others that have added up to 16,5 million Euros. Our university ranked 17 in the THE 2012 index (universities under 50 years old) and has recently been listed as the most productive in Spain in the U-ranking, an achievement to which the contribution of the research done in the DCEXS is fundamental. During the 2012-2013 period, we could highlight an ERC Starting grant, 4 COFUND postdoctoral fellows or 142 PhDs who defended their theses.

We have also undertaken new exciting initiatives. For instance, a new Research Office, part of the UPFs Research Service, has been established in our premises and a new Scientific Promotion Officer has been incorporated to help us foster our research and transference. In addition, with the new Medicine degree already in place, we are consolidating an even newer degree in Biomedical Engineering and have already recruited one junior and one senior group leaders to add up to our existing strength in that area. Also, we started a new series of yearly Symposia which, in 2012 and 2013, were devoted to Calcium Channels and to Perspectives in Evolutionary Biology. The increasing success of these and other events encourages us to keep doing and disseminating our research. This very Memoir is our first one and, thus, it is a novelty in itself. We try to reflect in its pages our recent accomplishments as well as the relatively new structure of the DCEXS in Research Programmes, established in 2011 after our first external evaluation.

In summary, the two last years have been tough but great. After a bit more than half a year in my post as Director, I feel I am starting to understand how we have managed to thrive under the circumstances. It is our unrelenting determination to cooperate, to collectively work to get the best of ourselves. Crucially, we are not alone in that endeavor. I happily realize that the PRBB, with the top research centers it hosts, has become a wonderful example of how to support each other in the face of difficulties. The 1,400-strong, international and vibrant community of PRBB neighbors, the members of CREAL, CMRM, CRG, DCEXS, FPM, IBE and IMIM, do not only share great views over the Mediterranean but also ideas, projects, facilities, funding, training, dissemination and even sports and entertainment. How could not do great with all these qualities in our favor? Thanks to all of you for making our job even better than we could dream!

Arcadi Navarro,

Director

The DCEXS:
A department committed to be excellent in research and innovative in education

Mission and vision

The Department of Experimental and Health Sciences (DCEXS) was founded by Universitat Pompeu Fabra (UPF) in 1998, along with the launching of the new degree in Human Biology. Later two new degrees were initiated in DCEXS, Medicine (2008) and Biomedical Engineering (2011).

The scientific goal of the DCEXS is to become a research centre with international presence and recognition in the fields of molecular biology and biomedicine. Our research faculty are hired after a rigorous process of selection and evaluated regularly according to their performance. A good number of young researchers have been recruited through competitive calls such as ICREA or the Ramón y Cajal programme and after an additional evaluation by the Department's External Scientific Advisory Board. Over the last few years, the DCEXS has achieved a remarkable presence in different research fields and a growing research output. The DCEXS is publishing over 500 research articles annually, with more than 75% in journals that fall in the first quartile.

The great challenge of the DCEXS has been to successfully develop a project where research and teaching are firmly integrated. Scientific research is lived by our students, both undergraduates and postgraduates, as an essential tool in their studies. The DCEXS's goals in education are to pioneer pedagogical innovation and to commit with the European Education Space and the spirit of Bologna. We currently run different Masters in the fields of biology, biotechnology, bioinformatics, health and medical sciences, and we are responsible of three undergraduate degrees in full integration with the UPF's Facultat de Ciències de la Salut i de la Vida. Additionally, the DCEXS contributes to the PRBB and the Research and Development system of Catalonia with its great capacity to train future researchers through its PhD Programme in Biomedicine, fully taught in English and recognized by independent agencies. We believe we are achieving our goal of being innovative and fostering a steady flow of state-of-the-art science to our students.

Direction (until June 2013)

Director:
Francesc Posas

Deputy Directors:
Cristina Pujades and Josep M. Antó

Secretary:
Baldo Oliva

Direction (from July 2013 onwards)

Director:
Arcadi Navarro

Deputy Directors:
José Aramburu and Francisco J. Muñoz

Secretary:
Baldo Oliva

Composition of the External Scientific Advisory Board

President:
Carlos López Otín

Members:
Francisco Sánchez Madrid
José Luis Fernández Piqueras
Alfonso Valencia
José Luis López Barneo
Fernando Rodríguez Artalejo
Jaume Bosch
Isabel Fariñas

Location:
Strategic location within a big scientific park, the PRBB.

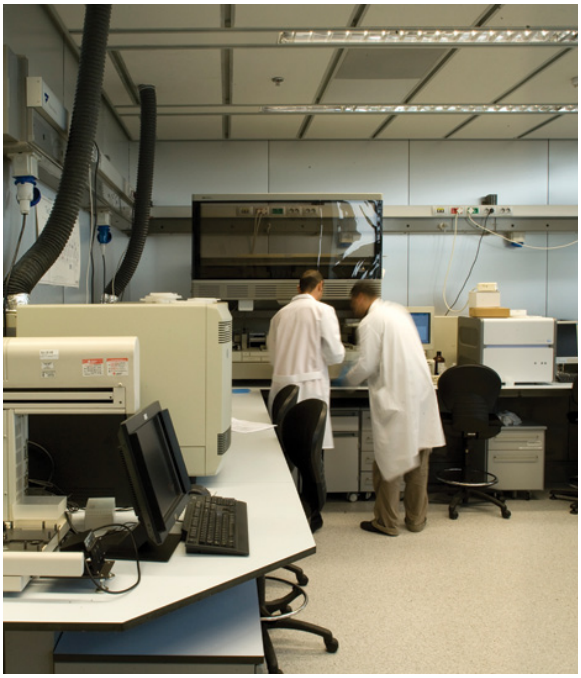
Barcelona's Biomedical Research Park **(PRBB)** is a large scientific infrastructure that gathers together several public research centres and is physically connected to Barcelona's 'Hospital del Mar', thus being one of the largest hubs of biomedical research in southern Europe.

The seven centres located in the park conduct science of excellence in a wide diversity of fields, with a critical mass of 1,400 people from 55 different countries, an accumulated R&D budget of approximately 80 M€ per year and cutting-edge scientific equipment. This allows our community to explore, in a unique building, the most relevant questions in life sciences and biomedicine today, from the molecular to the populational perspective. The close connection and shared faculty between the PRBB and the Hospital del Mar also provides an excellent insight into clinical reality.

This close contact has allowed us to establish strategic alliances with surrounding research institutes affiliated to the UPF such as **Centre for Research in Environmental Epidemiology (CREAL)**, **Centre for Genomic Regulation (CRG)** or **the Hospital del Mar Medical Research Institute (IMIM)**.

The PRBB strives to remain competitive and incorporate scientific talent from top centres. The organizational model is cooperative, with common spaces that facilitate the interrelationship between the centres as well as shared advanced scientific-technical services. The animal facility of the park is outstanding and considered to be one of the most modern in Europe, as are other services in the centres such as the advanced light microscopy, proteomics and flow cytometry units.

The PRBB provides us with a high excellence scientific environment, regular scientific seminars and a Continuing Professional Development Programme.



Core facilities

Our faculty has access **cutting-edge Core Facilities** offering the latest technologies in their fields. Some of them are run directly by the DCEXS, and of course they are open to the whole PRBB community; while others are jointly managed with the CRG; and yet others belong to the rest of institutions in the PRBB. The facilities to which the UPF contributes include the Advanced Light Microscopy Unit, which covers the whole spectrum of advanced microscopy applications with a recent focus on super-resolution microscopy; the **Proteomics Unit** that focuses on ultimate technology mass spectrometry for hypothesis free as well as targeted proteomics. Applications include identification of proteins and posttranslational modifications, biomarker analysis, and quantitative proteomics using label free quantification, iTRAQ and SILAC; the **Genomics Unit**, that performs both Sanger and Next-generation Sequencing, featuring state-of-the-art instruments for high-throughput genetic analysis and functional genomics, as well as de novo sequencing; and the **Flow Cytometry Unit** that, with its six analyzers and two sorters, is one of the most comprehensive facilities and the largest Becton Dickinson site in Spain.

Among the many facilities ran by other institutions, we could mention the PRBB's animal facility, one of the most complex and automated in Europe, with capacity for 70,000 mice under SPF conditions and for 6,000 mice in standard conditions (UBIOMEX), as well as 50,000 zebrafish. As of June 2010, the programme of care and use of laboratory animals has the full accreditation from the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Indicators 2012-2013

Publications:
- *1014*

Competitive grants:
- *14 International projects*
- *96 National projects*
- *125 Contracts with Industry*

Theses:
- *142*

Personnel

- *38 Research groups*
- *43 PIs*
- *15 Senior Researchers*
- *102 Postdoctoral Researchers*
- *151 Predoctoral Researchers*
- *43 Laboratory Technicians*
- *8 Project managers*
- *11 Administrative Staff*

Awards

Núria López Bigas:
- Catalan National Award for Young Research Talent (Premi Nacional de Recerca al Talent Jove), February 2012 and University
- Pompeu Fabra Social Council Award for a research project with an important component on Knowledge Transfer (2012)

Tomàs Marquès:
- EMBO Young Investigator Award 2013

Pura Muñoz:
- Elected Member of The European Consortium for Stem Cell Research (EuroStemCell)

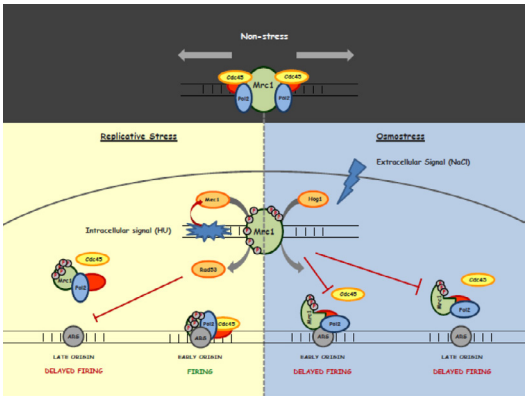
Luis Pérez Jurado:
- ICREA Acadèmia Award 2013

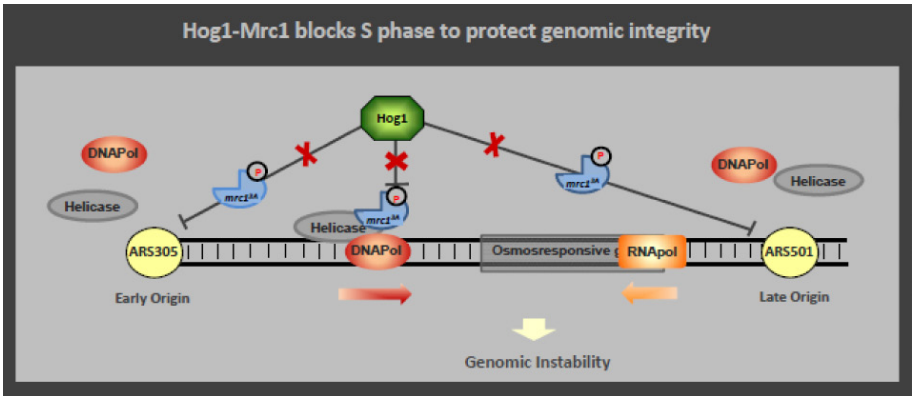
Khademul Islam:
- University Pompeu Fabra Social Council Award for a Thesis research project with an important component on Knowledge Transfer (2012)

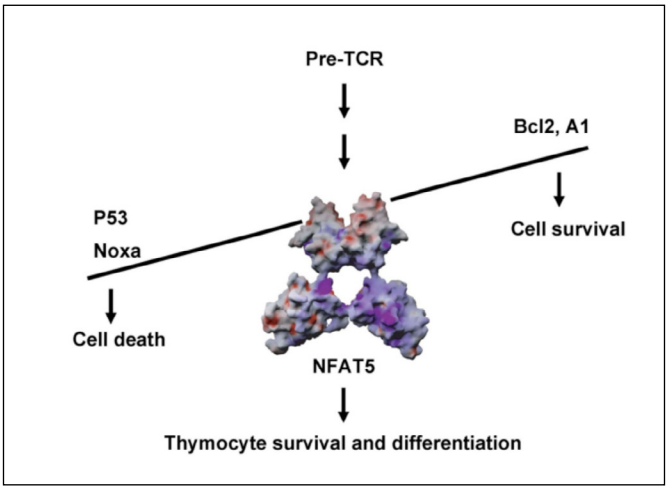
Scientific highlights 2012-2013:
Just a little taste of them!

Duch A, Felipe-Abrio I, Barroso S, Yaakov G, García-Rubio M, Aguilera A, Nadal E, Posas F (2013) ***Coordinated control of replication and transcription by a SAPK protects genomic integrity. Nature 493(7430):116-9.***

Upon environmental changes or extracellular signals, cells are subjected to marked changes in gene expression. Dealing with high levels of transcription during replication is critical to prevent collisions between the transcription and replication pathways and avoid recombination events. In response to osmostress, hundreds of stress-responsive genes are rapidly induced by the stress-activated protein kinase (SAPK) Hog1, even during S phase. In this work authors show in Saccharomyces cerevisae that a single signalling molecule, Hog1, coordinates both replication and transcription upon osmostress. Hog1 interacts with and phosphorylates Mrc1, a component of the replication complex. Mrc1 phosphorylation by Hog1 delays early and late origin firing by preventing Cdc45 loading, as well as slowing down replication-complex progression. Regulation of Mrc1 by Hog1 is completely independent of Mec1 and Rad53. Cells carrying a non-phosphorylatable allele of MRC1 (mrc13A) do not delay replication upon stress and show a marked increase in transcription-associated recombination, genomic instability and Rad52 foci. In contrast, mrc13A induces Rad53 and survival in the presence of hydroxyurea or methyl methanesulphonate. Therefore, Hog1 and Mrc1 define a novel S-phase checkpoint independent of the DNA-damage checkpoint that permits eukaryotic cells to prevent conflicts between DNA replication and transcription, which would otherwise lead to genomic instability when both phenomena are temporally coincident.





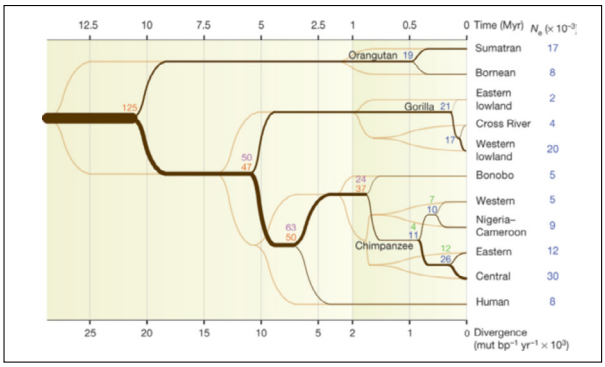


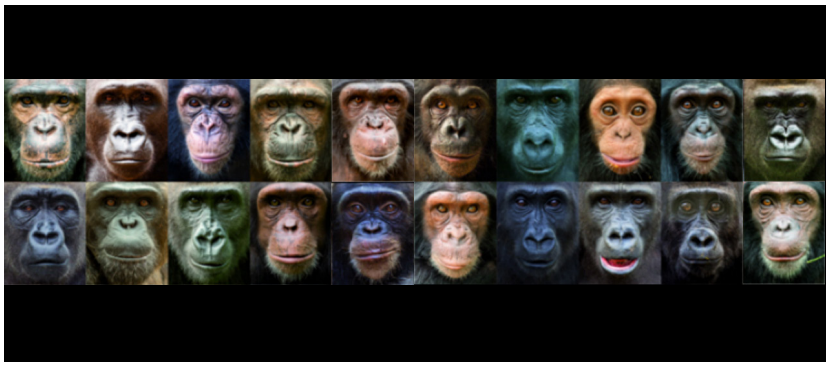
Berga-Bolaños R, Alberdi A, Buxadé M, Aramburu J, Cristina López-Rodríguez (2013) ***NFAT5 induction by the pre-T cell receptor serves as a selective survival signal in T lymphocyte development.*** **Proc Natl Acad Sci USA. 110(40):16091-6.**

This work identified that NFAT5 is positioned as a downstream transcriptional effector of the pre-T-cell receptor (pre-TCR) to selectively promote survival and allelic exclusion, two of the pre-TCR functions that ensure the lineage commitment of T lymphocyte precursors. Therefore, NFAT5 is identified as a key factor for the generation of T cells, essential regulators of adaptive immune responses. These findings reinforce the notion that the first stages in the generation of T lymphocytes require different and independent functions activated by a common receptor, the pre-TCR, to acquire the proper lineage fate determination.

Prado-Martinez J, Sudmant PH, Kidd JM, Li H, Kelley JL, Lorente-Galdos B, Veeramah KR, Woerner AE, O'Connor TD, Santpere G, Cagan A, Theunert C, Casals F, Laayouni H, Munch K, Hobolth A, Halager AE, Malig M, Hernandez-Rodriguez J, Hernando-Herraez I, Prüfer K, Pybus M, Johnstone L, Lachmann M, Alkan C, Twigg D, Petit N, Baker C, Hormozdiari F, Fernandez-Callejo M, Dabad M, Wilson ML, Stevison L, Camprubí C, Carvalho T, Ruiz-Herrera A, Vives L, Mele M, Abello T, Kondova I, Bontrop RE, Pusey A, Lankester F, Kiyang JA, Bergl RA, Lonsdorf E, Myers S, Ventura M, Gagneux P, Comas D, Siegismund H, Blanc J, Agueda-Calpena L, Gut M, Fulton L, Tishkoff SA, Mullikin JC, Wilson RK, Gut IG, Gonder MK, Ryder OA, Hahn BH, Navarro A, Akey JM, Bertranpetit J, Reich D, Mailund T, Schierup MH, Hvilsom C, Andrés AM, Wall JD, Bustamante CD, Hammer MF, Eichler EE, Marques-Bonet T (2013) *Great ape genetic diversity and population history*. Nature 499(7459):471-5.

For the first time, the genomes of a large number of individuals of the six species of great apes from Africa and south-east Asia have been sequenced. The greatest genetic diversity of wild specimens possible was included, due to the rapid decrease in the great ape population worldwide. The great apes -chimpanzees, gorillas and orang-utans- comprise the closest group of living species to humans. We share a common ancestor who lived some 14-16 million years ago, but we share a far more recent predecessor with chimpanzees, just six million years ago. This study provides the most comprehensive and detailed analysis to date of the genetic diversity of the great apes, and allows learning about the genetic diversity of the great apes in order to put the history of our genome in its context.



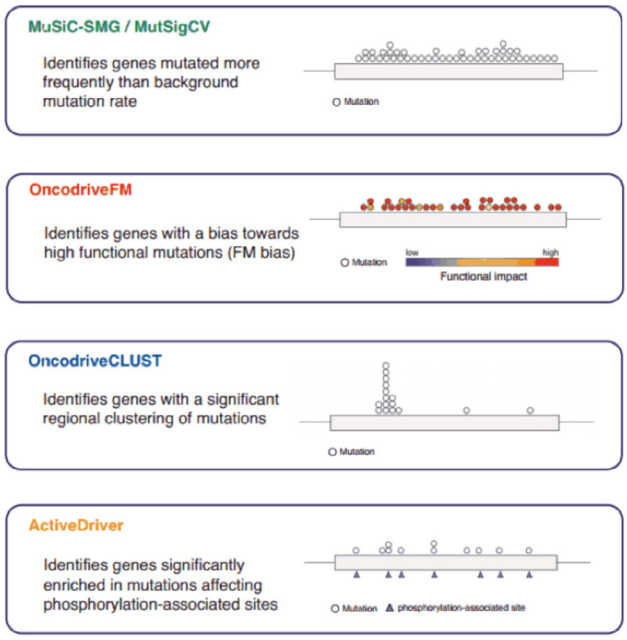


Gonzalez-Perez A, Perez-Llamas C, Deu-Pons J, Tamborero D, Schroeder MP, Jene-Sanz A, Santos A & Lopez-Bigas N (2013) *IntOGen-mutations identifies cancer drivers across tumor types*. Nature Methods (11):1081-2. http://www.nature.com/nmeth/journal/v10/n11/full/nmeth.2642.html

Identifying the complete list of genes involved in cancer development has been a major objective of cancer researchers for more than 30 years, and this is a first step towards the development of therapies that effectively and selectively target cancer genes to specifically kill tumour cells. In recent years systematic approaches to the quest for cancer genes have been undertaken. These involve sampling cancer genomes and sequencing most coding exons or the whole genome.

Thousands tumour genomes are being sequenced in the world. Most have been generated as part of large projects and consortia, such as the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA). When a tumour genome is sequenced, hundreds or even thousands of somatic mutations are detected; therefore, identifying which of those are involved in driving the tumourigenic process is a major challenge. With hundreds of available sequenced tumour genomes of each cancer type, this problem can be approached by identifying signals of positive selection in the pattern of mutations observed per gene across tumours. A computational approach to detect driver genes by combining multiple signals of positive selection has been developed and applied to 3,205 tumours from 12 different cancer types from the TCGA Pan-Cancer project. 291 high confident cancer driver genes have been identified. Among those genes, some have not been previously identified as cancer drivers and 16 have clear preference to sustain mutations in one specific tumour type. The novel driver candidates complement our current picture of the emergence of these diseases.

In addition the IntOGen-mutations, a novel web platform for cancer genomes interpretation has been described, which analyses not only TCGA pan-cancer data but also additional datasets generated by other initiatives such as those included within the ICGC. The resource allows users to identify driver mutations, genes and pathways acting on thousands of tumours from different cancer sites and to analyze newly sequenced tumour genomes and identify relevant mutations by putting them in the context of the accumulated knowledge.



Busquets-Garcia A., Gomis-González M., Guegan T., Agustín-Pavón C., Pastor A., Mato S, Pérez-Samartín A., Matute C., de la Torre R., Dierssen M., Maldonado R., Ozaita A. *" Targeting the endocannabinoid system in the treatme nt of fragile X syndrome"*. Nature Medicine 19(5):603-7.

Fragile X syndrome (FXS), a rare disease which is the most common inherited form of intellectual disability, is caused by an expansion in the FMR1 gene promoter which leads to silencing and loss of the "fragile X mental retardation protein".

The disease has no specific treatment to date, and it is only possible to alleviate some of the symptoms. This study shows that the endocannabinoid system is a new therapeutic target of great interest in the treatment of this disease.

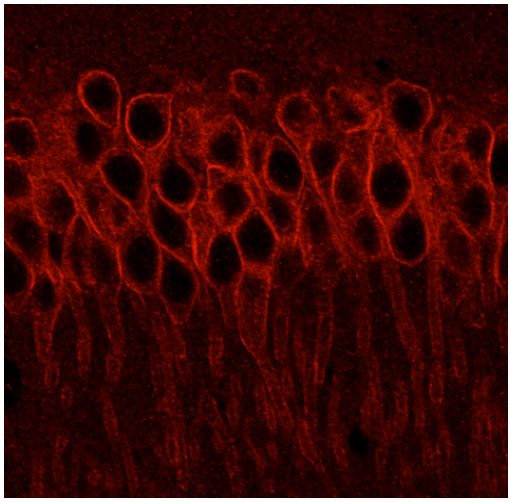
Using a murine model which reproduces many of the symptoms of FXS in humans, the researchers showed that cannabinoid receptors play a key role in the disease's pathophysiology. Previous studies by the NeuroPhar research group reported that signalling through the endocannabinoid system is important in cognitive performance, feeling pain, anxiety and neuronal plasticity.

Using genetic and pharmacological approaches, it was observed that blocking the CB1 cannabinoid receptor normalizes cognitive deficits, the lack of sensibility to painful stimuli and susceptibility to epileptic seizures that appear in the FXS mouse model. These behavioural improvements were accompanied by biochemical changes in the mTOR intracellular signalling pathway, which is essential to cognitive processing, and the regularization of the density and maturity of neuronal dendritic spines. Furthermore, the pharmacological blocking of CB2 cannabinoid receptors normalized the phenotype of reduced anxiety presented by mice with this syndrome.

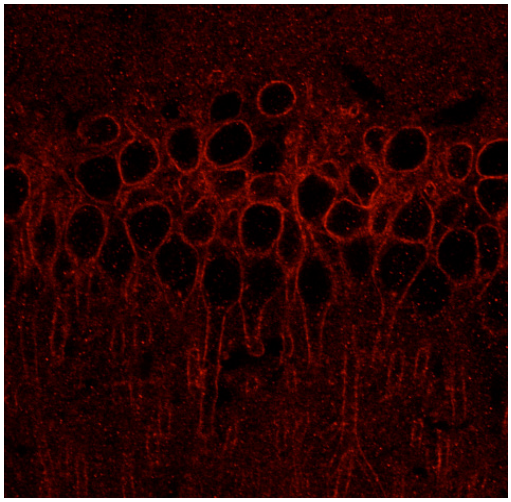
These results create an initial possible therapeutic approach for dealing with FXS by blocking the activity of the endocannabinoid system. The current lack of a treatment for this disease increases the interest in being able to validate the relevance of this new therapeutic straWtegy in the immediate future.

phospho-p70S6K(T389)

FXS



Wild-type



Immunodetection of phospho-p70SK(T389) in brain of a fragile X syndrome (FXS) mouse and a wild-type control. The immunostraining in the pyramidal neurons of the hypocampus denotes the basal enhanced activation of the mammalian target of rapamycin (mTOR) signaling pathway in the pathology, a characteristic that is normalized by targeting pharmacologically the endocannabinoid system.

DCEXS Symposiums

The symposiums are part of an initiative by the DCEXS to provide a forum for leading scientists working on topics included in the Department's Research Programmes to present and discuss the latest results, to promote the education of young scientists as well as catalysing scientific interactions between the DCEXS and other institutions. In addition, it is a good platform for the international visibility of the DCEXS and the work carried out in the department.

The symposiums are open to the scientific community, with no registration fee and UPF's students are actively invited to participate.

2012

The 2012 Symposium of the Department of Experimental and Health Sciences was devoted to Calcium Signalling and it was organised by the Cell and Molecular Biology Programme of the DCEXS.

Calcium signalling is one of the major mechanisms for transmitting information in the cell. It participates in the regulation of different cellular processes that ultimately will determine, among many other capabilities, how we move, sense our environment or think.

The program covered topics such as Ca2+-dependent control of transcription, Ca2+ handling in intracellular organelles, Ca2+ neurobiology and Ca2+ in disease pathophysiology.

The programme included the following talks:

- "Presenilins, calcium signalling and Alzheimer's Disease" by Ilya Bezprozvanny (UT Southwestern Medical Center)
- "Structural determinants of TRPV channel activation and desensitization" Rachelle Gaudet (Dept. of Molecular and Cellular Biology, Harvard University)
- "ASIC Channels and pain" David Julius (University of California, San Francisco)
- "Assessing the Role of Kainate receptor interacting proteins" Juan Lerma (CSIC-Universidad Miguel Hernández)
- "The role of Ca2+ protein sorting and secretion" Vivek Malhotra (Center for Genomic Regulation)
- "Is Calcium Homeostasis a Biomarker of Muscle Health and Disease?" Marco Brotto (University of Missouri)
- "Store Independent Calcium Signaling by Secretory Pathway Ca2+-ATPase, SPCA2" Rajini Rao (Johns Hopkins University School of Medicine)
- "SNAREing voltage-gated calcium channels: beyond the synprint site" José Manuel Fernández (DCEXS UPF)
- "New player on the T lymphocyte calcium homeostasis" Rubén Vicente (DCEXS UPF)

2013

The Second Symposium of the Department of Experimental and Health Sciences, entitled Perspectives in Evolutionary Biology, was held in the PRBB on the 26th November 2013.

The symposium was organised by the Evolutionary Biology and Complex Systems Programme of the DCEXS and it brought together leading researchers in the vibrant field of Evolutionary Biology.

The programme included the following talks:

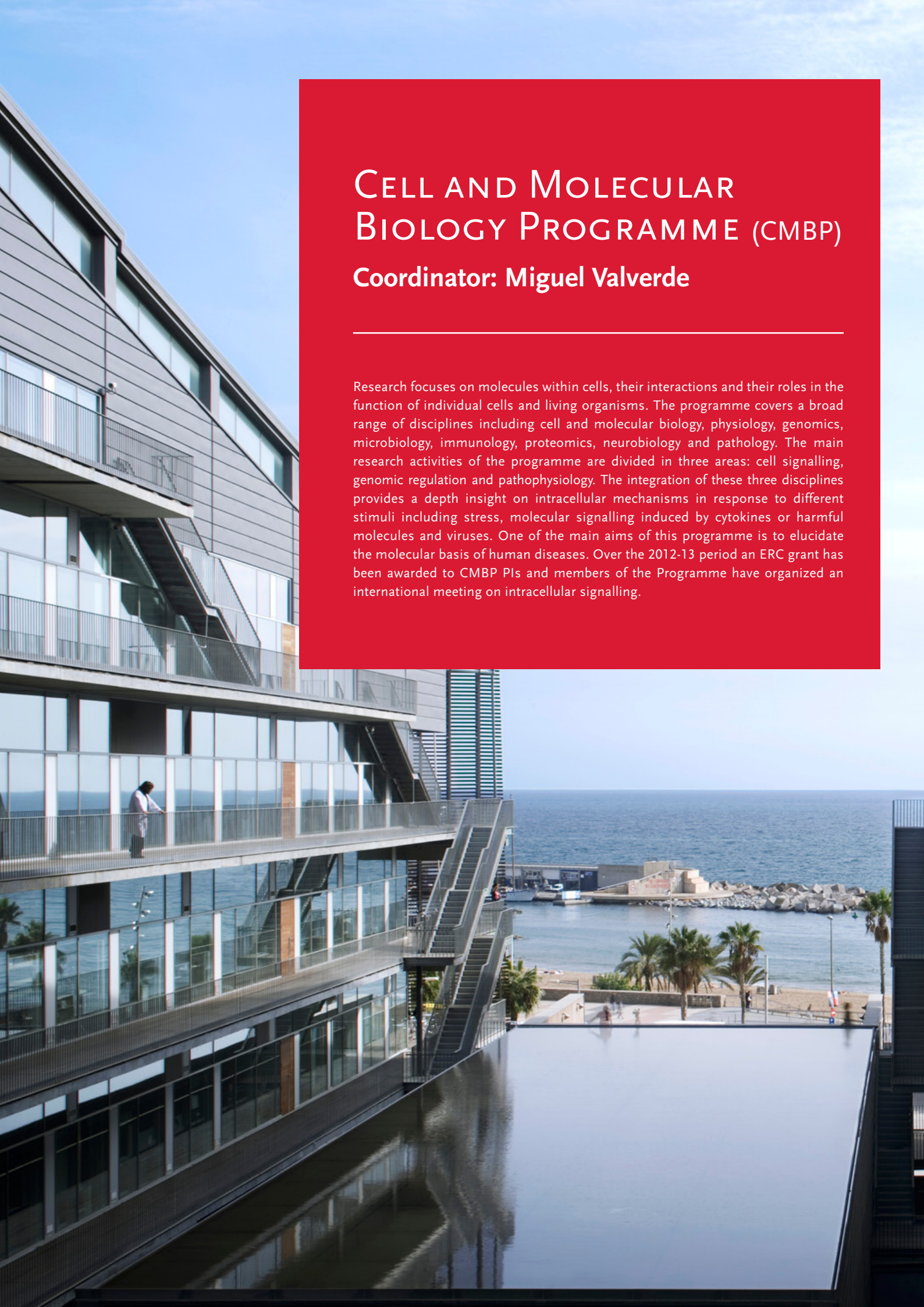
- "Solving the riddle of the evolution of language" by Luc Steels (IBE, Spain)
- "Stochastic epigenetic variation and the adaptation of malaria parasites to changes in their environment" by Alfred Cortés (CRESIB, Spain)
- "The evolution of imperfection and the imperfection of evolution: Tinkering and stochasticity in the human genome" by Dan Graur (University of Houston, USA)
- "Patterns of mutation and recombination in humans and chimpanzees" by Gilean McVean (University of Oxford, UK)
- "Paleogenomics and the Mesolithic-Neolithic transition in Europe"by Carles Lalueza (IBE, Spain)
- "Medicine without evolution is like engineering without physics" by Randolph Nesse (University of Michigan, USA)
  The participants presenting a poster entered a competition to win an ipad.

The awardee was Lidia Mateo, for her poster entitled "A transposable element insertion confers xenobiotic resistance in Drosophila".

Teaching

The Department of Experimental and Health Sciences is compromised with the teaching quality as well as the educative objectives of the Faculty of Health and Life Sciences. This Faculty was born on the premises of a common and innovative project which was initiated by the Dean with the technical support of a technical unit. This project has been very successful in achieving an excellent teaching of generic and specific competencies of the graduates of the Faculty.

The teaching of the members of the Department has been repeatedly recognized by several prizes that have been awarded by the Generalitat de Catalunya (four Vicens Vives awards in 2002, 2005, 2007 and 2013) as well as the Spanish Government (Prize to the Teaching Innovation in 2006).



Cell and Molecular Biology Programme (CMBP)

Coordinator: Miguel Valverde

Research focuses on molecules within cells, their interactions and their roles in the function of individual cells and living organisms. The programme covers a broad range of disciplines including cell and molecular biology, physiology, genomics, microbiology, immunology, proteomics, neurobiology and pathology. The main research activities of the programme are divided in three areas: cell signalling, genomic regulation and pathophysiology. The integration of these three disciplines provides a depth insight on intracellular mechanisms in response to different stimuli including stress, molecular signalling induced by cytokines or harmful molecules and viruses. One of the main aims of this programme is to elucidate the molecular basis of human diseases. Over the 2012-13 period an ERC grant has been awarded to CMBP PIs and members of the Programme have organized an international meeting on intracellular signalling.

Pura Muñoz-Cánoves

Cell Biology Group

www.upf.edu/cellbiology

Other PI: *Antonio Serrano.*

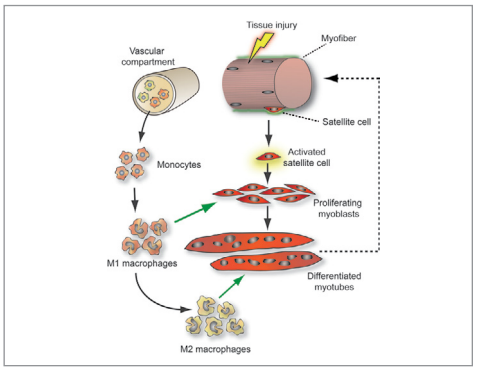
Senior Researcher: *Eusebio Perdiguero.*

Postdocs: *Yacine Kharraz, Patrizia Pessina, Chris Mann, Jessica Segalés and Mònica Zamora.*

PhD students: *Pedro Sousa-Victor, Laura García-Prat, Joana Guerra and Diana Mesquita.*

Technicians: *Vanessa Ruíz, Laura Ortet, Mercè Jardí, Susana Gutarra and Vera Lukesova.*

Project Manager: *Marina Raya.*



Research Outline

Our main objective is to understand the molecular mechanisms underlying adult muscle regeneration and growth. Muscle fiber degeneration and loss of muscle mass occurs in multiple settings, including cancer, cachexia, neuromuscular disorders (Duchenne Muscular Dystrophy -DMD-) and during aging, remaining a key factor contributing to morbidity. Understanding the molecular pathways that regulate muscle repair and gain/loss of muscle mass is therefore crucial for treating muscle wasting-associated disorders. Yet, the key molecular mediators of such processes are poorly understood. Thus, we have developed distinct experimental approaches to address our objective.

Current Projects/Research Lines

Mechanisms regulating skeletal muscle growth and regeneration in physiology and pathology

1. To gain insight into the mechanisms regulating muscle stem cell (satellite cell) transitional states during muscle regeneration; this is, what controls satellite cell activation from quiescence, proliferation, differentiation and return to the quiescent state (self renewal).

   Specific Focus: *Role and mechanisms of p38a-mediated genome organization in skeletal muscle stem cells. Neonatal versus adult muscle growth.*

2. To investigate the mechanisms controlling skeletal muscle growth and atrophy in the adult, with emphasis in aging.

   Specific Focus: *Role and mechanisms of action of a new regulator of skeletal muscle growth and wasting: Sestrin. Implications during physiological aging.*

3. To investigate the mechanisms leading to muscle fibrosis during Duchenne Muscular Dystrophy (DMD).

   Specific Focus: *Implication of inflammation in fibrosis progression in DMD. Cellular transdifferentiation as a fibrogenic mechanism.*

SELECTED PUBLICATIONS 2012 - 2013

- **Ardite E, Perdiguero E, Vidal E, Gutarra S, Serrano AL, Muñoz-Cánoves P (2012)** PAI-1-regulated miR-21 defines a novel age-associated fibrogenic pathway in muscular dystrophy. *J Cell Biol 196:163-75.*
- **Vidal B, Ardite E, Suelves M, Ruiz-Bonilla V, Janué A, Flick MJ, Degen JL, Serrano AL, Muñoz-Cánoves P (2012)** Amelioration of Duchenne muscular dystrophy in mdx mice by elimination of matrix-associated fibrin-driven inflammation coupled to the aMb2 leukocyte integrin receptor. *Hum Mol Genet 21:1989 – 2004.*
- **Liu QC, Zha X, Faralli H, Yin H; Louis-Jeune C, Perdiguero E, Muñoz-Cánoves P, Rudnicki MA, Brand M, Pranckeviciene E, Perez-Iratxeta C, Dilworth FJ (2012)** Comparative expression profiling identifies differential roles for Myogenin and p38alphaMAPK signaling in myogenesis. *J Mol Cell Biol 4:386-97.*
- **Kharraz Y, Guerra J, Mann CJ, Serrano AL, Muñoz-Cánoves P (2013)** Macrophage plasticity and the role of inflammation in skeletal muscle repair. *Mediators Inflamm 2013:491-497.*
- **García-Prat L, Sousa-Victor P, Muñoz-Cánoves P (2013)** Functional dysregulation of stem cells during aging: a focus on skeletal muscle stem cells. *FEBS J 280(17):4051-62.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Perdiguero E, Ruiz-Bonilla V, Gresh L, Hui L, Ballestar E, Sousa-Victor P, Baeza-Raja B, Jardi M, Bosch-Comas A, Esteller M, Caelles C, Serrano AL, Wagner EF, Munoz-Canoves P (2007)** Genetic analysis of p38 MAP kinases in myogenesis: fundamental role of p38alpha in abrogating myoblast proliferation. *EMBO J 26:1245-56.*
- **Suelves M, Vidal B, Serrano AL, Tjwa M, Roma J, López-Alemany R, Luttun A, Martínez de Lagrán M, Díaz MA, Jardí M, Roig M, Dierssen M, Dewerchin M, Carmeliet P, Muñoz-Cánoves P (2007)** uPA deficiency exacerbates muscular dystrophy in mdx mice. *J Cell Biol 178:1039-51.*
- **Serrano AL, Baeza-Raja B, Perdiguero E, Jardí M, Muñoz-Cánoves P (2008)** Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metab 7:33-44.*
- **Vidal B, Serrano AL, Tjwa M, Suelves M, Ardite E, De Mori R, Baeza B, Martínez de Lagrán M, Ruiz-Bonilla V, Jardí M, Gherardi R; Degen J, Christov C, Dierssen M, Dewerchin M, Carmeliet P, Muñoz-Cánoves P (2008)** Fibrinogen drives dystrophic muscle fibrosis via a TGFb/alternative macrophage activation pathway. *Genes Dev 22:1747-52.*
- **Perdiguero E, Sousa-Victor P, Ruiz-Bonilla V, Jardí M, Caelles C, Serrano A.L, Muñoz-Cánoves P (2011)** p38/MKP-1-regulated AKT coordinates macrophage transitions and resolution of inflammation during tissue repair. *J Cell Biol 195:307-22.*

Francesc Posas Garriga and Eulàlia de Nadal

Cell Signalling Research Group

www.upf.edu/cellsignaling

Senior Researchers: *Manel Joaquín and Carme Solé.*

Postdocs: *Alba Duch, Albert Gubern, Alberto González-Novo, Romilde Manzoni, Arnau Ulsamer, Gerhard Seisenbacher, Matteo Viganò, Andrea Silva, Klement Stojanovski and Silvia Velázquez.*

PhD students: *Núria Conde, Mariona Nadal, Ana Cristina Viéitez, Caterina Carbonell, Arturo Urrios, Berta Canal and Pedro Maseres.*

Technicians: *Laia Subirana and Aída Fernández.*

Project Manager: *Montse Morillas.*

Research Outline

Our group tries to understand how cells detect and respond to environmental changes. We have focused our studies in the characterization of the stress signal transduction pathways, especially those controlled by MAP kinases of the Hog1/p38 family, also known as the stress ativated MAP kinases (SAPK). Using the S. cerevisiae yeast as a model organism as well as higher eukaryotic cells, we study the molecular mechanisms of cells to respond to an extracellular stimulus and which are the generated adaptive responses. Proper adaptation to stress involves the modulation of several basic aspects of the cell biology, such as cell cycle and regulation of gene expression. Recently, the group has started to analyze the basic signaling properties of the HOG pathway and how to alter them, based on quantitative data collection and mathematical modeling, together with mutational analyses. A second line of research in the framework of synthetic biology addresses the feasibility of complex computation in biological systems. We have demonstrated that cellular communication using complex engineered networks can be implemented to perform in vivo cellular computation.

Current Projects/Research Lines

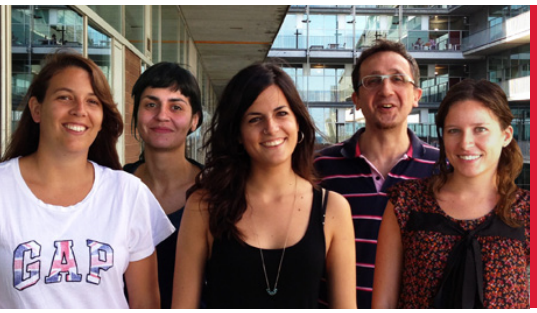
- **Function and regulation of SAPK signaling pathways in eukaryotic cells.** One of our main focuses is the study of the signaling properties of the p38/Hog1 SAPK pathway in response to cellular stress.
- **Identification and characterization of proteins under the control of the yeast Hog1 MAPK.** We are trying to define the substrates regulated by Hog1 and dissect the cellular processes involved in stress adaptation. We are using a combination of genetic screens and biochemical approaches.
- **Chromatin dynamics of transcriptional stress response in yeast.** Major issues are the identification of MAPK targets, as well as the identification of new transcriptional regulators or chromatin remodeling/modifying factors necessary for a proper transcriptional response upon osmostress. It is also important to characterize if the MAPK Hog1 regulates other aspects of mRNA biogenesis and translation.
- **Cell cycle control by Hog1 MAPK in yeast.** The Hog1 MAPK is able to induce cell cycle modulation at G1, S, G2 and exit from mitosis. We propose the existence of an osmocheckpoint: a complex response that could offer protection to cells during cell cycle.
- **Molecular basis to stress-adaptation by p38 MAPK in mammalian cells.** Our laboratory is trying to unravel whether the functions of the yeast Hog1 are also carried out by MAP kinases of the SAPK family, such as p38 and JNK, in mammalian cells.
- **Distributed Biological Computation.** In collaboration with Dr. Ricard Solé group (UPF) we aim at comprehensive understanding and implementation of biological computation. We are also involved in study cell communication systems that form building blocks for biological computation devices taking advantage of our signaling studies.

SELECTED PUBLICATIONS 2012 - 2013

- **Joaquin M, Gubern A, González-Nuñez D, Josué Ruiz E, Ferreiro I, de Nadal E, Nebreda AR, Posas F (2012)** The p57 CDKi integrates stress signals into cell-cycle progression to promote cell survival upon stress. *EMBO J 31(13):2952-64.*
- **Ruiz-Roig C, Noriega N, Duch A, Posas F, de Nadal E (2012)** The Hog1 SAPK controls the Rtg1/Rtg3 transcriptional complex activity by multiple regulatory mechanisms. *Mol Biol Cell 23(21):4286-96.*
- **Nadal-Ribelles M, Conde N, Flores O, González-Vallinas J, Eyras E, Orozco M, de Nadal E, Posas F (2012)** Hog1 bypasses stress-mediated down-regulation of transcription by RNA polymerase II redistribution and chromatin remodeling. *Genome Biol 13(11):R106.*
- **Duch A, Felipe-Abrio I, Barroso S, Yaakov G, García-Rubio M, Aguilera A, Nadal E, Posas F (2013)** Coordinated control of replication and transcription by a SAPK protects genomic integrity. *Nature 493(7430):116-9.*
- **Regot S, de Nadal E, Rodriguez-Navarro S, Gonzalez-Novo A, Perez-Fernandez J, Gadal O, Seisenbacher G, Ammerer G, Posas F (2013)** The Hog1 SAPK targets nucleoporins to control mRNA export upon stress. *J Biol Chem 288(24):17384-98.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **De Nadal E, Zapater M, Alepuz PM, Sumoy L, Mas G, Posas F (2004)** The MAPK Hog1 recruits Rpd3 histone deacetylase to activate osmoresponsive genes. *Nature 427(6972):370-4.*
- **Escoté X, Zapater M, Clotet J, Posas F (2004)** Hog1 mediates cell-cycle arrest in G1 phase by the dual targeting of Sic1. *Nat Cell Biol. 6(10):997-1002.*
- **Proft M, Mas G, de Nadal E, Vendrell A, Noriega N, Struhl K, Posas F (2006)** The stress-activated Hog1 kinase is a selective transcriptional elongation factor for genes responding to osmotic stress. *Mol Cell 23(2):241-50.*
- **Pelet S, Rudolf F, Nadal-Ribelles M, de Nadal E, Posas F, Peter M (2011)** Transient activation of the HOG MAPK pathway regulates bimodal gene expression. *Science 332(6030):732-5.*
- **Regot S, Macia J, Conde N, Peeters T, Kentaro F, Hohmann S, de Nadal E, Posas F, Solé S (2011)** Distributed Biological Computation with Multicellular Engineered Networks. *Nature 469:207-11.*



Francisco J. Muñoz

Ageing Brain Research Group

www.upf.edu/fisio

Postdocs: *Marta Tajes.*

PhD students: *Mònica Bosch-Morató, Biuse Guivernau and Victoria Valls-Comamala.*

Technicians: *Cristina Plata.*

Research Outline

Our research focuses in the pathophysiology of Alzheimer Disease (AD). AD is produced by the aggregation in beta-sheet of amyloid beta-peptide (Aß) forming small oligomers, which turns the peptide highly neurotoxic. Its neurotoxicity, and also its deleterious effects on brain vascular cells, is mostly due to oxidative stress. Therefore free radicals are playing a key role in AD at different levels. Free radicals activate intracellular signaling pathways to increase Aß production and apoptosis, yielding to the characteristic AD neurodegeneration. Moreover, they oxidize biomolecules and indirectly induce the nitrotyrosination of protein by the formation of peroxynitrite.

Current Projects/Research Lines

I. Activation of intracellular signalling pathways: BACE1 transcription and translation

1.1. Free radical production yields to GSK-3ß activation, a key enzyme in neuronal death in AD. We also study the activation of Stress Activated Kinases (p38 MAPK and JNK) and its role in Aß production by increasing the transcription of BACE1, a key enzyme that initiates Aß cleavage.

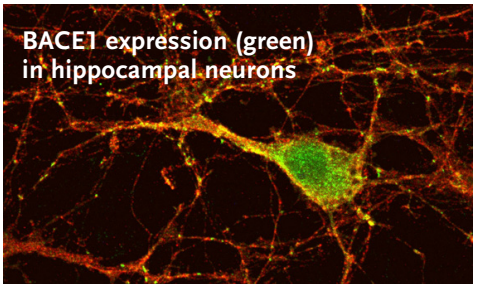
1.2. BACE1 physiological translation is initiated by glutamatergic stimulation. Nitric oxide (NO) activates the enzyme HRI phosphorylating eIF2-alpha that induces BACE1 translation. It contributes to dendritic spine growth and memory consolidation.

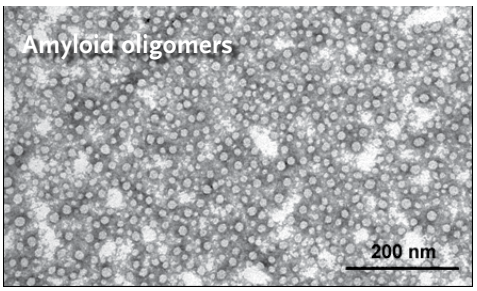
1.3. BACE1 is also translated under pathological situations such as oxidative stress, reticular stress or virus infection due to the activation of PKR and PERK, resulting in an abnormal trigger of Aß production initiating AD.

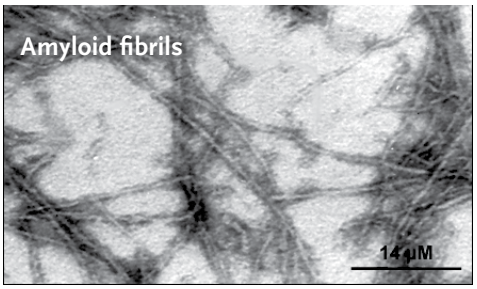
II. Mechanisms of amyloid neurotoxicity: protein nitrotyrosination

2.1. Aß activates NO production that reacts with superoxide anion generating peroxynitrite, which nitrotyrosinates proteins. The enzyme triose phosphate isomerase is strongly nitrotyrosinated in AD, which pdouces a decrease of the glycolityc flow and an increase of the toxic methylglyoxal. Its nitration induces its folding in ß-sheet and its intracellular aggregation. Its aggregation also induces the formation of neurofibrillary tangles of tau protein independently of its hyperphosphorylation.

2.2. In collaboration with neurologists we are carrying out a study on the role of nitro-oxidative stress in the brain damage after stroke demonstrating that nitrotyrosination is an early event after stroke and it would be strongly contributing to cell death after ischemic stroke.







SELECTED PUBLICATIONS 2012 - 2013

- **Guix FX, Wahle T, Vennekens K, Snellinx A, Chávez-Gutiérrez L, Ill-Raga G, Ramos-Fernandez E, Guardia-Laguarta C, Lleó A, Arimon M, Berezovska O, Muñoz FJ, Dotti CG, De Strooper B (2012)** Modification of gamma-secretase by nitrosative stress links neuronal ageing to sporadic Alzheimer's disease. *EMBO Mol Med 4:660-73.*
- **Aso E, Palomer E, Juvés S, Maldonado R, Muñoz FJ, Ferrer I (2012)** CB1 agonist ACEA protects neurons and reduces the cognitive impairment of APP/PS1 mice. *J Alzheimer Dis 30:439-59.*
- **Tajes M, Ill-Raga G, Palomer E, Ramos-Fernandez E, Guix FX, Bosch-Morató M, Guivernau B, Jiménez-Conde J, Ois A, Pérez-Asensio F, Reyes-Navarro M, Caballo C, Galán AM, Alameda F, Escolar G, Opazo C, Planas A, Roquer J, Valverde MA and Muñoz FJ (2013)** Nitro-oxidative stress after neuronal ischemia induces protein nitrotyrosination and cell death. *Oxid Med Cell Longev (in press; 2013)*
- **Tajes M, Guivernau B, Ramos-Fernández E, Bosch-Morató M, Palomer E, Guix FX, Muñoz FJ (2013)** The pathophysiology of triose phosphate isomerase dysfunction in Alzheimer's disease. *Histol Histopathol 28:43-51.*
- **Ill-Raga G, Köhler C, Radiske A, Lima RH, Rosen MD, Muñoz FJ, Cammarota M (2013)** Consolidation of object recognition memory requires HRI kinase-dependent phosphorylation of eIF2alpha in the hippocampus. *Hippocampus 23:431-6.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Coma M, Guix FX, Uribesalgo I, Espuna G, Sole M, Andreu D, Muñoz FJ (2005)** Lack of oestrogen protection in amyloid-mediated endothelial damage due to protein nitrotyrosination. *Brain 128:1613-1621.*
- **Coma M, Guix FX, Ill-Raga G, Uribesalgo I, Alameda F, Valverde MA, Muñoz FJ (2008)** Oxidative stress triggers the amyloidogenic pathway in human vascular smooth muscle cells. *Neurobiol Aging 29:969-80.*
- **Guix FX, Ill-Raga G, Bravo R, Nakaya T, de Fabritiis G, Coma M, Miscione GP, Villà-Freixa J, Suzuki T, Fernàndez-Busquets X, Valverde MA, de Strooper B, Muñoz FJ (2009)** Amyloid-dependent triosephosphate isomerase nitrotyrosination induces glycation and tau fibrillation. *Brain 132:1335-45.*
- **Ill-Raga G, Ramos-Fernández E, Guix FX, Tajes M, Bosch-Morató M, Palomer E, Godoy J, Belmar S, Cerpa W, Simpkins JW, Inestrosa NC, Muñoz FJ (2010)** Amyloid-β peptide fibrils induce nitro-oxidative stress in neuronal cells. *J Alzheimer Dis 22:641-52.*
- **Raga G, Palomer E, Wozniak MA, Ramos-Fernández E, Bosch-Morató M, Tajes M, Guix FX, Galán JJ, Clarimón J, Antúnez C, Real LM, Boada M, Itzhaki RF, Fandos C, Muñoz FJ (2011)** Activation of PKR causes amyloid ß-peptide accumulation via de-repression of BACE1 expression. *PLoS One 6(6):e21456.*

Miguel Ángel Valverde de Castro

Molecular Physiology and Channelopathies

www.upf.edu/fisio

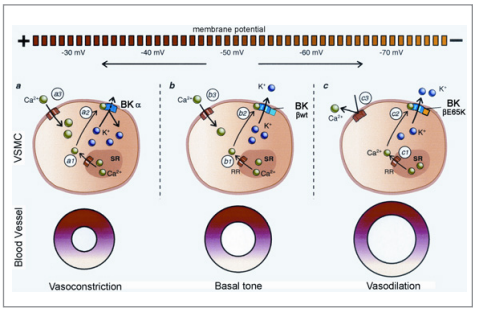
Other PI: *José M. Fernández-Fernández.*

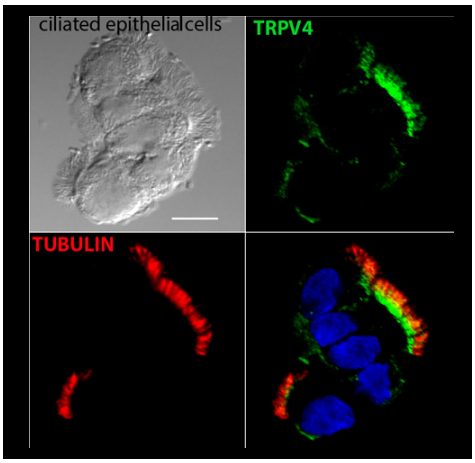
Senior Researcher: *Rubén Vicente.*

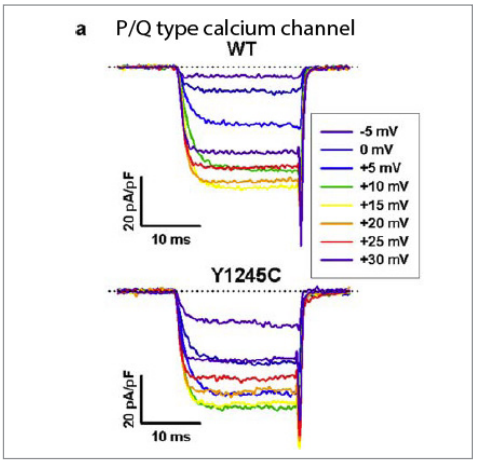
Postdocs: *Carole Jung, Francisca Rubio and Anna Garcia-Elias.*

PhD students: *Amado Carreras-Sureda, Sanela Mrkonjic, Gerard Cantero-Recasens, Anabel Fernández Mariño, Kerstin Kiefer and Carlos Pardo.*

Technicians: *Cristina Plata.*







Research Outline

The research interest of my laboratory is focused on the study of ion channels and regulatory proteins involved in the generation of intracellular calcium signals, with special interest in those participating in mechano-osmotic responses, the control of vascular tone, airways physiology and neurotransmission.

Current Projects/Research Lines

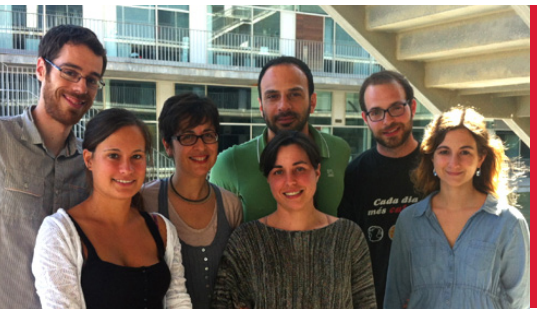
- **TRP channels and calcium signaling in health and disease.** The main goal of the project is to tackle aspects that are still poorly defined regarding the structural domains relevant to the generation of TRP-mediated Ca2+ signals, the mechano-osmotransduction in both epithelia and joints and the identification of genetic defects in TRP channels ("channelopathies") and other Ca2+ transport mechanisms that may occur in the context of ciliated epithelia and joint pathology.
- **Identification of new molecular determinants controlling the function of voltage-gated Ca2+ and K+ channels in physiology and pathology.** From the analysis of missense mutations in the CaV2.1 (P/Q) channel associated to familial hemiplegic migraine or episodic ataxia type 2, we aim to identify the role of different domains both in the gating of voltage-operated Ca2+ (CaV) channels and in their functional interaction with presynaptic exocytotic (SNARE) proteins. Also we search for new modulators of K+ channels controlling the arterial tone.

SELECTED PUBLICATIONS 2012 - 2013

- **Fernández-Mariño AI, Porras-González C, González-Rodríguez P, Selent J, Pastor M, Ureña J, Castellano A, Valverde MA, Fernández-Fernández JM (2012)** Tungstate activates BK channels in a ß subunit and Mg2+-dependent manner: relevance for arterial vasodilatation. *Cardiovasc Res 95(1):29-38.*
- **Von Blume J, Alleaume AM, Kienzle C, Carreras-Sureda A, Valverde MA, Malhotra V (2012)** Ca2+ dependent secretory cargo sorting at the Trans Golgi Network by Cab45. *J Cell Biol 199(7):1057-66.*
- **Carreras-Sureda A, Cantero-Recasens G, Rubio-Moscardo F, Kiefer K, Peinelt C, Niemeyer BA, Valverde MA, Vicente R (2013)** ORMDL3 modulates store-operated calcium entry and lymphocyte activation. *Hum Mol Genet 22(3):519-30.*
- **Mitrovic S, Nogueira C, Cantero-Recasens G, Kiefer K, Fernández-Fernández JM, Popoff JF, Casano L, Bard FA, Gomez R, Valverde MA, Malhotra V. (2013)** TRPM5-mediated calcium uptake regulates mucin secretion from human colon Goblet cells. *Elife 2:e00658.*
- **Garcia-Elias A, Mrkonjić S, Pardo-Pastor C, Inada H, Hellmich UA, Rubio-Moscardó F, Plata C, Gaudet R, Vicente R, Valverde MA (2013)** PIP2-dependent rearrangement of TRPV4 cytosolic tails enables channel activation by physiological stimuli. *PNAS 110(23):9553-8.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Fernández-Fernández JM, Tomás M, Vázquez E, Orio P, Latorre R, Sentí M, Marrugat J, Valverde MA (2004)** Gain-of-function mutation in the calcium-activated potassium channel b1 subunit associated with low prevalence of diastolic hypertension. *J Clin Invest 113:1032-39.*
- **Lorenzo IM, Liedtke W, Sanderson MJ, Valverde MA (2008)** TRPV4 channel participates in receptor-operated calcium entry and ciliary beat frequency regulation in mouse airways epithelial cells. *PNAS 105(34):12611-6.*
- **Fernandes J, Lorenzo IM, Andrade YN, Garcia-Elias A, Serra SA, Fernández-Fernández JM, Valverde MA (2008)** IP3 sensitizes TRPV4 channel to the mechado- and osmotransducing Messenger 5'-6'-epoxyeicosatrienoic acid. *J Cell Biol 181(1):143-55 .*
- **Serra SA, Cuenca-León E, Llobet A, Rubio-Moscardo F, Plata C, Carreño O, Fernàndez-Castillo N, Corominas R, Valverde MA, Macaya A, Cormand B, Fernández-Fernández JM (2010)** A mutation in the first intracellular loop of CACNA1A preventes P/Q channel modulation by SNARE proteins and lowers exocytosis. *PNAS 107(4):1672-7.*
- **Von Blume J, Alleaume AM, Cantero-Recasens G, Curwin A, Zimmermann T, Carreras-Sureda A, Van Galen J, Wakana Y, Valverde MA, Malhotra V (2011)** ADF/cofilin regulates the secretory cargo sorting at the TGN via the Ca2+ ATPase SPCA1. *Dev Cell 20:652-62.*



Juana Díez Antón

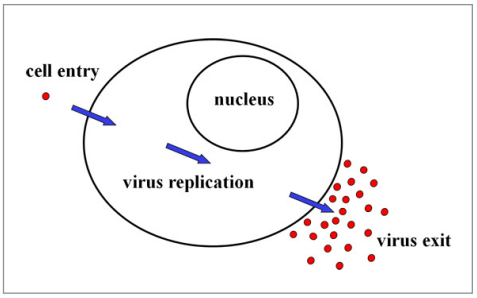
Molecular Virology

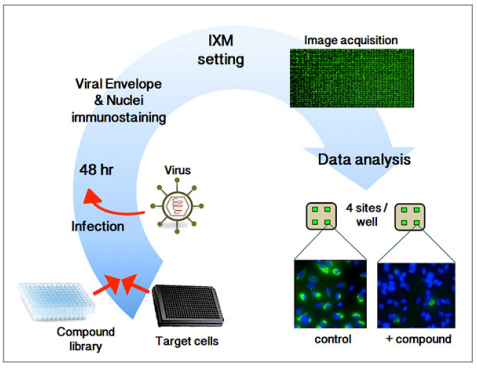
www.upf.edu/virologyunit

Postdocs: *Mireia Giménez Barcons, Nicoletta Scheller, Verónica Saludes and Georgios Koutsoudakis.*

PhD students: *Jennifer Jungfleisch, Bernat Blasco Moreno and Carlos Fernández.*

Lab Manager: *Gemma Pérez Vilaró.*





Research Outline

Viruses continue to threaten global human health. Special difficulties are associated with chronic infections like HCV or HIV, which affect hundreds of million people worldwide. Given their simplicity, viruses completely depend on cellular factors for expansion. Our aim is to understand fundamental common features of such intimate cell-virus interactions. This knowledge is essential to develop more effective virus control strategies and also provides novel insights into cellular regulatory pathways in non-infected cells.

Current Projects/Research Lines

1. **Identification of novel mechanisms to regulate gene expression.**

   Due to their evolutionary plasticity, viruses are invaluable tools to identify new mechanisms to modulate gene expression that are used not only by themselves but also by the host cell. We previously uncovered an unexpected role of host decay factors in promoting translation of viral RNAs. We are defining the mechanisms involved and testing whether these factors might exert a similar role on a specific subset of cellular mRNAs that share structural features with viral genomes such as mRNAs related to stress responses and cancer.

2. **Definition of viral and cellular translational landscapes.**

   Viruses hijack the cellular translation machinery to express their genomes and alter the host translational programme to favor initiation and progression of infection. We are using a system approach to decipher the temporal translation of the HCV genome and a genome wide characterization of the virus-induced changes in the cellular mRNA translation landscape. Aim is to uncover fundamental aspects of HCV-host interactions.

Translational research

3. **Development of broad-spectrum antivirals.**

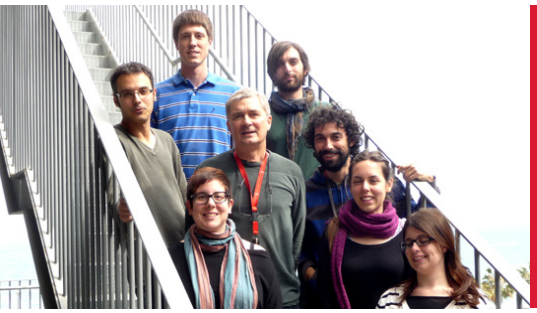
   They would allow to efficiently treat co-infections like HIV/HCV, whose treatment is particularly difficult, and to control novel pathogens. The basic idea is to target host factors with key roles in multiple viral life cycles. We have already identified chemically defined molecules capable of simultaneously inhibiting HIV and HCV. Aim is to characterize the mechanisms involved and to extend the screening to other viruses. This works has been done in collaboration with the Infection Biology group (UPF) and the Helmholtz Center of Infection Research (Braunschweig, Germany).

SELECTED PUBLICATIONS 2012 - 2013

- **Pérez-Vilaró G, Scheller N, Saludes V, Díez J (2012)** Hepatitis C virus infection alters P-body composition but is independent of P-body granules. *J Virol 86(16):8740-9.*
- **Diez J, Martinez JP, Mestres J, Sasse F, Frank R, Meyerhans A (2012)** Myxobacteria: natural pharmaceutical factories. *Microb Cell Fact 30;11:52.*
- **Huffman, T, Kathryn, L, Nardini; J, Poag, L, Flore, K, Banks, HT, Blasco, B, Jungfleisch, J, Diez J (2013).** A mathematical model of RNA3 recruitment in the replication cycle of Brome mosaic virus. *Journal of Pure and Applied Mathematics 89 (2), 251-274.*
- **Martínez JP, Pérez-Vilaró G, Muthukumar Y, Scheller N, Hirsch T, Diestel R, Steinmetz H, Jansen R, Frank R, Sasse F, Meyerhans A, Díez J (2013)** Screening of small molecules affecting mammalian P-body assembly uncovers links with diverse intracellular processes and organelle physiology. *RNA Biol 10(11):1661-9.*
- **Giménez-Barcons M, Alves-Rodrigues I, Jungfleisch J, Van Wynsberghe PM, Ahlquist P, Díez J (2013)** The cellular decapping activators LSm1, Pat1, and Dhh1 control the ratio of subgenomic to genomic Flock House virus RNAs. *J Virol 87(11):6192-6200.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Mas A, Alves-Rodríguez I, Noueiry A, Ahlquist P, Díez J (2006)** Host deadenylation-dependent mRNA decapping factors are required for a key step in brome mosaic virus RNA replication. *J Virol 80(1):246-251.*
- **Alves-Rodrigues I, Mas, A, Díez, J (2007)** Xenopus Xp54 and human RCK/p54 helicases functionally replace yeast Dhh1p in Brome Mosaic Virus RNA replication. *J. Virol. 81(8): 4378-80.*
- **Scheller N, Mina LB, Galão RP, Chari A, Giménez-Barcons M, Noueiry A, Fischer U, Meyerhans A, Díez J (2009)** Translation and replication of hepatitis C virus genomic RNA depends on ancient cellular proteins that control mRNA fates. *Proc Natl Acad Sci USA 106(32):13517-22.*
- **Galão RP, Chari A, Alves-Rodrigues I, Lobão D, Mas A, Kambach C, Fischer U, Díez J (2010)** LSm1-7 complexes bind to specific sites in viral RNA genomes and regulate their translation and replication. *RNA 16 (4):817-27.*
- **Reiter J, Pérez-Vilaró G, Scheller N, Mina LB, Díez J, Meyerhans A (2011)** Hepatitis C virus RNA recombination in cell culture. *J Hepatol 55(4):777-783.*



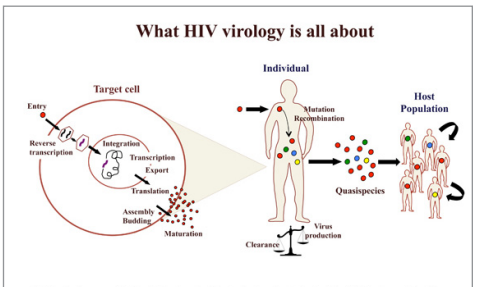
Andreas Meyerhans

Infection Biology

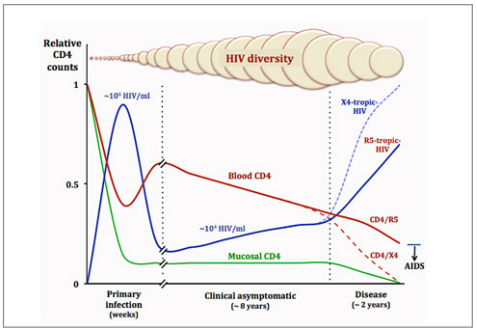
www.upf.edu/infection-biology

Postdocs: *Jordi Argilaguet, Javier Martinez, Irene Latorre and Clay Thompson.*

PhD students: *Cristina Peligero Cruz and Eric Fleta.*



Main features of HIV at the level of infected cells, infected individuals and in the human population.



Research Outline

The outcome of a virus infection is determined by a complex, dynamic interplay between the infecting virus and the induced host responses. The overall interest of our group is (i) to understand quantitatively this dynamic interplay, (ii) to define crucial factors that decide whether an infection is acutely resolved or becomes persistent, and (iii) to develop novel approaches of how to influence infection fates for host benefit.

Current Projects/Research Lines

Fundamental Research

1. Virus infection fate decisions.

Lymphocytic choriomeningitis virus (LCMV) infections of mice may result in acute or persistent infections depending on the specific infection conditions and LCMV strains used. With this model system, we are in the process of analyzing transcriptome changes over time in order to identify those factors that determine the infection outcome.

2. Dynamic responsiveness of T lymphocytes and their antiviral control potential.

Virus-specific T lymphocytes are an important component of adaptive immune responses. Their proliferative capacity and effector function are essential for virus control. Both properties may be severely compromised during persistent infections like those with the human immunodeficiency virus (HIV). We are studying the dynamic responsiveness of T cells including their effector/repressor function in persistent human infections and correlate these with the disease stage of the infected host. Aim is to generate a concise model of infection control.

Translational research

3. Towards development of broad-spectrum antiviral drugs.

Viruses of different groups can depend on the same cellular host factor for their replication. Targeting such common host factors with small chemical compounds may thus allow inhibiting several viruses with the same compound. We follow this idea in collaboration with Juana Diez´group at the UPF and the Helmholtz Center of Infection Research (HZI) in Braunschweig, Germany. Natural product and chemical library screening campaigns against HIV, Dengue virus, West Nile virus etc. and hit evaluations are ongoing.

SELECTED PUBLICATIONS 2012 - 2013

- **Schultz A, Sopper S, Sauermann U, Meyerhans A, Suspène R (2012)** Stable multi-infection of splenocytes during SIV infection--the basis for continuous recombination. *Retrovirology 9:31.*
- **Schuetz A, Dirks J, Sester U, Haule A, Elias N, Geldmacher C, Sanga E, Maboko L, Reither K, Hoelscher M, Meyerhans A, Sester A (2012)** Pathogen prevalence may determine maintenance of antigen-specific T-cell responses in HIV-infected individuals. *AIDS 26(6):695-700.*
- **Diez J, Martinez JP, Mestres J, Sasse F, Frank R, Meyerhans A (2012)** Myxobacteria: natural pharmaceutical factories. *Microb Cell Fact 11:52.*
- **Chereshnev VA, Bocharov G, Bazhan S, Bachmetyev B, Gainova I, Likhoshvai V, Argilaguet JM, Martinez JP, Rump JA, Mothe B, Brander C, Meyerhans A (2013)** Pathogenesis and Treatment of HIV Infection: The Cellular, the Immune System and the Neuroendocrine Systems Perspective. *Int Rev Immunol 32(3):282-306.*
- **Banks HT, Kapraun DF, Thompson WC, Peligero C, Argilaguet J, Meyerhans A (2013)** A novel statistical analysis and interpretation of flow cytometry data. *J Biol Dyn 7(1):96-132.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Jung A, Maier R, Vartanian JP, Bocharov G, Jung V, Fischer U, Meese E, Wain-Hobson S, Meyerhans A (2002)** Recombination: Multiply infected spleen cells in HIV patients. *Nature 418:144.*
- **Scheller N, Furtwängler R, Sester U, Maier R, Breinig T, Meyerhans A (2008)** Human Cytomegalovirus protein pp65: an efficient protein carrier system into human Dendritic Cells. *Gene Therapy 15:318-325.*
- **Scheller N, Mina LB, Galão RP, Chari A, Giménez-Barcons M, Noueiry A, Fischer U, Meyerhans A, and Díez J (2009)** Translation and replication of hepatitis C virus genomic RNA depends on ancient cellular proteins that control mRNA fates. *Proc Natl Acad Sci USA 106(32):13517-22.*
- **Ehrhardt M, Leidinger P, Keller A, Baumert T, Díez J, Meese E, and Meyerhans A (2011)** Profound differences of microRNA expression patterns in hepatocytes and hepatoma cell lines commonly used in hepatitis C virus studies. *Hepatology 54(3):1112-3.*
- **Reiter J, Pérez-Vilaró G, Scheller N, Mina LB, Díez J, and Meyerhans A (2011)** Hepatitis C virus RNA recombination in cell culture. *J Hepatol 55(4):777-83.*

Elena Hidalgo and José Ayté

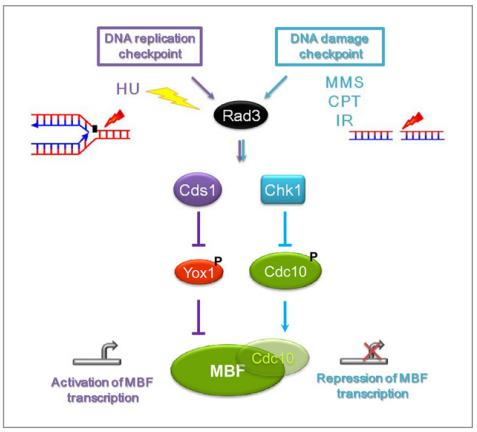
Oxidative Stress and Cell Cycle Group

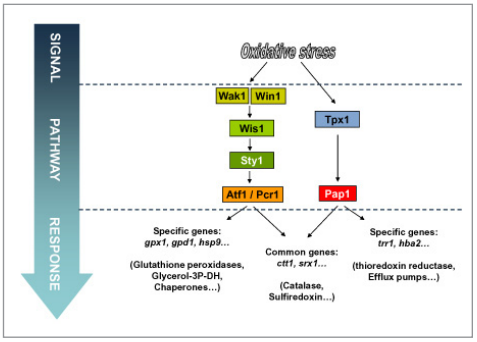
www.upf.edu/osccg

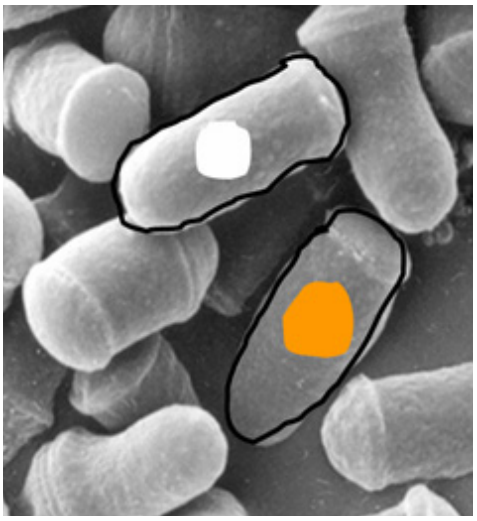
Postdocs: *Susanna Boronat, Isabel Alves-Rodrigues, Angel Guerra-Moreno, Maribel Marquina, Patricia García, Jorge Fernández-Vázquez and Javier Encinar.*

PhD students: *Maria Isabel Calvo, Sarela García-Santamarina, Tsvetomira Ivanova, Iva Knezevic and Esther Paulo.*

Technicians: *Mercè Carmona.*







Research Outline

Our main interest is the characterization of cellular responses to oxidative stress and cell cycle control in the fission yeast, Schizosaccharomyces pombe, using cutting edge approaches in molecular biology, proteomics/mass spectrometry and live cell imaging, as well as traditional genetics.

Current Projects/Research Lines

a) Reactive oxygen species are side-products of oxidative metabolism, and oxidative stress occurs as a consequence of unbalances between production and degradation of ROS. For instance, hydrogen peroxide (H_2O_2) can induce damage to all biomolecules, specifically to proteins. We aim to study both toxicity and signalling linked to H_2O_2. Currently, the main aims of our lab are:

- **i)** to study the toxic consequences of oxidative stress at proteins, analyzing at the proteome level disulfide bond formation (reversible modification) and carbonylation (irreversible modification), to better understand reactivity of peroxides;
- **ii)** to determine the participation of the thioredoxin system in both general disulfide formation and activation of the Pap1 sensor; and
- **iii)** to study the transcriptional and post-transcriptional events which allow cells to tolerate H_2O_2 stress in a MAP kinase Sty1-dependent manner.

b) Our research aims on characterizing how cell cycle regulates gene expression and how alterations of gene expression can also modulate cell cycle progression. In particular:

- **i)** Cdc10 is part of a multimeric transcription factor, the MBF complex, which is the functional homolog of mammalian RB/E2F. We are analyzing how MBF is regulated in an unperturbed cell cycle, and how this complex is regulated upon DNA damage. We are also isolating and characterizing new components of the MBF complex.
- **ii)** Meiosis is a specialized cell cycle that, at least in unicellular organisms, takes place when cells are under nutrient deprivation. We are characterizing how transcription and splicing factors regulate the organized meiotic cell cycle.

SELECTED PUBLICATIONS 2012 - 2013

- **Calvo IA, García P, Ayté J, Hidalgo E (2012)** The transcription factors Pap1 and Prr1 collaborate to activate antioxidant, but not drug tolerance, genes in response to H_2O_2. *Nucleic Acids Res 40:4816-24.*
- **Guerra-Moreno A, Alves-Rodrigues I, Hidalgo E, Ayté J (2012)** Chemical genetic induction of meiosis in Schizosaccharomyces pombe. *Cell Cycle 11:1620-24.*
- **Calvo IA, Boronat S, Domènech A, García-Santamarina S, Ayté J, Hidalgo E (2013)** Dissection of a redox relay: H_2O_2-dependent activation of the transcription factor Pap1 through the peroxidatic Tpx1-thioredoxin cycle. *Cell Rep 5:1413-24.*
- **Ivanova T, Alves-Rodrigues I, Gómez-Escoda B, Dutta C, DeCaprio JA, Rhind N, Hidalgo E, Ayté J (2013)** The DNA Damage and the DNA Replication Checkpoints Converge at the MBF Transcription Factor. *Mol Biol Cell 24:3350-57.*
- **Fernández-Vázquez J, Vargas-Pérez I, Sansó M, Buhne K, Carmona M, Paulo E, Hermand D, Rodríguez-Gabriel M, Ayté J, Leidel S, Hidalgo E (2013)** Modification of tRNALysUUU by Elongator is essential for efficient translation of stress mRNAs. *PLoS Genet 9:e1003647.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Vivancos AP, Castillo EA, Biteau B, Nicot C, Ayté J, Toledano MB, Hidalgo E (2005)** A cysteine-sulfinic acid in peroxiredoxin regulates H_2O_2-sensing by the antioxidant Pap1 pathway. *Proc Nat Acad Sci USA 101:8875-8880.*
- **Moldón A, Malapeira J, Gabrielli N, Gogol M, Gómez-Escoda B, Ivanova T, Seidel C, Ayté J (2008)** Promoter-driven splicing regulation in fission yeast. *Nature 455:997-1000.*
- **Moldón A, Ayté J (2009)** At the (3') end, you'll turn to meiosis. *Nat Struct Mol Biol 16:350-51.*
- **Zuin A, Carmona M, Gabrielli N, Morales-Ivorra I, Vivancos AP, Ayté J, Hidalgo E (2010)** Life-span extension by calorie restriction relies on the Sty1 MAP kinase stress pathway. *EMBO J 29:981-991*
- **Gómez-Escoda B, Ivanova T, Calvo IA, Alves-Rodrigues I, Hidalgo E, Ayté J (2011)** Yox1 links MBF-dependent transcription to completion of DNA synthesis. *EMBO Rep 12:84-9.*

Miguel López-Botet Arbona

Inhibitory and activating receptors of the innate immune system

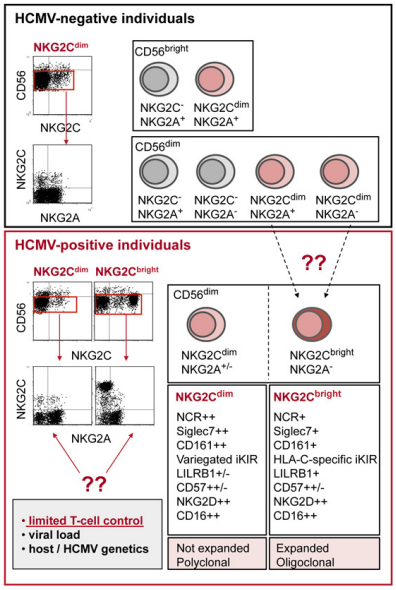
www.upf.edu/immuno

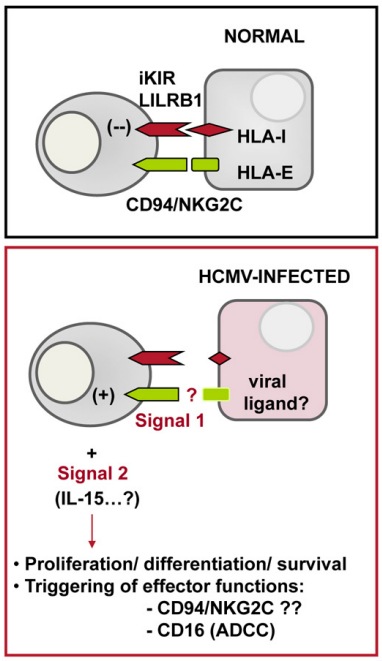
Senior Researcher: *Aura Muntasell Castellví.*

Postdocs: *Jordi Síntes Castro and Jordi Pou Sánchez.*

PhD students: *Diogo Baia, María López Montañés and Aldi Pupuleku.*

Technicians: *Gemma Heredia Díaz and Andrea Vera Barrón.*





Research Outline

Our research has focused for over 20 years on human Natural Killer (NK) cell inhibitory and activating receptors (NKR) which control their response against viral infections and tumors. The characterisation of CD94/NKG2 and ILT2 (LILRB1) receptors which interact with HLA class I molecules represent our most relevant past contributions. We currently study the role of NKR in the response to human cytomegalovirus (HCMV). This herpes virus establishing a prevalent and life-long persistent infection may cause severe congenital disorders, represents a common complication in immunocompromised patients, and may contribute to the pathogenesis of chronic inflammatory disorders (e.g. atherosclerosis).

Current Projects/Research Lines

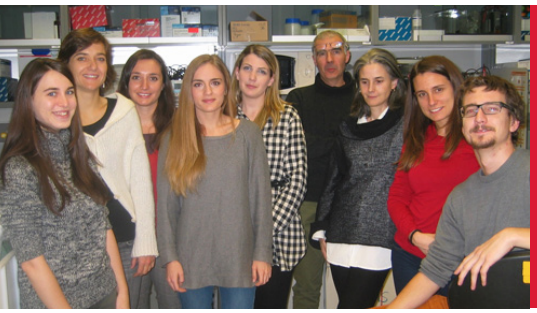
- NK cell-mediated response to HCMV infection in health and disease. We originally reported that HCMV may promote both in healthy individuals and under pathological conditions a variable and persistent reconfiguration of the human NK cell compartment, whose hallmark is the expansion of an NK subset expressing the CD94/NKG2C activating receptor specific for HLA-E. Regarding this process we currently explore: a) the nature of the underlying molecular and cellular mechanisms; b) the regulation by inhibitory and activating Killer Immunoglobulin-like Receptors (KIR); c) the implications in different clinical settings (e.g. organ transplantation, Multiple Sclerosis...); d) the putative impact in the response to other pathogens and tumors; e) the influence on specific antibody-dependent cell mediated cytotoxicity (ADCC) against infected cells; and f) the relation with the adaptive antiviral T cell-mediated function.
- Response to HCMV infection by myelomonocytic cells: We characterize the involvement of pathogen-recognition receptors (PRR) in the response of monocyte-derived macrophages to HCMV infection, analysing the participation of cytokines with inflammatory, anti-inflammatory and antiviral roles. Moreover, the regulatory role played in macrophages by the LILRB1 inhibitory receptor specific for HLA class I molecules is addressed.

SELECTED PUBLICATIONS 2012 - 2013

- **Noyola DE, Fortuny C, Muntasell A, Noguera-Julian A, Muñoz-Almagro C, Alarcón A, Juncosa T, Moraru M, Vilches C, López-Botet M (2012)** Influence of congenital human cytomegalovirus infection and the NKG2C genotype on NK-cell subset distribution in children. *Eur J Immunol 42:3256.*
- **Moraru M, Cisneros E, Gomez-Lozano N, de Pablo R, Portero F, Canizares M, Vaquero M, Roustan G, Millan I, Lopez-Botet M, Vilches C (2012)** Host genetic factors in susceptibility to herpes simplex type 1 virus infection: contribution of polymorphic genes at the interface of innate and adaptive immunity. *J Immunol 188: 4412.*
- **Muntasell A, López-Montañés M, Vera A, Heredia G, Romo R, Peñafiel J, Moraru M, Vila J, Vilches C, López-Botet M (2013)** NKG2C Zygosity Influences CD94/NKG2C Receptor Function and the NK-cell Compartment Redistribution in Response to Human Cytomegalovirus. *Eur J Immunol 3(12):3268-78.*
- **Muntasell A, Vilches C, Angulo A, López-Botet M (2013)** Adaptive reconfiguration of the human NK-cell compartment in response to cytomegalovirus: a different perspective of the host-pathogen interaction. *Eur J Immunol 43:1133.*
- **Muntasell A, Costa-Garcia M, Vera A, Marina-García N, Kirschning CJ, López-Botet M (2013)** Priming of NK cell anti-viral effector mechanisms by direct recognition of human cytomegalovirus. *Front Immunol 4:40.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Gumá M, Angulo A, Vilches C, Gómez-Lozano N, Malats N, López-Botet M (2004)** Imprint of human cytomegalovirus infection on the NK cell receptor repertoire. *Blood 104: 3664.*
- **Gumá M, Budt M, Sáez A, Brckalo T, Hengel H, Angulo A, López-Botet M (2006)** Expansion of CD94/NKG2C+ NK cells in response to human cytomegalovirus-infected fibroblasts. *Blood 107:3624.*
- **Sáez-Borderías A, Romo N, Magri G, Gumá M, Ángulo A, López-Botet M (2009)** IL-12-Dependent Inducible Expression of the CD94/NKG2A Inhibitory Receptor Regulates CD94/NKG2C(+) NK Cell Function. *J Immunol 182: 829.*
- **Muntasell A, Magri G, Pende D, Angulo A, López-Botet M (2010)** Inhibition of NKG2D expression in NK cells by cytokines secreted in response to human cytomegalovirus infection. *Blood 115:5170.*
- **Magri G, Muntasell A, Romo N, Sáez-Borderías A, Pende D, Geraghty DE, Hengel H, Angulo A, Moretta A, López-Botet M (2011)** NKp46 and DNAM-1 NK cell receptors drive the response to human cytomegalovirus infected myeloid dendritic cells overcoming viral immune evasion strategies. *Blood 117:848.*



Cristina López-Rodríguez and José Aramburu

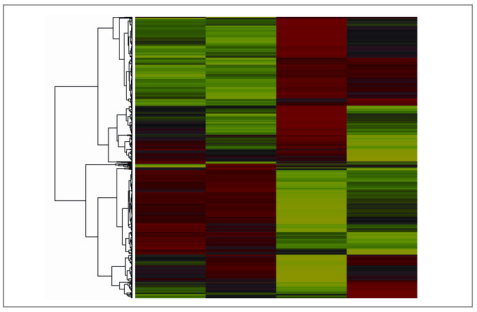
NFAT proteins and immune response

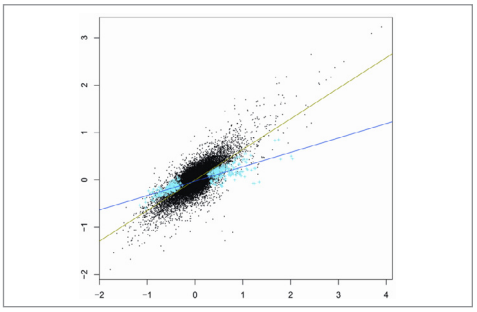
www.upf.edu/immuno/research

Postdocs: *Maria Buxadé.*

PhD students: *Maria Alberdi, Giulia Lunazzi (PhD since June 2013), Monika Tellechea, Sonia Tejedor, Hector Huerga and Mari Ortells (until 2013).*

Technicians: *Anna Almor.*





Research Outline

The immune system plays an essential role in the organism, both in the defense against pathogens and tumors as in regulating the function of multiple tissues. Immune cells continuously sense a wide variety of inputs from other cells and their environment, and use transcription factors and chromatin regulatory mechanisms to integrate this information into specific gene expression patterns that shape their activity and functional specialization.

In our group we are broadly interested in understanding gene expression regulatory mechanisms that allow immune cells to respond to stimuli such as pathogens and differentiation cues and to maintain functional competence under stress.

Current Projects/Research Lines

- **Regulation of macrophage and T lymphocyte functions by the transcription factor NFAT5.**

  NFAT5 belongs to the Rel family of transcription factors, which comprises the NF-kappaB and the calcineurin-dependent NFAT proteins. These factors regulate a wide variety of processes in immune cells, as well as in other tissues and organs. NFAT5 was initially characterized as a factor that conferred resistance to hyperosmotic stress (salt stress) in mammalian cells, but later works have revealed osmostress-independent NFAT5 functions. We have shown that NFAT5 regulates T cell activation and survival under osmotic stress in vitro and in vivo, and identified an osmostress-independent role of NFAT5 in thymocyte development. In addition, we have uncovered a novel function of NFAT5 in enhancing macrophage capability to detect low concentrations of microbial and pathogen-derived products, which makes NFAT5 a significant regulator of macrophage antimicrobial and inflammatory responses. We are currently investigating the involvement of NFAT5 in a wider range of immune functions.

- **Adaptive mechanisms used by T lymphocytes and macrophages to maintain their functionality under stress.**

  Accurate immune responses require that leukocytes are able to respond appropriately to specific signals such as cytokines and maintain this capability under a variety of stress conditions. We have found that osmotic stress activates a stress survival programme in T cells, but also induces the expression of immunologically relevant surface receptors and cytokines in a manner regulated by NFAT5 and growth signals. We are investigating the transcriptional mechanisms that allow immune cells to maintain their functionality under stress.

SELECTED PUBLICATIONS 2012 - 2013

- **Ortells MC, Morancho B, Drews-Elger K, Viollet B, Laderoute KR, López-Rodríguez C, Aramburu J (2012)** Transcriptional regulation of gene expression during osmotic stress responses by the mammalian target of rapamycin (mTOR). *Nucleic Acids Res 40:4368-4384.*
- **Buxadé M, Lunazzi G, Minguillón J, Iborra S, del Val M, Aramburu J, López-Rodríguez C (2012)** Gene expression induced by Toll-like receptors in macrophages requires the transcription factor NFAT5. *J. Exp Med. 209:379-393.*
- **Berga-Bolaños R, Alberdi A, Buxadé M, Aramburu J, Cristina López-Rodríguez (2013)** NFAT5 induction by the pre-T cell receptor serves as a selective survival signal in T lymphocyte development. *Proc Natl Acad Sci USA.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **López-Rodríguez C, Aramburu J, Jin L, Rakeman AS, Michino M, Rao A (2001)** Bridging the NFAT and NF-kappaB families: NFAT5 dimerization regulates cytokine gene transcription in response to osmotic stress. *Immunity 15:47-58.*
- **López-Rodríguez C, Antos CL, Shelton J, Richardson JA, Fangming L, Novobrantseva TI, Bronson RT, Igarashi P, Rao A, Olson EN (2004)** Loss of NFAT5 results in renal atrophy and lack of tonicity-responsive gene expression. Proc Natl Acad of Sci USA 101:2392-2397.
- **Minguillón J, Morancho B, Kim S-J, López-Botet M, Aramburu J (2005)** Concentrations of cyclosporin A and FK506 that inhibit IL-2 induction in human T cells do not affect TGF-β1 biosynthesis, whereas higher doses of cyclosporin A trigger apoptosis and release of preformed TGF-β1. *J Leukocyte Biol 77:748-758.*
- **Drews-Elger K, Ortells MC, Rao A, López-Rodríguez C, and Aramburu J (2009)** The Transcription Factor NFAT5 Is Required for Cyclin Expression and Cell Cycle Progression in Cells Exposed to Hypertonic Stress. *PLoS ONE 4:e5245.*
- **Berga-Bolaños R, Drews-Elger K, Aramburu J, López-Rodríguez C (2010)** NFAT5 regulates T lymphocyte homeostasis and CD24-dependent T cell expansion under pathologic hypernatremia. *J Immunol 185:6624-6635.*

David Andreu Martínez

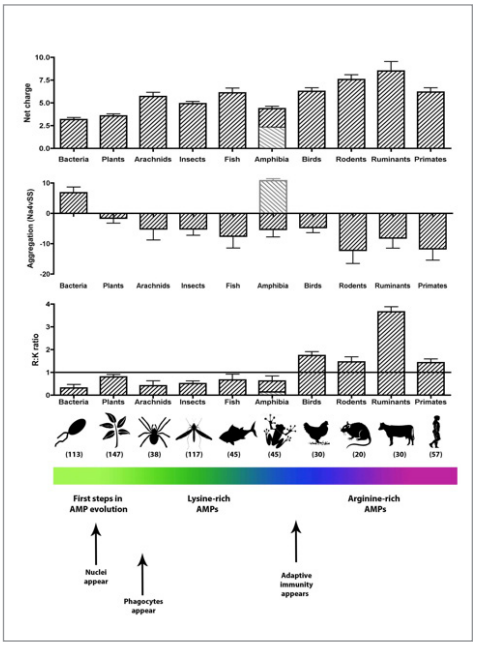
Proteomics and protein chemistry

www.upf.edu/uprot

Senior Researcher: *Beatriz G. de la Torre.*

PhD students: *Marta Monsó, Sira Defaus, Ainhoa Mascaraque, Ermelinda Vernieri and Francesca Pedretti.*

Technicians: *Javier Valle, Yolanda Tor and Jorge Esteban.*



Research Outline

Our group uses analytical and synthetic approaches to understand the role of proteins in various biological processes. Thus, we apply mass spectrometry (MS)-based proteomics to identify proteins involved in microbial resistance and oocyte fertilization processes. We also make extensive use of synthetic peptides as vaccine candidates against animal viral diseases, as intracellular delivery vectors or as antimicrobial agents.

Current Projects/Research Lines

- **Peptide-based vaccines against foot-and-mouth disease virus (FMDV) and classical swine fever virus (CSFV).**

  We have developed novel scaffolds for displaying clinically relevant B- and T-cell epitopes of these viruses, one of which (FMDV) causes the economically most devastating animal disease worldwide. Our original FMDV vaccine candidate induced a fully protective response in swine; an improved version has been developed and successfully tested in mice before extensive field trials and commercial application in China. A similar approach is applied for CSFV, with slower but encouraging progress.

- **Antimicrobial peptides (AMPs)**

  Long-standing work in this field focuses now on (i) identifying AMP pharmacophores and hence developing better-than-native AMP versions; (ii) host-defense role of evolutionarily conserved N-terminal domain of mammalian RNases; (iii) possible evolutionary pathways for generating AMP activity, particularly the transition from aggregating to membrane-active sequences; (iv) bioinformatic tools for predicting antimicrobial regions in proteins.

- **Studying sugar-protein interactions by surface and MS-based approaches**

  A novel platform for sugar display by surface plasmon resonance is used as a lectin capture and ID system, and can be conveniently complemented by MS-based analysis of the carbohydrate recognition domains of lectins. This technology is now applied to identifying proteins from bovine sperm putatively implicated in fertilization processes.

- **Cell-penetrating peptides (CPPs)**

  We are using CPPs for delivering poorly absorbed drugs into parasites and/or macrophages, there by defeating drug resistance and making new inroads for trypanosomatid chemotherapy. We are also investigating uptake mechanisms of NrTPs, a new class of CPPs discovered in our laboratory.

SELECTED PUBLICATIONS 2012 - 2013

- **Torrent M, Nogués MV, Andreu D, Boix E (2012)** The "CPC clip motif": a conserved structural signature for heparin-binding proteins. *PLoS ONE, 7, e42692.*
- **Luque-Ortega JR, de la Torre BG, Hornillos V, Bart JM, Rueda C, Navarro M, Amat-Guerri F, Acuña AU, Andreu D, Rivas L (2012)** Defeating Leishmania resistance to Miltefosine (hexadecylphosphocholine) by peptide-mediated drug smuggling: a proof of concept for trypanosomatid chemotherapy. *J Control Release 161:835-842.*
- **Jiménez-Castells C, Defaus S, Moise A, Przybylski M, Andreu D, Gutiérrez-Gallego R (2012)** Surface-based and mass spectrometric approaches to deciphering sugar-protein interactions in a galactose-specific agglutinin. *Anal Chem 84:6515-6520.*
- **Torrent M, Di Tomasso P, Nogués MV, Notredame C, Boix E, Andreu D (2012)** AMPA: An automated web server for prediction of protein antimicrobial regions. *Bioinformatics 28:130-131.*
- **Monsó M, de la Torre B, Blanco E, Moreno N, Andreu D (2013)** Influence of conjugation chemistry and B epitope orientation on the immune response of branched peptide antigens. *Bioconjugate Chem 24:578-585.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Cubillos C, de la Torre BG, Jakab A, Clementi G, Borràs E, Bárcena J, Andreu D, Sobrino F, Blanco E (2008)** Enhanced mucosal IgA response and solid protection against foot-and-mouth disease virus challenge induced by a novel dendrimeric peptide. *J Virol 82:7223-7230.*
- **Roda O, Ortiz-Zapater E, Martínez-Bosch N, Gutiérrez-Gallego R, Vila-Perelló M, Ampurdanès C, Gabius HJ, André S, Andreu D, Real FX, Navarro P (2009)** Galectin-1 is a novel functional receptor for tissue plasminogen activator in pancreatic cancer. *Gastroenterology 136:1379-1390, e1-5.*
- **Fernández-Reyes M, Rodríguez-Falcón M, Chiva C, Pachón J, Rivas L, Andreu D (2009)** The cost of resistance to colistin in Acinetobacter baumannii: a proteomic perspective. *Proteomics 9:1632-1645.*
- **Torrent M, Valle J, Nogués MV, Boix E, Andreu D (2011)** The generation of antimicrobial peptide activity: a trade-off between charge and aggregation? *Angew Chemie Int Ed Engl 50:10686-10689.*
- **Rodrigues M, De la Torre BG, Rádis-Baptista G, Santos NC, Andreu D (2011)** Efficient cellular delivery of β-galactosidase mediated by NrTPs, a new family of cell-penetrating peptides. Bioconjugate Chem 22:2339-2344.

Olga Valverde Granados

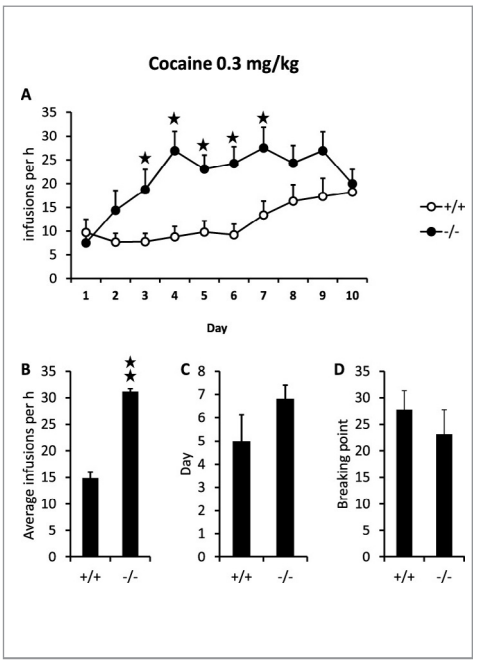
Neurobiology of Behavior Research Group (GReNeC)

www.upf.edu/grenec

Postdocs: *Jessica Ruiz-Medina, Marta González-Sepúlveda and Emily Johansson.*

PhD students: *Irene Gracia-Rubio, Maria Moscoso Castro and Anna Esteve Arenys.*

Technicians: *Neus Toro Ortiz.*



Research Outline

The research of our team is devoted to identify the neurobiological basis underlying several psychiatric disorders, in particular drug addiction, affective disorders, cognitive deficits, chronic pain and more recently neurotoxicity. For our studies, we employ behavioral models using mice combined with neurochemical, immunohistochemical and molecular tools for the appropriate interpretation of the data. We also use genetically modified mice as experimental tools, in particular, we are interested in the influence of specific targets in the above mentioned pathologies such as the adenosine A2a receptors, the endocannabinoid system and the orphan G protein coupled receptor GPR3. Our integrative strategy helps us to identify appropriate markers to characterize the mental diseases and for proposing new preventives strategies and therapeutical applications.

Current Projects/Research Lines

1. **The neurobiological substrate involved in drug addiction.**

   The study of the specific contribution of neurotransmission systems and GPCR in the processes associated to motivation and drug addiction, in particular adenosine A2a receptors, cannabinoid receptors and orphan GPRC receptors. More recently we have focused our research in the long-term toxicity associated to chronic drug consumption regarding emotion and cognition.

2. **Emotional control and the alterations leading to depressive disorders.**

   The identification and development of animal models of depression, using behavioral, pharmacological, molecular tools and genetically modified mice.

3. **Co-morbidity between drug addiction and depression.**

   The characterization of different models of psychiatric co-morbidity (drug addiction and depression) using different approximations. We investigated early-life adverse events, like maternal deprivation, in the later development (periadolescent period) on mood, anxiety and addictive disorders. We also focused in the identification of biomarkers to characterize the primary disease in the co-morbidity (depression and drug addiction).

4. **Co-morbidity between drug addiction and depression.**

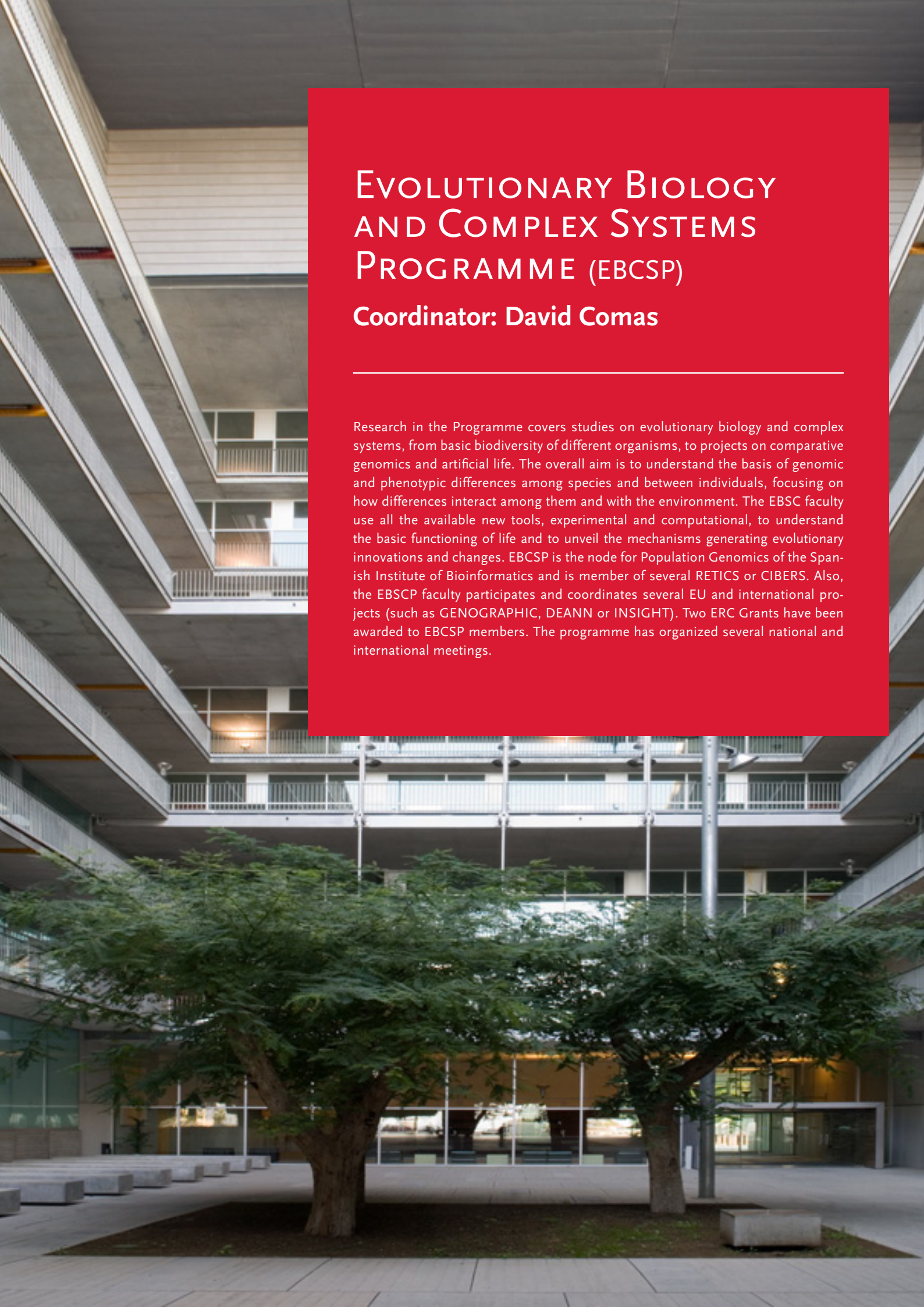
   The role of neurotransmitter systems in the development and expression of neuropathic pain after sciatic nerve ligature, and the evaluation of the inflammatory reaction in the central nervous system. Hyperalgesia to noxious thermal stimulus and allodynia to different stimuli are evaluated using behavioral models and immunohistochemistry in mice.

SELECTED PUBLICATIONS 2012 - 2013

- **Touriño C, Valjent E, Ruiz-Medina J, Herve D, Ledent C, Valverde O (2012)** The orphan receptor GPR3 modulates the early phases of cocaine reinforcement. *Br J Pharmacol 167(4):892-904.*
- **Madroñal N, Gruart A, Valverde O, Espadas I, Moratalla R, Delgado-García JM (2012)** Involvement of cannabinoid CB1 receptor in associative learning and in hippocampal CA3-CA1 synaptic plasticity. *Cereb Cortex 22(3):550-66.*
- **Ros-Simó C, Moscoso-Castro M, Ruiz-Medina J, Ros J, Valverde O (2013)** Memory impairment and hippocampus specific protein oxidation induced by ethanol intake and 3, 4-Methylenedioxymethamphetamine (MDMA) in mice. *J Neurochem 125(5):736-46.*
- **Ruiz-Medina J, Pinto-Xavier A, Rodríguez-Arias M, Miñarro J, Valverde O (2013)** Influence of chronic caffeine on MDMA-induced behavioral and neuroinflammatory response in mice. *Psychopharmacology (Berl) 226(2):433-44.*
- **Valverde O, Rodríguez-Árias M (2013)** Modulation Of 3, 4-Methylenedioxymethamphetamine Effects By Endocannabinoid System. *Curr Pharm Des 19(40):7081-91.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Valverde O, Karsak M, Zimmer A (2005)** Analysis of the endocannabinoid system by using CB1 cannabinoid receptor knockout mice. *Handb Exp Pharmacol (168):117-45.*
- **Bilkei-Gorzo A, Racz I, Valverde O, Otto M, Michel K, Sastre M, Zimmer A (2005)** Early age-related cognitive impairment in mice lacking cannabinoid CB1 receptors. *Proc Natl Acad Sci USA 102(43):15670-5.*
- **Laurent P, Becker JA, Valverde O, Ledent C, de Kerchove d'Exaerde A, Schiffmann SN, Maldonado R, Vassart G, Parmentier M (2005)** The prolactin-releasing peptide antagonizes the opioid system through its receptor GPR10. *Nat Neurosci 8(12):1735-41.*
- **Touriño C, Ledent C, Maldonado R, Valverde O (2008)** CB1 cannabinoid receptor modulates 3,4-methylenedioxymethamphetamine acute responses and reinforcement. *Biol Psychiatry 63(11):1030-8.*
- **Ruiz-Medina J, Ledent C, Valverde O (2011)** GPR3 orphan receptor is involved in neuropathic pain after peripheral nerve injury and regulates morphine-induced antinociception. *Neuropharmacology 61(1-2):43-50.*



Evolutionary Biology and Complex Systems Programme (EBCSP)

Coordinator: David Comas

Research in the Programme covers studies on evolutionary biology and complex systems, from basic biodiversity of different organisms, to projects on comparative genomics and artificial life. The overall aim is to understand the basis of genomic and phenotypic differences among species and between individuals, focusing on how differences interact among them and with the environment. The EBSC faculty use all the available new tools, experimental and computational, to understand the basic functioning of life and to unveil the mechanisms generating evolutionary innovations and changes. EBCSP is the node for Population Genomics of the Spanish Institute of Bioinformatics and is member of several RETICS or CIBERS. Also, the EBSCP faculty participates and coordinates several EU and international projects (such as GENOGRAPHIC, DEANN or INSIGHT). Two ERC Grants have been awarded to EBCSP members. The programme has organized several national and international meetings.

Jaume Bertranpetit

Evolutionary systems biology

www.ibe.upf-csic.es/research/research-labs/bertranpetit.html

Postdocs: *Ferran Casals, Hafid Laayouni and Ludovica Montanucci.*

PhD students: *Giovanni dall'Olio, Pierre Luisi, Brandon Invergo, Marc Pybus and Mayukh Mondal.*

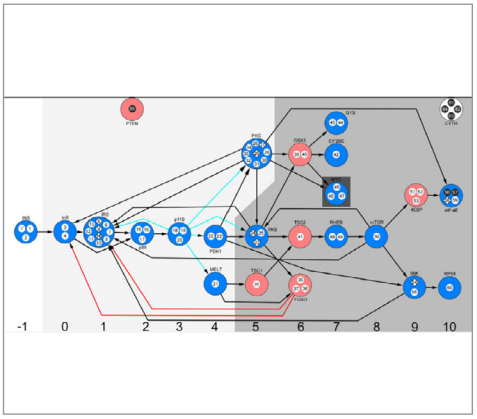


Figure: *Structure of the insulin/TOR signal transduction pathway. Each node represents a paralogous group. The distribution of signals of Positive selection is analyzed through the pathway structure (Luisi et al 2013)*

Research Outline

Our main research focuses on understanding the role of the structure of the interactions within a network in shaping the evolution of genes, to reveal patterns of adaptation in biological networks that are not observable in single gene studies and, ultimately to unravel principles that drive evolution that takes place in a highly interacting, complex system. Elucidating how and through which rules and dynamics can the evolution of genes takes place within a highly interacting system. We have also ongoing work in reconstructing population history by studying human genetic diversity with projects in India, Gypsies and Sudan and collaborations with Carles Lalueza-Fox, Francesc Calafell, David Comas, and with Tomàs Marquès-Bonet on detecting selection in the genome of apes.

Current Projects/Research Lines

Our main research focuses on how to use molecular pathways to understand the biology of adaptation through the measures of natural selection in genes and other genomic regions. The different forms of selection (purifying, balancing and positive) are analyzed at two levels: among human populations in order to detect population-specific adaptations, and among primates in order both to recognize species-specific adaptive selection and to measure the relative strength of purifying selection.

The action of selection is measured and understood not in terms of single lists of genes, but integrated in molecular physiological pathways or networks and the aim is, in a given pathway, to understand the complex basis of adaptation and how networks have been shaped by natural selection. For the analysis of selection we have developed a pipeline for the detection of positive selection that calculates 21 tests and, through simulation, are integrated in a machine learning algorithm (boosting) that produces a single score for specific selection footprints. The initial goal is to produce a map of positive selection in the human genome for three populations (Europe, Asia and Africa) that after will be used for other studies, mainly for the analysis of the ape genomes.

The pathways that we have analyzed are: N-glycosylation pathway; innate immunity; phototransduction; obesity through adiposity signals; and the whole human metabolome. Special attention has been put in the quality of databases for metabolic pathways, as their quality is worse than most studies assume and manual curation is needed in all cases.

SELECTED PUBLICATIONS 2012 - 2013

- **Melé M, Javed A, Pybus M, Zalloua P, Haber M, Comas D, Netea MG, Balanovsky O, Balanovska E, Jin L, Yang Y, Pitchappan RM, Arunkumar G, Parida L, Calafell F, Bertranpetit J, The Genographic Consortium (2012)** Recombination gives a new insight in the effective population size and the history of the Old World human populations. *Mol Biol Evol 29(1):25-30.*
- **Luisi P, Alvarez-Ponce D, Dall'Olio GM, Sikora M, Bertranpetit J, Laayouni H.** Network-level and population genetics analysis of the insulin/TOR signal transduction pathway across human populations**.** *Mol Biol Evol. 2012 May;29(5):1379-92.*
- **Casals F, Bertranpetit J (2012)** Human Genetic Variation, Shared and Private. *Science 337(6090):39-40.*
- **Invergo BM, Montanucci L, Laayouni H, Bertranpetit J (2013)** A system-level, molecular evolutionary analysis of mammalian phototransduction. *BMC Evol Biol 13(1):52.*
- **Pybus M, Dall'Olio GM, Luisi P, Uzkudun M, Carreño-Torres A, Pavlidis P, Laayouni H, Bertranpetit J, Engelken J (2013)** 1000 Genomes Selection Browser 1.0: a genome browser dedicated to signatures of natural selection in modern humans. *Nucleic Acid Res [Epub ahead of print] PMID: 24275494.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **González-Neira A, Ke X, Lao O, Calafell F, Navarro A, Comas D, Cann H, Bumpstead S, Ghori J, Hunt S, Deloukas P, Dunham I, Cardon LR, Bertranpetit J (2006)** The portability of tagSNPs across populations: a worldwide survey. *Genome Res 16(3):323-30.*
- **Bosch E, Laayouni H, Morcillo-Suarez C, Casals F, Moreno-Estrada A, Ferrer-Admetlla A, Gardner M, Rosa A, Navarro A, Comas D, Graffelman J, Calafell F, Bertranpetit J (2009)** Decay of linkage disequilibrium within genes across HGDP-CEPH human samples: most population isolates do not show increased LD. *BMC Genomics 10(1):338.*
- **Melé M, Javed A, Pybus M, Calafell F, Parida L, Bertranpetit J, The Genographic Consortium (2010)** A new method to reconstruct recombination events at a genomic scale. *PLOS Comput Biol 6(11):e1001010.*
- **Montanucci L, Laayouni H, Dall'Olio GM and Bertranpetit J (2011)** Molecular evolution and network-level analysis of the N-Glycosylation metabolic pathway across primates. *Mol Biol Evol 28(1):813-23.*
- **Casals F, Sikora M, Laayouni H, Montanucci L, Muntasell A, Lazarus R, Calafell F, Awadalla P, Netea MG, Bertranpetit J (2011)** Genetic adaptation of the antibacterial human innate immunity network. *BMC Evol Biol 11(1):202.*

David Comas

Human Genome Diversity Group

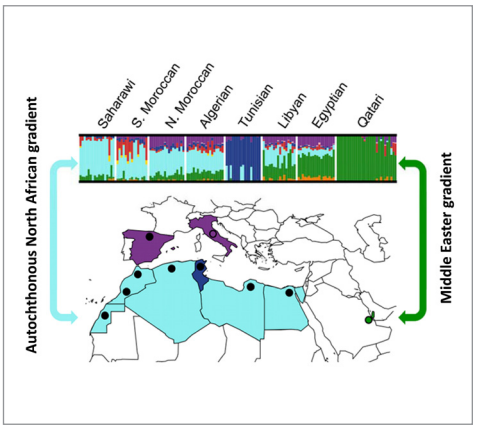
http://bhusers.upf.edu/dcomas

Postdocs: *Isabel Mendizabal.*

PhD students: *Laura Rodríguez-Botigué, Marc Haber, Arturo Silveyra, Lara R. Arauna and Gerard Serra.*

Technicians: *Paula Sanz and Mònica Vallés.*

Project Manager: *Judit Sainz.*



Research Outline

Our group is focused on the analysis of the human genome and related species in order to understand the processes that have modelled the extant genetic diversity of humans. We are interested in unravelling the demographic and adaptive processes that have given place to the genetic composition of human populations and their consequences in health and disease.

Current Projects/Research Lines

- **Tracing human migrations and admixture through the analysis of the genome**

  We analyze the genetic diversity in human populations in order to unravel the migration and admixture processes that have modelled the extant human variation.

- **Evolutionary history and adaptations in humans**

  Genetic adaptations to different climatic, pathogenic, and cultural environments have left a footprint in our genomes that gives us information about the evolutionary history of human populations and the natural history of disease.

- **Population genetic structure of human populations**

  The genetic variants within populations are not always distributed at random due to sub-structure in human populations. The knowledge of possible substructure in populations is of key relevance in genetic association and forensic studies.

- **Correlation between genes, languages and cultural traits**

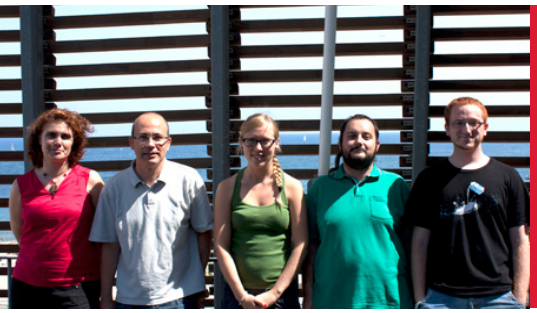
  The genetic variation in our species might be conditioned by cultural traits. The correlation between human variation and cultural traits such as languages, life-style, religion or surnames might give us hints about the processes that have modelled the distribution of genetic variants and predict genetic frequencies in unstudied samples.

SELECTED PUBLICATIONS 2012 - 2013

- **Mendizabal I, Lao O, Marigorta UM, Wollstein A, Gusmão L, Ferak V, Ioana M, Jordanova A, Kaneva R, Kouvatsi A, Kučinskas V, Makukh H, Metspalu A, Netea MG, de Pablo R, Pamjav H, Radojkovic D, Rolleston SJ, Sertic J, Macek M Jr, Comas D, Kayser M (2012)** Reconstructing population history of European Romani from genome-wide data. *Curr Biol 22:2342-2349.*
- **Campbell CL, Palamara PF, Dubrovsky M, Botigué LR, Fellous M, Atzmon G,Oddoux C, Pearlman A, Hao L, Henn BM, Burns E, Bustamante CD, Comas D, Friedman E, Pe'er I, Ostrer H (2012)** North African Jewish and non-Jewish populations form distinctive, orthogonal clusters. *Proc Natl Acad Sci USA 109(34):13865-70.*
- **Henn BM, Botigué LR, Gravel S,Wang W, Brisbin A, Byrnes JK, Fadhlaoui-Zid K, Zalloua PA, Moreno-Estrada A, Bertranpetit J, Bustamante CD, Comas D (2012)** Genomic Ancestry of North Africans Supports Back-to-Africa Migrations. *PLoS Genetics 8(1)e1002397.*
- **Botigué LR, Henn BM, Gravel S, Maples BK, Gignoux CR, Corona E, Atzmon G, Burns E, Ostrer H, Flores C, Bertranpetit J, Comas D, Bustamante CD (2013)** Gene flow from North Africa contributes to differential human genetic diversity in Southern Europe. *Proc Natl Acad Sci USA 110:11791-11796.*
- **Haber M, Gauguier D, Youhanna S, Patterson N, Moorjani P, Botigué LR, Platt DE, Matisoo-Smith E, Soria-Hernanz DF, Wells S, Bertranpetit J, Tyler-Smith C, Comas D, Zalloua PA (2013)** Genome-wide diversity in the Levant reveals recent structuring by culture. *PLoS Genetics 9(2)e1003316.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Gardner M, González-Neira A, Lao O, Calafell F, Bertranpetit J, Comas D (2006)** Extreme population differences across Neuregulin 1 gene, with implications for association studies. *Mol Psychiatry 11: 66-75.*
- **Enattah NS, Jensen TGK, Nielsen M, Lewinski R, Kuokkanen M, Rasinpera H, El-Shanti H, Seo JK, Alifrangis M, Khalil IF, Natah A, Ali A, Natah S, Comas D, Mehdi SQ, Groop L, Vestergaard EM, Imtiaz F, Rashed MS, Meyer B, Troelsen J, Peltonen L (2008)** Independent introduction of two lactase persistence alleles into human populations reflect different history of adaptation to milk culture. *Am J Hum Genet 82(1):57-72.*
- **Berniell-Lee G, Calafell F, Bosch E, Heyer E, Sica L, Mouguiama-Daouda P, van der Veen L, Hombert JM, Quintana-Murci L, Comas D (2009)** Genetic and demographic implications of the Bantu expansion: insights from human paternal lineages. *Mol Biol Evol 26:1581-1589.*
- **Behar DM, Yunusbayev B, Metspalu M, Metspalu E, Rosset S, Parik J, Rootsi S, Chaubey G, Kutuev I, Yudkovsky G, Khusnutdinova EK, Balanovsky O, Semino O, Pereira L, Comas D, Gurwitz D, Bonne-Tamir B, Parfitt T, Hammer MF, Skorecki K, Villems R (2010)** The genome-wide structure of the Jewish people. *Nature 466(7303):238-242.*
- **Henn BM, Gignoux CR, Jobin M, Granka JM, Macpherson JM, Kidd JM, Rodríguez-Botigué L, Ramachandran S, Hon L, Brisbin A, Lin AA, Underhill P, Comas D, Kidd KK, Parham P, Norman PJ, Bustamante CD, Mountain JL, Feldman MW (2011)** African Hunter-Gatherer Populations Maintain the Highest Levels of Human Genomic Diversity. *Proc Natl Acad Sci USA 108:5154-5162.*

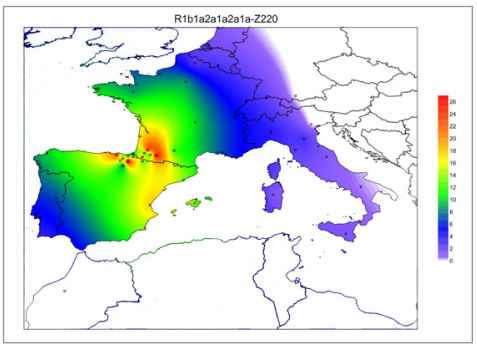


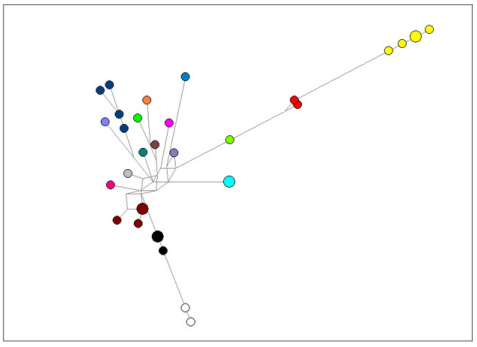
Francesc Calafell

Genomics of individuality

http://bhusers.upf.edu/fcalafell

Postdocs: *Koldo Garcia Exteberria.*
PhD students: *Marc Garcia-Garcerà.*
Technicians: *Cristina de Vasconcelos.*





Research Outline

The general topics that interest us revolve around the genomics of individuality: what is there in our genomes that make us the way we are? What does it tell about our ancestry? How does it affect our susceptibility to diseases? How can this be applied in practical settings, i.e., in forensic genetics? This is implemented in practice in three main projects: 1) we are characterizing the skin microbiome in healthy and psoriatic skin to reveal whether psoriasis has a microbial trigger; 2) we are working in a case-control association study to detect any host genetic determinant of a poor progression in 2009 A(H1N1) influenza, and 3) we are investigating Y-chromosome genetic diversity within samples of men carrying the same surname.

Current Projects/Research Lines

1. **The skin microbial biota in health and disease.**

   We are studying the skin microbial flora to try to comprehend the skin as a complex ecosystem. We are characterizing bacterial diversity, as well as performing bacterial metagenomics in samples from healthy individuals. We seek to establish a baseline and detect how it is affected in individuals with skin conditions such as psoriasis.

2. **Genetic susceptibility factors in poor influenza progression.**

   Taking the opportunity created by the 2009 A(H1N1) influenza pandemic, we collected confirmed influenza cases that required hospitalization and had no obvious risk factors, and comparing them with milder cases. By genotyping a whole genome array, we hope to discover genetic susceptibility factors for poor progression in influenza.

3. **A genetic atlas of Catalan surnames.**

   Given their transmission, surnames behave as alleles at a locus in the Y chromosome, but they also carry linguistic, social, and historic information. We have selected a list of 50 Catalan surnames and intend to gather a sample of 50 men for each of those surnames. We will type STRs and UEPs in those samples, and we want to answer these questions: 1) how are surname frequency and genetic diversity related? The frequency of a surname may be the result of polyphiletism; in that case, surname frequency and its internal genetic diversity should be positively correlated. Alternatively, certain surnames may have become more common by natural selection: surnames may be markers of social status, which, quite often, determined survival and fertility. 2) Were the carriers of German patronymic surnames of a different genetic origin form the rest of the population? 3) Is that also the case for ethnonym surnames?

SELECTED PUBLICATIONS 2012 - 2013

- **Martínez-González LJ, Martínez-Espín E, Alvarez JC, Albardaner F, Rickards O, Martínez-Labarga C, Calafell F, Lorente JA (2012)** Surname and Y chromosome in Southern Europe: a case study with Colom/Colombo. *Eur J Hum Genet 20(2):211-216.*
- **Melé M, Javed A, Pybus M, Zalloua P, Haber M, Comas D, Netea MG, Balanovsky O, Balanovska E, Jin L, Yang Y, Pitchappan R, Arunkumar G, Parida L, Calafell F, Bertranpetit J; The Genographic Consortium (2012)** Recombination gives a new insight in the effective population size and the history of the Old World human populations Molecular Biology and Evolution. *Mol Biol Evol 29:25-30.*
- **Javed A, Melé M, Pybus M, Zalloua P, Haber M, Comas D, Netea MG, Balanovsky O, Balanovska E, Jin L, Yang Y, Pitchappan R, ArunKumar G, Bertranpetit J, Calafell F, Parida L; The Genographic Consortium (2012)** Recombination Networks as Genetic Markers in A Human Variation Study of the Old World. *Hum Genet 131:601-613.*
- **Garcia-Garcerà M, Coscollà M, Garcia-Etxebarria K, Martín-Caballero J, González-Candelas F, Latorre A and Calafell F (2012)** Staphylococcus prevails in the skin microbiota of long-term immunodeficient mice. *Environ Microbiol, 14:2087-2098.*
- **Garcia-Garcerà M, Garcia-Etxebarria K, Coscollà M, Latorre A, Calafell F (2013)** A new method for extracting skin microbes allows metagenomic analysis of whole-deep skin. *PLoS ONE, 8(9):e74914.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Calafell F (2003)** Classifying humans. *Nat Genet 33:435-436.*
- **Calafell F, Roubinet F, Ramírez-Soriano A, Saitou N, Bertranpetit J, Blancher A (2008)** Evolutionary dynamics of the human ABO gene. *Hum Genet 124:123-135.*
- **Garagnani P, Laayouni H, González-Neira A, Sikora M, Luiselli D, Bertranpetit J, Calafell F (2009)** Isolated populations as treasure troves in genetic epidemiology: the case of the Basques. *Eur J Hum Genet 17:1490-1494.*
- **Sazzini M, Zuntini R, Farjadian S, Quinti I, Ricci G, Romeo G, Ferrari S, Calafell F, Luiselli D (2009)** An evolutionary approach to the medical implications of the tumor necrosis factor receptor superfamily member 13B (TNFRSF13B) gene. *Genes Immun 10:566-78.*
- **Calafell F, Almasy L, Sabater-Lleal M, Buil A, Mordillo C, Ramírez-Soriano A, Sikora M, Souto JC, Blangero J, Fontcuberta J, Soria JM (2010)** Sequence variation and genetic evolution at the human F12 locus: mapping quantitive trait nucleotides that influence FXII plasma levels. *Hum Mol Genet 19:517-525.*

Elena Bosch Fusté

Evolutionary Population Genetics

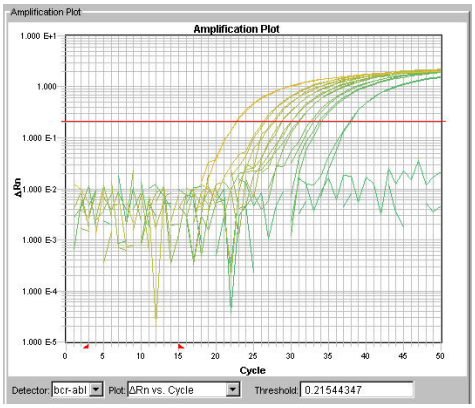
http://biologiaevolutiva.org/ebosch

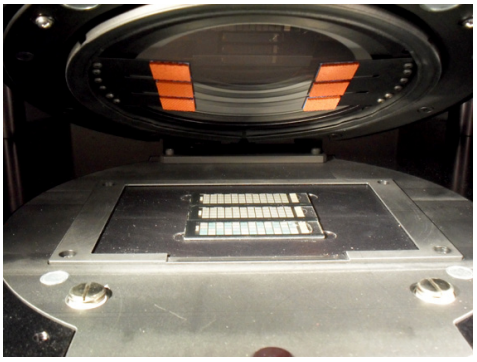
Postdocs: *Johannes Engelken.*

PhD students: *Elena Carnero, Nino Spataro and Juan Antonio Rodriguez.*

Technicians: *Mònica Vallés.*

Project Manager: *Judit Sainz.*





Research Outline

Our research focuses on investigating different aspects of human genetic diversity. In particular, we are interested in: (i) human adaptation, that is, in identifying traits that have undergone positive selection during human evolution in order to understand the adaptive events that have shaped our genomes; and (ii) the architecture of the genetic predisposition to complex disease. The search for genetic signatures of selection is pursued at different levels using comparative data and exploring intraspecific diversity patterns. As for complex disease, we believe that the application of population genetic models can help in unraveling the genetic contribution to them.

Current Projects/Research Lines

1. Human adaptation and the immune system. We want to explore whether there are genetic adaptations of the immune system in human populations exposed to different geographical environments. Beyond the detection of the footprint of natural selection into the genome itself, we experimentally investigate the phenotypical functional consequences of the genetic variants suspected under natural selection.
2. Human adaptation and nutrition. Similarly, we want to functionally characterize the variants of genes related to the metabolism of micronutrients for which we have previously shown that are subjected to distinct selective pressures in different geographical areas.
3. Role of selection in coding and non-coding regions of the genome. We are obtaining sequence data at both intraspecific and interespecific levels in order to investigate the role of natural selection in all coding and regulatory elements of particular gene pathways selected a priori for their pattern of divergence in coding regions or their relation to complex disease.
4. The role of rare variants in the etiology of complex diseases. Our hypothesis is that an excess of rare variants may indicate the involvement of a gene in a complex disease such as Parkinson's disease. Using an evolutionary approach and resequencing data in candidate genes we attempt to evaluate the expected deviation of the spectrum of allele frequencies between cases and controls if such an excess is present.

SELECTED PUBLICATIONS 2012 - 2013

- **Carnero-Montoro, E; Bonet, L; Engelken, J; Bielig, T; Martínez-Florensa, M; Lozano, F; Bosch, E (2012)** Evolutionary and functional evidence for positive selection at the human CD5 immune receptor gene. *Mol Biol Evol 29(2):811–823.*
- **Farfán M, Spataro N, Sanglas A, Albarral V, Lorén JG, Bosch E, Fusté MC (2013)** Draft genome sequence of the Aeromonas diversa type strain. *Genome Announc 1(3):e00330-13.*
- **Spataro N, Farfán M, Albarral V, Sanglas A, Lorén JG, Fusté MC, Bosch E (2013)** Draft genome sequence of Aeromonas molluscorum strain 848TT, isolated from bivalve molluscs. *Genome Announc 1(3):e00382-13*.

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Bosch E, Hurles ME, Navarro A, Jobling MA (2004)** Dynamics of a human interparalog gene conversion hotspot. *Genome Research 14 (5):835-844.*
- **Moreno-Estrada A, Casals F, Ramírez-Soriano A, Oliva B, Calafell F, Bertranpetit J, Bosch E (2008)** Signatures of selection in the human olfactory receptor OR5I1 gene. *Mol Biol Evol 25(1):144-154.*
- **Adams SM, Bosch E, Balaresque PL, Lee AC, Arroyo E, López-Parra AM, Aler M, Grifo MSG, Brion M, Carracedo A, Lavinha J, Martínez-Jarreta B, Quintana-Murci LI, Picornell A, Ramon M, Skorecki K, Behar D, Calafell F, Jobling MA (2008)** The genetic legacy of religious diversity and intolerance: paternal lineages of Christians, Jews and Muslims in the Iberian Peninsula. *Am J Hum Genet 83:725-736.*
- **Moreno-Estrada A, Tang K, Sikora M, Marquès-Bonet T, Casals F, Navarro A, Calafell F, Bertranpetit J, Stoneking M, Bosch E (2009)** Interrogating 11 fast-evolving genes for signatures of recent positive selection in worldwide human populations. *Mol Biol Evol 26(10):2285-2297.*
- **Moreno-Estrada A, Aparicio-Prat E, Sikora M, Engelken J, Ramírez-Soriano A, Calafell F, Bosch E (2010)** African signatures of recent positive selection in human FOXI1. *BMC Evol Biol 10:267.*

Arcadi Navarro i Cuartiellas

Evolutionary Genomics

http://biologiaevolutiva.org/anavarro

Postdocs: *Rui Faria, Carlos Morcillo, Natalia Petit and Gabriel Santpere.*

PhD students: *Diego Hartasanchez, Belén Lorente, Urko Martinez, Juan Antonio Rodriguez and Marco Telford.*

Technicians: *Angel Carreño, Juan Manuel Fuentes and Jordi Rambla.*

Project Manager: *Judit Sainz.*

Research Outline

Life as we see it in our planet today has been shaped by many different biological processes during billions of years. These processes leave a signature in our genomes in the form of differences between species, or between individuals of the same species. We interrogate these differences to gain knowledge about the forces behind such various phenomena as biodiversity, human emotions or the differential susceptibility of different people to certain diseases.

Current Projects/Research Lines

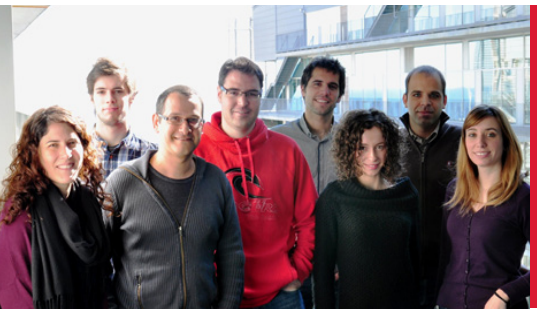
- **Chromosomal evolution and speciation**
  We study how large chromosomal rearrangements affect many aspects of genome structure and evolution, including how they may drive the generation of new species.
- **Molecular evolution of Structural Variants**
  The genomes of humans and other species present many Structural Variants (SVs) with high sequence identity that can vary in copy number from one individual to another; they are generally known as Segmental Duplications or Copy Number Variants. SVs are fundamental for the creation of novel genes and may have been key in the evolution of our lineage. We use both experimental and computational techniques to try understanding the evolutionary dynamics of the nucleotide content of SDs.
- **Detecting positive selection in the human lineage**
  We study the signature of adaptive changes out the usual paradigm of new mutations that arise in single-copy protein-coding regions. Recently we have been focusing on two questions: how natural selection may have shaped regulatory regions and the functional content of SDs and how prevalent epistatic selection or, more generally, context-dependent selection, has been in the recent history of our lineage.
- **Geographic and temporal distribution of human disease**
  We study World-wide and temporal patterns of disease susceptibility distribution to ascertain how these may have been influenced by recent human evolution.
- **Genoeconomics**
  Complex human traits that are exclusive of our lineage are the basis of our societies and have huge socio-economic impact. We deploy the latest tools of genomics for the dissection of human economic traits.

SELECTED PUBLICATIONS 2012 - 2013

- **Dickhaus T, Straßburger K, Schunk D, Morcillo-Suarez C, Illig T, Navarro A (2012)** How to analyze many contingency tables simultaneously in genetic association studies. *Stat Appl in Gen and Mol Biol 11(4):1544-6115.*
- **Muñiz-Fernandez, F., A. Carreño-Torres, C. Morcillo-Suarez and A. Navarro (2012)** Application of Array-Oriented Scientific Data Formats (NetCDF) to Genotype Data, GWASpi as an Example. In: Bioinformatics in Personalized Medicine. Series: Lecture Notes in Computer Science. Subseries: Lecture Notes in Bioinformatics. Eds Freitas A T and A Navarro. *Lecture Notes in Computer Science 6620:8-20.*
- **Prado-Martinez, J., P. H. Sudmant, J. M. Kidd, H. Li, J. L. Kelley, B. Lorente-Galdos, K. R. Veeramah, A. E. Woerner, T. D. O'Connor, G. Santpere, A. Cagan, C. Theunert, F. Casals, H. Laayouni, K. Munch, A. Hobolth, A. E. Halager, M. Malig, J. Hernandez-Rodriguez, I. Hernando-Herraez, K. Prüfer, M. Pybus, L. Johnstone, M. Lachmann, C. Alkan, D. Twigg, N. Petit-Marty, C Baker, F. Hormozdiari, M. Fernandez-Callejo, M. Dabad, M. L. Wilson, L. Stevison, C. Camprubí, T. Carvalho, A. Ruiz-Herrera, L. Vives, M. Mele, T. Abello, I. Kondova, R. E. Bontrop, A. Pusey, F. Lankester, J. A. Kiyang, R. A. Bergl, E. Lonsdorf, S. Myers, M. Ventura, P. Gagneux, D. Comas, H. Siegismund, J. Blanc, L. Agueda-Calpena, M. Gut, L. Fulton, S. A. Tishkoff, J. C. Mullikin, R. K. Wilson, I. G. Gut, M. K. Gonder, O. A. Ryder, B. H. Hahn, A. Navarro, J. M. Akey, J. Bertranpetit, D. Reich, T. Mailund, M. H. Schierup, C. Hvilsom, A. M. Andrés, J. D. Wall, C. D. Bustamante, M. F. Hammer, E. E. Eichler, T. Marques-Bonet (2013)** Great ape genetic diversity and population history. *Nature 499:471-475.*
- **Marigorta UM, Navarro A (2013)** High Trans-ethnic replicability of GWAS results implies common causal variants. *PLoS Genet 9(6): e1003566.*
- **Lorente-Galdos B, Bleyhl J, Santpere G, Vives L, Ramírez O, Hernández J, Anglada R, Cooper GM, Navarro A, Eichler EE, Marques-Bonet T (2013)** Accelerated exon evolution within primate segmental duplications. *Genome Biol 14:R9.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Navarro A, Barton NH (2003)** Chromosomal speciation and molecular divergence. Accelerated evolution of genes in rearranged chromosomes. *Science 300:321-324.*
- **Morcillo-Suarez C, Alegre J, Sangros R, Gazave E, de Cid R, Milne R, Amigo J, Ferrer-Admetlla A, Moreno-Estrada A, Gardner M, Casals F, Pérez-Lezaun A, Comas D, Bosch E, Calafell F, Bertranpetit J, Navarro A (2008)** SNP Analysis To Results (SNPator): a web-based environment oriented to statistical genomics analyses upon SNP data. *Bioinformatics 24(14):1643-4.*
- **Faria R, Navarro A (2010)** Chromosomal speciation: rearranging theory with pieces of evidence. *Trends Ecol Evol 25:660-669.*
- **The Orangutan Genome Consortium (Including A Navarro and 6 other members of my team) (2011)** Comparative and demographic analysis of orang-utan genomes. Nature 469: 529–533.



Tomàs Marquès Bonet

Comparative Genomics Lab

http://bhusers.upf.edu/tmarques

Postdocs: *Belén Lorente, Javier Quilez and Andrés Medrano Muñoz.*

PhD students: *Javier Prado, Irene Hernando, Tiago Carvalho, Raquel Garcia, Gabriela Palacios Verdú, Débora Pérez García and Cristina Borralleras Fumaña.*

Computational Support: *Marcos Fernández.*

Experimental Support: *Jessica Hernadez.*

Other PIs: *Victoria Campuzano Uceda and Miguel del Campo Casanelles.*

Research Outline

Our main line of research is centred in the discovery of the extent of all kinds of genome variation within humans, great ape species and other mammalian genomes. The goal is to create an integrated view of genome evolution by studying changes in the composition, frequency, size and location at every major branch point of human divergence from other primates. Adding other organisms (such as canids) we aim to infer rates of genome variation, characterize regional deletions and copy-number expansions with functional consequences, as well as determine the patterns of selection acting upon them and whether the diversity of these segments is consistent with other forms of genetic variation.

Current Projects/Research Lines

1. **Genomic variation in apes and canid genomes.**

   Despite international efforts to characterize thousands of human genomes to understand the extent of structural variants in the human species, primates (our closest relatives) have somehow been forgotten. Yet, they are the ideal set of species to study the evolution of these features from both mechanistic and adaptive points of view. Most genome projects include only one individual as a reference, but in order to understand the impact of structural variants in the evolution of every species we need to re-sequence multiple individuals of each species. We can only understand the origins of genomic variants and phenotypical differences among species if we can model variation within species and compare it to a proper perspective with the differences among species.

2. **Epigenetics and transcriptomics of non-human primates.**

   The recognition of post-genomic modifications with high biological impact has been a focus of research in model and non-model organisms in the last years. However, little has been done combining a three way analysis going from genomic variants, to gene expression and epigenetics in non-human primates. In the next years I am planning to use different tissues from the same individual comparing human, chimps and rhesus macaque to explore the relationship of these three layers of complexity.

SELECTED PUBLICATIONS 2012 - 2013

- **Prüfer K, Munch K, Hellmann I, Akagi K, Miller JR, Walenz B, Koren S, Sutton G, Kodira C, Winer R, Knight JR, Mullikin JC, Meader SJ, Ponting CP, Lunter G, Higashino S, Hobolth A, Dutheil J, Karakoç E, Alkan C, Sajjadian S, Catacchio CR, Ventura M, Marques-Bonet T, Eichler EE, André C, Atencia R, Mugisha L, Junhold J, Patterson N, Siebauer M, Good JM, Fischer A, Ptak SE, Lachmann M, Symer DE, Mailund T, Schierup MH, Andrés AM, Kelso J, Pääbo S (2012)** The bonobo genome compared with the genomes of chimpanzee and human. *Nature 486(7404):527-31.*
- **Prado-Martinez J, Sudmant PH, Kidd JM, Li H, Kelley JL, Lorente-Galdos B, Veeramah KR, Woerner AE, O'Connor TD, Santpere G, Cagan A, Theunert C, Casals F, Laayouni H, Munch K, Hobolth A, Halager AE, Malig M, Hernandez-Rodriguez J, Hernando-Herraez I, Prüfer K, Pybus M, Johnstone L, Lachmann M, Alkan C, Twigg D, Petit N, Baker C, Hormozdiari F, Fernandez-Callejo M, Dabad M, Wilson ML, Stevison L, Camprubí C, Carvalho T, Ruiz-Herrera A, Vives L, Mele M, Abello T, Kondova I, Bontrop RE, Pusey A, Lankester F, Kiyang JA, Bergl RA, Lonsdorf E, Myers S, Ventura M, Gagneux P, Comas D, Siegismund H, Blanc J, Agueda-Calpena L, Gut M, Fulton L, Tishkoff SA, Mullikin JC, Wilson RK, Gut IG, Gonder MK, Ryder OA, Hahn BH, Navarro A, Akey JM, Bertranpetit J, Reich D, Mailund T, Schierup MH, Hvilsom C, Andrés AM, Wall JD, Bustamante CD, Hammer MF, Eichler EE, Marques-Bonet T (2013)** Great ape genetic diversity and population history. *Nature 499(7459):471-5.*
- **Hernando-Herraez I, Prado-Martinez J, Garg P, Fernandez-Callejo M, Heyn H, Hvilsom C, Navarro A, Esteller M, Sharp AJ, Marques-Bonet T (2013) Dynamics of DNA Methylation in Recent Human and Great Apes Evolution. PLOS Genetics 9(9):e1003763.**
- **Lorente-Galdos B, Bleyhl J, Santpere G, Vives L, Ramirez O, Hernandez J, Anglada R, Copper GM, Navarro A, Eichler E, Marques-Bonet T (2013)** Fast exon evolution in duplicated regions in hominids. *Genome Biol 14(1):R9.*
- **Prado-Martinez J, Hernando-Herraez I, Lorente-Galdos B, Dabad M, Ramirez O, Baeza-Delgado C, Morcillo-Suarez C, Alkan C, Hormozdiari F, Raineri E, Estellé J, Fernandez-Callejo M, Valles M, Ritscher L, Schöneberg T, de la Calle-Mustienes E, Casillas S, Rubio-Acero R, Melé M, Engelken J, Caceres M, Gomez-Skarmeta JL, Gut M, Bertranpetit J, Gut IG, Abello T, Eichler EE, Mingarro I, Lalueza-Fox C, Navarro A, Marques-Bonet T (2013)** The genome sequencing of an albino Western lowland gorilla reveals inbreeding in the wild BMC. *Genomics 14:363.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

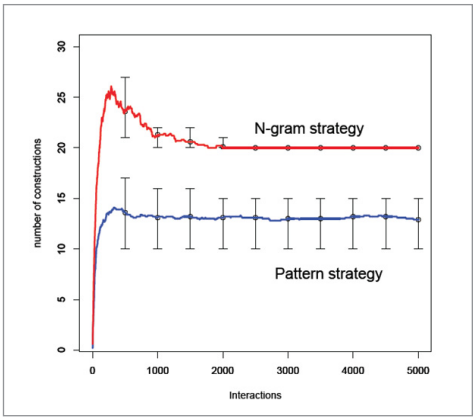
- **Marquès-Bonet T, Cáceres M, Bertranpetit J, Preuss TM, Thomas JW, Navarro A (2004)** Genomic distribution of gene expression divergence in humans and chimpanzees. *Trends Genet 20(11):524-9.*
- **Marques-Bonet T, Kidd JM, Ventura M, Graves TA, Cheng Z, Hillier LW, Jiang Z, Baker C, Malfavon-Borja R, Fulton LA, Alkan C, Aksay G, Girirajan S, Siswara P, Chen L, Cardone MF, Navarro A, Mardis ER, Wilson RK, Eichler EE (2009)** A Burst of Segmental Duplications in the African Great Ape Genome Ancestor. *Nature 457(7231):877-81.*
- **Neandertal Consortium (2010)** A draft sequence of the Neandertal genome. *Science 328(5979):710-22.*
- **Reich D, Green RE, Kircher M, Krause J, Patterson N, Durand EY, Viola B, Briggs AW, Stenzel U, Johnson PL, Maricic T, Good JM, Marques-Bonet T, Alkan C, Fu Q, Mallick S, Li H, Meyer M, Eichler EE, Stoneking M, Richards M, Talamo S, Shunkov MV, Derevianko AP, Hublin JJ, Kelso J, Slatkin M, Pääbo S (2010)** A Draft Genome Sequence and Dental Morphology of an Archaic Hominin group from Denisova in Siberia. *Nature 468(7327):1053-60.*
- **Orangutan Genome Consortium (2011)** Comparative and demographic analysis of orang-utan genomes. *Nature (Cover) 469(7331):529-33.*

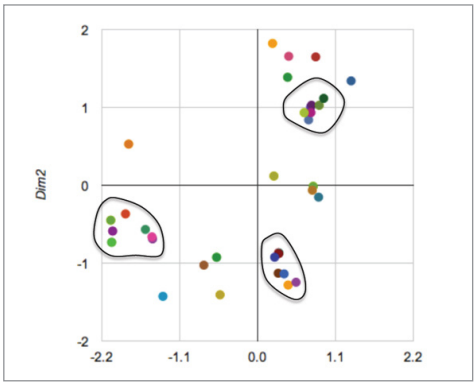
Luc Steels

Language Evolution

http://biologiaevolutiva.org/lsteels

PhD students: *Emília García Casademont and Miquel Cornudella Gaya.*





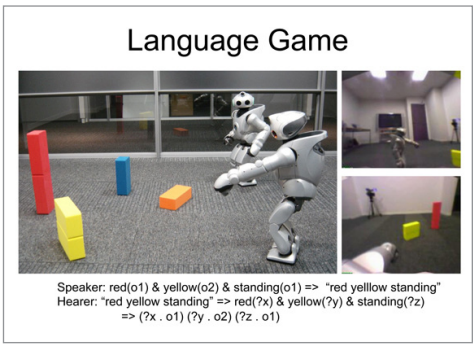


Figure 2: A two-dimentional MDS plot of the different categories of the agents. Clusters emerge, showing that agents have developed similar lexical categories

Figure 3: Luc Steels. A self-organizing spatial vocabulary. Artificial Life Journal, 2(3): 319-332, 1995.
Steels, L. (2005) The Emergence and Evolution of Linguistic Structure: From Lexical to Grammatical Communication Systems. Connection Science. 17(3).

Research Outline

The goal of our research is to develop a theory for the origins and evolution of language. Such a theory necessarily involves three aspects: social, cultural, and biological. The social aspect should give us answers to the question 'Why did humans start to talk?'. The cultural aspect should answer how new language forms arise in language and keep on changing over time. The biological aspect addresses how the biological foundations for language may have arisen. We focus mostly on the cultural aspect, developing and testing agent-based models explaining how features of language, such as agreement systems, arise and culturally evolve.

Current Projects/Research Lines

1. **Origins and evolution of grammatical structures.**

   Although there is a lot of data about the historical change in language, there is virtually no theory of the fundamental processes underlying this kind of evolution. We try to understand the cognitive mechanisms, interaction patterns, and collective dynamics that could explain how grammatical structures arise in human language by building agent-based models and using the hypothesis that self-organization and (linguistic) selection are the primary driving forces. We analyze the behavior of our models using the tools of complex systems science, and compare the results with phenomena observed in human languages. At this point we focus in particular on the origins of agreement systems and of grammatical patterns (such as noun phrases).

2. **Fluid Construction Grammar (FCG).**

   In order to conduct agent-based experiments in language evolution it is necessary to have a computational formalism that is capable to handle variation, flexibility, and change. We are therefore working in collaboration with other research centers on the development of such formalism. The formalism takes a construction grammar viewpoint which is more appropriate for modeling language evolution. It consists of data structures for representing linguistic knowledge and mechanisms for parsing, production, and language learning. FCG has been released in open source and is being used by a growing community (http://www.fcg-net.org/).

3. **Neural implementations of Fluid Construction Grammar .**

   To bridge the gap between computational models and neurobiology, we are investigating how a replicator dynamics model of the brain could potentially be used to implement the highly complex operations that Fluid Construction Grammar demands.

SELECTED PUBLICATIONS 2012 - 2013

- **Steels L (2012)** Interactions between cultural, social and biological explanations for language evolution. *Phys Life Rev 9(1):5-8.*
- **Van Trijp R, Steels L (2012)** Multilevel alignment maintains language systematicity. *Adv Complex Syst 15:3-4.*
- **Beuls K, Steels L (2013)** Agent-based models of strategies for the emergence and evolution of grammatical agreement. *PLoS ONE: 8(3).*
- **Steels, L. (2013)** How language emerges in situated embodied interactions. In: Lefebvre C, Comrie B. *New Perspectives on the Origins of Language. Cambridge University Press, Cambridge.*
- **Steels, L. (2013) Breaking down barriers. In: Dor D, Knight C, Lewis J (2013)** The Social Origins of Language: Early Society, Communication and Polymodality. Oxford *University Press, Oxford.*

Ricard Solé
Complex Systems Lab

http://complex.upf.edu/publications

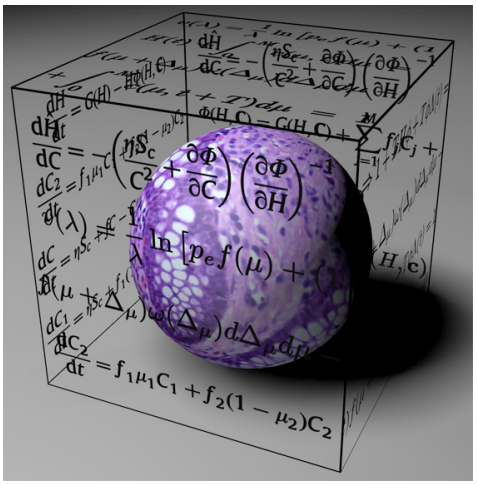
Senior Researchers: *Javier Macía, Carlos rodríguez-Caso and Sergi Valverde.*

Postdocs: *Dani Rodríguez-Amor and Raul Montañez.*

PhD students: *Adriano Bonforti, Max Carbonell, Núria Conde, Salvador Durán, Luis Seoane and Ben Shirt-Ediss.*

Technicians: *Eva García Ramallo.*

Project Manager: *Jesus Gonzalez.*



Research Outline

The Complex Systems Lab is an interdisciplinary research team exploring the evolution of complex systems, both natural and artificial, searching for their common laws of organization. We closely work in collaboration with the Santa Fe Institute (USA) and the European Centre of Living Technology (IT). Our research spans a broad range of systems, with special attention to biological computation, protocell biology, synthetic systems and network biology.

Current Projects/Research Lines

1. **Evolutionary innovations.**

   We explore theoretical approaches to the origins of evolutionary innovations and major transitions in biological, artificial and technological systems. Using methods from statistical physics we explore potential scenarios for the development of innovations and the potential patterns of universality common to all these disparate classes of systems. Simulated artificial ecosystems, information technology systems, language networks and other case studies are considered.

2. **Multicellularity: origins, maintenance and decay.**

   We want to develop a general theoretical framework for the origins and development of complex multicellular systems, including early emergence through evolution (evo-devo), the elegiac of tissue organization and the role played by evolution in cancer development. We also have a theoretical/experimental research approach based on synthetic multicellularity, involving the development of synthetic, engineered cell-cell communication in order to force cells to behave as multicellular entities.

3. **Emergence of complex behavior.**

   We explore the emergence of communication, collective intelligence and language in natural and artificial systems. The main goal here is to understand the nature of the major transitions associated to the shift from single individuals to cooperative systems, as well as the emergence of a complex language as a result of interactions among words. Here we also use synthetic biology to study the potential collective behaviors arising from manipulated, single-cell bacterial communities.

4. **Biological computation.**

   We study the nature, origins and evolution of living computational systems, both natural and synthetic. Using a number of methods from complex systems theory, we want to make a map of the landscape of computational processes that can occur in nature and figure out how we can move beyond that landscape.

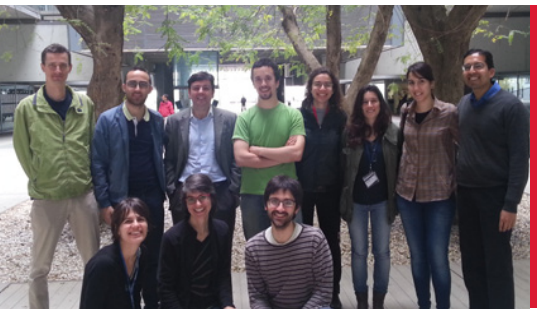
This work has several branches, both theoretical and applied to biomedical research.

SELECTED PUBLICATIONS 2012 - 2013

- **Macía J, Posas F, Solé R (2012)** Distributed computation: the new wave of synthetic biology devices. *Trends Biotechnol 30:342-49.*
- **Macía J, Solé R, Elena S (2012)** The causes of epistasis in genetic networks. *Evolution 66:586-96.*
- **Widder S, Solé R, Macía J (2012)** Evolvability of feed-forward loop architecture biases its abundance in transcription networks. *BMC Syst Biol 6 (1):7.*
- **Solé R, Valverde S, Rosas Casals M, Kauffman S, Farmer D, Eldredge N (2013)** The evolutionary ecology of technological innovations. *Complexity 18:15-27.*
- **Corominas-Murtra B, Goñi J, Solé R, Rodriguez-Caso C (2013)** On the origins of hierarchy in complex networks. *Proc Natl Acad Sci USA 110:13316-21.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Ferrer R, Solé R (2003)** Least effort and the origins of scaling in human language. *PNAS 100:788-91.*
- **Solé R, Bascompte J (2006)** Self-organization in complex ecosystems. *Monographs in Population Biology, Princeton University Press.*
- **Montoya JM, Pimm S, Solé R (2006)** Ecological networks and their fragility. *Nature 442:259-64.*
- **Regot S, Macía J, Conde N, Furukawa K, Kjellen J, Peeters T, Hohmann S, de Nadal E, Posas F, Solé R (2011)** Distributed Biological Computation with Multicellular Engineered Networks. *Nature 469:207-11.*
- **Solé R (2011)** Phase transitions. *Princeton University Press, New York.*



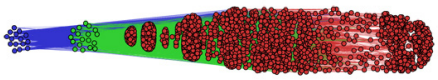
Jordi Garcia Ojalvo

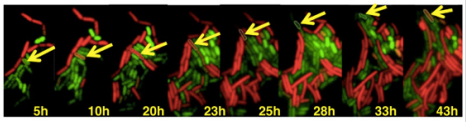
Dynamical Systems Biology

http://dsb.upf.edu

Postdocs: *Elena Abad and Nara Guisoni.*

PhD students: *Alessandro Barardi, Marta Dies, Marçal Gabaldà, Maciej Jedynak, Pau Rué and Belén Sancristóbal.*





Research Outline

Our lab is interested in the dynamics of living systems, from unicellular organisms to human beings. We use dynamical phenomena to identify the molecular mechanisms of cellular processes, such as decision making in bacteria, signaling in the immune system, and pluripotency and tissue homeostasis in stem cells. Using a combination of theoretical modeling and experimental tools such as time-lapse fluorescence microscopy and microfluidics, we investigate dynamical phenomena like biochemical pulses and oscillations, and study how these processes coexist inside the cell in a coordinated way. We also study the emergence of collective rhythms in cortical and brain networks.

Current Projects/Research Lines

- **Dynamics of gene regulation in bacteria.**
  In spite of their seeming simplicity, bacteria are able to exhibit nontrivial dynamical behavior. We monitor this behavior by time-lapse microscopy using fluorescence proteins as gene-expression reporters, which in combination with theoretical modeling allows us to unravel the molecular mechanisms of diverse cellular functions at the single-cell level.
- **Dynamics of pluripotency in embryonic stem cells**
  Pluripotency in embryonic stem cells is characterized by strong dynamical signatures, according to which certain key pluripotency factors exhibit large fluctuations in their activity. We aim to understand the interaction between dynamics and signaling in these cells.
- **Dynamics of cell signaling in the immune response**
  We study how immune system cells respond to external signals. We are studying the oscillatory response of these cells to cytokine stimulation, with the goal of determining its molecular mechanism, and understanding the response to therapy in autoimmune diseases such as multiple sclerosis.
- **Mesoscopic description of brain dynamics**
  Brain activity is naturally dynamical. We aim to relate the functional measures of brain activity, as measured by fMRI and EEG, with the underlying connectivity structure of the brain. Our models allow us to search for dynamical correlates of neurodegenerative diseases such as Alzheimer's disease, and to study the neurological consequences of multiple sclerosis.
- **Collective oscillations in neuronal populations**
  We are investigating how the dynamical properties of individual neurons impact the nature of cortical oscillations, how these oscillations are affected by noise, and are used to communicate information in an effective manner across distant brain areas.

SELECTED PUBLICATIONS 2012 - 2013

- **Asally M, Kittisopikul M, Rue P, Du Y, Hu Z, Cagatay T, Robinson A, Lu H, Garcia-Ojalvo J, Süel GM (2012)** Localized cell death focuses mechanical forces during 3D patterning in a biofilm. *Proc Natl Acad Sci USA 109:18891.*
- **Garcia-Ojalvo J, Martinez Arias A (2012)** Towards a statistical mechanics of cell fate decisions. *Curr Opin Genet Dev 22:619–626.*
- **Rue P, Garcia-Ojalvo J (2013)** Modeling gene expression in time and space. *Annual Review of Biophysics 43:605–627.*
- **Espinar L, Dies M, Cagatay T, Süel GM, Garcia-Ojalvo J (2013)** Circuit-level input integration in bacterial gene regulation. *Proc Natl Acad Sci USA 110:7091–7096.*
- **Sancristóbal B, Vicente R, Sancho JM, Garcia-Ojalvo J (2013)** Emergent bimodal firing patterns implement different encoding strategies during gamma-band oscillations. *Front Comput Neurosci 7:18.*

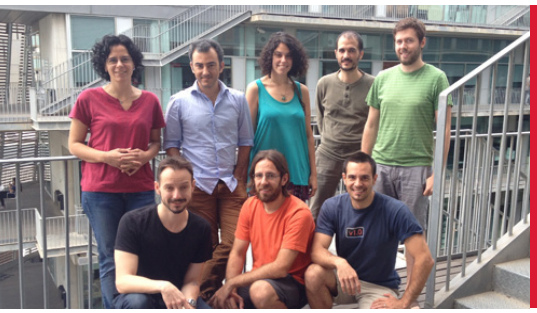
OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Garcia-Ojalvo J, Elowitz MB, Strogatz SH (2004)** Modeling a synthetic multicellular clock: repressilators coupled by quorum sensing. *Proc Natl Acad Sci USA 101:10955-10960*
- **Süel GM, Garcia-Ojalvo J, Liberman LM, Elowitz MB (2006)** An excitable gene regulatory circuit induces transient cellular differentiation. *Nature 440:545-550.*
- **Süel GM, Kulkarni RP, Dworkin J, Garcia-Ojalvo J, Elowitz MB (2007)** Tunability and noise-dependence in differentiation dynamics. *Science 315:1716-1719.*
- **Kalmar T, Lim C, Hayward P, Muñoz-Descalzo S, Nichols J, Garcia-Ojalvo J, Martinez-Arias A (2009)** Regulated fluctuations in Nanog expression mediate cell fate decisions in embryonic stem cells. *PLoS Biology 7:e1000149.*
- **Cagatay T, Turcotte M, Elowitz MB, Garcia-Ojalvo J, Suel GM (2009)** Architecture-dependent noise discriminates functionally analogous differentiation circuits. *Cell 139:512-522.*

Biomedical Informatics Programme (GRIB)

Coordinator: Ferran Sanz

The GRIB (from the Catalan Grup de Recerca en Informàtica Biomèdica) is a joint research programme of IMIM-Hospital del Mar Medical Research Institute and Universitat Pompeu Fabra (UPF), organized in seven research groups which are: Biomedical Genomics, Computational Biophysics, Computational Genomics, Functional Genomic, Integrative Biomedical Informatics, PharmacoInformatics and Structural Bioinformatics. Ferran Sanz, head of the IBI group is also the coordinator of GRIB. The GRIB mission is to develop and apply computational methods and information technologies for a better understanding and prediction of biological phenomena, giving especial emphasis to those related to the human diseases, their prevention, diagnosis and pharmacological treatment. GRIB faculty members have wide experience in the participation and coordination of research projects funded by the European Commission and other international agencies. Some of the on-going EC projects are: eTOX, for the in-silico prediction of drug toxicities; OpenPhacts, about computational extraction, integration and exploitation of open source knowledge to support drug discovery: INBIOMEDvision, to monitor the evolution of the BMI field and to address its scientific challenges; and EMIF to develop a common information framework of patient-level data.



Núria López-Bigas

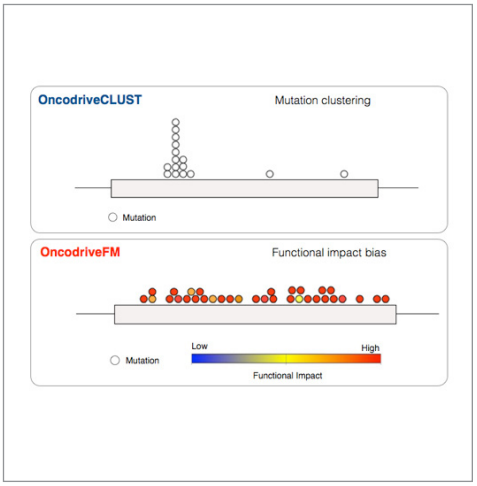
Biomedical Genomics Group

http://bg.upf.edu

Postdocs: *Abel González-Pérez, David Tamborero and Loris Mularoni.*

PhD students: *Christian Pérez Llamas, Carlota Rubio and Michael Schroeder.*

Technicians: *Jordi Deu-Pons.*



Research Outline

Our group is focused on the study of cancer from a genomics perspective. Specifically, our group is interested in the development of computational approaches to analyse cancer genomes to identify mutations, genes and pathways driving tumorigenesis. We are also interested in the study of the involvement of specific pathways in cancer, in particular pRB/JARID1 pathway, Hippo and E2F pathways.

Current Projects/Research Lines

1. Development of methods to identify cancer drivers. We are interested in identifying cancer driver mutations and driver genes. With that purpose we have developed various complementary methods: OncodriveFM and oncodriveCLUST identify signals of positive selection in the mutational pattern of genes in a cohort of tumors, pointing to candidate driver genes. OncodriveCIS identifies genes that accumulate copy number alterations in tumors with a high effect on its expression. TransFIC predicts the functional impact of non-synonymous variants for cancer cells.
2. Systematic identification of cancer driver genes (IntOGen-mutations). A large number of tumor genomes are being sequenced and this is expected to continue due to the reduced costs of sequencing and the large value of this data. This opens the possibility for the first time to have a comprehensive view of mutations, genes and pathways involved in cancer development in diferent tumor types. With this objective in mind we have developed IntOGen-mutations, a platform that implements methods developed in our lab to identify cancer driver mutations, genes and pathways. We have analyzed over 7000 tumors across various cancer types using this platform and the results are provided at http://www.intogen.org/mutations. We have also focused on the analysis of chromatin regulatory factors acting as drivers across tumors.
3. Cancer genomics data visualization. One important challenge in cancer genomics is how to explore and visualize the large amount a complex data being generated to extract meaningful knowledge. We have developed Gitools and jHeatmap, which use interactive heatmaps to visualize multidimensional cancer genomics data, and we have recently written a review on this topic.

SELECTED PUBLICATIONS 2012 - 2013

- **Gonzalez-Perez A, Lopez-Bigas N (2012)** Functional Impact Bias Reveals Cancer drivers. *Nucleic Acids Research:1-10. 10.1093/nar/gks743.*
- **Gonzalez-Perez A, Perez-Llamas C, Deu-Pons J, Tamborero D, Schroeder MP, Jene-Sanz A, Santos A & Lopez-Bigas N (2013)** IntOGen-mutations identifies cancer drivers across tumor types. *Nat Methods (11):1081-2.*
- **The Cancer Genome Atlas Research Network (including David Tamborero, Abel Gonzalez-Perez and Nuria Lopez-Bigas) (2013)** The Cancer Genome Atlas Pan-Cancer analysis project. *Nat Genet 45:1113–20.*
- **Gonzalez-Perez A, Jene-Sanz A, Lopez-Bigas N (2013)** The mutational landscape of chromatin regulatory factors across 4623 tumor samples. *Genome Biol 14(9):r106.*
- **Gonzalez-Perez A, Mustonen V, Reva B, Ritchie GR, Creixell P, Karchin R, Vazquez M, Fink JL, Kassahn KS, Pearson JV, Bader GD, Boutros PC, Muthuswamy L, Ouellette BF, Reimand J, Linding R, Shibata T, Valencia A, Butler A, Dronov S, Flicek P, Shannon NB, Carter H, Ding L, Sander C, Stuart JM, Stein LD, Lopez-Bigas N; International Cancer Genome Consortium Mutation Pathways and Consequences Subgroup of the Bioinformatics Analyses Working Group (2013)** Computational approaches to identify functional genetic variants in cancer genomes. *Nat Methods 10:723–72.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Lopez-Bigas N, Kisiel TA, DeWaal D, Holmes KB, Volkert TL, Gupta S, Love J, Murray HL, Young RA, Benevolenskaya EV (2008)** Genome-wide Analysis of the H3K4 Histone Demethylase RBP2 Reveals a Transcriptional Programme Controlling Differentiation. *Mol Cell, 31(0):520-530.*
- **Gundem G, Perez-Llamas C, Jene-Sanz A, Kedzierska A, Islam A, Deu-Pons J, Furney S and Lopez-Bigas N (2010)** IntOGen: Integration and data-mining of multidimensional oncogenomic data. *Nat Methods 7:92-93.*
- **Gonzalez-Perez A, Lopez-Bigas N (2011)** Improving the assessment of the outcome of non-synonymous SNVs with a Consensus deleteriousness score (Condel). *Am J Hum Genet 88(4):440-9.*
- **Tamborero, D., Gonzalez-Perez, A., Perez-Llamas, C., Deu-Pons, J., Kandoth, C., Reimand, J., Lawrence, M.S., Getz, G., Bader, G.D., Ding, L., et al. (2013a)** Comprehensive identification of mutational cancer driver genes across 12 tumor types. *Sci. Rep. 3, 2650.*
- **Perez-Llamas C, Lopez-Bigas N (2011)** Gitools: analysis and visualization of genomic data using interactive heat-maps. *PLoS One 6(5):e19541.*

Gianni de Fabritiis
Computational Biophysics Group

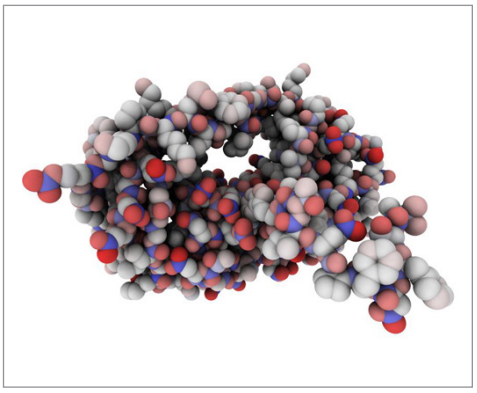
www.multiscalelab.org

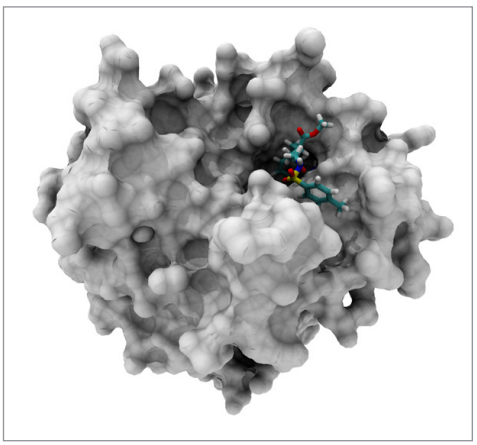
Postdocs: *Toni Giorgino, Kashif Sadiq and David Soriano.*

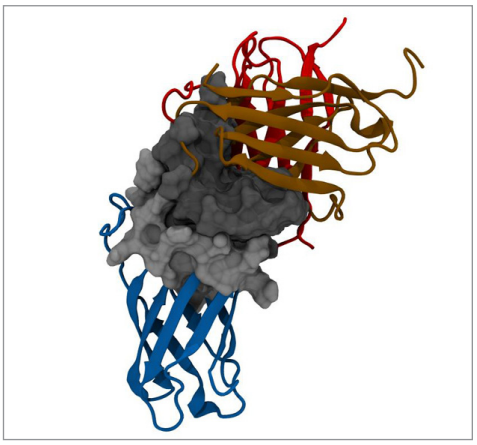
PhD students: *Stefan Doerr, Noelia Ferruz, Nathaniel Stanley and Gerard Martinez.*

Visiting students: *Paola Bisignano and Gianluigi Lauro.*

Visiting postdocs: *Ludovico Sutto and Santiago Esteban.*







Research Outline

Our group shares interests in the range of physical phenomena produced by the interplay of different scales, for instance between single and collections of molecules (mesoscale). We study protein dynamics, kinetics and energetics using mainly molecular dynamics simulations (ACEMD) on graphics processing units (GPUs) and GPUGRID.net (http://www.gpugrid.net). In our research, we attempt to solve new scientific problems by developing new methodologies, software and ideas for bridging between the atomistic scale (femtoseconds, nanometers) and the biological molecular scale (micro- to milli-seconds and hundreds of nanometers).

Current Projects/Research Lines

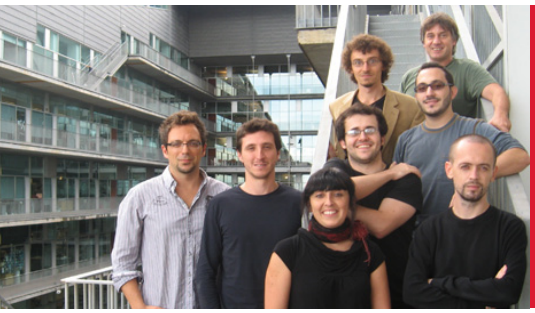
- In-silico protein-ligand binding, kinetics and thermodynamics
- In-silico fragment based drug design
- Intrinsically disordered proteins, multistate proteins, folding
- Ligand binding to GCPRs
- Accelerated and distributed computing
- Markov state model analysis and machine learning for molecular simulations

SELECTED PUBLICATIONS 2012 - 2013

- **Giorgino T, Buch I, De Fabritiis G (2012)** Visualizing the Induced Binding of SH2-Phosphopeptide. *J Chem Theory Comput 8(4): 1171-1175.*
- **Wright DW, Sadiq SK, De Fabritiis G, Coveney PV (2012)** Thumbs down for HIV: Domain level rearrangements do occur in the NNRTI bound HIV-1 Reverse Transcriptase. *J Am Chem Soc 134(31):12885-8.*
- **Harvey MJ, De Fabritiis G (2012)** High-throughput molecular dynamics: The powerful new tool for drug discovery. *Drug Discov Today 17(19-20):1059-62.*
- **Sadiq SK, Noé F, De Fabritiis G (2012)** Kinetic characterization of the critical step in HIV-1 protease maturation. *Proc Natl Acad Sci USA 109(50):20449-54.*
- **Perez-Hernandez G, Paul F, Giorgino T, De Fabritiis G, Noe F (2013)** Identification of slow molecular order parameters for Markov model construction. *J Chem Phys 139(1):015102.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **De Fabritiis G, Delgado-Buscalioni R, Coveney PV (2006)** Modelling the mesoscale with molecular specificity. *Phys Rev Lett 97:134501.*
- **Harvey M, Giupponi G, De Fabritiis G (2009)** ACEMD: Accelerating bio-molecular dynamics in the microsecond time-scale. *J Chem Theory Comput 5, 1632.*
- **Harvey M, de Fabritiis G (2009)** An Implementation of the Smooth Particle Mesh Ewald Method on GPU Hardware. *J Chem Theory Comput 5(9):2371-2377.*
- **Buch I, Harvey MJ, Giorgino T, Anderson DP, De Fabritiis G (2010)** High-Throughput All-Atom Molecular Dynamics Simulations Using Distributed Computing. *J Chem Inf Model 50(3):397-403.*
- **Buch I, Giorgino T, De Fabritiis G (2011)** Complete reconstruction of an enzyme-inhibitor binding process by molecular dynamics simulations. *PNAS 108 (25):10184-9.*



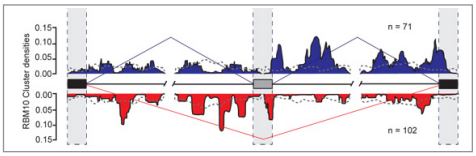
Eduardo Eyras

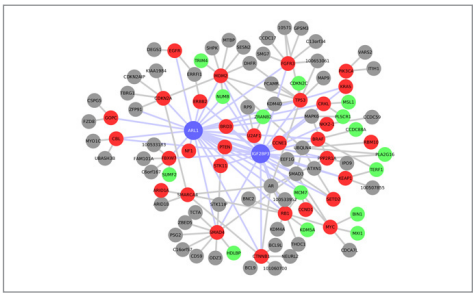
Computational Genomics Group

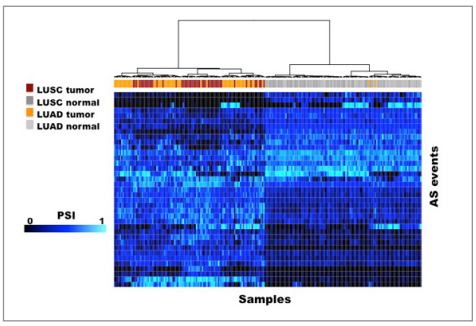
http://regulatorygenomics.upf.edu

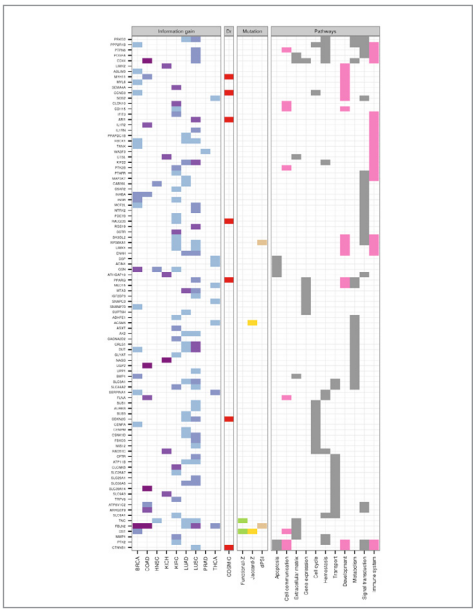
Postdocs: *Endre Sebestyen and Nicolás Bellora.*

PhD students: *Eneritz Agirre, Juan González-Vallinas, Amadís Pagés, Isaac Kremsky and Babita Singh.*









Research Outline

Our group focuses on the development of computational predictive models for the study of RNA biology, in particular, to investigate the role of chromatin and non-coding RNAs in the regulation of splicing, and the relevance of these mechanisms in cancer.

Current Projects/Research Lines

- We study the alterations in alternative splicing in different breast cancer types and evaluate how these alterations impact the network of protein-protein interactions, with the aim to uncover novel mechanisms of tumorigenesis specific of each cancer type.
- We apply Machine Learning methods to RNA sequencing data to find novel splicing signatures that characterize different cancers, with the aim to find novel prognostic markers and therapeutic targets.
- We investigate the mechanisms of post-transcriptional regulation of RNA in cancer. In particular we study RNA binding proteins that regulate the processing of RNA and how these mechanisms are altered in tumours.
- We investigate the interplay between the chromatin and RNA processing. In particular, we study how SR proteins, which are regulators of splicing, may interact with the transcriptional regulatory machinery.
- We study the role of epigenetic modifications in breast cancer and how these modifications affect splicing.

SELECTED PUBLICATIONS 2012 - 2013

- **Althammer S, Pagès A, Eyras E (2012)** Predictive models of gene regulation from high-throughput epigenomics data. *Comp Funct Genomics:284786.*
- **Macias S, Plass M, Stajuda A, Michlewski G, Eyras E, Cáceres JF (2012)** DGCR8 HITS-CLIP reveals novel functions for the Microprocessor. *Nat Struct Mol Biol 19(8):760-6.*
- **Plass M, Codony-Servat C, Ferreira PG, Vilardell J, Eyras E (2012)** RNA secondary structure mediates alternative 3'ss selection in Saccharomyces cerevisiae. *RNA 18(6):1103-15.*
- **Zhang Z, Falaleeva A, Agranat-Tamir L, Pages A, Eyras E, Sperling J, Sperling R, Stamm A (2013)** The 5' untranslated region of the serotonin receptor 2C pre-mRNA generates miRNAs and is expressed in non-neuronal cells. *Exp Brain Res 230(4):387-94.*
- **Ballaré C, Castellano G, Gaveglia L, Althammer S, González-Vallinas J, Eyras E, Le Dily F, Zaurin R, Soronellas D, Vicent GP, Beato M (2013)** Nucleosome-driven transcription factor binding and gene regulation. *Molecular Cell 49(1):67-79.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

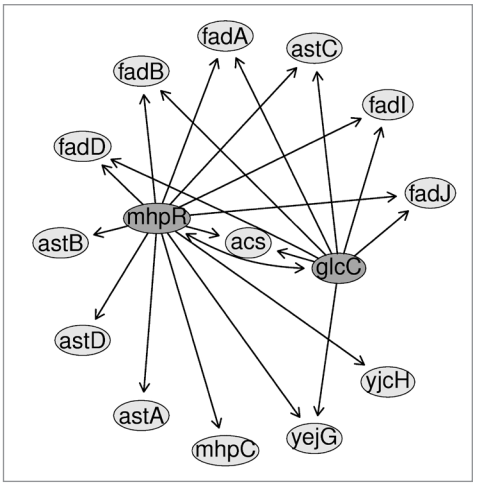
- **Plass M, Agirre E, Reyes D, Camara F, Eyras E (2008)** Co-evolution of the branch site and SR proteins in eukaryotes. *Trends Genet 24(12):590-4.*
- **Corvelo A, Eyras E (2008)** Exon creation and establishment in human genes. *Genome Biol 9(9):R141.*
- **Gal-Mark N, Schwartz S, Ram O, Eyras E, Ast G (2009)** The pivotal roles of TIA proteins in 5' splice-site selection of alu exons and across evolution. *PLoS Genet. 2009 5(11):e1000717.*
- **Corvelo A, Hallegger M, Smith CW, Eyras E (2010)** Genome-wide association between branch point properties and alternative splicing. *PLoS Comput Biol 6(11):e1001016.*
- **Althammer S, González-Vallinas J, Ballaré C, Beato M, Eyras E (2011)** Pyicos: a versatile toolkit for the analysis of high-throughput sequencing data. *Bioinformatics 27(24):3333-40.*

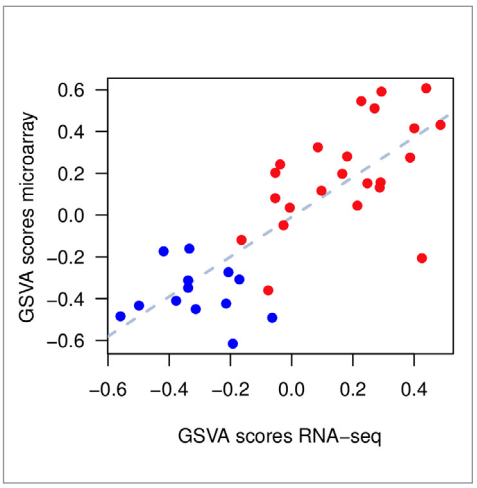
Robert Castelo

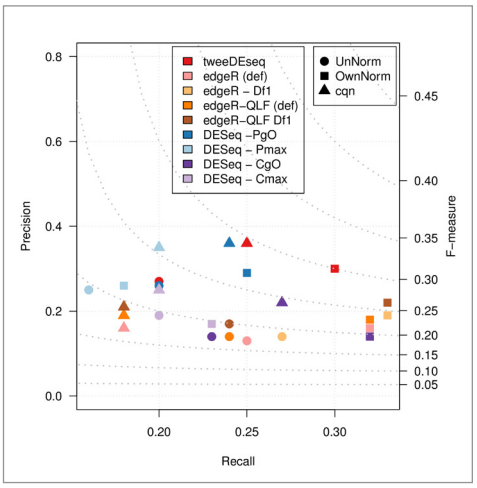
Functional Genomics Group

http://functionalgenomics.upf.edu

PhD students: *Sonja Hänzelmann and Inma Tur.*







Research Outline

We aim at contributing to narrow the gap between sequence and function by developing computational tools to build network models of molecular regulatory mechanisms from high-throughput genetics and genomics data.

Current Projects/Research Lines

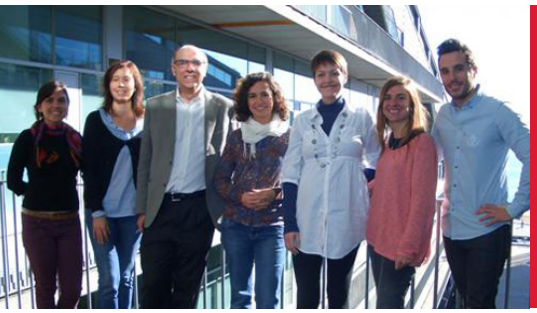
- **Reverse engineering the genotype-phenotype map.**
  Genes and molecules are activated in a coordinated manner under finely tuned regulatory programmes. High-throughput genetics and genomics data offer a unique opportunity to witness this phenomenon by monitoring the simultaneous action of thousands of genes and millions of genotypes. We try to embrace this complexity by developing computational tools that enable estimating multivariate statistical models from these data, which have the potential to disentangle direct from indirect or spurious effects.

SELECTED PUBLICATIONS 2012 - 2013

- **Mahdi T, Hänzelmann S, Salehi A, Muhammed SJ, Reinbothe TM, Tang Y, Axelsson AS, Zhou Y, Jing X, Almgren P, Krus U, Taneera J, Blom AM, Lyssenko V, Esguerra JL, Hansson O, Eliasson L, Derry J, Zhang E, Wollheim CB, Groop L, Renström E, Rosengren AH (2012)** Secreted frizzled-related protein 4 reduces insulin secretion and is overexpressed in type 2 diabetes. *Cell Metabolism, 16(5):625-633.*
- **Roverato A, Castelo R (2012)** Learning undirected graphical models from multiple datasets with the generalized non-rejection rate. *International Journal of Approximate Reasoning, 53(9):1326-1335.*
- **Castelo R, Roverato A (2012)** Inference of regulatory networks from microarray data with R and the Bioconductor package qpgraph. *In Next Generation Microarray Bioinformatics, J. Wang, A.C. Tan and T. Tian, Eds., pp. 215-233, Methods in Molecular Biology Series, Humana Press, USA, ISBN 978-1-61779-399-8.*
- **Esnaola M, Puig P, Gonzalez D, Castelo R, Gonzalez JR (2013)** A flexible count data model to fit the wide diversity of expression profiles arising from extensively replicated RNA-seq experiments. *BMC Bioinformatics 14:254.*
- **Hänzelmann S, Castelo R, Guinney J (2013)** GSVA: gene set variation analysis for microarray and RNA-Seq data. *BMC Bioinformatics 14:7.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Castelo R, Guigó R (2004)** Splice Site Identification by idlBNs. *Bioinformatics, 20(1):i69-i76.*
- **Castelo R, Roverato A (2006)** A robust procedure for Gaussian graphical model search from microarray data with p larger than n. *Journal of Machine Learning Research, 7(Dec):2621-2650.*
- **The ENCODE Project Consortium (including R. Castelo) (2007)** Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature, 447:799-816.*
- **Castelo R, Roverato A (2009)** Reverse engineering molecular regulatory networks from microarray data with qp-graphs. *Journal of Computational Biology, 16(2):213-227.*
- **Hartmann B, Castelo R, Miñana B, Peden E, Blanchette M, Rio DC, Singh R, Valcarcel J (2011)** Distinct regulatory programmes establish widespread sex-specific alternative splicing in Drosophila melanogaster. *RNA, 17:453-468.*



Ferran Sanz

Integrative Biomedical Informatics Group

http://ibi.imim.es

Senior Researcher: *Laura I. Furlong.*

Postdocs: *Montse Cases, Miguel Angel Mayer, Nuria Queralt and Solene Grosdidier.*

PhD students: *Alex Bravo, Janet Piñero and Alba Gutierrez .*

Project Manager: *Maria Saarela.*

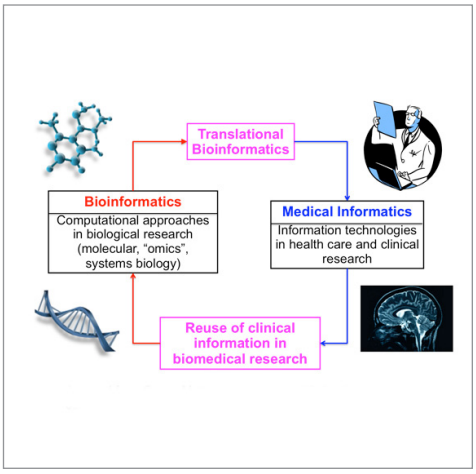


Figure: *Adapted from Cases M et al. J Intern Med. 2013;274:321-8*

Research Outline

Our group promotes and tackles synergistic and integrative strategies for affording biomedical problems, making use of approaches developed within the IBI group but also fostering the collaboration between research groups of the GRIB. Currently, an increasing wealth of information, particularly the one generated by biomedical research, is left unused. There is a great difficulty in both the identification and use of clinically actionable information. The goal of our group is to develop methods and tools to help to solve this problem, with a special focus in methods that promote an understanding of human health and disease.

Current Projects/Research Lines

The current research lines of the group are:

- Development of new strategies and tools for knowledge extraction and linkage from biomedical literature and other publicly available sources.
- Network biology for the study of human diseases and drug toxicity.
- Integrative knowledge management and exploitation in drug discovery and development, including multi-level and multi-scale modelling and simulation.

The group is currently coordinating two large scale scientific initiatives:

- The IMI project eTOX that integrates bioinformatics and chemoinformatics approaches for the development of expert systems allowing the in silico prediction of drug toxicity.
- The FP7 coordination and support action INBIOMEDvision that promotes biomedical informatics by means of the permanent monitoring of the scientific state-of-the-art and existing activities in the theme, prospective analysis of the emerging challenges and opportunities, and dissemination of the knowledge in the field.

The group participates in other EU-funded projects, like the ongoing IMI project Open PHACTS which aim is to develop an open access innovation platform, called Open Pharmacological Space (OPS), via a semantic web approach, and the IMI project EMIF, dealing with the creation and exploitation of a European Medical Information Framework.

SELECTED PUBLICATIONS 2012 - 2013

- **Briggs K, Cases M, Heard DJ, Pastor M, Pognan F, Sanz F, Schwab CH, Steger-Hartmann T, Sutter A, Watson DK, Wichard JD (2012)** Inroads to Predict in Vivo Toxicology—An Introduction to the eTOX Project. *Int J Mol Sci 13(3):3820-3846.*
- **Bauer-Mehren A, van Mulligen EM, Avillach P, Carrascosa MC, Garcia-Serna R, Piñero J, Singh B, Lopes P, Oliveira JL, Diallo G, Ahlberg Helgee E, Boyer S, Mestres J, Sanz F, Kors JA, Furlong LI (2012)** Automatic Filtering and Substantiation of Drug Safety Signals. *PLoS Comput Biol 8(4).*
- **Beck T, Gollapudi S, Brunak S, Graf N, Lemke HU, Dash D, Buchan I, Díaz C, Sanz F, Brookes AJ (2012)** Knowledge engineering for health: A new discipline required to bridge the "ICT gap" between research and healthcare. *Hum Mutat 33 (5):797-802.*
- **Furlong LI (2012) Human diseases through the lens of network biology.** *Trends Gen 29 (3):150-159.*
- **Cases M, Furlong LI, Albanell J, Altman RB, Bellazzi R, Boyer S, Brand A, Brookes AJ, Brunak S, Clark TW, Gea J, Ghazal P, Graf N, Guigo R, Klein TE, Lopez-Bigas N, Maojo V, Mons B, Musen M, Oliveira JL, Rowe A, Ruch P, Shabo A, Shortliffe EH, Valencia A, van der Lei J, Mayer MA, Sanz F (2013)** Improving data and knowledge management to better integrate health care and research. *J Intern Med 274 (4):321-8.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Fontaine F, Pastor M, Sanz F (2004)** Incorporating Molecular Shape into the Alignment-free GRid-INdependent Descriptors (GRIND). *J Med Chem 47:2805-15.*
- **Fontaine F, Pastor M, Zamora I, Sanz F (2005)** Anchor-GRIND: Filling the Gap between Standard 3D QSAR and the GRid-INdependent Descriptors. *J Med Chem 48:2687-94.*
- **Furlong LI, Dach H, Hofmann-Apitius M, Sanz F (2008)** OSIRISv1.2: a named entity recognition system for sequence variants of genes in biomedical literature. *BMC Bioinformatics 9:1-32.*
- **Bauer-Mehren A, Furlong LI, Sanz F (2009)** Pathway databases and tools for their exploitation: benefits, current limitations and challenges. *Mol Syst Biol 5:290.*
- **Bauer-Mehren A, Rautschka M, Sanz F, Furlong LI (2010)** DisGeNET: a Cytoscape plugin to visualize, integrate, search and analyze gene-disease networks. *Bioinformatics 26(22):2924-6.*

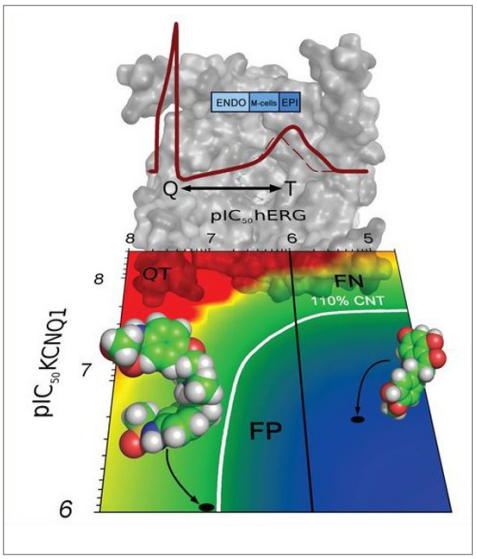
Manuel Pastor
PharmacoInformatics Group

http://phi.imim.es/phi/publications

Senior Researchers: *Núria B. Centeno, Jana Selent and Ismael Zamora.*

Postdocs: *Agnieszka Kaczor.*

PhD students: *Pau Carrió, Ramón Guixa, Oriol López, Ivan Rodriguez and Maria Martí.*



Research Outline

Our group is devoted to the development and application of computational methodologies in the area of drug design and development.
Nowadays, computational methodologies are widely applied in many steps of the drug discovery and development; from the structural modeling of a pharmacological target to the prediction of the ligand binding affinity. However, in the vast majority of cases the limitations of the current technology allow only to obtain approximate representations of the complex biological phenomena that are the subject of interests in the development of new drugs.
Our group aims to improve the current state-of-the-art with a pragmatic approach. We want to develop useful tools that increase the efficiency of the pharmaceutical R&D process. At the same time, the need of producing robust models led us to overcome reductionist approaches and to develop multi-scale methods, depicting richer and more realistic representations of the phenomena under study than those produced by classical computational methods.

Current Projects/Research Lines

1. **In silico methods for drug safety assessment**
   Drug safety assessment is one of the most important bottlenecks in today's drug development. Computational (in silico) methods offer a very interesting alternative to other experimental methods for ealy drug safety screening; they are faster, cheaper and require no amount of your valuable compound to obtain a prediction that sometimes has comparable quality with those obtained using high-throughput in vitro methods.
   In this area we are coordinating the project eTOX, a public-private partnership within the framework of the European Innovative Medicines Initiative Joint Undertaking (IMI-JU) aiming to produce in silico predictions of in vivo toxicity endpoints for novel drug candidates.

2. **Multi-scale models in drug discovery**
   Classical approaches for the discovery of new drugs based on the "one target, one drug" paradigm are exhausted and fail to deliver new candidates with the desirable efficiency. The same, simplistic approaches are limited in the evaluation of the drug safety and other areas. For these reasons, we aim to expand the scale of current computational models to allow a richer description of the physiological phenomena involved, crossing the scales that separate molecular from cellular level and tissue from organ level.
   Such methodological approach has been applied to different areas of drug development, like for example in studies involving the evaluation of drug cardiotoxicity or the prediction of the side effects of antipsychotic drugs.

SELECTED PUBLICATIONS 2012 - 2013

- **Bruno A, Costantino G, Fabritiis G, Pastor M, Selent M (2012)** Membrane-Sensitive Conformational States of Helix 8 in the Metabotropic Glu2 Receptor, a Class C GPCR. *PLoS ONE 7(8):e42023.*
- **Briggs K, Cases M, Heard DJ, Pastor M, Pognan F, Sanz F, Schwab CH, Steger-Hartmann T, Sutter A, Watson DK, Wichard JD (2012)** Inroads to Predict In Vivo Toxicology. An Introduction to the eTOX Project. *Int J Mol Sci 13(3):3820-46.*
- **Azzaoui K, Jacoby E, Senger S, Rodríguez EC, Loza M, Zdrazil B, Pinto M, Williams AJ, de la Torre V, Mestres J, Pastor M, Taboureau O, Rarey M, Chichester C, Petiffer S, Blomberg N, Harland L, Williams-Jones B, Ecker GF (2013)** Scientific competency questions as the basis for semantically enriched open pharmacological space development. *Drug Discov Today 18:843-852.*
- **Martí-Solano M, Guixà-González R, Sanz F, Pastor M, Selent J (2013)** Novel Insights into Biased Agonism at G Protein-Coupled Receptors and their Potential for Drug Design. *Curr Pharm Des 19 (28):5156-5166.*
- **Sadiq SK, Guixa-Gonzalez R, Dainese E, Pastor M, De Fabritiis G, Selent J (2013)** Molecular modeling and simulation of membrane lipid-mediated effects on GPCRs. *Curr Med Chem 20(1):22-38.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Obiol-Pardo C, Gomis-Tena J, Sanz F, Saiz J, Pastor M (2011)** A Multiscale Simulation System for the Prediction of Drug-Induced Cardiotoxicity. *J Chem Inf Model 51(2):483-92.*
- **Obiol-Pardo C. López L, Pastor M, and Selent J (2011)** Progress in the structural prediction of G protein-coupled receptors: D3 receptor in complex with eticlopride. *Proteins 79(6):1695-703.*
- **Selent J, Sanz F, Pastor M, Fabritiis G (2010)** Induced effects of sodium ions binding on dopaminergic G-protein coupled receptors. *PLOS Comput Biol 6(8) pii:e1000884.*
- **Selent J, Bauer-Mehren A, López L, Loza MI, Sanz F, Pastor M (2010)** A novel multilevel statistical method for the study of the relationships between multi-receptorial binding affinity profiles and in vivo endpoints. Mol Pharmacol 77(2):149-58
- **Novensa L, Selent J, Pastor M, Sandberg K, Heras M, Dantas AP (2010)** Equine estrogens impair nitric oxide production and endothelial nitric oxide synthase transcription in human endothelial cells compared with the natural 17beta-Estradiol. *Hypertension 56: 405-11.*

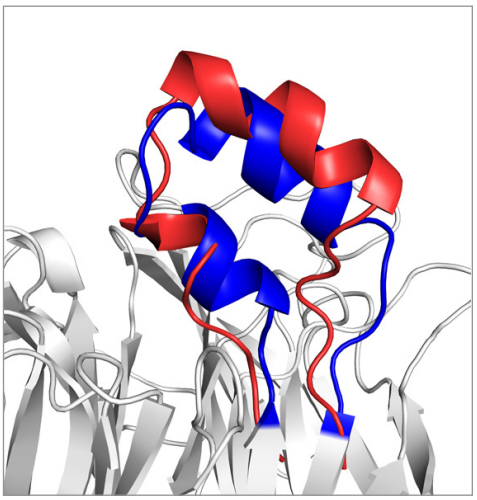
Baldo Oliva

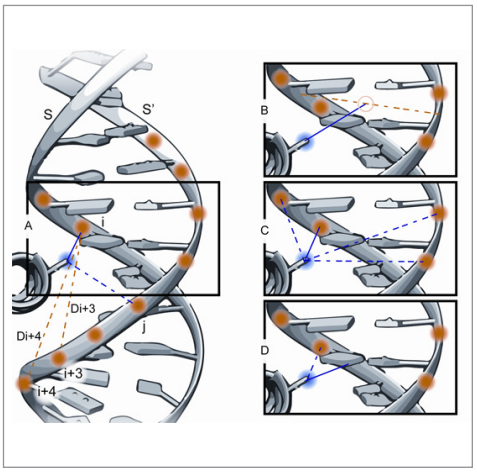
Structural Bioinformatics group

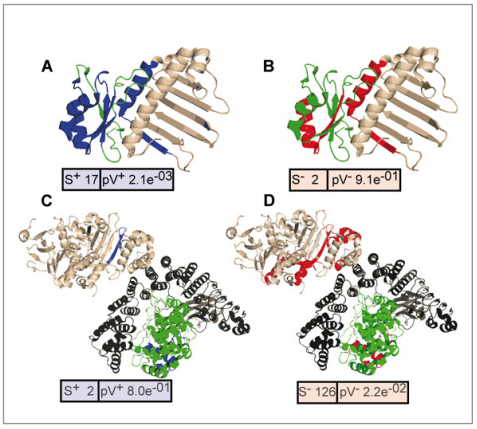
http://sbi.imim.es/web

Postdocs: *Daniel Aguilar and Joan Planas.*

PhD students: *Javier García-García, Jaume Bonet, Oriol Fornés, Manuel Alejandro Marín, Bernat Antón and Daniel Poglayen.*







Research Outline

Protein-protein interactions play a relevant role among the different functions of a cell. Identifying the protein-protein interaction network of a given organism (interactome) is useful to shed light on the key molecular mechanisms within a biological system. A paradox in protein-protein binding is to explain how the unbound proteins of a binary complex recognize each other among a large population within a cell and how they find their best docking interface in a short time-scale. We interrogate protein structure to unveil its function, generate the network of interactions and to relate genes/proteins with diseases by means of exploiting the topology of the network.

Current Projects/Research Lines

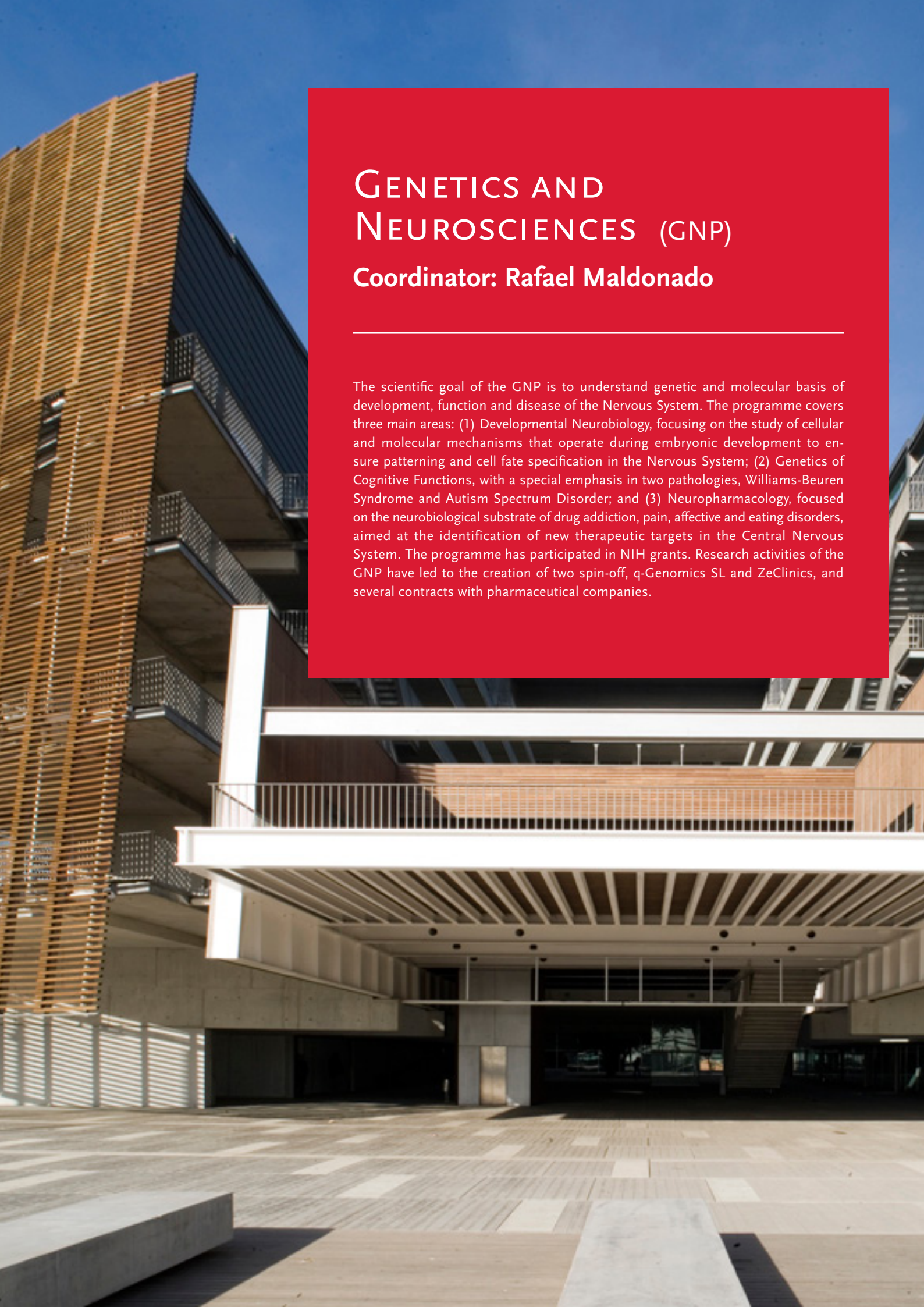
- Study of the relationship between sequence, structure and function of proteins. Characterization of the structural motifs involved in the function and interactions between proteins. Development of statistical potentials and analysis of physico-chemical potentials helping to describe the fold and function of proteins and its interactions with other macro-molecules.
- Prediction of protein-protein and protein-DNA interations. Structural analysis of docking aproaches and development of new techniques towards the prediction of binding sites and the mechanisms of interface selection of protein-protein and protein-DNA interactions.
- Analysis of protein interaction networks and its use on bio-medicine, helping to detect potential targets and prioritization of candidate disease-genes. Development of methods to study and integrate information for different types of networks and application on the study of metastasis. Prediction of signalling networks, such as the phosphorylation network and other post-transcriptional modifications, and integration with genomic data, such as microarrays.

SELECTED PUBLICATIONS 2012 - 2013

- **Wright RH, Castellano G, Bonet J, Le Dily F, Font-Mateu J, Ballaré C, Nacht AS, Soronellas D, Oliva B, Beato M (2012)** CDK2-dependent activation of PARP-1 is required for hormonal gene regulation in breast cancer cells. *Genes Dev 26(17):1972-83.*
- **Garcia-Garcia J, Schleker S, Klein-Seetharaman J, Oliva B (2012)** BIPS: BIANA Interolog Prediction Server. *A tool for protein-protein interaction inference Nucleic Acids Res 40 (W1):W147-W151.*
- **Guney E, Oliva B (2012)** Exploiting Protein-Protein Interaction Networks for Genome-Wide Disease-Gene Prioritization. *PLoS One 7 (9) e43557.*
- **Santana-Codina N, Carretero R, Sanz-Pamplona R, Cabrera T, Guney E, Oliva B, Clezardin P, Olarte OE, Loza-Alvarez P, Méndez-Lucas A, Perales JC, Sierra A (2013)** A transcriptome-proteome integrated network identifies ERp57 as a hub that mediates bone metastasis. *Mol Cell Proteomics 12(8): 2111-2125.*
- **Planas-Iglesias J, Bonet J, García-García J, Marín-López MA, Feliu E, Oliva B (2013)** Understanding protein-protein interactions using local structural features. *J Mol Biol 425 (7):1210-1224.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Espadaler J, Aragüés R, Narayanan E, Marti-Renom MA, Querol E, Avilés FX, Sali A, Oliva B (2005)** Detecting Remotely Related Proteins by Their Interactions and Sequence Similarity. *Proc Natl Acad Sci USA 17;102(20):7151-6.*
- **Espadaler J, Romero-Isarto O, Jackson RM, Oliva B (2005)** Prediction of protein-protein interactions using distant conservation of sequence patterns and structure relationships. *Bioinformatics. 21(16):3360-8.*
- **Aragüés R, Sali A, Bonet J, Marti-Renom MA, Oliva B (2007)** Characterization of Protein Hubs by Inferring Interacting Motifs from Protein Interactions. *PLOS Computational Biology 3(9):1761-1771.*
- **Gitter A, Siegfried Z, Klutstein M, Fornés O, Oliva B, Simon I, Bar-Joseph Z (2009)** Backup in gene regulatory networks explains differences between binding and knockout results. *Mol Syst Biol. 5:276.*
- **García-García J, Guney E, Aragüés R, Planas-Iglesias J, Oliva B (2010)** Biana: a software framework for compiling biological interactions and analyzing networks. *BMC Bioinformatics. 11(1):56.*



Genetics and Neurosciences (GNP)

Coordinator: Rafael Maldonado

The scientific goal of the GNP is to understand genetic and molecular basis of development, function and disease of the Nervous System. The programme covers three main areas: (1) Developmental Neurobiology, focusing on the study of cellular and molecular mechanisms that operate during embryonic development to ensure patterning and cell fate specification in the Nervous System; (2) Genetics of Cognitive Functions, with a special emphasis in two pathologies, Williams-Beuren Syndrome and Autism Spectrum Disorder; and (3) Neuropharmacology, focused on the neurobiological substrate of drug addiction, pain, affective and eating disorders, aimed at the identification of new therapeutic targets in the Central Nervous System. The programme has participated in NIH grants. Research activities of the GNP have led to the creation of two spin-off, q-Genomics SL and ZeClinics, and several contracts with pharmaceutical companies.

Rafael Maldonado López

Laboratory of Neuropharmacology-NeuroPhar

www.upf.edu/neurophar

Other PIs: *Fernando Berrendero Díaz and Andrés Ozaita Mintegui.*

Postdocs: *Blanca Rubí Galobart, José Manuel Trigo Díaz, Xavier Nadal Roura, Elena Martín García, Javier Gutiérrez Cuesta, Simona Adreea Bura, Lola Galeote González, Antonio Ortega Álvaro, Emma Puighermanal Puigvert, Andrea Herrera Solís and Konstantin Kuteykin-Teplyakov.*

PhD students: *Thomas Mathieu Guegan, Aurelijus Burokas, Xavier Viñals Álvarez, Carmen La Porta, Elk Kossatz de Mello, Pol Cuscó Pons, Samantha Mancino, Míriam Gutiérrez Martos and Victoria Salgado Medialdúa.*

Technicians: *Raquel Martín García, Cristina Fernández Avilés, Dulce Real Muñoz, Marta Linares López, Roberto Cabrera Ortega, Francisco Porrón López and Neus Morgui Valls.*

Project Manager: *Miquel-Àngel Serra Beltrán.*

Research Outline

Our main interest is the development of research lines aimed at the identification of new therapeutical targets at the nervous system level. The group has focused its activities in the neurochemical and neuroanatomical bases of the dependence to opioids and cannabinoids, addressing possible physical aspects as well as the motivational components of the continuous consumption of such substances of abuse. We have also studied the possible use of some of these compounds in the treatment of pain, cognitive, affective and food disorders. Therefore, classical pharmacological strategies complemented with the use of genetically modified animals are employed.

Current Projects/Research Lines

The aim of our current project is to evaluate the involvement of some specific components of the endogenous opioid system in the mechanisms underlying nicotine and cocaine relapse. We will extend these studies to the behavioural alterations promoted by food that are closely related to the addictive process. Addiction is a chronic brain disorder characterized by the occurrence of relapse due to an impaired ability to regulate the drive to obtain and use the drug. We have validated new operant models to evaluate the reinstatement of extinguished cocaine, nicotine and palatable food-seeking behaviour in mice. We will use these new behavioural models in constitutive and conditional – with site-specific deletions in precise brain areas- knockout mice deficient in specific genes of the endogenous opioid system that play a crucial role on drug addiction. We will also use c-fos mapping to identify activated neurons and ballistic delivery techniques to evaluate in the knockout mice the structural plasticity induced by cocaine, nicotine and palatable food that is involved in the alterations of the reward-seeking observed. We have identified GPR88 as a potential candidate in the development of nicotine addiction. We will now use constitutive knockouts deficient in GPR88 to study its specific involvement in the acquisition, extinction and reinstatement of cocaine and nicotine self-administration. This project will provide new insights for better understanding the neurobiological mechanisms leading to drug addiction and eating disorders and will facilitate the identification of new targets for the possible development of a more effective therapeutic approach.

SELECTED PUBLICATIONS 2012 - 2013

- **Cutando L, Busquets-Garcia A, Puighermanal E, Gomis-González M, Delgado-García JM, Gruart A, Maldonado R, Ozaita A (2013)** Mechanisms underlying the cerebellar deficits produced by repeated cannabis exposure. *J Clin Invest 123(7):2816-2831.*
- **Maldonado R, Robledo P, Berrendero F (2013)** Role of the endogenous cannabinoid system in addiction using genetic animal models. *Curr Opinion Neurobiol 23(4):480-486.*
- **La Porta C, Bura SA, Aracil-Fernández A, Manzanares J, Maldonado R (2013)** Role of cannabinoid CB1 and CB2 cannabinoid receptors in the development of joint pain induced by monosodium acetate. *Pain 154:160-174.*
- **Busquets-Garcia A, Gomis-González M, Guegan T, Agustín-Pavón C, Pastor A, Mato S, Pérez-Samartín A, Matute C, de la Torre R, Dierssen M, Maldonado R, Ozaita A (2013)** Targeting the endocannabinoid system in the treatment of fragile X syndrome. *Nature Med 19(5):603-607.*
- **Plaza-Zabala A, Flores A, Maldonado R, Berrendero F (2012)** Hypocretin/Orexin Signaling in the Hypothalamic Paraventricular Nucleus is Essential for the Expression of Nicotine Withdrawal. *Biol Psych 71(3):214-23.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Laurent P, Becker J.A, Valverde O, de Kerchove A, Schiffmann S.N, Maldonado R, Vassart G, Parmentier** M. The prolactin-releasing peptide acts as a functional antagonist of the opioid system through its receptor GPR10. Nature Neurosci. 8: 1735-1741, 2005. *PMID: 16299503*
- **Maldonado R, Valverde O, Berrendero F (2006)** Involvement of CB1 cannabinoid receptors in drug addiction. *Trends Neurosci 29:225-232.*
- **Trigo JM, Renoir T, Lanfumey L, Hamon M, Lesch K.P, Robledo P, Maldonado R (2007)** 3,4-methylenedioxymethamphetamine self-administration is abolished in serotonin transporter knockout mice. *Biol Psych 62:669-679.*
- **Racz I, Nadal X, Alfernik J, Baños JE, Rehnelt J, Martín M, Pintado B, Gutierrez-Adan A, Sanguino E, Manzanares J, Zimmer A, Maldonado R (2008)** Crucial role of cb2 cannabinoid receptor in the regulation of central immune responses during neuropathic pain. *J Neurosci 28:12125-12135.*
- **Puighermanal E, Marsicano G, Busquets-Garcia A, Lutz B, Maldonado R, Ozaita A (2009)** Cannabinoid modulation of hippocampal long-term memory is mediated by mTOR signaling. *Nat Neurosci 12(9):1152-1158.*

Luis Alberto Pérez Jurado

Human Genetics

www.upf.edu/genetica
www.qgenomics.com

Senior Researchers: *Ivon Cuscó Martí and Lluís Armengol Dulcet.*

Other PIs: *Victoria Campuzano Uceda and Miguel del Campo Casanelles.*

Postdocs: *Benjamín Rodríguez-Santiago, Olaya Villa Marcos, Cristina Hernando Davalillo, Clara Serra Juhé and Andrés Medrano Muñoz.*

PhD students: *Aïda Homs Raubert, Marta Codina Solà, Armand Gutiérrez Arumí, Judith Reina Castillón, Gabriela Palacios Verdú, Débora Pérez García and Cristina Borralleras Fumaña.*

Technicians: *Raquel Flores Peirats, Manel García Aragonés and Sònia Cano Redondo.*

Informatics: *Xavier Armengol Dulcet.*

Assistant: *Mª Jesús Rodríguez-Carretero.*

Research Outline

The main focuses of our research are the genetic disorders caused by genomic mutations, mutational mechanism of the human genome, and some monogenic diseases of development, integrating clinical and molecular research along with cellular and animal models. We search for better biomarkers for early diagnosis of germline and somatic disease, and provide appropriate genetic counselling to families. Translation and transfer of the generated knowledge is achieved through clinical services in the linked hospitals and the Spin-off qGenomics, developing specific tools for early translation into clinical diagnosis, prognosis and personalize medicine.

Current Projects/Research Lines

- **Structural human genome variation and disease susceptibility.**

  We develop and apply improved tools for detection of complex variants including mosaic changes, genomic inversions and gene conversions, to investigate molecular mechanisms of somatic and germline genome instability and its role in disease.

- **Mutational & pathogenic mechanisms of Williams-Beuren syndrome (WBS).**

  WBS is a recurrent genomic disorder caused by haploinsufficiency for several genes affecting the cardiovascular system, cognition and behavior, with a prevalence of 1:7500. Detailed clinical and molecular definition in patients and the identification of genetic modifiers are used with the goal to identify novel therapeutic options.

- **Molecular bases of autistic spectrum, related disorders and human malformations.**

  Through the integration of clinical, genomic, transcriptomic and methylomic data, we attempt to unravel the causes of these multifactorial disorders affecting human development, in order to develop better biomarkers for early diagnosis, as well as to define novel genes and pathways, and help families with genetic counseling. We also generate models for some of these disorders by iPS cell reprogramming.

- **Diagnosis of genetic diseases and personalized medicine.**

  The Spin-off qGenomics offers valuable products and services of high throughput DNA and RNA analysis, mostly structured around interpretation, addressed to investigators and clinicians. The company also develops specific tools for early translation into clinical diagnosis, prognosis and personalize medicine.

SELECTED PUBLICATIONS 2012 - 2013

- **Campuzano V, Segura M, Terrado V, Sánchez-Rodríguez C, Coustest M, Menacho-Márquez M, Nevado J, Bustelo XR, Francke U, Pérez Jurado LA (2012)** Reduction of NADPH-oxidase activity ameliorates the cardiovascular phenotype in a mouse model of Williams-Beuren syndrome. *PLoS Genet, 8(2):e1002458.*
- **Jacobs K, Yeager M, Zhou W, Wacholder S, Wang Z, Rodríguez-Santiago B, Hutchinson A, Villa O,..(180 more authors), Pérez-Jurado LA*, Chanock SJ* (* co-last authors) (2012)** Detectable clonal mosaicism and its relationship to aging and cancer. *Nat Genet 44(6):651-8.*
- **Armengol L, Nevado J, Serra-Juhé C, Plaja A, Mediano C, García-Santiago FA, García-Aragonés M, Villa O, Mansilla E, Preciado C, Fernández L, Mori MA, Lapunzina PD, Pérez-Jurado LA (2012)** Clinical Utility and Cost-Efficiency of Chromosomal Microarray Analysis in Invasive Prenatal Diagnosis. *Hum Genet, 131(3):513-523.*
- **Serra-Juhé C, Rodríguez-Santiago B, Cuscó I, Vendrell T, Camats N, Torán N, Pérez-Jurado LA (2012)** Contribution of Rare Copy Number Variants to Isolated Human Malformations. *PLoS ONE 7(10): e45530.*
- **Sailani MR1, Makrythanasis P, Valsesia A, Santoni FA, Deutsch S, Popadin K, Borel C, Migliavacca E, Sharp AJ, Duriaux Sail G, Falconnet E, Rabionet K, Serra-Juhé C, Vicari S, Laux D, Grattau Y, Dembour G, Megarbane A, Touraine R, Stora S, Kitsiou S, Fryssira H, Chatzisevastou-Loukidou C, Kanavakis E, Merla G, Bonnet D, Pérez-Jurado LA, Estivill X, Delabar JM, Antonarakis SE (2013)** The complex SNP and CNV genetic architecture of the increased risk of congenital heart defects in Down syndrome. *Genome Res 23(9):1410-21.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Antonell A, de Luis O, Domingo-Roura X, Pérez Jurado LA (2005)** Evolutionary mechanisms shaping the genomic structure of the Williams-Beuren syndrome chromosomal region at human 7q11.23. *Genome Res 15:1179-88.*
- **Del Campo M, Antonell A, Magano LF, Muñoz FJ, Flores R, Bayès M, Pérez Jurado LA (2006)** Hemizygosity at the NCF1 locus in Willimas-Beuren syndrome prevents their risk of hypertension. *Am J Hum Genet 78:533-42.*
- **Cuscó I, Medrano A, Gener B, Vilardell M, Gallastegui F, Villa O, González E, Rodríguez-Santiago B, Vilella E, Del Campo M, Pérez-Jurado LA (2009)** Autism-specific copy number variants further implicate the phosphatidylinositol signaling pathway and the glutamatergic synapse in the etiology of the disorder. *Hum Mol Genet 18:1795-804.*
- **Rodríguez-Santiago B, Malats N, Rothman N, Armengol L, Garcia-Closas M, Kogevinas M, Villa O, Hutchinson A, Earl J, Marenne G, Jacobs K, Rico D, Tardón A, Carrato A, Thomas G, Valencia A, Silverman D, Real FX, Chanock SJ, Pérez-Jurado LA (2010)** Mosaic Uniparental Disomies and Aneuploidies as Large Structural Variants of the Human Genome. *Am J Hum Genet, 87:129-138.*
- **Rodríguez-Santiago B, Brunet, A, Sobrino B, Serra-Juhé C, Flores R, Armengol L, Vilella E, Gabau E, Guitart M, Guillamat R, Martorell L, Valero J, Gutiérrez-Zotes A, Labad A, Carracedo A, Estivill X, Pérez-Jurado LA (2010)** Association of Common Copy Number Variants at the Glutathione-S Transferase Genes and Rare Novel Genomic Changes with Schizophrenia. *Mol Psychiatry 15:1023-33.*

Berta Alsina

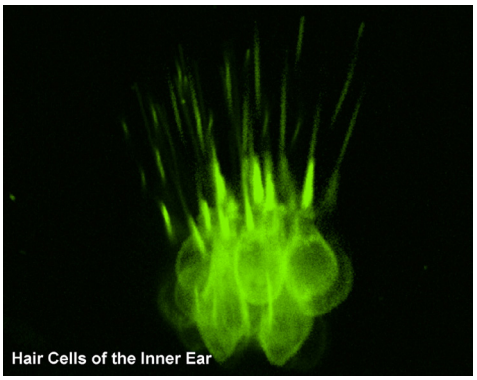
Developmental Biology Group

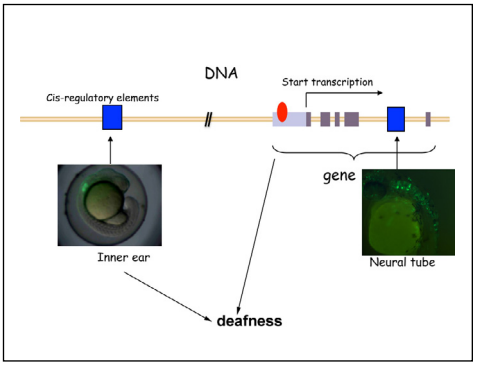
http://lavandula.imim.es/AL

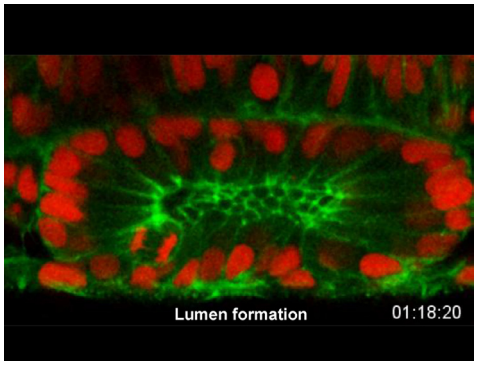
Postdocs: *Esteban Hoijman.*

PhD students: *Davide Rubbini and Laura Fargas.*

Technicians: *Miquel Sas and Marta Linares.*







Research Outline

The inner ear is a central sensory organ responsible for the senses of hearing and balance. The study of the genetics and cellular processes underlying the generation of sensory neurons and hair cells is key to understand basic developmental questions, regeneration and neurosensory diseases. Many genes involved in ear patterning and cell specification have been disclosed, however less is known on their interactions and genomic regulation in time and space.

Our goal is to understand the molecular, cellular and biomechanical mechanisms that control the development of the inner ear. The lab combines cell tracing, genetic, life imaging and computational approaches in several organisms.

Current Projects/Research Lines

- **Neurogenesis and neural patterning of the inner ear.**

  The otic primordium is early patterned into distinct neurogenic and sensory territories. We are studying the role of on different signalling pathways (Fgf, RA, Notch) and transcription factors in the establishment of these domains and in the acquisition of cell identity.
- **Characterization of novel cis-regulatory elements for the inner ear.**

  Cis-regulatory elements control the spatiotemporal dynamics of gene expression. Computational approaches to elucidate common transcription factor signatures, combined with ChIP approaches are being conducted in the lab for the identification and characterization of novel inner ear cis-regulatory elements.
- **Morphogenesis of the inner ear.**

  The cells of the inner ear primordium remodel at high speed to transition from a 2D epithelial sheet to a 3D organ filled with fluid. We are interested in understanding several aspects of inner morphogenesis such as how a cavity is generated and the cellular reorganization required to obtain the mature organ. The project involves high spatial and temporal resolution life-imaging of the otic vesicle together with biological manipulation.
- **Regeneration and Differentiation of Hair Cells.**

  Hearing loss in humans is a major problem in our society. Progressive deafness is irreversible due to our incapacity to regenerate hair cells. Zebrafish instead have retained the ability to regenerate hair cells, which provides us with a great model to study the signals and pluripotency programmes that mediate regeneration. We are currently studying the role of retinoic acid pathway in this process and well as its target genes.

SELECTED PUBLICATIONS 2012 - 2013

- **Mora N, Almudi I, Alsina B, Corominas M, Serras F (2013)** The ss-amyloid protein precursor like (Appl) is a Ras1/MAPK regulated gene required for axonal targeting in Drosophila photoreceptor neurons. *J Cell Sci 126(1):53-9.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

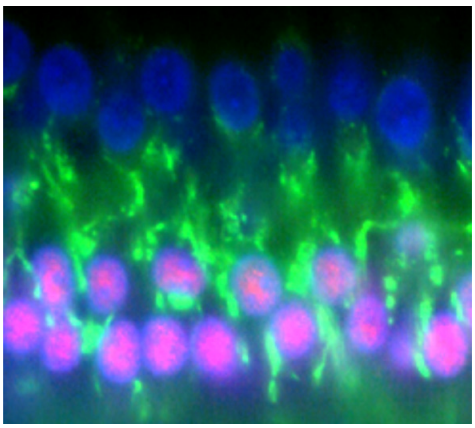
- **Alsina B, Abelló G, Ulloa E, Pujades C, Giráldez F (2004)** FGF signaling is required for determination of otic neuroblasts in the chick embryo. *Dev Biol 267(1):119-34.*
- **Abelló G, Giráldez F, Alsina B (2007)** Early regionalization of the otic placode and its regulation by Notch signaling pathway. *Mechanisms of Development, 124(7-8):631-45.*
- **Naranjo S, Voesenek K, de la Calle-Mustienes E, Robert-Moreno A, Kokotas H, Grigoriadou M, Economides J, Van Camp G, Hilgert N, Moreno F, Alsina B, Petersen M, Kremer H , Gomez-Skarmeta JL (2010)** Multiple enhancers located in a 1 Mb region upstream of POU3F4 promote expression during inner ear development and may be required for hearing. *Hum Genet 128(4):411-9.*
- **Abelló G, Khatri S, Scotting P, Giráldez F, Alsina B (2010)** Independent regulation of Sox3 and Lmx1b by FGF and BMP signaling gradients determines the neurogenic and non-neurogenic domains in the otic placode. *Dev Biol 339(1):166-78.*
- **Radosevic M, Robert-Moreno A, Coolen M, Bally-Cuif L and Alsina B (2011)** Her9, a zebrafish Hes1 ortholog, represses neurogenic fate in the inner ear downstream of Tbx1 and RA. *Development 138(3):397-408.*

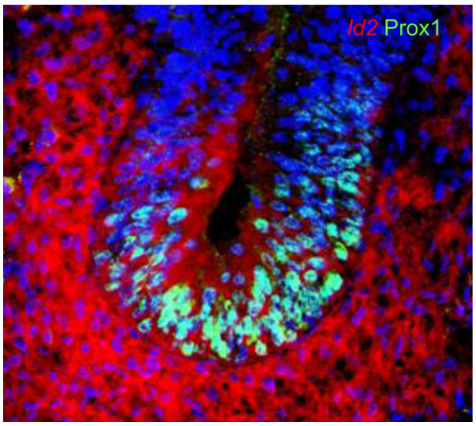
Fernando Giraldez

Developmental Biology: Ear Development

www.upf.edu/devbiol/projectes/progenitors.html

Postdocs: *Gina Abelló.*
PhD students: *Jelena Petrovic and Héctor Gálvez.*
Technicians: *Marta Linares and Miquel Sas.*





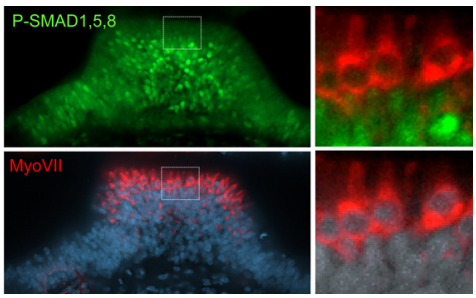


Figure 1: SOX2 expression in the supporting cells of the utricular macula. By Joana Neves.

Figure 2: Id2 mRNA and Prox1 expression in a E4 crista. By Andrés Kamaid.

Figure 3: P-SMAD1,5,8 immunodetection and MyoVII expression in an E7 crista of the chick embryo. By Joana Neves.

Research Outline

One basic problem in development is to understand how specific cell types are generated from pluripotent progenitors throughout embryonic life. We address this question by exploring the developmental origin of neurons and hair cells in the inner ear. We want to deepen into the major genetic pathways that dictate neuronal and hair cell fates during development. This knowledge is crucial for developing new tools for regenerative therapies directed to alleviate hear impairment.

Current Projects/Research Lines

- The specification of neuronal and hair cell fates depend on yet unknown interactions between proneural genes Neurog1 and Atoh1 and other upstream factors. Sox2 and Notch play a crucial role in sensory development and they have complex interactions during sensory specification. Our goal is to understand the regulation of Atoh1 in sensory precursors and the production of hair cells. We want to dissect the mechanisms that link Sox2 and Notch functions with neuronal and sensory development, and to identify the molecular interactions between Notch downstream targets and Atoh1. This work is supported by MINECO.
- The research on the molecular nature of sensory competence and the properties of ear progenitors is an essential background for developing hair cell regeneration techniques. The studies on the molecular regulation of Atoh1, the master gene for hair cell development, are focused on finding the conditions that favour its activation. This knowledge will lead to develop better transdifferentiation and regeneration procedures. For this purpose we collaborate with Thomas Schimmang (IBGM, CSIC-UVA) and Marcelo Rivolta within a project financed by MINECO and La Marató TV3.

SELECTED PUBLICATIONS 2012 - 2013

- **Neves J, Uchikawa M, Bigas A, Parada C, Chamizo M, Giraldez F (2012)** The Prosensory Function of Sox2 in the Chicken Inner Ear Relies on the Direct Regulation of Atoh1. *PLoSONE 7(1): 1-11.*
- **Duran B, Feijoo A, Conde de Felipe M, Carnicero E, Sanchez A, García-Sancho J, Rivolta MN, Giraldez F, Schimmang T (2012)** Generation of Inner Ear Sensory Cells from Bone-Marrow derived Human Mesenchymal Stem Cells. *Regenerative Medicine 7(6):769-83.*
- **Neves J, Vachkov I, Giraldez F (2013)** Sox2 regulation of hair cell development: incoherence makes sense, Special Issue Inner "Ear Development and Regeneration". *Ed by Stefan Heller Hearing Research 297:20-29.*
- **Neves J, Abelló G, Petrovic J, Giraldez F (2013)** Patterning and cell fate in the inner ear: a case for Notch in the chicken embryo. *Ed by R. Ladher and T. Suzuki Development Growth & Differentiation 55(1):96-112.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Bell D, Streit A, Gorospe, Varela-Nieto I, Alsina B, Giraldez F (2008)** Spatial and temporal segregation of auditory and vestibular neurons in the otic placode. *Dev Biol 322:109–120.*
- **Abelló G, Khatri S, Radosevic M, Scotting PJ, Giráldez F, Alsina B (2010)** Independent regulation of Sox3 and Lmx1b by FGF and BMP signaling determines the neurogenic and non-neurogenic domains in the chick otic placode. *Dev Biol 339: 166-178.*
- **Kamaid A, Neves J, Giráldez F (2010)** Id gene regulation and function in the prosensory domains of the chicken inner ear: a link between BMP signaling and Atoh1. *J Neurosci 30(34):11426-11434.*
- **Dominguez-Frutos E, Lopez-Hernandez I, Vendrell V, Neves J, Gallozzi M, Gutsche K, Quintana L, Sharpe J, Knoepfler P, Eisenman R, Trumpp A, Giraldez F, Schimmang T (2011)** N-myc controls proliferation, morphogenesis and patterning of the inner ear. *J Neurosci 11;31(19):7178-89.*
- **Neves J, Parada C, Chamizo M, Giraldez F (2011)** "Jagged1 regulates the restriction of Sox2 expression in the developing chicken inner ear: a mechanism for sensory organ specification". *Development 138: 735-744.*

Cristina Pujades

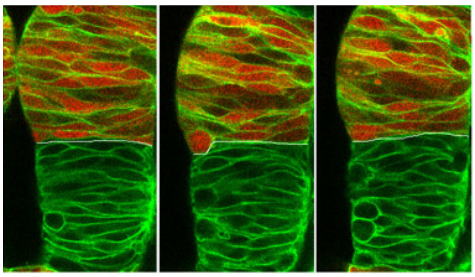
Developmental Biology

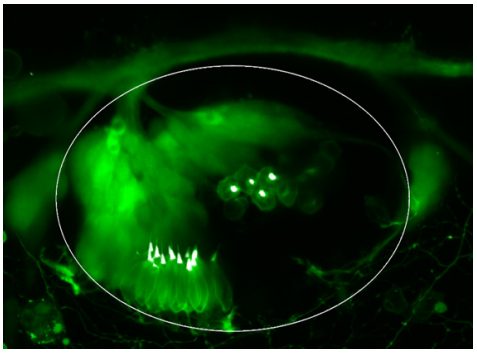
www.upf.edu/devbiol/projectes/cns.html

Postdoc: *Javier Terriente.*

PhD students: *Simone Calzolari, Sylvia Dyballa, Andrea Zecca and Adrià Voltes.*

Technicians: *Marta Linares and Miquel Sas.*





Research Outline

A long-standing goal of developmental biology is to understand how multiple cell types are generated and maintained in highly organized spatial patterns. Our group explores the mechanisms underlying the organization of cells into highly developed structures in the Nervous System, with special attention to the patterning of cell lineages. Clonal analyses, which describe the derivatives of a single cell, provide insights into the mode of growth of a tissue and its regionalization, and reveal the diversity of cell behavior that underlies progression along a lineage tree. Cell lineage follows the normal fate of a cell and its daughters, leading to genealogical trees of cells with increasingly restricted cell fate choices as development proceeds.

Current Projects/Research Lines

We want to address three fundamental questions in neural development: i) how cell diversity is generated from single precursors (cell lineage reconstruction); ii) how cell fate decisions are taken and regulated; and iii) how cell fate affects cell behavior. We tackle these questions in two structures, which are interconnected by neuronal circuits: the hindbrain and the inner ear. We use zebrafish embryos as model system because permits functional genetic studies to be combined with 3D+time in vivo imaging.

Our current projects are the following:

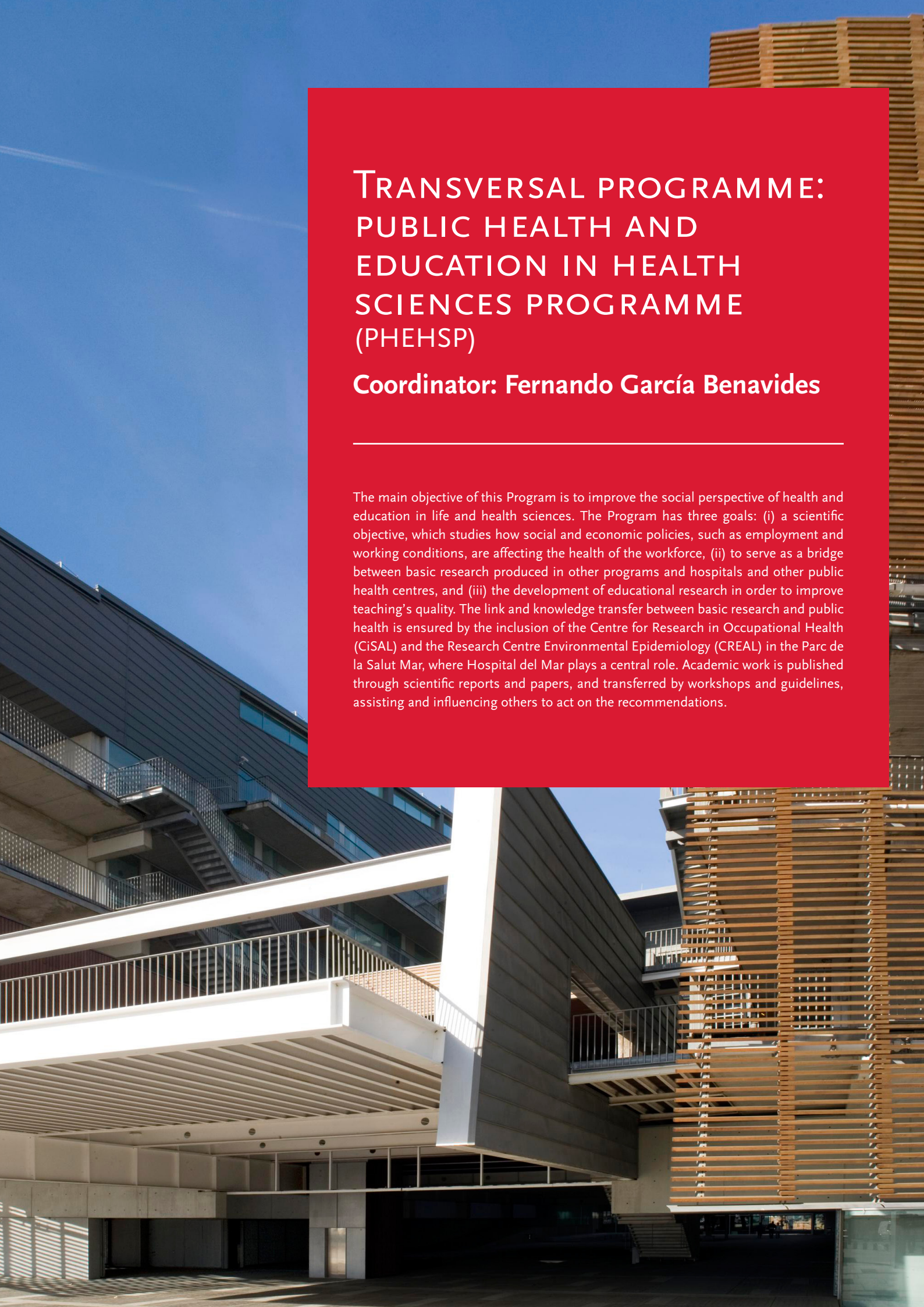
1. Global cell lineage reconstitution of the otic vesicle during early embryonic development. Our aim is to generate the complete lineage tree of the neurosensory elements of the inner ear by high spatial and temporal resolution 2-photon 3D+time imaging. We correlate the progenitor potentials to the temporal and spatial proneural gene requirements.
2. Deciphering the topographical representation of the sensory information at central levels. We investigate the selective innervation of hindbrain regions by somatosensory afferents and the gene requirements. An extended goal is the study of how changes or variations in the behavior are reflected in the underlying neuronal activity and perform brain-wide neuronal dynamics in response to sensory stimuli.
3. Understanding morphomechanics during hindbrain segmentation. We have recently shown the role of actomyosin cables acting downstream of EphA/Ephrin signaling in the segregation of rhombomeric cell populations. We are currently exploring the cellular machinery and the molecular players responsible of the assembly of the mechanical barrier.
4. Exploring the fate of the Boundary Cell Population (BCP). The BCP is generated at interface between two rhombomeres, and displays a specific gene expression landscape. We study the biological BCP behaviour and seek its lineage combining in vivo imaging techniques with the generation of new transgenic lines by the CRISPR/Cas9 genome edition system.

SELECTED PUBLICATIONS 2012 - 2013

- **Sapède D, Dyballa S, Pujades C (2012)** Cell lineage analysis reveals three different progenitor pools for neurosensory elements in the otic vesicle. *J Neurosci 32(46):16424-34.*
- **Calzolari S, Terriente J, Pujades C (2013)** Cell segregation in the rhombomeric boundaries relies in physical mechanisms based in an actomyosin cable. *EMBO J, in press.*
- **Terriente J, Pujades C (2013)** The use of zebrafish embryos for small molecule screening related to cancer. *Dev Dyn 242(2):97-107.*
- **Vendrell V, Vázquez-Echeverría C, López-Hernández I, Durán B, Alonso MT, Martinez S, Pujades C, Schimmang T (2013)** Roles of Wnt8a during formation and patterning of the murine inner ear. *Mech Dev 130(2-3):160-8.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Lecaudey V, Ulloa E, Anselme I, Stedman A, Schneider-Maunoury S, Pujades C (2007)** Role of the hindbrain in patterning the otic vesicle: a study of the zebrafish vhnf1 mutant. *Dev Biol 303:134-43.*
- **Vázquez-Echeverría C, Dominguez-Frutos E, Charnay P, Schimmang T, Pujades (2008)** Analysis of kreisler mutants reveals new roles of the hindbrain-derived signals in the establishment of the otic neurogenic domain. *Dev Biol 322(1):167-78.*
- **Sapède D, Pujades C (2010)** Hedgehog signaling governs the development of sensory epithelium and its associated innervation in the zebrafish inner ear. *J Neurosci 30:3612-23.*
- **Jimenez-Guri E, Udina F, Colas JF, Sharpe J, Padrón L, Torres M, Pujades C (2010)** Clonal analysis in mice underlines the importance of positional information during hindbrain segmentation. *PLoS ONE 5(4):e10112.*
- **Jimenez-Guri E, Pujades C (2011)** An ancient mechanism of hindbrain patterning has been conserved in vertebrate evolution. *Evol Dev 13(1):38–46.*



Transversal programme: public health and education in health sciences programme (PHEHSP)

Coordinator: Fernando García Benavides

The main objective of this Program is to improve the social perspective of health and education in life and health sciences. The Program has three goals: (i) a scientific objective, which studies how social and economic policies, such as employment and working conditions, are affecting the health of the workforce, (ii) to serve as a bridge between basic research produced in other programs and hospitals and other public health centres, and (iii) the development of educational research in order to improve teaching's quality. The link and knowledge transfer between basic research and public health is ensured by the inclusion of the Centre for Research in Occupational Health (CiSAL) and the Research Centre Environmental Epidemiology (CREAL) in the Parc de la Salut Mar, where Hospital del Mar plays a central role. Academic work is published through scientific reports and papers, and transferred by workshops and guidelines, assisting and influencing others to act on the recommendations.

Fernando G. Benavides

Center for Research in Occupational Health (CISAL)

www.ufp.edu/cisal
www.upf.edu/cisal/Publicaciones

Senior Researchers: *Consol Serra, George L. Delclos and David Gimeno.*

Postdocs: *Javier Campos Serna.*

PhD students: *Isabel Tora Rocamora, María Lopez Ruiz, Mónica Ubalde López, María Carmen Gonzales Galarzo, Carmen Clara Gual Llorens, Maria Andree Lopez Gomez, Jose María Ramada Rodilla, Sergio Vargas-Prada and Xavier Duran Jorda.*

Technicians: *Montserrat Fernandez Busquets and Sandra Garrido Salmeron.*

Project Manager: *Emily Felt.*

Research Outline

The objective of the CiSAL is to study occupational health issues and their implications for employees, businesses and governments, all of them particularly relevant for Social Welfare Systems. Our group aims to serve as an academic venue producing and disseminating useful scientific knowledge to inform policy with the ultimate goal of improving the health of workers.

Research at the CiSAL focuses on a range of workplace-related health problems including musculoskeletal disorders (MSDs); sickness absence and permanent disability; workplace injuries and prevention programmes.

Current Projects/Research Lines

Central American Survey of Working Conditions and Health (ECCTS); in collaboration with seven other Central American Universities (SALTRA), evaluates formal vs. informal working conditions and the prevalence of MSDs in Central America.

Cultural and Psychosocial influences on Disability (CUPID); in collaboration with Southampton University and seventeen other countries, explores the hypothesis that common MSDs and associated disability are influenced by culturally determined health beliefs.

Participatory Ergonomics (ERGOPAR); in collaboration with the University of Valencia and Parc Salut Mar, studies the impact of participatory ergonomic interventions in work settings on employee health in relation to MSDs.

Immigration, Work and Health (ITSAL) II; in collaboration with the University of Alicante, evaluates the impact of the economic crisis on migrant workers in Spain from Colombia, Ecuador, Morocco and Romania.

Occupational Pathology Unit (UPL); in collaboration with Parc Salut Mar, involves the adaptation of the Work Role Functioning Questionnaire (WRFQ) for the Spanish workforce. CISAL is also involved in the COST ModerNET and E-Capacit8 projects, which are EU funded actions, focused on identifying new trends in occupational diseases and training of occupational health professionals.

Continuous Working Lives Cohort (MCVL); in collaboration with the Institut Català d'Avaluacions Mèdiques (ICAM), analyses the relation between labour market trajectories and disability of a cohort of workers affiliated to the Social Security System.

Spanish Job Exposure Matrix (MatEmESp); in collaboration with the University of Valencia and ISTAS-COO, we have developed an adaptation of the Finnish Job Exposure Matrix to Spanish job characteristics based on official Spanish job.

SELECTED PUBLICATIONS 2012 - 2013

- **Ronda Pérez E, Benavides FG, Levecque K, Love JG, Felt E, Van Rossem R (2012)** Differences in working conditions and employment arrangements among migrant and non-migrant workers in Europe. *Ethn Health 17(6):563-77.*
- **Coggon D, Ntani G, Palmer KT, Felli VE, Harari R, Barrero LH, Felknor SA, Gimeno D, Cattrell A, Serra C, Bonzini M, Solidaki E, Merisalu E, Habib RR, Sadeghian F, Kadir M, Warnakulasuriya SS, Matsudaira K, Nyantumbu B, Sim MR, Harcombe H,Cox K, Marziale MH, Sarquis LM, Harari F, Freire R, Harari N, Monroy MV, Quintana LA, Rojas M, Salazar Vega EJ, Harris EC,Vargas-Prada S, Martinez JM, Delclos G, Benavides FG, Carugno M, Ferrario MM, Pesatori AC, Chatzi L, Bitsios P, Kogevinas M, Oha K, Sirk T, Sadeghian A, Peiris-John RJ, Sathiakumar N, Wickremasinghe AR, Yoshimura N, Kielkowski D, Kelsall HL, Hoe VC, Urquhart DM, Derett S, McBride D, Gray A (2012)** The CUPID (Cultural and Psychosocial Influences on Disability) Study: Methods of Data Collection and Characteristics of Study Sample. *PLoS One.;7(7):e39820.*
- **Ubalde-Lopez M, Delclos GL, Calvo E, Benavides FG (2013)** Influence of new secondary diagnoses on the duration of non-work related sickness absence episodes. *J Occup Environ Med 55(4):460-4.*
- **Coggon D, Ntani G, Vargas-Prada S, Martinez JM, Serra C, Benavides FG, Palmer KT, et al (2013)** International variation in absence from work attributed to musculoskeletal illness: findings from the CUPID study. *Occup Environ Med 70(8):575-84.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

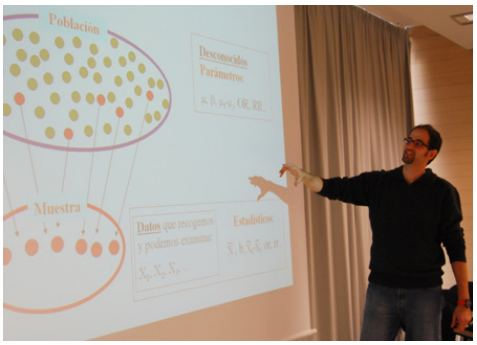
- **Benavides FG, Castejón J, Gimeno D, Porta M, Mestres J, Simonet P (2005)** Certification of occupational diseases as common diseases in a primary health care setting. *Am J Ind Med, 47(2), 176-80.*
- **Benavides FG, Benach J, Muntaner C, Delclos GL, Catot N, Amable M (2006)** Associations between temporary employment and occupational injury: what are the mechanisms? *Occup Environ Med 63(6):416-21.*
- **Ahonen EQ, Benavides FG, Benach J (2007)** Immigrant populations, work and health – a systematic literature review. *Scand J Work Environ Health, 33(2):96-104.*
- **Delclos Gl, Gimeno D, Arif AA, Benavides FG, Zock JP (2009)** Occupational exposures and asthma in health-care workers: comparison of self-reports with a workplace-specific job exposure matrix. *Am J Epidemiol 169(5):581-7.*
- **Benavides FG, Serra C, Dominguez R, Martinez JM, Plana M, Despuig M, Sampere M, Gimeno D (2009)** Does return to work occur earlier after work-related sick leave episodes than after non-work-related sick leave episodes? A retrospective cohort study in Spain. *Occup Environ Med, 66(1): 63-7.*

José Miguel Martínez Martínez

Center for Research in Occupational Health (CISAL)

www.upf.edu/cisal
www.upf.edu/cisal/Publicaciones

PhD students: *Maria Buxó Pujolràs, Isabel Torá Rocamora, Vanessa Puig i Barrachina, Sergio Vargas-Prada, Xavier Durán, Maria López Ruiz, Maria Andree López Gómez and Elena Zaballa Lasala.*



Research Outline

Research Outline Epidemiology and biostatistics are two very important disciplines in public and occupational health. In the last 10 years there have been a number of important methodological advances to improve the design and analysis of epidemiological studies. We seek to contribute to the advancement of epidemiology research by developing innovative biostatistical methods.

Current Projects/Research Lines

Statistical methods for epidemiological investigations (funded by the Canadian Institutes for Health Research -CIHR-).

- This project will develop and apply statistical methods in epidemiological research. Specifically, we have developed a so-called integrated design. This new epidemiological design is shown as an alternative to improve multilevel analysis in certain situations. In recent years, so-called design and multilevel analysis has emerged as a powerful epidemiological technique which allows studying the simultaneous relationship of individual and group factors on the health of populations.

Other research lines (please see professor Fernando G. Benavides's current projects/research lines outline for more details):

- Cultural and Psychosocial Influences on Disability (CUPID).
- Immigration, Work and Health (ITSAL) II.
- Continuous Working Lives Cohort (MCVL).
- Central American Survey of Working Conditions and Health (ECTS).

SELECTED PUBLICATIONS 2012 - 2013

- **Cleries R, Ribes J, Buxo M, Ameijide A, Marcos-Gragera R, Galceran J, Martínez JM, Yasui Y (2012)** Bayesian approach to predicting cancer incidence for an area without cancer registration by using cancer incidence data from nearby areas. *Stat Med 31(10):978-87.*
- **Torá-Rocamora I, Gimeno D, Delclos G, Benavides FG, Manzanera R, Jardí J, Alberti C, Yasui Y, Martínez JM (2013)** Heterogeneity and event dependence in the analysis of sickness absence. *BMC Med Res Methodol 13:114.*
- **Benach J, Malmusi D, Yasui Y, Martínez JM (2013)** A new typology of policies to tackle health inequalities and scenarios of impact based on rose's population approach. *J Epidemiol Community Health 67(3):286-91.*
- **Vargas-Prada S, Martínez JM, Coggon D, Delclos G, Benavides FG, Serra C (2013)** Health beliefs, low mood, and somatizing tendency: contribution to incidence and persistence of musculoskeletal pain with and without reported disability. *Scand J Work Environ Health 39(6):589-98.*
- **Clèries R, Martínez JM, Moreno V, Yasui Y, Ribes J, Borràs JM (2013)** Predicting the change in breast cancer deaths in Spain by 2019: a bayesian approach. *Epidemiology 24(3):454-60.*

OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Martínez JM, Benach J, Ginebra J, Benavides FG, Yasui Y (2007)** An integrated analysis of individual and aggregated health data: an estimating equation approach. *Int J Biostat 3(1):10.*
- **Martínez JM, Benach J, Benavides FG, Muntaner C, Cleries R, Zurriaga O, Martínez-Beneito MA, Yasui Y (2009)** Improving multilevel analyses: the integrated epidemiologic design. *Epidemiology 20(4):525-32.*
- **Buxó-Pujolràs M, Martínez JM, Yasui Y, Borrell C, Martín JC, Vergara M, Cervantes M, Benach J (2012)** Monitoring the cluster of high-risk mortality areas in the southwest of Spain. *Geospat Health 7(1):73-81.*
- **Torá-Rocamora I, Delclos GL, Martínez JM, Jardí J, Alberti C, Manzanera R, Yasui Y, Clèries R, Tobías A, Benavides FG (2012)** Occupational health impact of the 2009 H1N1 flu pandemic: surveillance of sickness absence. *Occup Environ Med 69(3):205-10.*

Jordi Pérez Sánchez and Josep Eladi Baños

Research Group in Health Sciences Education

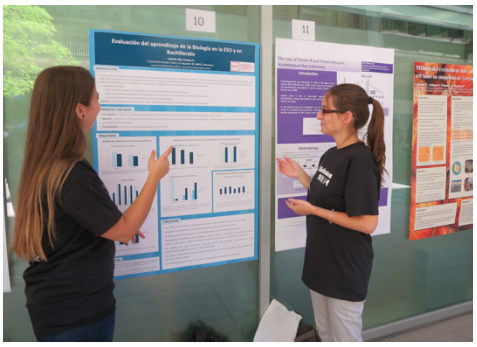
www.upf.edu/grecs

Senior Researchers: *Meritxell Girvent, Mariano Sentí, Núria B. Centeno, Mar Carrió and Elisabeth Moyano.*

PhD student: *Vanessa Soria.*

Postdocs: *Laia Agell, Eva Baillés, Silvia Lope, and Mireia Valero.*

Technician: *Pilar Larramona.*



Research Outline

The Group of Research on Education in Health Sciences (GRECS) has three main objectives:

1. To improve the educational project of the FCSV of UPF
2. To enhance the initiatives which improve the university teaching
3. To facilitate the contact with secondary education through an increase of scientific interest of young students

To achieve these aims, GRECS has three domains of activities:

1. Evaluation of the teaching projects of the bachelors of the FCSV of UPF
2. Activities in educational research
3. Innovation and development in education

Current Projects/Research Lines

a) Evaluation of teaching projects at FCSB of UPF

- The programme of Problem-based learning (PBL)
- The programme of students' mentoring
- The implementation of portfolio for generic competencies
- The programme of preparation for professional work

b) Research in education:

- Secondary education: use of inquiry-based methods and the contextualization of science in daily life, use of social and scientific facts to promote the interests of young people in science, the outcome of Salters project in PAS exams
- University education: use of inquiry-based learning methods (PBL), evaluation of learning (effects of PBL, initial performance as a prediction factor of subsequent performance, continuous evaluation and final outcomes, learning styles and recall), academic stress (stress sources and psychological and physical discomfort)

c) Innovation and educative development

- Creation of teaching material (good practices guidelines)
- Design of interdisciplinary didactic units (PBL texts)
- Use of communication and information technologies to stimulate the cooperative work of teachers
- Activities to enhance the interest of science for young students (many in collaboration with PRBB)

SELECTED PUBLICATIONS 2012 - 2013

- **Carrillo-de-la-Peña MT, Pérez J (2012)** Continuous Assessment Improved Academic Achievement and Satisfaction of Psychology Students in Spain. *Teach of Psychology 39:45-7.*
- **Farré M, Arribas S, Pérez J, Baños JE (2013)** Bioethical principles, clinical research and popular movies. *Med Education 47:1141-2.*
- **Pérez J, Girvent M, Moyano E (2013)** La evaluación de los aprendizajes en la Facultad de Ciencias de la Salud y de la Vida de la Universidad Pompeu Fabra (UPF) de Barcelona. Una tarea colectiva. *RECS 10:127-32.*
- **Carrió M, Branda L, Baños JE (dir) (2013)** El aprendizaje basado en problemas en sus textos. Ejemplos de su empleo en biomedicina. *Barcelona: Fundación Dr. Antoni Esteve.*
- **Baños JE, Farré M (2013)** La docencia de la farmacología en el marco del Espacio Europeo de Educación Superior. *Revista de Farmacología de Chile 6:11-8.*

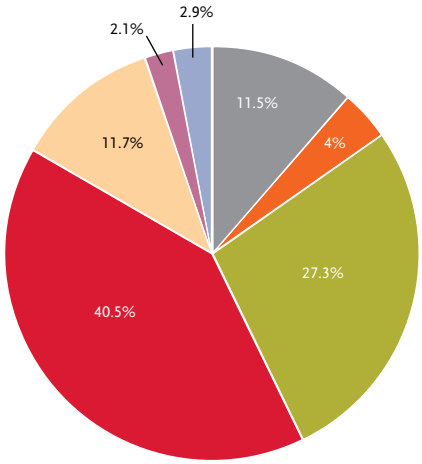
OTHER 5 RELEVANT PUBLICATIONS FROM LAST 10 YEARS

- **Carrillo de la Peña MT, Baillès E, Caseras X, Martínez A, Ortet G, Pérez J (2009)** Formative assessment and academic achievement in pre-graduate students of health sciences. *Adv Health Sci Educ Theory Pract 14:61-7.*
- **Carrio M, Larramona P, Baños JE, Pérez J (2011)** The effectiveness of the hybrid problem-based learning approach in the teaching of biology: a comparison with lecture-based learning. *Journal Biol Educ 45:229-35.*
- **Hernández-Leo D, Romeo L, Carralero MA, Chacón J, Carrió M, Moreno P, Blat J (2011)** LdShake: Learning design solutions sharing and co-edition. *Computers & Education, 57: 2249-2260.*
- **Baños JE, Miralles R, Sentí M (2011)** Contacto precoz con la realidad asistencial: una experiencia piloto en medicina. *Educación Médica 14:39-47.*

The DCEXS in numbers

Personnel

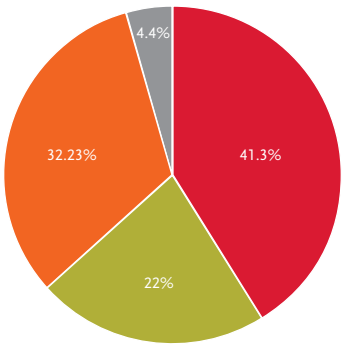
Principal Investigators	43
Senior Researchers	15
Postdoctoral Researchers	102
Predoctoral Researchers	151
Laboratory Technicians	43
Project Managers	8
Administrative staff	11



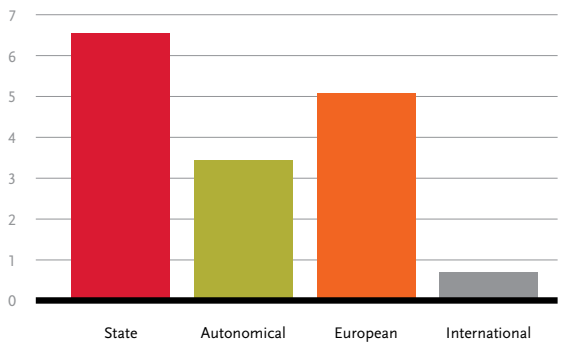
Competitive funding obtained in 2012-13

Origin	(Milion €)
State administration	6.51
Autonomical administration	3.47
European administration	5.08
International administration	0.702
TOTAL:	**15.76**

Origin of the competitive funding obtained in 2012-13



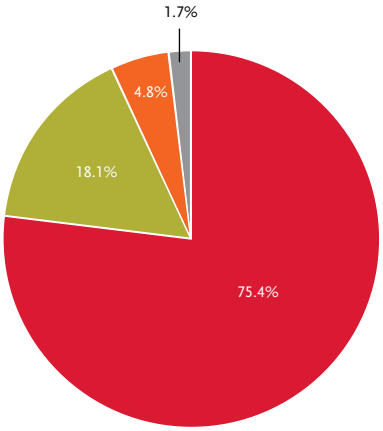
Competitive funding obtained in 2012-13 (Milion €)

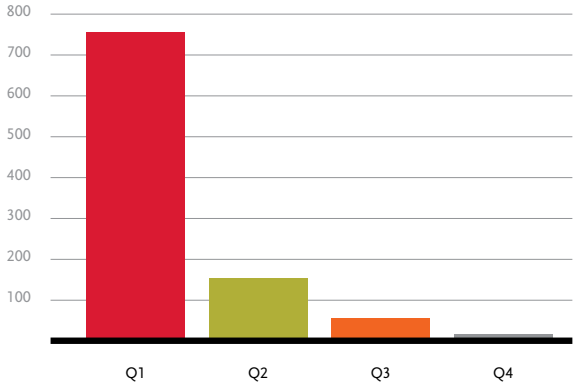


Publications (2012-13)

	Distribution of articles per Quartile
Q1	755
Q2	157
Q3	49
Q4	18

Distribution of articles per quartile





Universitat
Pompeu Fabra
Barcelona

Department
of Experimental and Health
Sciences

Barcelona Biomedical Research Park
Doctor Aiguader, 88 | 08003 Barcelona
www.upf.edu/cexs