ANNUAL REPORT 2015-2016

Department of Experimental and Health Sciences

EXCELENCIA MARÍA DE MAEZTU

upf. Universitat Pompeu Fabra Barcelona

Department of Experimental and Health Sciences

Main menu

Foreword of the Director

David Comas
DCEXS Director

Research and educational centers follow the evolutionary principle of the Red Queen's Race from Lewis Carroll's character in *Through the Looking-Glass*: "It takes all the running you can do, to stay in the same place". We should move constantly, progress without stopping at any time, because if we stop changing, we would lose the momentum. Despite the difficulties, species should adapt to new challenges and new environments. In this sense, during 2015 and 2016 the DCEXS has moved, facing new challenges and trying to overcome the general limitations given the country's economic situation. But as done in the past years, we have managed to keep up the hard work and, in doing so, we have been rewarded.

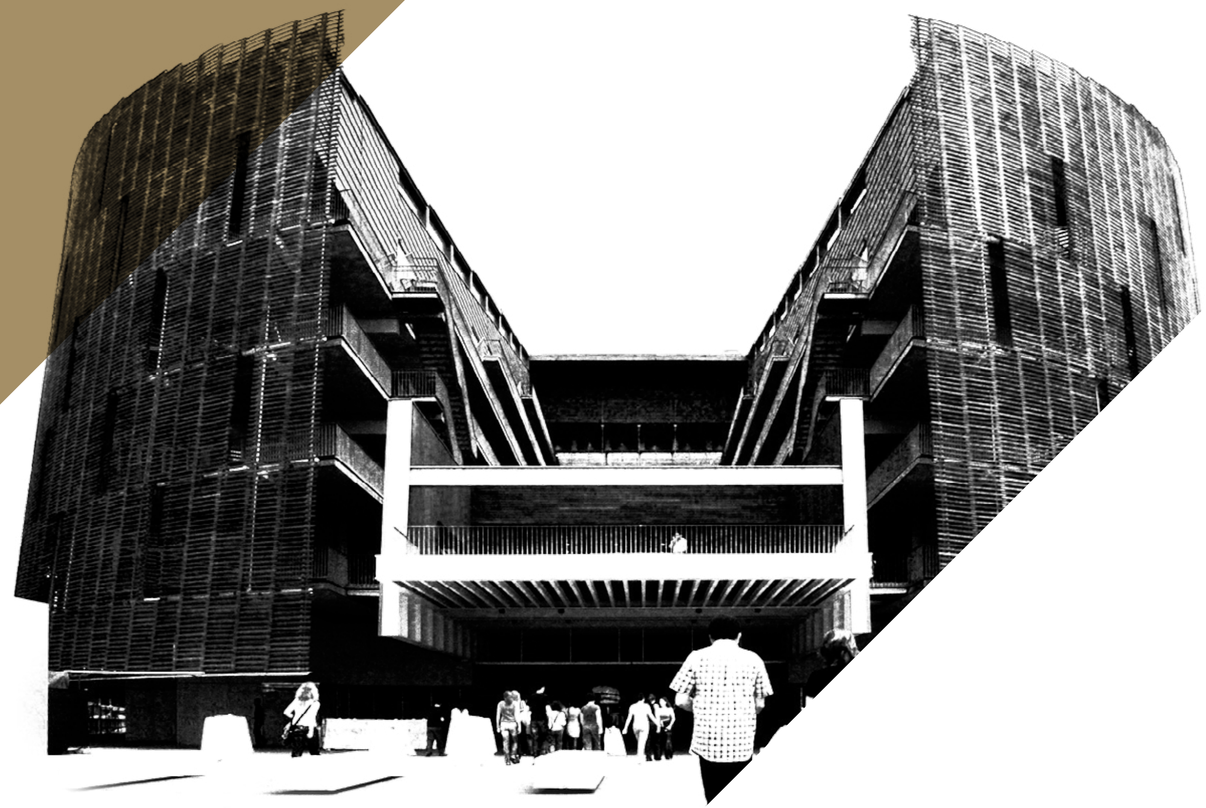
For instance, 2015 was a turning point in the DCEXS trajectory: the first call of the Units of Excellence *María de Maeztu*, an initiative of the Spanish Ministry of Economy and Competitiveness to foster excellence in scientific and technical research, awarded the DCEXS and recognized the quality of the research performed in our center. The financial support provided by the *María de Maeztu* has allowed us the development of strategic research programs within the Department, launching new initiatives towards gender balance and equality, and the creation of new collaboration efforts between research groups and scientific programs. Moreover the award *María de Maeztu* has allowed us to create the new Systems Bioengineering program (the seventh in our department), which will start in 2017, directed to acquire and interpret quantitative knowledge of biological processes using systems-level approaches. Besides the collective effort of the *María de Maeztu*, the individual research of the investigators in the DCEXS during this period has also yielded a significant number of competitive extramural grants, both in state and international calls; and the quality of the research groups was evaluated for the first time at the University level in 2015 by external evaluation panels with excellent results. Our outreach has not only been devoted to attract international attention but also local dissemination. It is worth noting the DCEXS symposiums organized with diverse topics, such as Innovative strategies in silico in Biomedical Research (2015) and Quantitative Biology (2016) with the participation of national and international experts. At a local level, we also hosted the first *Biology Night* organized by the *Societat Catalana de Biologia*.

Our teaching assets were also quite satisfying with the consolidation of the degrees in Human Biology and Medicine, and the first graduates of the Biomedical Engineering during 2015. More recently, we launched the new degree on Bioinformatics at the end of 2016 as a joint effort of the DCEXS, the ESCI, the UB and the UPC, which makes us quite excited about its future projection and results. We have also completed an exhaustive assessment of our Degrees and several of our Masters by independent external accreditation agencies with a very positive evaluation. This excellent result has been possible due to the commitment of all our community: our faculty, administrative personnel, and of course the main protagonists, our students. Moreover, we have created new teaching programs for postdoctoral researchers (Teaching Mentorship Program) and predoctoral students (Teaching Training Program) in order to provide teaching skills to the future scientific generations.

In summary, the last two years have been times of change and evolution, which have allowed us to keep improving. However, we are aware of the dangers of complacency, which stimulate us to keep running as the Red Queen character in order to foresee better results in the forthcoming years.

I would like to express my gratitude to all of you for making it possible.

The DCEXS



The Department of Experimental and Health Sciences (DCEXS) was founded in 1998 by the Pompeu Fabra University (UPF), a young, public and modern university born in 1990 and called to become one of the leading European universities. Within this framework, the great challenge of the DCEXS has been to successfully develop a project where research and teaching are firmly integrated. Together with the UPF's Faculty of Health and Life Sciences, the DCEXS is responsible for three undergraduate degrees: Human Biology (since 1998), Medicine (2008), Biomedical Engineering (2011) and Bioinformatics (2016). The Department also runs Master's degrees in the fields of biomedicine, pharmaceutical and biotechnology industries, clinical laboratory sciences, and public health, and PhD Programme in Biomedicine, fully taught in English and recognized by independent agencies. Scientific research is perceived by the students, both undergraduates and postgraduates, as an essential tool in their studies. The DCEXS is strategically located within the Barcelona's Biomedical Research Park (PRBB), a large scientific infrastructure that gathers together several public research centers and is physically connected to Barcelona's Hospital del Mar, thus being one of the largest hubs of biomedical research in southern Europe. This close contact has allowed DCEXS to establish strategic alliances with surrounding research institutes affiliated to the UPF such as the Barcelona Institute for Global Health (ISGLOBAL), the Centre for Genomic Regulation (CRG) or the Hospital del Mar - Medical Research Institute (IMIM). Over the last few years, the DCEXS has achieved a remarkable presence in different research fields and a growing research output and impact. DCEXS researchers have published 383 research articles in 2015 and 2016, 86 % of which in journals that fall in the first quartile, and 61 % in the first decile.

Remarkably, the DCEXS was awarded the "María de Maeztu" distinction and grant in its first call (2014). The grant provides 2 M € over 4 years to develop a strategic programme to promote the department's research, training, outreach, and technology transfer.

Regarding participation in international projects, an excellent example is the H2020 project HEIRRI, awarded in 2015. Its aim is to integrate the concept of "Responsible Research and Innovation" (RRI) in the science and engineering degrees, mainly focusing in universities and other higher education institutions (HEI). Gema Revuelta, director of the Studies Centre on Science, Communication and Society (SCS-UPF), from the UPF Department of Experimental and Health Sciences (DCEXS), is the coordinator of the project.

In recognition of the excellence of the department, several DCEXS researchers received the ICREA Academia Award: Elena Bosch Fusté, Elena Hidalgo Hernando, Cristina Pujades Corbi, Rafael Maldonado in 2015; and David Comas, Juana Díez Antón and Andres Ozaita in 2016. Furthermore, Pura Muñoz-Cánoves obtained the Science Award from La Vanguardia in 2015 for her work on muscle regeneration published in Nature.

Management team

Direction

Director:

David Comas

Vice Directors:

José Aramburu, Francisco J. Muñoz, and Eulàlia de Nadal

External Scientific Advisory Board

President:

Isabel Fariñas (Universitat de València)

Members:

Cosima Tatiana Baldari (Università di Siena)
Carmen Birchmeier (Max-Delbrück-Center for Molecular Medicine)
Søren Brunak (Technical University of Denmark)
José Luis López Barneo (Universidad de Sevilla)
Trudy McKay (NC State University)
Francisco Sánchez Madrid (Universidad de Madrid)
Alfonso Valencia (CNIO)

Teaching

The Department of Experimental and Health Sciences is committed to 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 under the support of a technical unit. This project has been very successful in achieving an excellent teaching of generic and specific competences of the Faculty graduates. The teaching of Department members has been repeatedly recognized by several prizes 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). The degree in Human Biology began in 1998 with an innovative teaching methodology. Small size classes, problem-based learning, student tutoring, high content of practical skills and continued evaluation were combined for a high quality education. DCEXS study programmes became the reference at UPF because of the implementation of European Higher Education Area (EHEA) methodology. According to the U-Ranking 2015 (Fundación BBVA-Ivie, which integrates indicators in teaching, research and technological innovation), the UPF is the first choice for Medicine and Human Biology studies. The first cohort of Medicine students graduated in 2014 and all of them passed the qualifying state exam for clinical specialisation (MIR), with 90% of our students having obtained positions in major hospitals and clinical centers.

Types of Studies

- Bachelor Degrees
- Master’s programmes
- PhD in Biomedicine
- Bringing Science to young students Programme

Teaching

Bachelor Degrees

HUMAN BIOLOGY

The degree in Human Biology is especially designed to enable graduates to work professionally in three major fields: the pharmaceutical and biotechnological industry, clinical laboratories and biomedical research.

MEDICINE (UPF-UAB)

The Faculty's MD studies are characterized by the strong relationship between biomedical research and clinical practice.

BIOMEDICAL ENGINEERING

An interdisciplinary degree that provides with education in the fields of biomedicine, technology and biomedical computational modelling.

Teaching

Master's programmes

BIOINFORMATICS FOR HEALTH SCIENCES

The Master's programme in Bioinformatics for Health Sciences is designed to provide professionals and researchers with skills and abilities geared towards the development of new computational strategies and IT systems for their use in biomedical research.

PHARMACEUTICAL INDUSTRY AND BIOTECHNOLOGY

The primary aim of this Master's programme is to train students in the area of companies dedicated to the research of drugs and biotechnology products to prevent and treat human diseases.

BIOMEDICAL RESEARCH

The Master's degree in Biomedical Research focuses on the study of the molecular, cellular, physiological and evolutionary bases of biological processes and their pathological or adaptive alterations, and is mainly aimed at students who wish to obtain a PhD in different fields of Biomedicine.

CLINICAL ANALYSIS LABORATORY

The Master's programme in Bioinformatics for Health Sciences is designed to provide professionals and researchers with skills and abilities geared towards the development of new computational strategies and IT systems for their use in biomedical research.

PUBLIC HEALTH

The primary aim of this Master's programme is to train students in the area of companies dedicated to the research of drugs and biotechnology products to prevent and treat human diseases.

PRE-SERVICE SCIENCE TEACHER TRAINING

The Master's degree in Biomedical Research focuses on the study of the molecular, cellular, physiological and evolutionary bases of biological processes and their pathological or adaptive alterations, and is mainly aimed at students who wish to obtain a PhD in different fields of Biomedicine.

GENETIC COUNSELLING

This is the only course in Spain officially accredited by the European Board of Medical Genetics to train professional genetic consultants. The Master's in Genetic Counselling provides professionals to inform patients about genetic diseases and advises them on family planning issues related to them (understand their heritage, know the risk of transmission to offspring, etc.). In addition, DCEXS Faculty coordinates participates in different courses in several Master's coordinated by other universities: Neurosciences (UB), Clinical and Biomedical Research (UB), and Workplace Health and Safety (UPC).

Teaching

PhD in Biomedicine

The PhD Programme in Biomedicine forms part of the UPF Doctoral School and provides graduate students a training framework to develop a research project and complete a doctoral thesis in the fields of health and life sciences that allows them to become scientists. More than 400 doctoral students are currently enrolled in the programme, most of them conducting their research in public institutions within the PRBB. All its training activities are carried out in English and every year the programme attracts a large number of students from abroad. The awarded PhD degree complies with the requirements of the Spanish National Agency for the Evaluation, Quality and Accreditation (ANECA) and on October, 2011, the Spanish Ministry of Education awarded the 'Mention towards Excellence' (MEE2011-0323).

Teaching

Bringing Science to young students Programme

The DCEXS, in collaboration with PRBB, has the Bringing Science to young students Programme, which aims at encouraging scientific vocations and encompasses several scientific dissemination activities addressed to school children.
The main actions are:

PRBB AWARD

For high school research projects, celebrated yearly since 2005 *(http://premi.prbb.org/)*.

ESCOLAB ACTIVITIES

Visits to labs are organised for high school students since 2008 *(http://escolab.bcn.cat/)*.

PLAY DECIDE DEBATES

Role play in which high school students debate about socio-scientific topics.

UPF JUNIOR CAMPUS

A course on molecular biology addressed to high school students took place in 2013 and 2014.

SCIENTIFIC TALKS FOR HIGH SCHOOL STUDENTS IN THE PRBB AUDITORIUM

More than 350 students per year attend scientific talks about topics such as genomics, evolution or neuropharmacology.

DCEXS Sympo-siums

This initiative seeks to present the department's research programmes and promote the education of young scientists and provide a place where researchers can discuss and discuss their latest results. The Fourth Symposium of the DCEXS, entitled "Innovative in silico strategies in biomedical research" took place on the 11th of November 2015 at the Barcelona Biomedical Research Park. It was organized by the Bioinformatics Research Programme and it brought together leading researchers in the field. The programme included the following talks:

- **Alfonso Valencia**, Spanish National Cancer Research Centre. *"The mESC epigenetics network as an example of the combination of network and evolutionary analysis"*
- **Mihaela Zavolan**, Biozentrum, University of Basel. *"Exploiting single cell level heterogeneity to uncover in vivo hierarchies of miRNA targets"*
- **Caroline Gubser Keller**, Novartis Institutes for BioMedical Research. *"The splice is right: RNA-seq analysis to impact drug discovery for spinal muscular atrophy"*
- **Marta Filizola**, Structural and Chemical Biology, ISMMS. *"New Strategies for a New Era in G Protein-couples Receptor Drug Discovery"*
- **Gerhard Ecker**, Pharmaceutical Chemistry, University of Vienna. *"Prediction of drug - transporter interaction and its exploitation in biomedical research"*
- **Bart Vannieuwenhuyse**, Health Information Sciences, The Janssen Pharmaceutical Companies of Johnson & Johnson. *"Unlocking the value of Real World Data for lifesciences"*
- **Joaquín Dopazo**, Computational Genomics, Centro de Investigación Príncipe Felipe. *"Digging into thousands of variants to find disease genes in Mendelian and complex diseases"*

The Fifth Symposium took place on the 9th of September 2016. It was entitled "Quantitative Biology: a systems-level approach to life" and it was devoted to the emerging field of systems biology, whose goal is to understand living cells and organisms as a whole, using an interdisciplinary combination of theory, numerical simulations, and detailed quantitative measurements of biological processes. The symposium also served as the closing event of the 2016 International Conference on Systems Biology, organized in Barcelona by the UPF and the CRG *(http://www.icsb2016barcelona.org/)*.

- **Galit Lahav**, Harvard Medical School. *"Dynamics of Cancer Pathways in Single Cells"*
- **Buzz Baum**, University College London. *"The origins of eukaryotic cell organisation"*
- **Ruth Baker**, University of Oxford. *"Cell biology processes: model building and validation using quantitative data"*
- **Michael Elowitz**, California Institute of Technology. (Perspective talk), *"Signaling, memory, and fate at the single-cell level"*
- **David Sprinzak**, Tel Aviv University. *"The interplay between cell-cell signaling and cell morphology"*
- **Ala Trusina**, Niels Bohr Institute. *"Asymmetric Damage Segregation: when history and stress matter"*
- **Marta Ibañes**, Universitat de Barcelona. *"Redundancy and cooperation in signaling for patterning"*

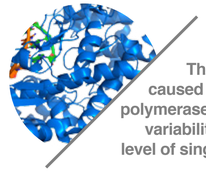
One of the main aims of the symposiums is to promote the education of young scientists, therefore students are actively invited to participate and encouraged to present their data in the poster sessions. Each year, 300 people registered for the symposium, and over 20 PhD and Master's students participated in the poster competition.

Scientific Highlights

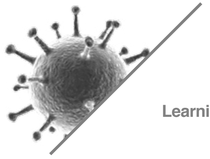
Cell autophagy, a key process in muscle regeneration during ageing

New ancestor to humans discovered

The way to reduce the adverse cognitive effects of cannabis has been identified



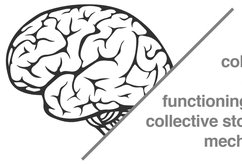
The errors caused by RNA polymerase induce variability at the level of single cells



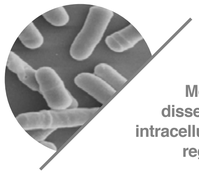
Learning from viruses

A new and efficient method discovers switches predictive of cancer

The forces that contribute to the inner ear development



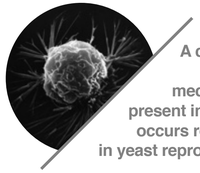
The coherence of brain functioning due to collective stochastic mechanisms



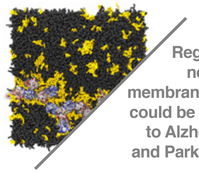
Molecular dissection of intracellular iron regulation

Genome sequencing reveals ancient interbreeding between chimpanzees and bonobos and creates new conservation opportunities

Social changes due to the economic crisis



A complex genetic mechanism present in cancer occurs routinely in yeast reproduction



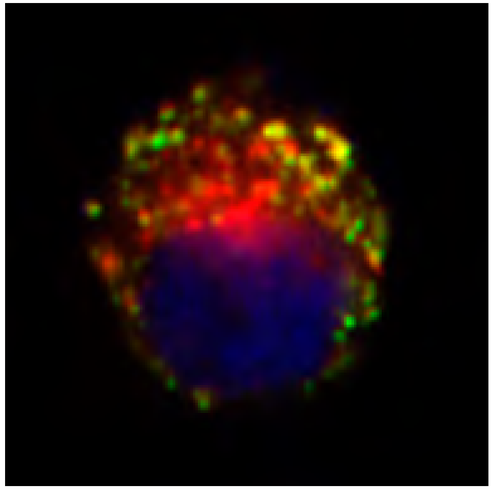
Regulating neuronal membrane lipids could be the key to Alzheimer's and Parkinson's

The economic crisis accentuates the existing gender differences in periods of time off work

Scientific Highlights

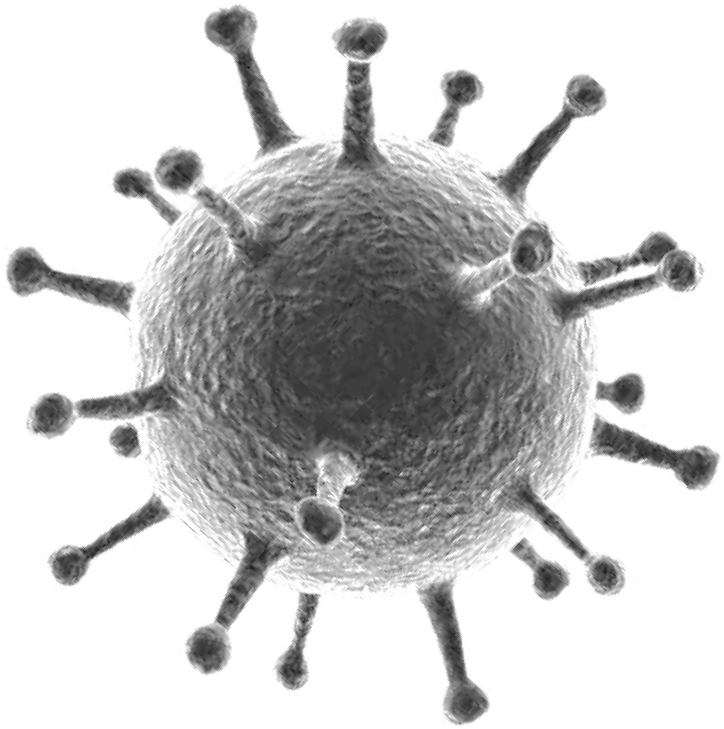
Cell autophagy, a key process in muscle regeneration during ageing

García-Prat L, Martínez-Vicente M, Perdiguero E, Ortet L, Rodríguez-Ubreva J, Rebollo E, Ruiz-Bonilla V, Gutarra S, Ballestar E, Serrano AL, Sandri M, Muñoz-Cánoves P (2016) Autophagy maintains stemness by preventing senescence. Nature 529, 37–42.

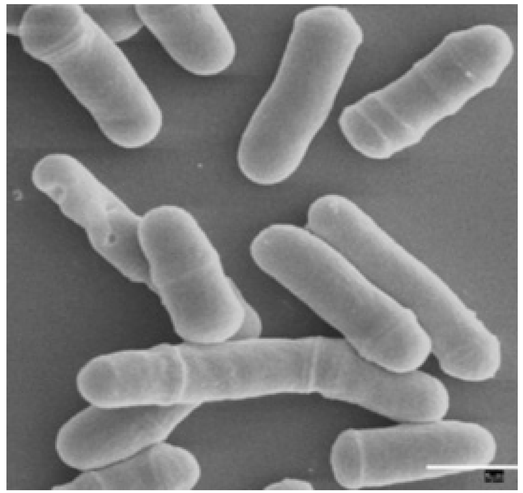


Learning from viruses

Jungfleisch J, Nedialkova DD, Dotu I, Sloan KE, Martinez-Bosch N, Brüning L, Raineri E, Navarro P, Bohnsack MT, Leidel SA, Díez J (2016) A novel translational control mechanism involving RNA structures 1 within coding sequences. Genome Res 27(1):95-106.

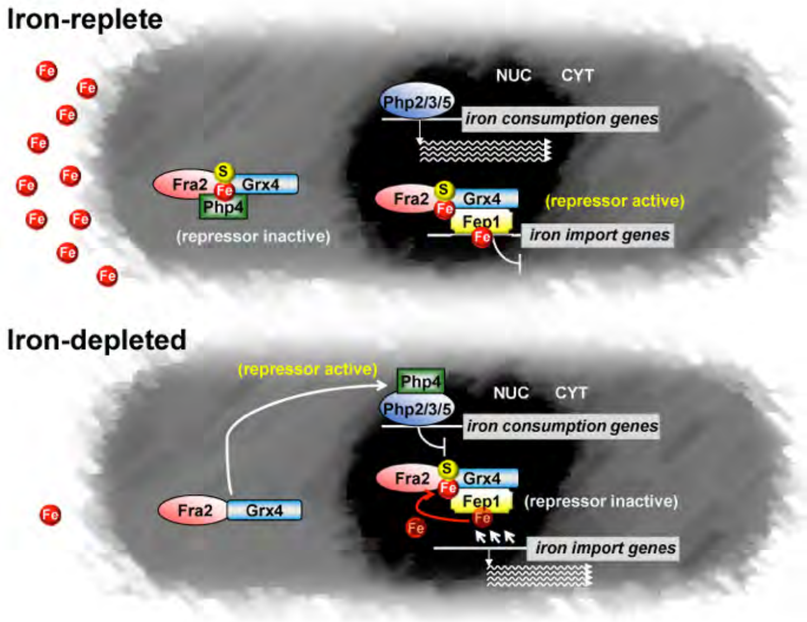


Scientific Highlights



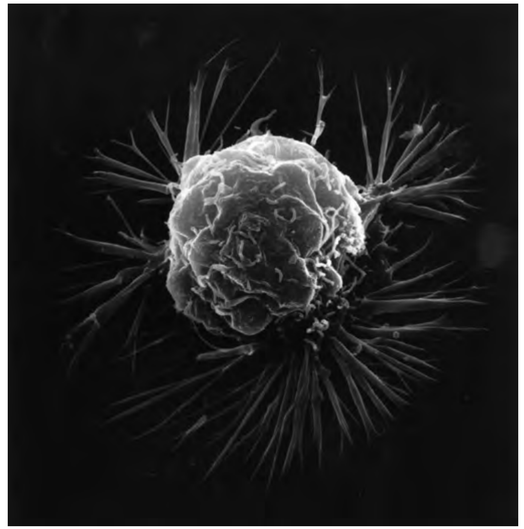
Molecular dissection of intracellular iron regulation

Encinar del Dedo J, Gabrielli N, Carmona M, Ayté J, Hidalgo E (2015) A cascade of iron-containing proteins governs the genetic iron starvation response to promote iron uptake and inhibit iron storage in fission yeast. PLoS Genet 25;11(3):e1005106.



A complex genetic mechanism present in cancer occurs routinely in yeast reproduction

Alves-Rodrigues I, Ferreira PG, Moldón A, Vivancos AP, Hidalgo E, Guigó R, Ayté J (2016) Spatiotemporal Control of Forkhead Binding to DNA Regulates the Meiotic Gene Expression Program. Cell Rep 14(4):885-95.



Scientific Highlights

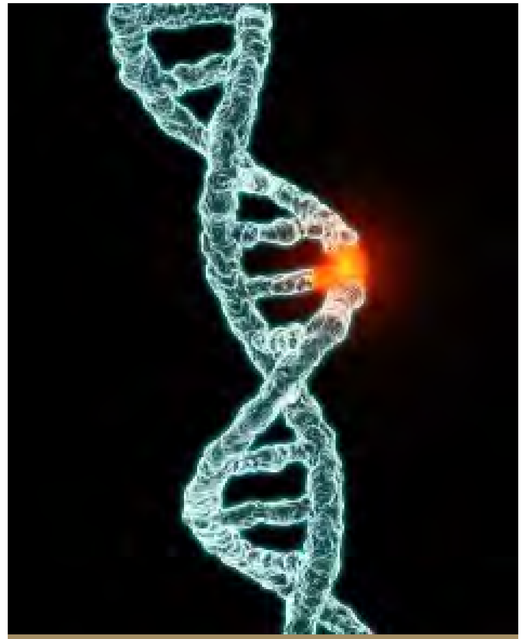
New ancestor to humans discovered

Mondal M, Casals F, Zheng H, Dall'Olio GM, Pybus M, Netea MG, Comas D, Laayouni H, Li Q, Majumder PP, Bertranpetit J (2016) Genomic analysis of the Andamanese provides new insights into the spread of humans in Asia and their local adaptations. Nat Genet 48(9):1066-70.

Andamesos. *Font: Mueso Pitt Rivers, Oxford*

A new and efficient method discovers switches predictive of cancer

Sebestyén E, Singh B, Miñana B, Pagès A, Mateo F, Pujana MA, Valcárcel J, Eyras E (2016) Large-scale analysis of genome and transcriptome alterations in multiple tumors unveils novel cancer-relevant splicing networks . Gen Res 26(6):732-44.



Kaden11a (CC)

Scientific Highlights

Ngogo Chimpanzee Project (Uganda) - *Kevin Kevin Langergraber*

Genome sequencing reveals ancient interbreeding between chimpanzees and bonobos and creates new conservation opportunities

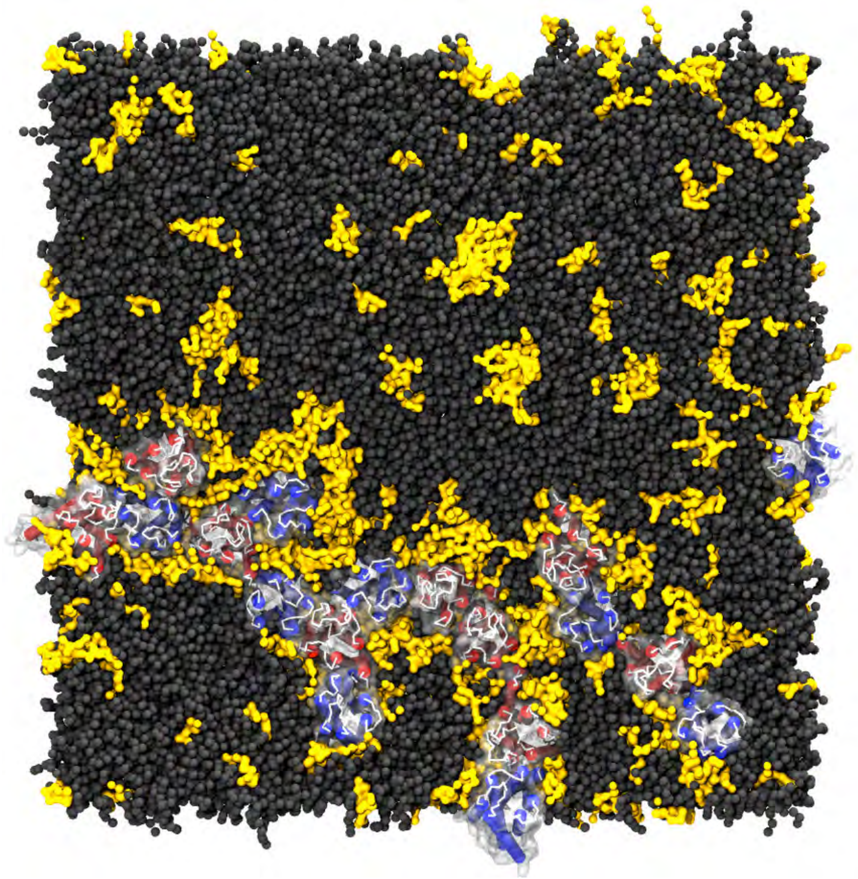
De Manuel M, Kuhlwilm M, Frandsen P, Sousa VC, Desai T, Prado-Martinez J, Hernandez-Rodriguez J, Dupanloup I, Lao O, Hallast P, Schmidt JM, Heredia-Genestar JM, Benazzo A, Barbujani G, Peter BM, Kuderna LFK, Casals F, Angedakin S, Arandjelovic M, Boesch C, Kühl H, Vigilant L, Langergraber K, Novembre J, Gut M, Gut I, Navarro A, Carlsen F, Andrés AM, Siegismund HR, Scally A, Excoffier L, Tyler-Smith C, Castellano S, Xue Y, Hvilsom C, Marques-Bonet T. Chimpanzee genomic diversity reveals ancient admixture with bonobos. Science 354(6311):477-81.

Ngogo Chimpanzee Project (Uganda) - *Kevin Kevin Langergraber*

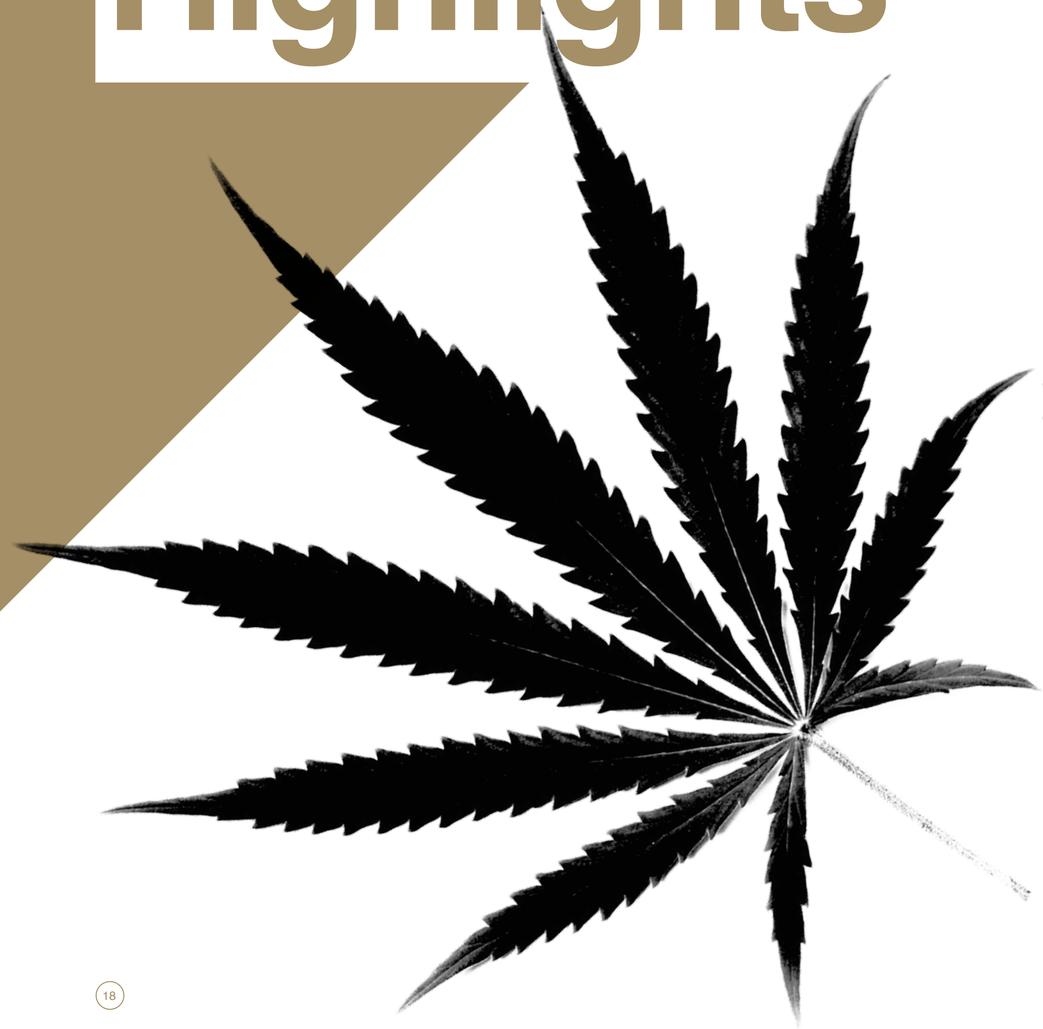
Scientific Highlights

Regulating neuronal membrane lipids could be the key to Alzheimer's and Parkinson's

Guixà-González R, Javanainen M, Gómez-Soler M, Cordobilla B, Domingo JC, Sanz F, Pastor M, Ciruela F, Martinez-Seara H, Selent J (2016) Membrane omega-3 fatty acids modulate the oligomerisation kinetics of adenosine A2A and dopamine D2 receptors membrane levels of docosahexaenoic acid. Scientific Reports 6:19839.

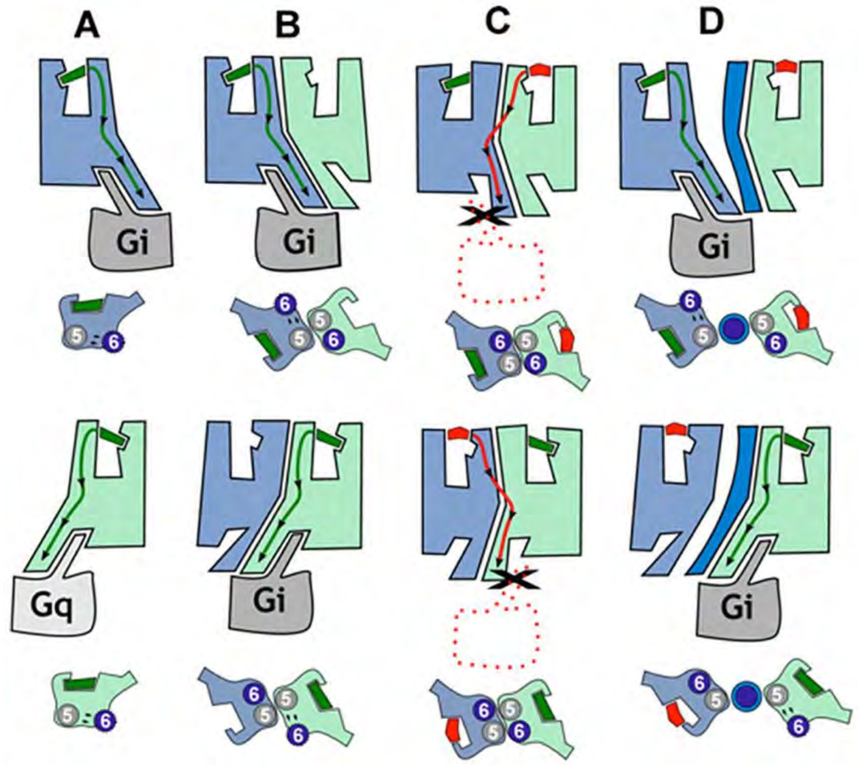


Scientific Highlights

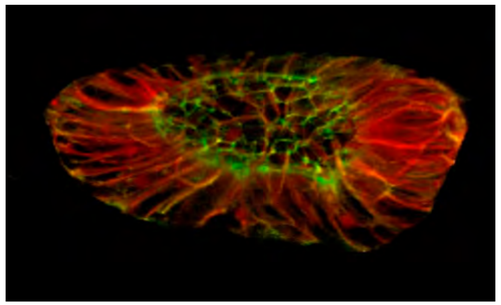


The way to reduce the adverse cognitive effects of cannabis has been identified

Moreno E, Lanfumey L, Cordomí A, Pastor A, de La Torre R, Gasperini P, Navarro G, Howell LA, Pardo L, Lluís C, Canela EI, McCormick PJ, Maldonado R, Robledo P (2015) Cognitive Impairment Induced by Delta9- tetrahydrocannabinol Occurs through Heteromers between Cannabinoid CB1 and Serotonin 5-HT2A Receptors PLoS Biol 13(7): e1002194.



Scientific Highlights



The forces that contribute to the inner ear development

Hoijman E, Rubbini D, Colombelli J, Alsina B (2015) How epithelial cells use forces and fluids to sculpt cavities during development. Mitotic cell rounding and epithelial thinning regulate lumen growth and shape. Nat Commun 6:7355.

Social changes due to the economic crisis

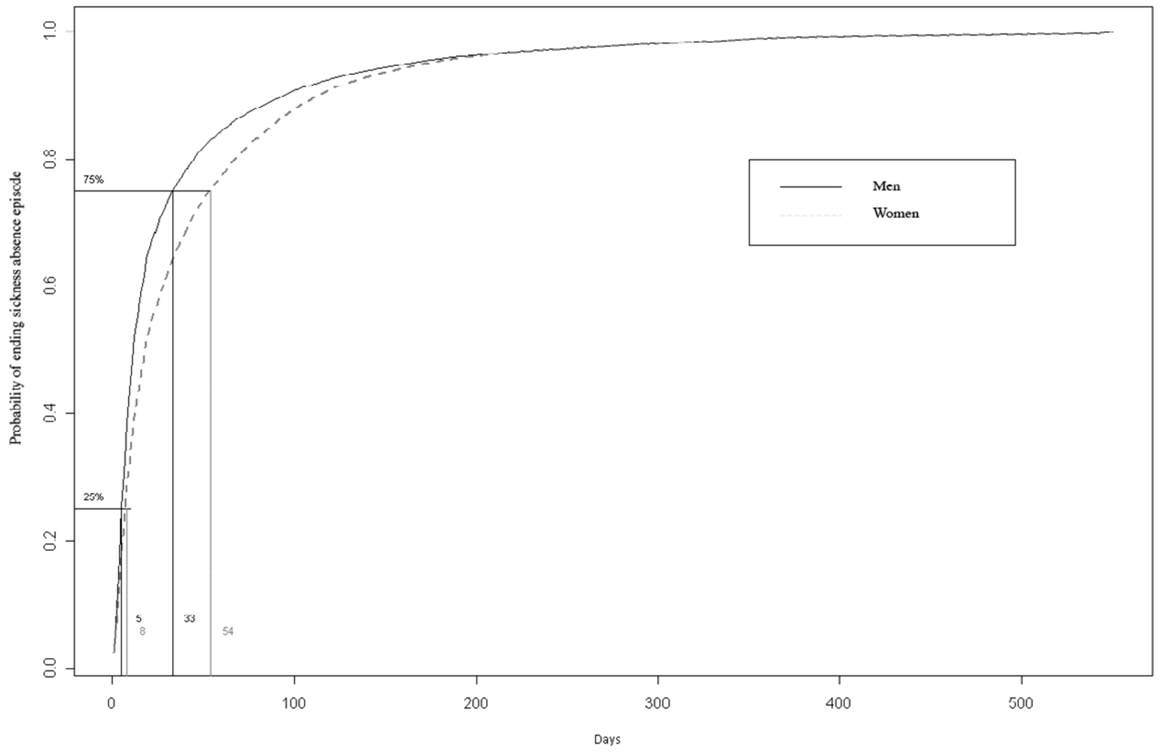
Colell E, Sánchez-Niubò A, Delclos GL, Benavides FG, Domingo-Salvany A (2015) Economic crisis and changes in drug use in the Spanish economically-active population. Addiction 110(7):1129-37.

Scientific Highlights

The economic crisis accentuates the existing gender differences in periods of time off work

Murcia López G, Delclós Clanchet J, Ubalde López M, Calvo Bonacho E, Benavides FG (2016) Has the Spanish economic crisis affected the duration of sickness absence episodes? Soc Sci Med 160:29-34.

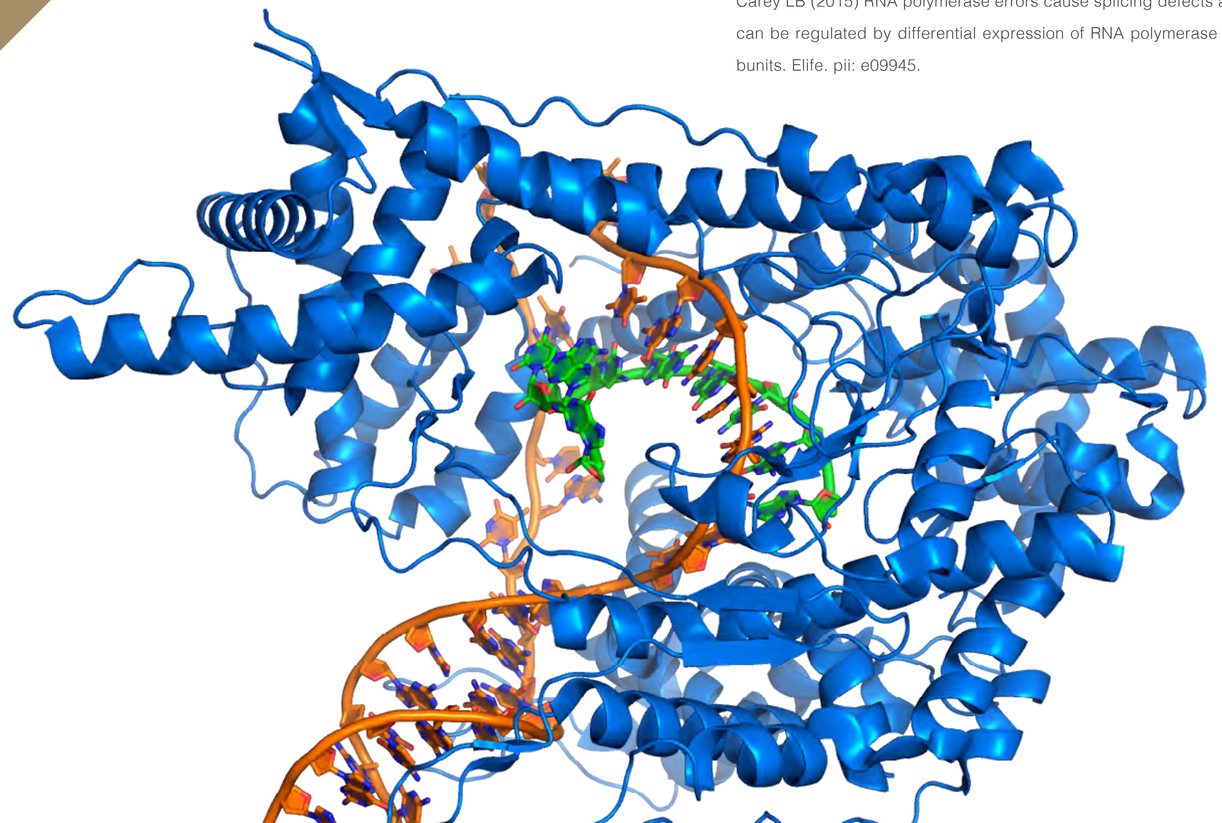
Figure 1. Probability distribution (Wang Chang estimation) of ending a nonwork-related sickness absence episode due to musculoskeletal disorders by sex. Integrated System for Sickness Absence Management of the ICAMS 2007-2008



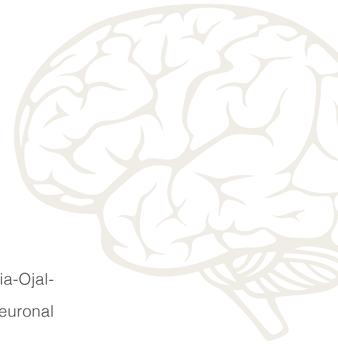
Scientific Highlights

The errors caused by RNA polymerase induce variability at the level of single cells

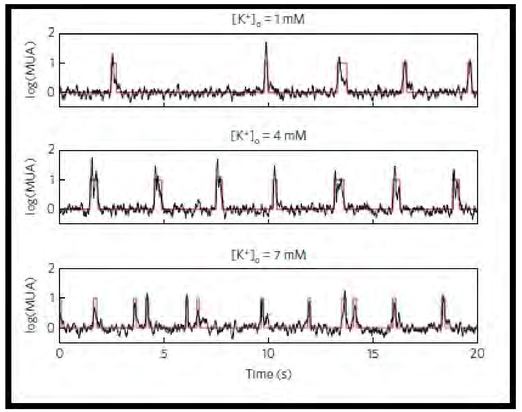
Carey LB (2015) RNA polymerase errors cause splicing defects and can be regulated by differential expression of RNA polymerase subunits. Elife. pii: e09945.



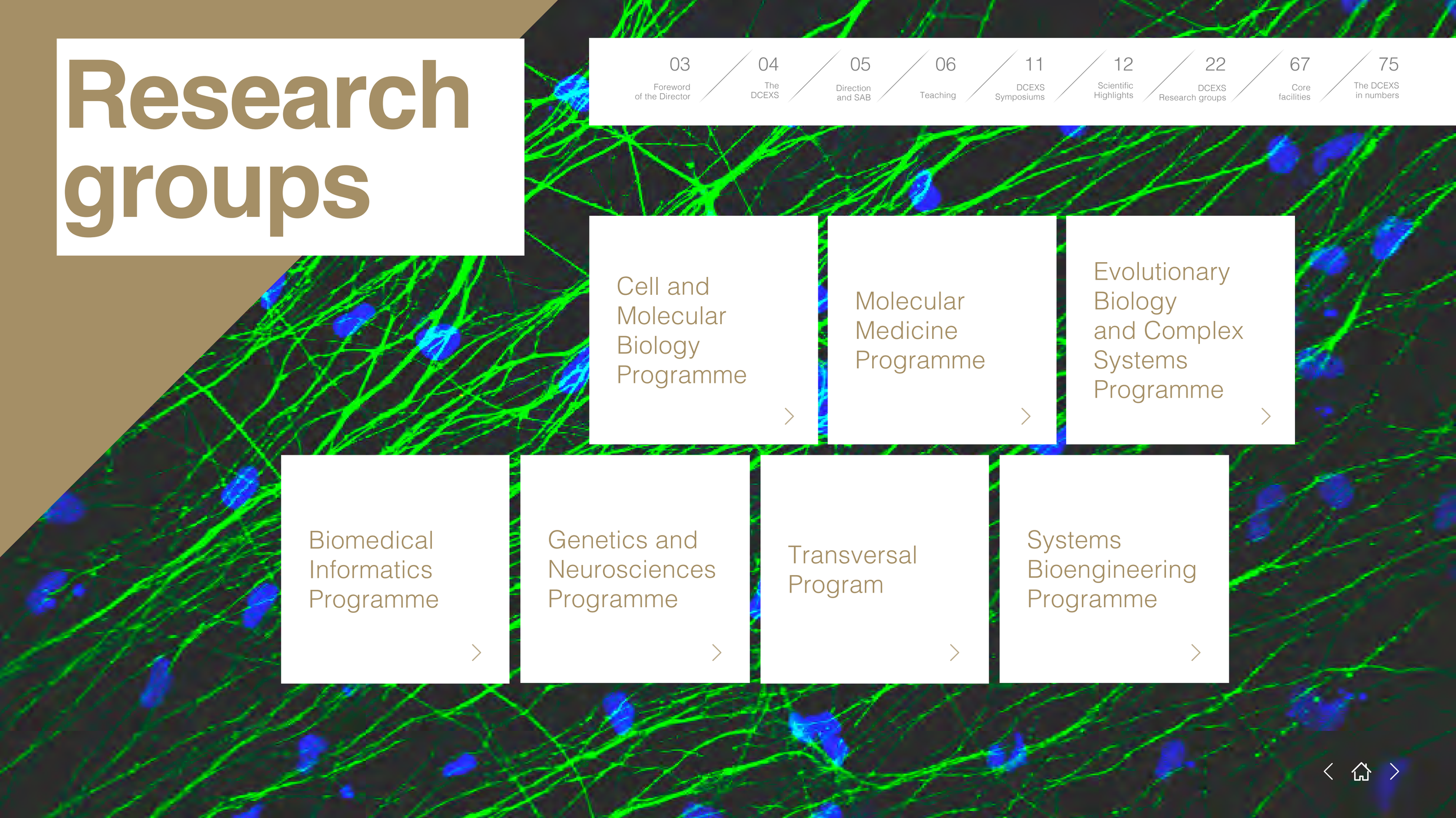
The coherence of brain functioning due to collective stochastic mechanisms



Sancristóbal B, Rebollo B, Boada P, Sanchez-Vives MV, Garcia-Ojalvo J (2016) Collective stochastic coherence in recurrent neuronal networks. Nat Phys 12: 881-7.



Research groups



Cell and Molecular Biology Programme

Molecular Medicine Programme

Evolutionary Biology and Complex Systems Programme

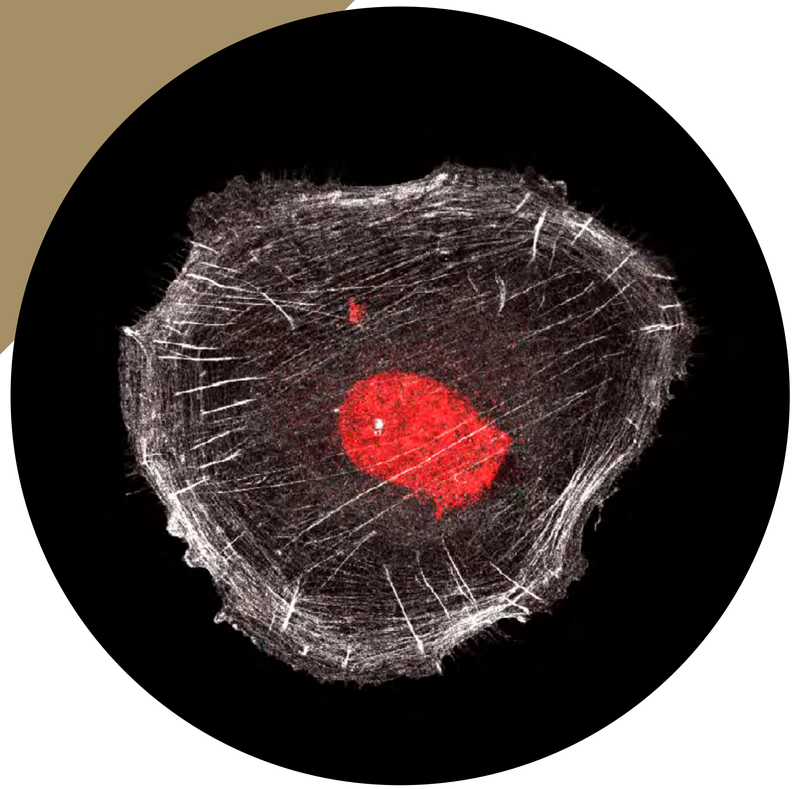
Biomedical Informatics Programme

Genetics and Neurosciences Programme

Transversal Program

Systems Bioengineering Programme

Research groups



Cell and Molecular Biology Programme

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 and pathology. The main research activities of the programme are divided in three areas: cell signaling, genomic regulation and pathophysiology. The integration of these three disciplines provides a depth insight on intracellular mechanisms in response to different stimuli including stress or harmful molecules and viruses. One of the main aims of this programme is to elucidate the molecular basis of human diseases.

COORDINATOR

Miguel Valverde

- Cell Biology Group
- Cell Signaling Research Group
- Molecular physiology
- Ageing Brain Research Group
- Biophysics of the Immune System
- Infection Biology Group
- Molecular Virology

Cell Biology Group

Pura Muñoz-Cánoves

Awards

- La Vanguardia of Science Award (2015)
- Pfizer Award on Basic Research in Biomedicine (2015)
- Elected EMBO Member (2015)
- City of Barcelona Award on Life Sciences (2015)
- City of Gandia Award on Scientific Research (2016)

Website

www.upf.edu/cellbiology

Transfer activities

Prospera Biotech

Research Outline

How do stem cells maintain quiescence, activate, proliferate, differentiate or self-renew? How do they interact with the external inflammatory environment? Our research is aimed to understand the mechanisms regulating stem cell homeostasis and regenerative functions, focusing specially on stem cells of skeletal muscle. Our studies have a direct impact on regenerative medicine. In particular, we want to shed light on: the age-associated muscle decline and wasting (sarcopenia) and loss of stem-cell regenerative functions with aging; and the physiopathology of muscular dystrophies, with a specific interest in the contribution of inflammation and fibrosis to dystrophy progression.

Current Projects / Research Lines

- **Skeletal muscle regenerative decline with aging: causes and potential reversal**

Analysis of autophagy in aging muscle stem cells and relationship with defective regeneration.
Analysis of signalling pathways driving aging of muscle stem cells.
Analysis of the impact of nutritional regimes on stem cell rejuvenation in aging muscle.

- **Inflammation and fibrosis in muscle regeneration: implications for Duchenne muscular dystrophy progression.**

Genetic demonstration of the role of inflammation in regenerating and dystrophic muscle.
Genetic tracing analysis to demonstrate the cellular origin of myofibroblasts (i.e. fibrosis) in fibrosis progression in dystrophic muscle.

Team during 2015-16

Other PIs (Associate / Assistant Professors at UPF): Antonio L. Serrano, Eusebio Perdiguero.

Postdocs: Laura García Prat, Joana Guerra Badell, Yacine Kharraz, Patrizia Pessina, Jessica Segalés.

PhD students: Laura García-Prat, Joana Guerra Badell, Diana Mesquita, Beatriz de Lucas, Victoria Moiseeva, Antonio Martínez García, Pedro Maseres Javaloy.

Technicians: Vanessa Ruíz, Laura Ortet, Merce Jardí, Susana Gutarra, Vera Lukesova, Begoña Ampudia.

Project Manager: Marina Raya.

Selected publications 2015-16

García-Prat L, Martínez-Vicente M, Perdiguero E , Ortet L, Garcia-Ubreva J, Rebollo E, Ruiz-Bonilla V, Gutarra S, Ballestar E, Serrano AL, Sandri M, Muñoz-Cánoves P (2016) Autophagy maintains stemness by preventing senescence. Nature 529: 37-42.

Gómez-Del Arco P, Perdiguero E, Yunes-Leites PS, Acín-Pérez R, Zeini M, Segalés J, López-Maderuelo D, Ornés B, Enshell-Seijffers D, Morgan B, Georgopoulos K, Islam AB, Braun T, de la Pompa JL, Kim J, Enriquez JA, Ballestar E, Muñoz-Cánoves P, Redondo JM (2016) The Chromatin Remodeling Complex Chd4/NuRD Controls Striated Muscle Identity and Metabolic Homeostasis. Cell Metab. 5:881-92.

Segalés J, Islam AB, Kumar R, Liu QC, Sousa-Victor P, Dilworth FJ, Ballestar E, Perdiguero E, Muñoz-Cánoves P (2016) Chromatin-wide and transcriptome profiling integration uncovers p38α MAPK as a global regulator of skeletal muscle differentiation. Skelet Muscle. 6:9.

Sousa-Victor P, García-Prat L, Serrano AL, Perdiguero E, Muñoz-Cánoves P (2015) Muscle stem cell aging: regulation and rejuvenation. Trends Endocrinol Metab. 26(6):287-96

Pessina P, Kharraz Y, Jardí M, Fukada SI. Serrano AL, Perdiguero E, Muñoz-Cánoves P (2015) Fibrogenic cell plasticity blunts tissue regeneration and aggravates muscular dystrophy. Stem Cell Reports 4:1046-60.

Other relevant publications from last 10 years

Sousa-Victor P, Gutarra S, García-Prat L, Rodriguez-Ubreva J, Ortet L, Ruiz-Bonilla V, Jardí M, Ballestar E, González S, Serrano AL, Perdiguero E, Muñoz-Cánoves P (2014) Geriatric muscle stem cells switch reversible quiescence into senescence. Nature 506:316-21.

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-Raja B, Lafuste P, Ruiz-Bonilla V, Jardí M, Gherardi R, Christov C, Dierssen M, Carmeliet P, Degen JL, Dewerchin M, Muñoz-Cánoves P (2008) Fibrinogen drives dystrophic muscle fibrosis via a TGFbeta/alternative macrophage activation pathway. Genes Dev 22:1747-52.

Other relevant information 2015-16

Organization of International Conferences

International Advisory Committeee of The Batsheva de Rothschild Workshop on Skeletal and Cardiac Myogenesis The David Lopatie Conference Centre, Weizmann Institute of Science, Rehovot, Israel (2016).

Cell Signaling Research Group

Francesc Posas and Eulàlia de Nadal

Website

www.upf.edu/cellsignaling

Patents

"Control of Cancer Progression by Retinoblastoma Phosphorylation"
(submitted on April 7, 2016; EP16382156.4).

Participation in agreements with private bodies

Cooperation agreement on support technology transfer in the field of biotechnology.
Fundación Botín (2014-2018).

Research Outline

Our group studies how cells detect and respond to environmental changes. We investigate the molecular mechanisms required to respond to changes in the extracellular environment and which are the adaptive responses required for cell survival. Specifically, we focus on signal transduction pathways related to stress responses. Using the S. cerevisiae yeast and higher eukaryotic cells as model organisms, we study stress adaptation across eukaryotes. We focus on the modulation of several aspects of the cell physiology, such as the control of cell cycle and regulation of gene expression. We also analyse the basic signalling properties of the HOG/p38 pathway. Last, using complex engineered networks we implement cellular communications to perform in vivo cellular computation.

Current Projects / Research Lines

- **Regulation of SAPK signalling pathways in eukaryotic cells**

Study of the signalling properties of the p38/Hog1 SAPK pathway in response to cellular stress. Signal integration and crosstalk during the dynamic stress response in single cells.

- **Defining the functional landscape for a SAPK in a eukaryotic organism**

Definition of the substrates regulated by Hog1 and dissection of the cellular processes involved in stress adaptation.

- **Molecular basis for stress-adaptation by the p38 MAPK in mammalian cells**

Unravelling whether the functions of the yeast Hog1 are also conserved by p38 in mammalian cells.

- **Chromatin dynamics of transcriptional stress response**

Characterization of the regulatory mechanisms required for modulation of gene expression in response to stress by the Hog1 and p38 SAPKs.

- **Cell cycle control by Hog1 and p38 MAPKs**

Characterization of the role of Hog1 and p38 in the regulation of cell cycle progression in response to stress.

- **Distributed Biological Computation**

Comprehensive understanding of biological computation and its implementation to the relevant problem of the Diabetes.

Team during 2015-16

Postdocs: Alba Duch, Silvia Tognetti, Manel Joaquin, Albert Gubern, Arnau Ulsamer, Ramon Amat, Gerhard Seisenbacher, Romilde Manzoni, Jana Sánchez, Silvia Vázquez, Carme Solé, Jorge Pérez, René Böttcher, David Canadell.

PhD students: Caterina Carbonell, Arturo Urrios, Berta Canal, Gerard Martínez, Pedro Maseres.
Technicians: Santiago Cavero, Laia Subirana, Aída Fernández.
Project Manager: Montse Morillas.

Selected publications 2015-16

González-Novo A, Jiménez J, Clotet J, Nadal-Ribelles M, Cavero S, de Nadal E*, Posas F* (2015) Hog1 targets Whi5 and Msa1 transcription factors to down-regulate cyclin expression upon stress. Mol Cell Biol. 35(9):1606-18.

Nadal-Ribelles M&, Mas G&, Millan G, Solé C, Ammerer G, Chavez S, Posas F*, de Nadal E* (2015) H3K4 Monomethylation Dictates Nucleosome Dynamics and Chromatin Remodeling at Stress-Responsive Genes. Nucleic Acids Res. 43(10):4937-49.

Macia J&, Manzoni R&, Conde N&, Urrios A, de Nadal E, Solé R*, Posas F* (2016) Implementation of complex biological logic circuits using spatially distributed multicellular consortia. PLOS Comput. Biol. 12(2):e1004685.

Studer RA, Rodriguez-Mias RA, Haas KM, Hsu JI, Viéitez C, Solé C, Swaney DL, Stanford LB, Liachko I, Böttcher R, Dunham MJ, de Nadal E, Posas F, Beltrao P, Villén J (2016) Evolution of protein phosphorylation across 18 fungal species. Science 354(6309):229-232.

Gubern A, Joaquin M, Marquès M, Maseres P, Garcia-Garcia J, Amat R, González-Nuñez D, Oliva B, Real FX, de Nadal E*, Posas F* (2016) The N-terminal phosphorylation of RB by p38 bypasses its inactivation by CDKs and prevents proliferation in cancer cells. Mol Cell. 64(1):25-36.

& Authors contributed equally to the work; * Corresponding Author

Other relevant publications from last 10 years

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.

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.

Nadal-Ribelles M&, Solé C&, Xu Z, Steinmetz LM, de Nadal E*, Posas F* (2014) Control of Cdc28 CDK1 by a stress-induced lncRNA. Mol Cell. 53(4):549-61.

Molecular physiology

Miguel Ángel Valverde de Castro and José Manuel Fernández Fernández

Website

www.upf.edu/web/lmp

Organization of the V RECI

Present and Future in Ion Channel Research"
(Barcelona, 2015).

Research Outline

Ion channels and regulatory proteins involved in the generation of intracellular calcium signals focus our research. Our group has a special interest in those participating in mechano-osmotic responses, the control of vascular tone, airways physiology and neurotransmission.

Current Projects / Research Lines

- **MECHANICA project: MEchano / osmosensitive CHAnNels in epIthelia, Cancer and Asthma**

Study of ion channels of the Transient Receptor Potential (TRP) and Piezo families, their molecular determinants for gating and regulation, and their role in epithelial physiology and pathology.

- **Structure-Function relationship and Pharmacology of Ion Channels**

Functional characterization of novel genetic, molecular and cellular mechanisms underlying the pathogenesis of cardiovascular and neurological disorders, with focus on hemiplegic migraine (HM), different forms of ataxia and stroke-like episodes. Our work is focused on the BK_{Ca} channel, Piezo channels and the high-voltage activated $Ca_V2.1$ (P/Q) Ca^{2+} channel and the characterization of the molecular determinants controlling channel function/dysfunction, and modulation.
In collaboration with the Sussex Drug Discovery Centre (University of Sussex, United Kingdom), we are developing novel $Ca_V2.1$ selective tool molecules capable of reversing the functional consequences of channel mutations linked to neurological disorders, and exploring their potential therapeutic use.

Team during 2015-16

Postdocs: Fanny Rubio Moscardó, Selma A. Serra Pascual, Carole Jung, Alejandro Berna Erro, Mercè Izquierdo Serra ("Juan de la Cierva-Formación" Fellow).
PhD students: Pablo Doñate Macián, Carlos Pardo Pastor, Julia Carrillo García.
Technicians: Cristina Plata Fernández.

Selected publications 2015-16

Hung WC, Yang JR, Yankaskas CL, Wong BS, Wu PH, Pardo-Pastor C, Serra SA, Chiang MJ, Gu Z, Wirtz D, Valverde MA, Yang JT, Zhang J, Konstantopoulos K. (2016) Confinement Sensing and Signal Optimization via Piezo1/PKA and Myosin II Pathways. *Cell Rep* 15(7):1430-41.

Bahamonde MI, Serra SA, Drechsel O, Rahman R, Marcé-Grau A, Prieto M, Ossowski S, Macaya A, Fernández-Fernández JM. (2015) A Single Amino Acid Deletion (ΔF1502) in the S6 Segment of CaV2.1 Domain III Associated with Congenital Ataxia Increases Channel Activity and Promotes Ca2+ Influx. *PLoS One* 10(12):e0146035.

Garcia-Elias A, Berna-Erro A, Rubio-Moscardo F, Pardo-Pastor C, Mrkonjić S, Sepúlveda RV, Vicente R, González-Nilo F, Valverde MA. (2015) Interaction between the Linker, Pre-S1, and TRP Domains Determines Folding, Assembly, and Trafficking of TRPV Channels. *Structure* 23(8):1404-13.

Fernández-Mariño AI, Cidad P, Zafra D, Nocito L, Domínguez J, Oliván-Viguera A, Köhler R, López-López JR, Pérez-García MT, Valverde MÁ, Guinovart JJ, Fernández-Fernández JM. (2015) Tungstate-targeting of BKαβ1 channels tunes ERK phosphorylation and cell proliferation in human vascular smooth muscle. *PLoS One* 10(2):e0118148.

Mrkonjić S, Garcia-Elias A, Pardo-Pastor C, Bazellières E, Trepat X, Vriens J, Ghosh D, Voets T, Vicente R, Valverde MA. (2015) TRPV4 participates in the establishment of trailing adhesions and directional persistence of migrating cells. *Pflügers Arch* 467(10):2107-9.

Other relevant publications from last 10 years

Garcia-Elias A, Mrkonjic S, Pardo-Pastor C, Inada H, Hellmich UA, Rubio-Moscardó F, Plata C, Gaudet R, Vicente R, Valverde MA. (2013) Phosphatidylinositol-4,5-biphosphate-dependent rearrangement of TRPV4 cytosolic tails enables channel activation by physiological stimuli. *Proc Natl Acad Sci USA* 110(23):9553-8.

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 prevents P/Q channel modulation by SNARE proteins and lowers exocytosis. *Proc Natl Acad Sci USA* 107(4):1672-7.

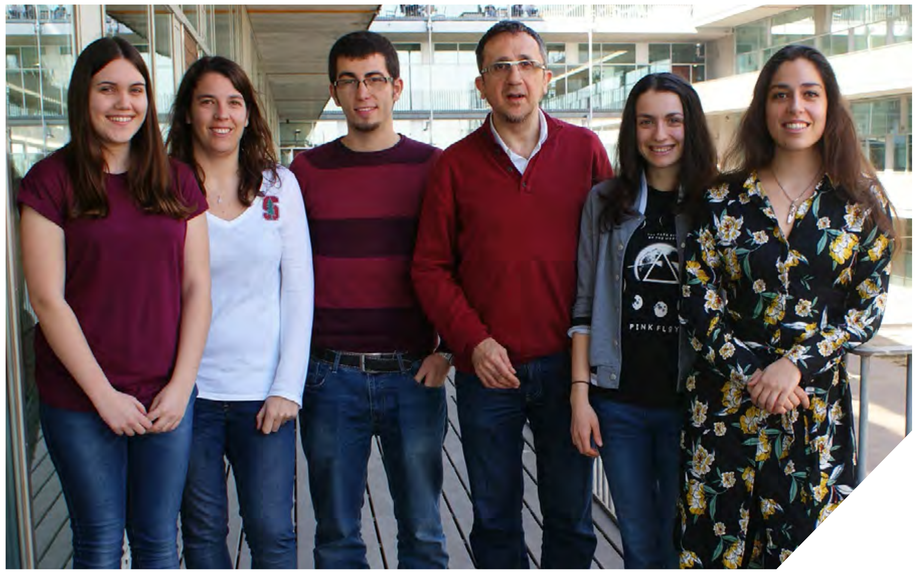
Fernandes J, Lorenzo IM, Andrade YN, Garcia-Elias A, Serra SA, Fernández-Fernández JM, Valverde MA. (2008) IP_3 sensitizes TRPV4 channel to the mechano- and osmotransducing messenger 5'-6'-epoxyeicosatrienoic acid. *J Cell Biol* 181(1):143-55.

Ageing Brain Research Group

Francisco J. Muñoz

Website

www.upf.edu/fisio



Research Outline

Free radicals production generated by fibrillar aggregates of Aß lead to neuronal death in Alzheimer's Disease (AD). Aß activates nitric oxide (NO) production which reacts to form peroxynitrite that nitrotyrosine proteins, mainly the triose phosphate isomerase (TPI) producing the toxic methylglyoxal (MG). We have demonstrated that MG is the major intracellular effector of neuronal apoptosis in AD through the activation of caspase-3 and bax, and the decrease of bcl-2 and mitochondrial potential. We have also found that albumin, an extracellular protein, is also significantly nitrotyrosinated in brain, cerebrospinal fluid and plasma of AD patients contributing to the progression of the disease.

Current Projects / Research Lines

- **Study of the effect of the ß-galactosidase decrease and the consequent increase in the ganglioside GM1 in neurons on the production and aggregation of the amyloid ß-peptide**

APP could be localized in GM1 clusters preventing its processing by α-secretase. Moreover GM1 clusters could be promoting BACE1 amiloydogenic activity. An increase of the concentration of Aβ in neuron extracellular matrix will favour Aβ oligomerization by the interaction with GM1 especially in the asialyzated state.

- **Study of the role of nitro-oxidative stress in the formation of Aß oligomers and fibers and their toxicity in skeletal muscle in Inclusion Body Miopathy type 2**

The Aß binding to GM1 is regulated by sialic acid. Interestingly GNE (Bifunctional UDP-N- acetylglucosamine 2-epimerase / N-acetylmannosamine kinase) myopathy (GNE-m) is a degenerative disease that affects to skeletal muscle due to unusual intracellular aggregation of Aß. The mutation in GNE impairs protein syalization in cells.

Team during 2015-16

PhD students: Mònica Bosch-Morató, Biuse Guivernau, Victòria Valls-Comamala.

Selected publications 2015-16

Guivernau B, Bonet J, Valls-Comamala V, Bosch-Morató M, Godoy JA, Inestrosa NC, Perálvarez-Marín A, Fernández-Busquets X, Andreu D, Oliva B, Muñoz FJ (2016) Amyloid-β peptide nitrotyrosination stabilizes oligomers and enhances NMDAR-mediated toxicity. J Neurosci. 36:11693-703.

Ramos-Fernández E, Tajes M, Ill-Raga G, Vargas L, Busquets-García A, Bosch-Morató M, Guivernau B, Valls-Comamala V, Gomis M, Grau C, Fandos C, Rosen MD, Rabinowitz MH, Inestrosa N, Maldonado R, Altafaj X, Ozaita A, Alvarez A, Vicente R, Valverde MA, Muñoz FJ (2016) Glutamatergic stimulation induces GluN2B translation by the nitric oxide-Heme-Regulated eIF2α kinase in cortical neurons. Oncotarget. 7(37):58876-92.

Bosch-Morató M, Iriondo C, Guivernau B, Valls-Comamala V, Vidal N, Olivé M, Querfurth H, Muñoz FJ (2016) Increased amyloid β-peptide uptake in skeletal muscle is induced by hyposialylation and may account for apoptosis in GNE myopathy. Oncotarget. 7:13354-71.

Ill-Raga G, Tajes M, Busquets-García A, Ramos-Fernández E, Vargas LM, Bosch-Morató M, Guivernau B, Valls-Comamala V, Eraso-Pichot A, Guix FX, Fandos C, Rosen MD, Rabinowitz MH, Maldonado R, Alvarez AR, Ozaita A, Muñoz FJ (2015) Physiological Control of Nitric Oxide in Neuronal BACE1 Translation by Heme-Regulated eIF2α Kinase HRI Induces Synaptogenesis. Antioxid Redox Signal 22: 1295-1307.

Ill-Raga G, Palomer E, Ramos-Fernández E, Guix FX, Bosch-Morató M, Guivernau B, Tajes M, Valls-Comamala V, Jiménez-Conde J, Ois A, Pérez-Asensio F, Reyes-Navarro M, Caballo C, Gil-Gómez G, Lopez-Vilchez I, Galan AM, Alameda F, Escolar G, Opazo C, Planas AM, Roquer J, Valverde MA, Muñoz FJ (2015) Fibrinogen nitrotyrosination after ischemic stroke impairs thrombolysis and promotes neuronal death. Biochim Biophys Acta Mol Basis Dis, 1852:421-8.

Other relevant publications from last 10 years

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-beta peptide fibrils induce nitro-oxidative stress in neuronal cells. J Alzheimer Dis, 22:641-52.

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.

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.

Biophysics of the Immune System

Rubén Vicente

Website

www.upf.edu/web/lmp/biphysics-of-the-immune-system

Research Outline

The main interest of our group is to understand the role of ion fluxes and membrane composition regulation in the physiology of immune cells, having a special interest in calcium signalling, zinc fluxes and de novo ceramide synthesis.

Current Projects / Research Lines

- **ORMDL3 in immune cells**

Genome Wide Studies have associated ORMDL3 with asthma, inflammatory bowel diseases, type 1 diabetes among others. The family of proteins ORMDLs is involved in calcium signalling and sphingolipid synthesis. Our laboratory has been pioneer in doing functional studies of ORMDL proteins and is running projects in order to offer new insights into the pathophysiological relevance of ORMDL3 in the immune system.

- **Zinc transport in immune cells**

Zinc deficiency causes impairment in body growth, neurological disorders and immunosuppression, leading to morbidity and an increased infection rate. In our laboratory we are interested in exploring the function and regulation of zinc fluxes in immune cells in order to have a better understanding of zinc signals and its consequences.

Team during 2015-16

PhD students: Roberto García López and Kerstin Kiefer.

Selected publications 2015-16

Kiefer K, Carreras-Sureda A, García-López R, Rubio-Moscardó F, Casas J, Fabriàs G, Vicente R. (2015) *Coordinated regulation of the orosomucoid-like gene family expression controls de novo ceramide synthesis in mammalian cells.* J Biol Chem 290(5):2822-30.

Garcia-Elias A, Berna-Erro A, Rubio-Moscardo F, Pardo-Pastor C, Mrkonjić S, Sepúlveda RV, Vicente R, González-Nilo F, Valverde MA (2015) *Interaction between the Linker, Pre-S1, and TRP Domains Determines Folding, Assembly, and Trafficking of TRPV Channels.* Structure 23(8):1404-13.

Orta-Mascaró M, Consuegra-Fernández M, Carreras E, Roncagalli R, Carreras-Sureda A, Alvarez P, Girard L, Simões I, Martínez-Florensa M, Aranda F, Merino R, Martínez VG, Vicente R, Merino J, Sarukhan A, Malissen M, Malissen B, Lozano F (2016) *CD6 modulates thymocyte selection and peripheral T cell homeostasis* J Exp Med 213(8):1387-97.

Ramos-Fernández E, Tajes M, Ill-Raga G, Vargas L, Busquets-García A, Bosch-Morató M, Guivernau B, Valls-Comamala V, Gomis M, Grau C, Fandos C, Rosen MD, Rabinowitz MH, Inestrosa N, Maldonado R, Altafaj X, Ozaita A, Alvarez A, Vicente R, Valverde MA, Muñoz FJ (2016) *Glutamatergic stimulation induces GluN2B translation by the nitric oxide-Heme-Regulated eIF2α kinase in cortical neurons.* Oncotarget 7(37):58876-58892.

Carreras-Sureda A, Rubio-Moscardo F, Olvera A, Argilaguet J, Kiefer K, Mothe B, Meyerhans A, Brander C, Vicente R (2016) *Lymphocyte Activation Dynamics Is Shaped by Hereditary Components at Chromosome Region 17q12-q21.* PLoS One 11(11):e0166414.

Other relevant publications from last 10 years

Cantero-Recasens G, Fandos C, Rubio-Moscardo F, Valverde MA, Vicente R (2010) *The asthma-associated ORMDL3 gene product regulates endoplasmic reticulum-mediated calcium signaling and cellular stress.* Hum Mol Genet. 19, 111-21.

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 22:519-30.

Engelken J, Carnero-Montoro E, Pybus M, Andrews GK, Lalueza-Fox C, Comas D, Sekler I, de la Rasilla M, Rosas A, Stoneking M, Valverde MA, Vicente R*, Bosch E* (2014)*Extreme population differences in the human zinc transporter ZIP4 (SLC39A4) are explained by positive selection in Sub-Saharan Africa.* PLoS Genet 10(2):e1004128.

Infection Biology Group

Andreas Meyerhans

Website

www.upf.edu/web/virology-unit

Patent

"Meyerhans and J. Martinez are co-inventors of the patent application "**Human helicase DDX3 inhibitors as therapeutic agents**" (EP15167177.3). Filing date: 11/05/2015. Applicants: University Siena, Italy.

Patent

Meyerhans and J. Martinez are co-inventors of the patent application "**Neosoraphens**" (WO 2015154883). Filing date: 10.04.2015. Applicants: Helmholtz-Zentrum für Infektionsforschung (Braunschweig, Germany) and Twincore (Hannover, Germany).

Research Outline

We are aimed at understanding the factors that regulate the decision between an acute versus a persistent infection course, defining the factors that control the dynamic balance of virus expansion and immune control in persistent infections and identifying small chemical compounds with broad-spectrum antiviral activities.

Current Projects / Research Lines

- **Virus infection fate regulation: underlying mechanisms and therapeutic strategies of intervention**

Identification of the mechanisms that determine infection outcomes, gain of detailed insights into infection control mechanisms and setting of the basis for the development of new antiviral drugs.

- **Broad-spectrum antiviral drugs**

Together with an international team of research groups, we aim to test the antiviral properties of diverse natural products, and develop promising candidates further into broad-spectrum antiviral drugs.

- **Multi-scale mathematical models of virus-host interactions**

Together with the groups of Gennady Bocharov (Moscow, Russia), Vitaly Volpert (Lyon, France) and Boris Bachmetyev (Perm, Russia) we aim to describe the dynamics and pathogenesis of virus infections within their hosts by quantitative mathematical models.

Team during 2015-16

Postdocs: Jordi Argilaguet, Javier Martinez, Kashif Sadiq.
PhD students: Mireia Pedragosa, Graciela Riera, Katarina Smutna, Cristina Peligero, Eric Fleta.

Selected publications 2015-16

Tsunetsugu-Yokota Y, Kobayahi-Ishihara M, Wada Y, Terahara K, Takeyama H, Kawana-Tachikawa A, Tokunaga K, Yamagishi M, Martinez JP, Meyerhans A (2016) Homeostatically Maintained Resting Naive CD4(+) T Cells Resist Latent HIV Reactivation. Front Microbiol 7:1944.

Peligero C, Argilaguet J, Güerri-Fernandez R, Torres B, Ligero C, Colomer P, Plana M, Knobel H, García F, Meyerhans A (2015) PD-L1 Blockade Differentially Impacts Regulatory T Cells from HIV-Infected Individuals Depending on Plasma Viremia. PLoS Pathog 11(12):e1005270.

Martinez JP, Sasse F, Brönstrup M, Diez J, Meyerhans A (2015) Antiviral drug discovery: broad-spectrum drugs from nature. Nat Prod Rep 32(1):29-48.

Latorre I, Leidinger P, Backes C, Domínguez J, de Souza-Galvão ML, Maldonado J, Prat C, Ruiz-Manzano J, Sánchez F, Casas I, Keller A, von Briesen H, Knobel H, Meese E, Meyerhans A (2015) A novel whole-blood miRNA signature for a rapid diagnosis of pulmonary tuberculosis. Eur Respir J 45(4):1173-6.

Koutsoudakis G, Romero-Brey I, Berger C, Pérez-Vilaró G, Monteiro Perin P, Vondran FW, Kalesse M, Harmrolfs K, Müller R, Martinez JP, Pietschmann T, Bartenschlager R, Brönstrup M, Meyerhans A, Díez J (2015) Soraphen A: A broad-spectrum antiviral natural product with potent anti-hepatitis C virus activity. J Hepatol 63(4):813-21.

Other relevant publications from last 10 years

Brai A, Fazi R, Tintori C, Zamperini C, Bugli F, Sanguinetti M, Stigliano E, Esté J, Badia R, Franco S, Martinez MA, Martinez JP, Meyerhans A, Saladini F, Zazzi M, Garbelli A, Maga G, Botta M (2016) Human DDX3 protein is a valuable target to develop broad spectrum antiviral agents. Proc Natl Acad Sci U S A 113(19):5388-93.

Ehrhardt M, Leidinger P, Keller A, Baumert T, Díez J, Meese E, 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, Meyerhans A (2011) Hepatitis C virus RNA recombination in cell culture. J Hepatol 55(4):777-83.

Molecular Virology

Juana Díez Antón

Website

www.upf.edu/web/virology-unit

Patents filed as co-inventors

- Antiviral activity of Neosoraphens (Ref. PCT/EP2015/000757). 2015
- Antiviral agents comprising oligonucleotides containing G-quadruplexes. (Ref. ABG P7363EP00). 2015

Contracts with companies (White factor LC, 2015)

Research Outline

Positive-strand RNA ((+)RNA) viruses are a major threat to human health. Current key examples are the re-emerging mosquito-transmitted Dengue virus (DENV), Chikungunya virus (CHIKV) and Zika virus (ZIKV). (+)RNA viruses also provide a first-row view into cell biology since they completely depend on the infected cell to multiply. In our laboratory we are interested in understanding diverse aspects of these intimate interactions.

Current Projects / Research Lines

- **Definition of viral and cellular translation landscapes throughout infection**

A key step in the lifecycle of (+)RNA viruses is to translate their RNA genomes. How the mosquito-transmitted DENV, CHIKV and ZIKV efficiently adapt to the diverse requirements of human and mosquito translation machineries and how they subvert the host translation program to their benefit are still unknown. Elucidating these key questions is essential to understand how they multiply and cycle between the different hosts, a crucial aspect of their biology, and also to identify critical regulatory control points that may represent promising targets for novel antiviral strategies.

- **Development of broad-spectrum antivirals**

Such antivirals would allow to simplify and speed-up treatment of infections by DENV, CHIKV and ZIKV during outbreaks, as they share initial symptoms and geographical distribution. We are optimizing very promising hits and identifying novel ones by defining and analysing virus-cell interaction spaces.

Team during 2015-16

Postdocs / Researchers: Jennifer Jungfleisch, Gemma Pérez Vilaró, René Boettcher.
PhD students: Marc Talló Parra, Leire de Campos Mata.

Selected publications 2015-16

Jungfleisch J, Nedialkova DD, Dotu I, Sloan KE, Martinez-Bosch N, Brüning L, Raineri E, Navarro P, Bohnsack MT, Leidel SA, Diez J (2016) A novel translational control mechanism involving RNA structures within coding sequences. *Genome Res.* Nov 7. pii: gr.209015.116.

Koutsoudakis G, Romero-Brey I, Berger C, Pérez-Vilaró G, Monteiro Perin P, Vondran FW, Kalesse M, Harmrolfs K, Müller R, Martinez JP, Pietschmann T, Bartenschlager R, Brönstrup M, Meyerhans A, Díez J (2015) Soraphen A: A broad-spectrum antiviral natural product with potent anti-hepatitis C virus activity. *J Hepatol.* 63(4):813-21.

Pérez-Vilaró G, Fernández-Carrillo C, Mensa L, Miquel R, Sanjuan X, Forns X, Pérez-del-Pulgar S, Díez J (2015) Hepatitis C virus infection inhibits P-body granule formation in human livers. *J Hepatol.* 62(4):785-90.

Elsebai MF, Koutsoudakis G, Saludes V, Pérez-Vilaró G, Turpeinen A, Mattila S, Pirttilä AM, Fontaine-Vive F, Mehiri M, Meyerhans A, Diez J (2015) Pan-genotypic Hepatitis C Virus Inhibition by Natural Products Derived from the Wild Egyptian Artichoke. *J Virol.* 90(4):1918-30.

Jungfleisch J, Chowdhury A, Alves-Rodrigues I, Tharun S, Díez J (2015) The Lsm1-7-Pat1 complex promotes viral RNA translation and replication by differential mechanisms. *RNA.* 21(8):1469-79.

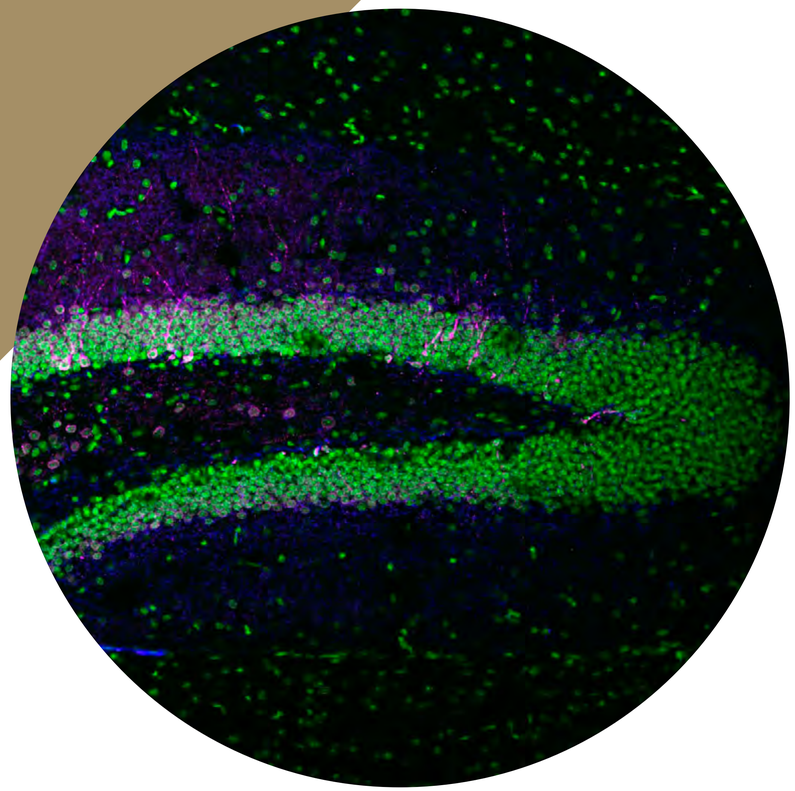
Other relevant publications from last 10 years

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.

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.

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 U S A.* 106(32):13517-22.

Research groups



Molecular Medicine Programme

The programme integrates several research groups with diverse, but overlapping scientific interests aiming to decipher the molecular mechanisms that underlie physiological processes and the diseases associated with them. Normal and pathological processes are studied from different disciplines (molecular biology, immunology, biochemistry, proteomics, and neurobiology) using unicellular and pluricellular model organisms. This enriched and diverse scientific environment together with a superb spectrum of stateof-the-art methodologies makes the Molecular Medicine Programme an exceptional training ground, for undergraduate students, graduate students and postdoctoral fellows, who in turn also contribute to the high vitality of the Programme.

COORDINATOR

José Ayté

- Oxidative Stress and Cell Cycle Group
- Human natural killer cell biology
- NFAT Proteins and Immune Cells
- Proteomics and Protein Chemistry
- Neurobiology of Behavior Research Group (GReNeC)

Oxidative Stress and Cell Cycle Group

Elena Hidalgo and José Ayté

Website

www.upf.edu/web/osccg

Research Outline

Using the fission yeast as a model system, our group is interested in studying the components and molecular mechanisms regulating the responses to oxidative stress and controlling the mitotic and meiotic cell cycle. We use cutting edge approaches in molecular biology, proteomics/mass spectrometry and live cell imaging, as well as traditional genetics.

Current Projects / Research Lines

- **Cellular responses to oxidative stress**

Study of the sensing and transcriptional outputs of signal transduction cascades and their influence on cell survival to stress and on aging.

- **Protein oxidation, protein misfolding and proteostasis network**

Part of the toxicity associated to oxidative stress and to aging is protein oxidation. We study the networks controlling the synthesis and degradation of carbonylated proteins.

- **Gene expression control at the G1/S transition of the cell cycle**

The MBF complex (the functional homolog of mammalian RB/E2F) controls the transcriptional wave during START. We are analysing how the MBF complex is regulated in an unperturbed cell cycle, using proteomic and genetic approaches.

- **Alternative splicing in fission yeast**

Several fission yeast genes have a specific splicing program during meiosis, which involves Prp2U2AF65, among several factors. We are dissecting splicing regulation during meiosis and during mitotic cell cycle, characterizing the role of several spliceosome components.

Team during 2015-16

Postdocs: Isabel Alves, Susanna Boronat, Margarita Cabrera, Cristina Corral, Javier Encinar, Patricia García, Stefan Hümmer, Laura Sánchez.
PhD students: Alba Doménech, Rodrigo Fraile, Alberto González, Iva Knezevic, Luis Marte, Esther Pazo, Clàudia Salat.
Technicians: Mercè Carmona.

Selected publications 2015-16

Boronat S, García-Santamarina S, Hidalgo E (2015) Gel-free proteomic methodologies to study reversible cysteine oxidation and irreversible protein carbonyl formation. Free Radic. Res. 49:494-510.

Alves-Rodrigues I, Ferreira PG, Moldón A, Vivancos AP, Hidalgo E, Guigó R, Ayté J (2016) Spatiotemporal control of forkheads binding to DNA regulates the meiotic gene expression program. **Cell** Reports 14:885-895.

Eckert D, Andrée N, Razanau A, Zock-Emmenthal S, Lützelberger M, Plath S, Schmidt H, Guerra-Moreno A, Cozzuto L, Ayté J, Käufer NF (2016) Prp4 kinase grants the license to splice: control of weak splice sites during spliceosome activation. PLoS Genet 12(1):e1005768.

Encinar del Dedo J, Gabrielli N, Carmona M, Ayté J, Hidalgo E (2015) A cascade of iron-containing proteins governs the genetic iron starvation response to promote iron uptake and inhibit iron storage in fission yeast. PLoS Genet 11(3):e1005106.

García P, Encinar del Dedo J, Ayté J, Hidalgo E (2016) Genome-wide Screening of Regulators of Catalase Expression: Role of a Transcription Complex and Histone and tRNA Modification Complexes on Adaptation to Stress. J Biol Chem 291:790-9.

Other relevant publications from last 10 years

García-Santamarina S, Boronat S, Domènech A, Ayté J, Molina H, Hidalgo E (2014) Monitoring in vivo reversible cysteine oxidation in proteins using ICAT and mass spectrometry. Nat Protoc 9:1131-45.

Zuin A, Carmona M, Morales-Ivorra I, Gabrielli N, Vivancos AP, Ayté J, Hidalgo E (2010) Life-span extension by calorie restriction relies on the Sty1 MAP kinase stress pathway. EMBO J 29:981-91.

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.

Human natural killer cell biology

Miguel López-Botet

Website

www.upf.edu/web/nkiller

Research Outline

We have a long-standing experience on the biology of human Natural Killer (NK) cells, which are involved in the immune response against infections and tumours. Most relevant past contributions were the characterization of CD94/NKG2 and ILT2 (LIR1, CD85j, LILRB1) receptors specific for HLA class I molecules. We are currently studying the role of NK cells in response to human cytomegalovirus (HCMV) infection. This herpesvirus may cause severe congenital neurological disorders in newborns, constitutes a common complication for immunocompromised individuals (e.g. transplant recipients) and has been associated to chronic inflammatory disorders, such as atherosclerosis, and immunosenescence.

Current Projects / Research Lines

- **Characterization of the human adaptive NK cell response to cytomegalovirus infection**

HCMV may promote in healthy individuals a marked and persistent reconfiguration of the NK cell compartment whose hallmark is the expansion of a subset bearing the CD94/NKG2C activating receptor specific for HLA-E (Gumá et al. Blood 2004, Blood 2006). We currently explore the underlying molecular and cellular mechanisms, the implications in different clinical settings (organ transplantation, Multiple Sclerosis…), the relation with the antiviral T cell mediated response and the putative impact in the response to other pathogens and tumors (breast cancer).
These issues are addressed at the experimental level and in collaboration with clinical teams (Dpts. of Nephrology, Oncology, and Neurology. Hospital del Mar). Specific funding has been recently obtained supporting an extension of our research in the context of cancer immunotherapy (coordinated by Dr. A. Muntasell, IMIM).

Team during 2015-16

Researcher (co-PI): Aura Muntasell (IMIM)
Postdocs: Jordi Pou, Dalia Raïch.
PhD students: Marcel Costa, Aldi Pupuleku, María López, Mariona Cabo.
Technicians: Gemma Heredia, Andrea Vera.

Selected publications 2015-16

Baía D, Pou J, Jones D, Mandelboim O, Trowsdale J, Muntasell A*, López-Botet M* (2016) Interaction of the LILRB1 inhibitory receptor with HLA class Ia dimers. Eur J Immunol. 46:1681-90. (*) shared credit.

Muntasell A, Pupuleku A, Cisneros E, Vera A, Moraru M, Vilches C, López-Botet M (2016) Relationship of NKG2C Copy Number with the Distribution of Distinct Cytomegalovirus-Induced Adaptive NK Cell Subsets. J Immunol. 196:3818-27.

Martínez-Rodríguez JE, Cobo-Calvo A, Villar LM, Munteis E, Blanco Y, Rasal R, Vera A, Muntasell A, Alvarez-Lafuente R, Saiz A, Alvarez-Cermeño JC, Martínez-Yélamos S, Roquer J, López-Botet M (2016) Adaptive natural killer cell response to cytomegalovirus and disability progression in multiple sclerosis. Mult Scler 22:741-52.

Costa-Garcia M, Vera A, Moraru M, Vilches C, López-Botet M*, Muntasell A*. (2015) Antibody-mediated response of NKG2Cbright NK cells against human cytomegalovirus. J Immunol. 194:2715-24. (*) shared credit.

Crespo M, Yelamos J, Redondo D, Muntasell A, Perez-Saéz MJ, López-Montañés M, García C, Torio A, Mir M, Hernández JJ, López-Botet M*, Pascual J*. (2015) Circulating NK-cell subsets in renal allograft recipients with anti-HLA donor-specific antibodies. Am J Transplant. 15:806-14. (*) shared credit.

Other relevant publications from last 10 years

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 117:848-56.

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. 115:5170-9.

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. 107:3624-31.

NFAT Proteins and Immune Cells

Cristina López-Rodríguez & Jose Aramburu

Website

www.upf.edu/web/genimmune

Awards

- ICREA acadèmia award, Catalan Institution for Research and Advanced Studies, **Cristina López-Rodríguez** (2015-2019)

Research Outline

The immune system plays an essential role in the organism, both in the defence against pathogens and tumours 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. We are interested in understanding gene regulatory mechanisms that allow immune cells to respond to diverse stimuli and differentiation cues and maintain functional competency under stress conditions such as those found in inflamed microenvironments and tumours.

Current Projects / Research Lines

- **Role of NFAT transcription factors in gene regulation in immune cells**

Identification of points of control in immune responses at the level of gene expression regulation. We have focused our recent work on NFAT5, a distinct Rel-like protein with hybrid features between NF-κB and the calcineurin-regulated NFATc. We have elucidated specific roles for NFAT5 in the development of the immune system, identified pathways connecting cell growth-regulatory mechanisms with stress adaptation responses, and uncovered roles for NFAT5 in anti-pathogen defences.

- **Stress adaptation responses in immune cell functions**

Adaptive stress responses are relevant in the immune system, whose cells must function in a variety of anatomical niches where they can be exposed to diverse stress sources. Our current work focuses on understanding how immune cells interpret specific stress signals in different growth and differentiation contexts to modify their functional capabilities in an organism.

Team during 2015-16

Postdocs: Maria Buxadé.
PhD students: Sonia Tejedor, Maria Val, Laura Garcia, Laia Traveset, Hèctor Huerga, Monika Tellechea.
Technicians: Maria García-Belando.

Selected publications 2015-16

Alberdi M, Iglesias M, Tejedor S, Merino R, López-Rodríguez C, Aramburu J (2017, published online 6th September 2016). Context-dependent regulation of Th17-associated genes and IFNγ expression by the transcription factor NFAT5. Immunol Cell Biol. 95:56-67.

López-Rodríguez C, Aramburu J, Berga-Bolaños R (2015) Transcription factors and target genes of pre-TCR signaling. Cell Mol Life Sci. 72:2305-2321.

Boland BS, Widjaja CE, Banno A, Zhang B, Kim SH, Stoven S, Peterson MR, Jones MC, Su HI, Crowe SE, Bui JD, Ho SB, Okugawa Y, Goel A, Marietta EV, Khosroheidari M, Jepsen K, Aramburu J, López-Rodríguez C, Sandborn WJ, Murray JA, Harismendy O, Chang JT (2015) Immunodeficiency and autoimmune enterocolopathy linked to NFAT5 haploinsufficiency. J Immunol 194:2551-2560.

Other relevant publications from last 10 years

Berga-Bolaños R, Alberdi M, Buxadé M, Aramburu J, López-Rodríguez C (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, 16091-16096.

Buxadé M, Lunazzi G, Minguillón J, Iborra I, Berga-Bolaños R, del Val M, Aramburu J, and López-Rodríguez C (2012) Gene expression induced by Toll-like receptors in macrophages requires the transcription factor NFAT5. J Exp Med 209, 379-393.

Ortells MC, Morancho B, Drews-Elger K, Viollet B, Laderoute KR, López-Rodríguez C, and Aramburu J (2012) Transcriptional regulation of gene expression during osmotic stress responses by the mammalian target of rapamycin. Nucleic Acids Res. 40, 4368-4384.

Proteomics and Protein Chemistry

David Andreu

Website

www.upf.edu/web/uprot

Research Outline

We use bioanalytical and synthetic approaches to understand and reproduce the role of proteins in biomedically relevant processes. In proteomics, for instance, we use affinity capture and mass spectrometric methods to identify proteins involved in fertilization. We also make extensive use of synthetic peptides as vaccines against animal viral diseases as well as antimicrobial agents and shuttles for intracellular delivery of otherwise poorly absorbed drugs.

Current Projects / Research Lines

- **Proteomics**

We have recently identified in bovine sperm 58 hitherto unreported lectins recognizing oocyte sugar epitopes involved in fertilization. This structural information could be used for diagnosing/treating infertility, or for developing vaccines for fertility control. We are also developing smart nanoparticles to enrich low-abundance proteins in blood samples.

- **Peptide vaccines**

A newly developed platform displays clinically relevant B and T epitopes of foot-and-mouth disease, the economically most devastating animal disease worldwide. Our candidate induces 100% protection in swine, readily adapts to new outbreaks and is efficiently produced. We look forward to extensive field trials in Asia.

- **Antimicrobial peptides (AMPs)**

Focus on: bioinformatic tools for AMP prediction, discovery and development of AMPs from snake venoms and refining AMP pharmacophores to develop better-than-native versions.

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

Study of CPPs as vectors for low-bioavailability antiparasitic drugs (miltefosine, paromomycin) with the aim of defeating resistance in Leishmania and other trypanosomatids.

Team during 2015-16

Postdocs: Sira Defaus, Gerard Such.
Senior associate: Ricardo Gutiérrez-Gallego.
PhD students: Clara Pérez-Peinado, Mar Forner, Maria Gallo, Ferran Nadal, Weiteng An, Greta Ripoll.
Technicians: Javier Valle, Yolanda Tor.

Selected publications 2015-16

Andreu D, Torrent M (2015) Prediction of bioactive peptides using artificial neural networks. Methods Mol Biol 1260, 101-18.

Falcão CB, Pérez-Peinado C, de la Torre BG, Mayol X, Zamora-Carreras H, Jiménez MA, Rádis-Baptista G, Andreu D* (2015) Structural dissection of crotalicidin, a rattlesnake venom cathelicidin, retrieves a fragment with antimicrobial and antitumor activity. J Med Chem 58, 8553-663.

Defaus S, Avilés M, Andreu D*, Gutiérrez-Gallego R (2016) Identification of bovine sperm surface proteins involved in carbohydrate-mediated fertilization interactions. Mol Cell Proteomics 15, 2236-51.

Blanco E, Guerra B, de la Torre BG, Defaus S, Dekker A, Andreu D*, Sobrino F (2016) Full protection of swine against foot-and-mouth disease by a bivalent B-cell epitope dendrimer peptide. Antiviral Res 129, 74-80.

Araújo-Bazán L, Ruiz-Avila LB, Andreu D, Huecas S, Andreu JM (2016)mCytological profile of antibacterial FtsZ inhibitors and synthetic peptide MciZ. Front Microbiol 7:1558.

Other relevant publications from last 10 years

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 mechanism for trypanosomatid chemotherapy. J Control Release 161, 835-42.

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 50, 10686-9.

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, 7223-30.

Neurobiology of Behavior Research Group (GReNeC)

Olga Valverde

Website

www.upf.edu/grenec

Research Outline

We are devoted to identify the neurobiological basis underlying several psychiatric disorders: drug addiction, affective disorders, cognitive impairments, chronic pain and neurotoxicity. We use mice behavioural models combined with neurochemical, immunohistochemical and molecular tools. The influence of specific targets related to the above mentioned pathologies like the adenosine A2a receptors, the endocannabinoid system and others G protein coupled receptors focus our interest. We are currently using new approaches such as proteomics techniques and biocomputational analysis for better understanding neurobehavioral outputs. Our integrative strategy helps us to identify appropriate biomarkers and to propose new preventives strategies and therapeutical applications for mental health.

Current Projects / Research Lines

- **The neurobiological substrate involved in drug addiction**

Study of psychostimulant use disorders, including the consumption of cocaine and other synthetic derivatives. We analyze participation of environmental vulnerability factors in the environmental consumption and the evaluation of new strategies for the management of the craving and relapse to the consumption after prolonged periods of abstinence. We also study the consequences of alcohol intake with a binge pattern of consumption in particular developmental periods, including pre-natal and adolescence and the role for the inflammatory factors.

- **Neurobiology of depressive disorders**

We investigated early-life adverse events, like maternal deprivation in the later development of mood and anxiety disorders. We further assess whether mood disorders could affect cognitive behaviours and attentional processes. Psychostimulants and alcohol consumption in adolescent using animal models.

- **Co-morbidity between drug different psychiatric disorders**

We have participated in the characterization of different models of psychiatric co-morbidity (drug addiction and depression as well as depression and Alzheimer's disease) using different approximations.

Team during 2015-16

Postdocs: Vincent Warnault, Ana Martín-Sánchez, Sandra Montagud.
PhD students: Lídia Cantacorps, Adriana Castro, Miguel-Angel Luján.
Technicians: Neus Mondragón.

Selected publications 2015-16

Moscoso-Castro M, Gracia-Rubio I, Ciruela F, Valverde O* (2016) Genetic blockade of adenosine A2A receptors induces cognitive impairments and anatomical changes related to psychotic symptoms in mice. Eur Neuropsychopharmacol 26(7):1227-40.

Gracia-Rubio I, Moscoso-Castro M, Pozo OJ, Marcos J, Nadal R, Valverde O* (2016) Maternal separation induces neuroinflammation and long-lasting emotional alterations in mice. Prog Neuropsychopharmacol Biol Psychiatry 65:104-17.

Gracia-Rubio I, Valverde O*, Martinez-Laorden E, Moscoso-Castro M, Milanés MV, Laorden ML (2016) Maternal Separation Impairs Cocaine-Induced Behavioural Sensitization in Adolescent Mice. PLoS One 11(12): e0167483.

González-Sepúlveda M, Pozo OJ, Marcos J, Valverde O* (2016) Chronic pain causes a persistent anxiety state leading to increased ethanol intake in CD1 mice. J Psychopharmacol 30(2):188-203.

Johansson EM, García-Gutiérrez MS, Moscoso-Castro M, Manzanares J, Valverde O* (2016) Reduced Contextual Discrimination following Alcohol Consumption or MDMA Administration in Mice. PLoS One 10(11):e0142978.

**corresponding author*

Other relevant publications from last 10 years

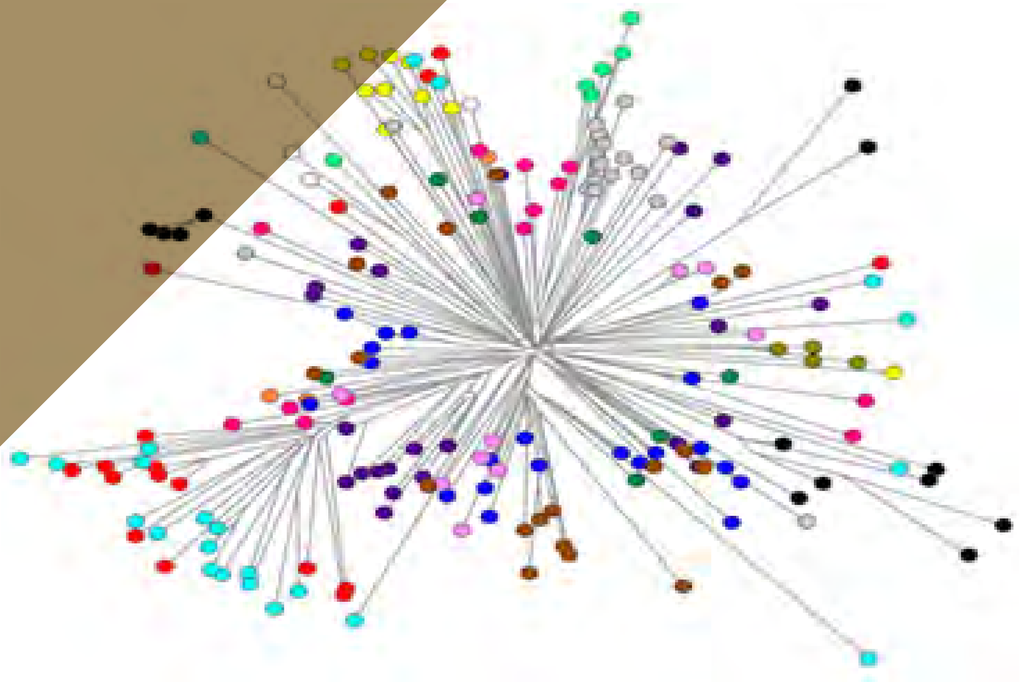
Ruiz-Medina J, Ledent C, Valverde O* (2011) GPR3 orphan receptor is involved in neuropathic pain after peripheral nerve injury and regulates morphine-induced antinociception. Neuropharmacology. 61(1-2):43-50.

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.

Bura SA, Nadal X, Ledent C, Maldonado R, Valverde O* (2008) A2A adenosine receptor regulates glia proliferation and pain after peripheral nerve injury. Pain 140(1):95-10.

**corresponding author*

Research groups



Evolutionary Biology and Complex Systems Programme

COORDINATOR

Elena Bosch

The analysis of processes and mechanisms generating diversity in biological and artificial entities including their organization and interactions are the main interests of this interdisciplinary programme. The entities under study cover a wide range of natural and artificial elements from single molecules, cells, genomes and organisms to whole ecosystems. The research challenges on this programme require both theoretical and experimental approaches with a remarkable computational input. Several disciplines are also required to achieve our scientific goals, such as genomics, physics, statistical and computational genetics, network theory, molecular and cell biology, linguistics, among others.

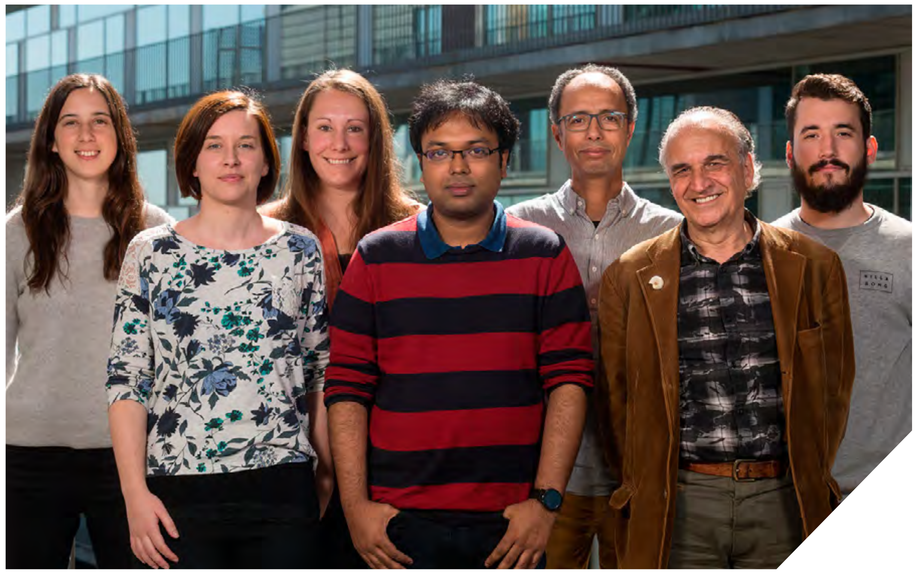
- Evolutionary systems biology
- Human Genome Diversity
- Genomics of Individuality
- Evolutionary Population Genetics Lab
- Comparative Genomics
- Complex Systems

Evolutionary systems biology

Jaume Bertranpetit

Website

biologiaevolutiva.org/jbertranpetit/



Research Outline

We are interested in evolution using genomics as a tool. Our goal is to approach our own evolutionary history and to understand the basic mechanisms that have been acting in shaping our past, which is the base for making our future. Understanding adaptation through the detection of positive (adaptive) selection in the genomes is one of our main interests. We are applying tools of network theory and systems biology to unravel the genetic bases of complex adaptations.

Current Projects / Research Lines

- **Understanding natural selection and adaptation in humans and in primates through the comparative analysis of genomes**

Analysis of the different forms of selection (purifying, balancing and positive) both among human populations in order to detect population-specific adaptations, and among primates in order to recognize species-specific adaptive selection and to measure the strength of purifying selection. The action of selection is measured and understood as integrated in molecular physiological pathways or networks to comprehend the basis of complex adaptations and how networks have been shaped by natural selection. In humans we try to identify population specific adaptations and in primates the places in the genome with human specificities. We have ongoing work in the following regions: Africa (Ethiopia, Nama), Asia and Pacific (Andaman, India, Australia), Europe (Gypsies) and in Apes. New projects are being developed on Asian Pygmies.

Team during 2015-16

Postdocs: Hafid Laayouni, Ludovica Montanucci (till end 2015), Mayukh Mondal (since 10-2016).
PhD students: Begoña Dobon, Jessica Nye, Sandra Walsh, Pablo Villegas.

Selected publications 2015-16

Luisi P, Alvarez-Ponce D, Pybus M, Fares M, Bertranpetit J, Laayouni H (2015) Positive selection in the human protein-protein interaction network. Genome Biology and Evolution 7(4):1141-54.

Dobon B, Hassan HY, Laayouni H, Luisi P, Ricano-Ponce I, Zhernakova A, Wijmenga C, Tahir H, Comas D, Netea DG, Bertranpetit J (2015) The genetics of East African populations: a Nilo-Saharan component in the African genetic landscape. Scientific Reports 5:9996.

Invergo BM, Montanucci L, Bertranpetit J (2015) A dynamic model of mammalian phototransduction reveals insights into the molecular evolution of systems. Proceedings of the Royal Society B 282(1820).

Pybus M, Luisi P, Dall'Olio G, Uzkudun M, Laayouni H, Bertranpetit J, Engelken J (2015) A Machine-Learning Framework to Detect and Classify Hard Selective Sweeps in Human Populations. Bioinformatics pii: btv493.

Mondal M, Casals F, Xu T, Dall'Olio GM, Pybus M, Netea MG, Comas D, Laayouni H, Li Q, Majumder PP, Bertranpetit J (2016) Genomic analysis of Andamanese provides insights into ancient human migration into Asia and adaptation. Nat Genet 48(9):1066-70

Cagan A, Theunert C, Laayouni H, Santpere G, Pybus M, Casals F, Prüfer K, Navarro A, Marques-Bonet T, Bertranpetit J, Andrés AM (2016) Natural Selection in the Great Apes. Mol Biol Evol 33(12): 3268-83.

Other relevant publications from last 10 years

Laayouni H, Oosting M, Luisi P, Ioana M, Alonso S, Ricaño-Ponce I, Trynka G, Zhernakova A, Plantinga T, Cheng SC, van der Meer JWM, BK T, Popp R, Sood A, Wijmenga C, Joosten LAB, Bertranpetit J, Netea MG (2014) The common evolutionary history of European and Rroma populations identifies convergent evolution exerted by plague on TLR1/TLR6/TLR10 pattern recognition system. PNAS 111(7): 2668-73.

Sikora M, Ferrer-Admetlla A, Laayouni H, Menendez C, Mayor A, Bardaji A, Sigauque B, Mandomando I, Alonso PL, Bertranpetit J, Casals F (2009) A variant in the gene FUT9 is associated with susceptibility to placental malaria infection. Human Molecular Genetics 18(16):3136-44.

Melé M, Javed A, Pybus M, Calafell F, Parida L, Bertranpetit J, and The Genographic Consortium (2010) A new method to reconstruct recombination events at a genomic scale. PLOS Computational Biology, Nov 24;6(11).

Human Genome Diversity

David Comas

Website

www.biologiaevolutiva.org/dcomas

Research Outline

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

Current Projects / Research Lines

- **Demographic history of European populations**

Detection of differential migrations and genetic composition of some European populations, with a focus on isolated groups and minorities, such as Roma (aka Gypsies).

- **Migrations and adaptations in North African populations**

The complex human population landscape of North Africa is the result of an amalgam of migrations in the region. The genome-wide analysis of North African groups allows us to date the sequential migrations in the area since Paleolithic times until historical movements, which explain the extant genomic pattern of North Africa.

- **Genomic composition of African populations**

Despite being the cradle of humankind, the genomic diversity within the African continent has been poorly analysed. The analysis of complete genomes allows us to describe the first splits and migrations within the continent, and a description of the demography and adaptation in the region, which helps to unravel the health and disease components of humans.

Team during 2015-16

PhD students: Simone Biagini, André Flores, Àlex Mas, Lara Rubio-Araúna, Gerard Serra, Neus Solé-Morata. **Technicians**: Mònica Vallés.

Selected publications 2015-16

Vargas-Pinilla P, Paixão-Côrtes VR, Paré P, Tovo-Rodrigues L, Vieira CM, Xavier A, Comas D, Pissinatti A, Sinigaglia M, Rigo MM, Vieira GF, Lucion AB, Salzano FM, Bortolini MC (2015) Evolutionary pattern in the OXT-OXTR system in primates: coevolution and positive selection footprints. PNAS USA 112:88-93.

Sudmant PH, et al. (2015) Global diversity, population stratification, and selection of human copy number variation. Science 349 (6253):aab3761.

Martínez-Cruz B, Mendizabal I, Harmant C, de Pablo R, Ioana M, Angelicheva D, Kouvatsi A, Makukh H, Netea MG, Pamjav H, Zalán A, Tournev I, Marushiakova E, Popov V, Bertranpetit J, Kalaydjieva L, Quintana-Murci L, Comas D, the Genographic Consortium (2016) Origins, admixture and founder lineages in European Roma. Eur J Hum Genet 24: 937-943.

Lazaridis I, et al. (2016) Genomic insights into the origin of farming in the ancient Near East. Nature 536:419-424.

Mallick S, et al. (2016) The Simons Genome Diversity Project: 300 genomes from 142 diverse populations. Nature 538:201-206.

Other relevant publications from last 10 years

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 Genet 8(1)e1002397.

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.

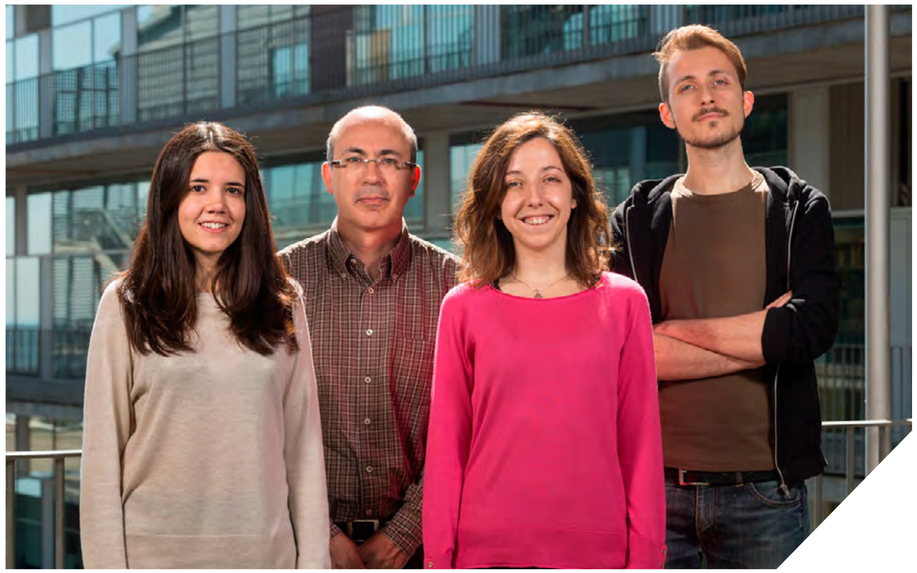
Botigué LR, Henn BM, Gravel S, Maples BK, Gignoux CR, Corona E, Atzmon G, Burns E, Ostrer H, Flores C, Bertranpetit J, Comas D*, Bustamante CD* (2013) Gene flow from North Africa contributes to differential human genetic diversity in Southern Europe. PNAS USA 110:11791-11796.

Genomics of Individuality

Francesc Calafell

Website

www.biologiaevolutiva.org/fcalafell



Research Outline

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)? We have applied this frame to a wider scope that views the individual as part of a genealogy, sharing lineages with individuals that are related to them. We focus on the Y chromosome, which marks paternal lineages, and on the Western Mediterranean.

Current Projects / Research Lines

- **Phylogeography of the Y chromosome in the Western Mediterranean**

R1b-DF27 and E-M81 are branches of the human Y-chromosome phylogeny with parallel lives: the former abounds in the Iberian Peninsula, while the latter is typical of NW Africa. Both have recent origins and have expanded explosively. We are characterizing their phylogeography to ascertain the demographic history that produced them and deeply affected the populations that host them.

- **Population genomics of the Western Mediterranean**

We are using whole genomes to characterize the human populations in the Western Mediterranean, in order to disentangle their mutual relationships, as well as any external contributions. For the first time, we are exploring French regional diversity. We have also found that one of the most divergent populations in the area is Eivissa, and we are trying to tease apart the contributions to this unexpected pattern of the Phoenician first settlement of the island versus its subsequent isolation.

Team during 2015-16

PhD students: Neus Solé, Simone Biagini.

Selected publications 2015-16

Solé-Morata N, Bertranpetit J, Comas D, Calafell F (2015) Y-chromosome diversity in Catalan surname samples: insights into surname origin and frequency. *European Journal of Human Genetics*, 23:1549-1557.

Garcia-Etxebarria K, Bracho MA, Galán JC, Pumarola T, Castilla J, Ortiz de Lejarazu R, Rodríguez-Dominguez M, Quintela I, Bonet N, Garcia-Garcerà M, Domínguez A, González-Candelas F, Calafell F, on behalf of the CIBERESP Cases and Controls in Pandemic Influenza Working Group (2015) No Major Host Genetic Risk Factor Contributed to A(H1N1)2009 Influenza Severity. *PLoS ONE*, 10(9): e0135983.

Calafell F, Anglada R, Bonet N, González-Ruiz M, Prats-Muñoz G, Lalueza-Fox C, Bertranpetit J, Malgosa A, Casals F (2016) An assessment of a massively parallel sequencing approach for the identification of individuals from mass graves of the Spanish Civil War (1936-1939). *Electrophoresis*, 37:2841-2847.

Other relevant publications from last 10 years

Ramírez-Soriano A, Ramos-Onsins SE, Rozas J, Calafell F*, Navarro A* (2008) Statistical power analysis of neutrality tests under demographic expansions, contractions and bottlenecks with recombination. *Genetics*, 179:555-567.

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. *Human Molecular Genetics*, 19:517-525.

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. *European Journal of Human Genetics*, 20(2):211-216.

Evolutionary Population Genetics Lab

Elena Bosch

Website

www.biologiaevolutiva.org/ebosch

Awards

Icrea Academia Award- Life and Medical Sciences (2015)

Research Outline

Our research focuses on investigating different aspects of human genetic diversity. In particular, we are interested in the architecture of the genetic predisposition to complex disease and in adaptive traits that have undergone positive selection during human evolution. In order to do so, we analyse full genome sequencing data from different control/case settings or geographically diverse populations and apply state-of-the-art methods for variant association and detection of selection. Furthermore, by using in silico predictions and relevant molecular biology techniques, we aim to elucidate the genetic variants and molecular phenotypes underlying the genetic basis of adaptations presumably related to pathogen interaction and diet.

Current Projects / Research Lines

- **Adaptation to the Neolithic**

During the transition from hunter-gatherer groups to agricultural societies, humans confronted major demographical and ecological challenges. We plan to apply several evolutionary strategies to detect differential modes of selection in full genomes from hunter-gatherers and neighbouring populations differing in their lifestyles.

- **Role of natural selection in disease genes**

We study the selective pressures acting in genes associated to Mendelian and complex diseases to understand differences in penetrance, age of onset, and risk allele frequencies between disorders. Also by identifying signatures of selection on pleiotropic disease variants we aim to understand the evolutionary causes of senescence.

- **Adaptation to zinc deficiency**

Zinc is an essential trace element that can only be obtained through the food chain. Since low levels of zinc in soil easily translate to this micronutrient deficiency, we aim to explore whether signatures of polygenic selection can be detected in populations living in zinc deficient areas.

Team during 2015-16

PhD students: Nino Spataro, Juan Antonio Rodríguez, Barbara Sinigaglia.
Technicians: Mònica Vallès.

Selected publications 2015-16

Spataro N, Calafell F, Cervera-Carles L, Casals F, Pagonabarraga J, Pascual-Sedano B, Campolongo A, Kulisevsky J, Lleó A, Navarro A, Clarimón J, Bosch E (2015) Mendelian genes for Parkinson's disease contribute to the sporadic forms of the disease. Hum Mol Genet 24(7): 2023-2034.

Santpere G, Carnero-Montoro E, Petit N, Serra F, Hvilsom C, Rambla J, Heredia-Genestar JM, Halligan DL, Dopazo H, Navarro A, Bosch E (2015) Analysis of five gene sets in chimpanzees suggests decoupling between the action of selection on protein-coding and on noncoding elements. Genome Biol Evol 7(6): 1490-1505.

Delgado J, Bielig T, Bonet L, Carnero-Montoro E, Puente XS, Colomer D, Bosch E, Campo E, Lozano F (2016) Impact of the functional CD5 polymorphism A471V on the response of chronic lymphocytic leukaemia to conventional chemotherapy regimens. Br J Haematol. doi: 10.1111/bjh.14037.

Engelken J, Espadas G, Mancuso FM, Bonet N, Scherr AL, Jímenez-Álvarez V, Codina-Solà M, Medina-Stacey D, Spataro N, Stoneking M, Calafell F, Sabidó E, Bosch E (2016) Signatures of evolutionary adaptation in quantitative trait loci influencing trace element homeostasis in liver. Mol Biol Evol 33(3): 738-754

Other relevant publications from last 10 years

Engelken J, Carnero-Montoro E, Pybus M, Andrews GK, Lalueza-Fox C, Comas D, Sekler I, de la Rasilla M, Rosas A, Stoneking M, Valverde MA, Vicente R, Bosch E (2014) Extreme Population Differences in the Human Zinc Transporter ZIP4 (SLC39A4) are Explained by Positive Selection in Sub-Saharan Africa. PLOS Genetics 10(2): e1004128.

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.

Moreno-Estrada A, Tang K, Sikora M, Marquès-Bonet T, Casals F, Navarro A, Calafell F, Bertranpetit J, Stoneking M and 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.

Comparative Genomics

Tomas Marques-Bonet and Arcadi Navarro

Website

www.biologiaevolutiva.org/tmarques

Awards

Icrea Academia Award- Life and Medical Sciences (2015)

Research Outline

Our labs are centred in the study of the many different biological processes, particularly natural selection, during millions of years. We focus on the discovery of the extent of all kinds of genome variation within different phenotypically genomes. We study genome variation (centred on CNVs), gene expression and epigenetic differences in the human species in the context of great ape evolution and other mammalian genomes such as canids. But also, interrogating these patterns of genome diversity we can infer what are the forces that affect living organisms, how and when they act, and how they affect such various things as biodiversity or the differential susceptibility of different persons to certain diseases.

Current Projects / Research Lines

- **Genomic variation in ape genomes**

Characterizing the variation of thousands of human genomes is standard today. However, primates (our closest relatives) are the ideal set of species to study the evolution of these features from both mechanistic and adaptive points of view. We use genomic approaches in humans and primates to understand the impact of variants in the evolution of every species to provide a proper perspective to the differences among species.

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

DNA methylation is an epigenetic modification involved in regulatory processes. However, the dynamics of DNA methylation changes between human and their closest relatives is still poorly understood. We evaluate methylation patterns in recent human evolution.

- **ELIXIR - the European life science Infrastructure for Biological Information**

Distributed organisation comprising national bioinformatics research infrastructures and the European Bioinformatics Institute (EMBL-EBI). This coordinated infrastructure includes data standards, exchange, interoperability, storage, security and training.

Team during 2015-16

Postdocs: Inna Povolotskaya, Martin Kuhlwilm, Esther Lizano, David de Juan, Gerard Muntané, Josephine Daub. **PhD students**: Raquel Garcia, Jessica Hernadez, Marc de Manuel, Irene Lobon, Lukas Kuderna, Claudia Fontsere, Aitor Serres, Sojung Han, Manuel Solís, Luis Ferrández, Diego A. Hartasánchez, Juan A. Rodriguez, Txema Heredia, Rajendra H. Mandage, Marco Telford, Marina Brasó.

Selected publications 2015-16

deManuel M, Kuhlwilm M, Frandsen P, Sousa VC, Desai T, Prado-Martinez J, Hernandez-Rodriguez J, Dupanloup I, Lao O, Hallast P, Schmidt JM, Heredia-Genestar JM, Benazzo A, Barbujani G, Peter BM, Kuderna LF, Casals F, Angedakin S, Arandjelovic M, Boesch C, Kühl H, Vigilant L, Langergraber K, Novembre J, Gut M, Gut I, Navarro A, Carlsen F, Andrés AM, Siegismund HR, Scally A, Excoffier L, Tyler-Smith C, Castellano S, Xue Y, Hvilsom C, Marques-Bonet T (2016) Chimpanzee genomic diversity reveals ancient admixture with bonobos. Science 354(6311):477-81.

Kuhlwilm M, de Manuel M, Nater A, Greminger MP, Krützen M, Marques-Bonet T (2016) Evolution and demography of the great apes. Curr Opin Genet Dev 41:124-9.

Hernando-Herraez et al. Tomas Marques-Bonet (2015) “A genome-wide comparative study of the DNA methylation landscape in great apes” Nucleic Acid Research.

Sonay TB et al (2015) “Human and great ape variation in tandem repeats population variation and its correspondence impact to on gene expression divergence” Genome Research.

Lappalainen I, Almeida-King J, Kumanduri V, Senf A, Spalding JD, Ur-Rehman S, Saunders G, Kandasamy J, Caccamo M, Leinonen R, Vaughan B, Laurent T, Rowland F, Marin-Garcia P, Barker J, Jokinen P, Torres AC, de Argila JR, Llobet OM, Medina I, Puy MS, Alberich M, de la Torre S, Navarro A, Paschall J, Flicek P (2015) “The European Genome-phenome Archive of human data consented for biomedical research.”. Nat Genet 47(7):692-5

Other relevant publications from last 10 years

Gazave E, Darré F, Morcillo-Suarez C, Petit-Marty N, Carreño A, Marigorta UM, Ryder OA, Blancher A, Rocchi M, Bosch E, Baker C, Marquès-Bonet T, Eichler EE, Navarro A (2011). Copy number variation analysis in the great apes reveals species-specific patterns of structural variation. Genome Res 10:1626-39.

Prado-Martinez J, et al. (2013) Great ape genetic diversity and population history”. Nature 499(7459):471-5.

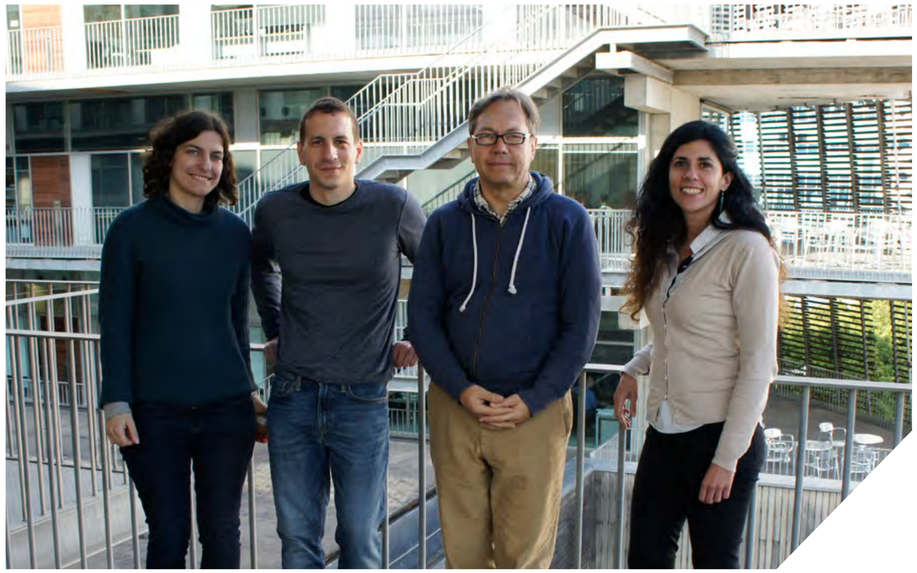
Marigorta et al. “High Trans-ethnic Replicability of GWAS Results Implies Common Causal Variants” Plos Genetics 2013.

Language Evolution

Luc Steels

Website

www.upf.edu/web/language-evolution



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 looks to explain 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 to explain how features of language, such as agreement systems, arise and culturally evolve.

Current Projects / Research Lines

- **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.

- **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 of handling variation, flexibility and change. FCG has been released as open source and has a growing community of users (http://www.fcg-net.org/).

- **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.

Team during 2015-16

PhD students: Emilia García-Casademont.
Research Collaborator: Miquel Cornudella.
Principal Investigator: Luc Steels.
Project Manager: Andrea Barquet.

Selected publications 2015-16

Steels L (2016) Agent-based models for the emergence and evolution of grammar. Phil. Trans. *Royal Society Journal 2016. Volume 371, issue 1701. 20150447.http://dx.doi.org/10.1098/rstb.2015.0447.*

Steels L (2016) Do languages evolve or merely change? *Journal of Neurolinguistics, Volume 39 pp. 1-5.*

Steels L (2016) Human language is a culturally evolving system. *Psychonomic Bulletin & Review. Volume 24, Issue 1, pp 190–193. DOI: 10.3758/s13423-016-1086-6.*

Steels L, Szathmary E (2016) Fluid Construction Grammar as a Biological System.*Linguistics Vanguard, Volume 2, Isssue 1, 20150022.*

Steels L, Garcia Casademont E (2015) *Ambiguity and the origins of syntax. The Linguistic Review; 32(1): 37-60.*

Other relevant publications from last 10 years

Beuls K, Steels L (2013) Agent-Based Models of Strategies for the Emergence and Evolution of Grammatical Agreement. PLOS ONE, 8(3), e58960.

Van Trijp R, Steels L (2012) Multilevel alignment maintains language systematicity. Advances in Complex Systems 15(3-4): 1250039-0.

Steels L (2011) Modeling the Cultural Evolution of Language (target article) Physics of Life 8(4). p. 339-356.

Complex Systems

Ricard Solé

Website

www.complex.upf.edu

Research Outline

The ICREA-Complex Systems Lab is formed by an interdisciplinary team that explores the evolution of complex systems, both natural and artificial, in search of their common laws of organization. We do both theoretical and experimental work, working in close collaboration with the Santa Fe Institute (USA). Using methods from statistical physics, synthetic/systems biology and network theory, we study the origins and evolution of complex systems, the boundaries of such complexity and how to break them.

Current Projects / Research Lines

Our current research focuses in understanding the evolutionary origins of complex systems, using both mathematical models and experimental approaches based on synthetic biology:

- **Synthetic Major Transitions**

We have proposed this concept as a unifying framework to explore the origins of innovation in evolution using a parallel approach, namely our potential for building or simulating synthetic systems that can recreate past evolutionary events. This includes the origin of protocells, multicellular systems, symbiosis, cognition and language.

- **Unstable Evolutionary dynamics**

Namely the dynamics of biological systems (particularly RNA viruses and cancer) that exhibit a tendency towards high genetic instability as part of their adaptation potential. We introduced the concept of "terraforming" endangered or human-made ecosystems to avoid catastrophic shifts. The success of this proposal will require the development of a new synthesis involving multiple scales and conceptual frameworks, from synthetic biology and cellular circuits to ecological communities.

Team during 2015-16

Other PIs: Javier Macía, Carlos Rodríguez-Caso, Sergi Valverde.
Postdocs: Núria Conde, Raúl Montañez, Dani Rodríguez-Amor, Josep Sardanyés Cayuela.
PhD students: Adriano Bonforti, Max Carbonell, Salvador Durán, Aina Ollé, Jordi Piñero, Luis Seoane, Ben Shirt-Ediss.
Technicians: Eva García Ramallo.

Selected publications 2015-16

Solé R (2016) Synthetic transitions: towards a new synthesis. Phil. Trans. Royal Soc B 371 (1701), 20150438.

Ollé-Vila A, Duran-Nebreda S, Conde-Pueyo N, Montañez R, Solé R (2016) Design principles for synthetic organs and organoids: the possible and the actual. Integrative Biology 8, 485 – 503.

Urrios A, Macia J, Manzoni R, Conde N, deNadal L, Posas F, Solé R (2016) A synthetic multicellular memory device. ACS Synthetic Biology 5: 862-73.

Sole R, Montañez R, Duran-Nebreda S (2015) Synthetic circuit designs for earth terraformation. Biology Direct 10:37.

Duran-Nebreda S, Solé R (2015) Emergence of multicellularity in a model of cell growth, death and aggregation under size-dependent selection. Royal Society Interface 12: 20140982.

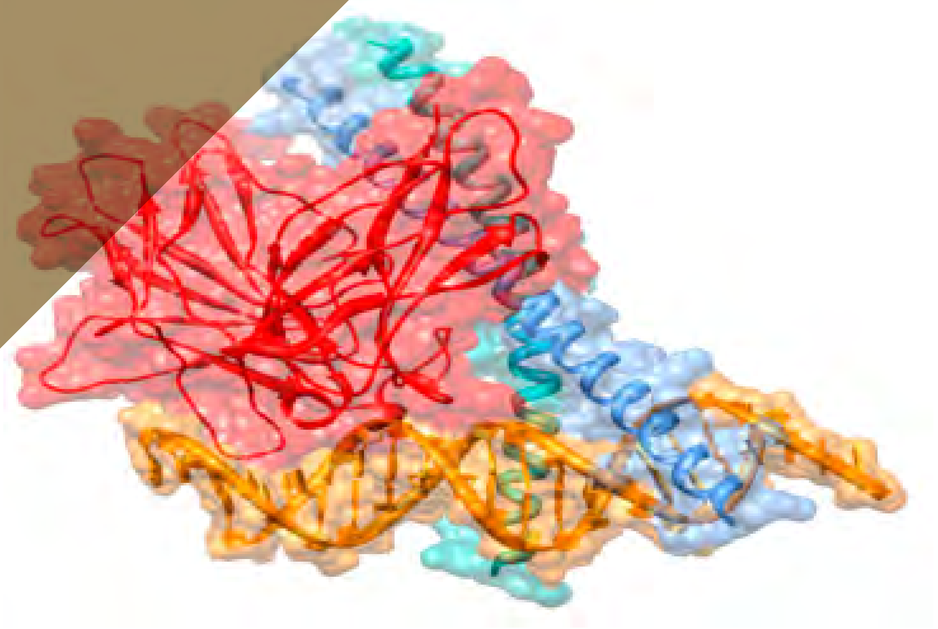
Other relevant publications from last 10 years

Mestres J, Gregori-Puigjané E, Valverde S, Solé R (2008) Data Completeness: the Achilles heel of Drug-Target Networks. Nature Biotechnology, 26, 983-4.

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: 207-211.

Corominas-Murtra B, Goñi J, Solé R, Rodríguez-Caso C (2013) On the origins of hierarchy in complex networks. PNAS 110(33): 13316-21.

Research groups



Biomedical Informatics Programme

The Research Programme on Biomedical Informatics (GRIB) is a joint research programme of the Department of Experimental and Health Sciences of the UPF and the Hospital del Mar Medical Research Institute (IMIM). The development and application of computational methods and information technologies for a better understanding and prediction of biological phenomena, giving especial emphasis to those related to the human diseases and pharmacological treatment, are the principal missions of the GRIB. GRIB faculty members have wide experience in the participation and coordination of research projects funded by the European Commission. EC-funded ongoing projects during the period 2015-16 were focused, among others, on drug discovery, data usage and toxicology.

COORDINATOR

Ferran Sanz

- Integrative Biomedical Informatics Group
- PharmacoInformatics Group
- Structural Bioinformatics Group
- Computational RNA Biology Group
- Biomedical Genomics Group
- Functional Genomics Group
- Computational Biophysics Group

Structural Bioinformatics Group

Ferran Sanz

Website

http://grib.imim.es/research/integrative-biomedical-informatics/index.html

http://ibi.imim.es/

Research Outline

The huge wealth of biomedical information that is currently available is underused because the difficulties in seeking, integrating, analysing the relevant one. There is also a great difficulty for the identification and priorisation of clinically actionable information. The goal of the Integrative Biomedical Informatics (IBI) group is to develop computational methods and tools to address these challenges, with the aim of better understanding human health and disease and contributing to the design of more effective and safe therapeutic interventions. This research group promotes and tackles integrative synergistic strategies for affording biomedical problems, making use of approaches developed within the IBI group and other research groups of the GRIB.

Current Projects / Research Lines

- New methods and tools for knowledge extraction and linkage from biomedical literature and other sources. Within this line, we coordinate the EU-funded project MedBioinformatics on translational bioinformatics and participated in the IMI project Open PHACTS on knowledge discovery in pharmaceutical R&D. The knowledge resources DisGeNET and PsyGeNET are key results of this research line.
- Development of strategies for the research reuse of clinical data. EMIF (European Medical Information Framework) in an IMI project on the matter in which we participate.
- Network biology for the study of human diseases (in MedBioinformatics) and drug toxicity (in several EU-funded projects, such as eTOX and EU-ToxRisk).
- Integrative knowledge management and exploitation in pharmaceutical research, including the coordination of the eTOX project on computational toxicology and the participation in the iPiE project on the prediction of the environmental impact of drugs.

We also participate in the ELIXIR-Excelerate platform, which supports the Europe's life-science data infrastructure.

Team during 2015-16

Postdocs: Miguel Angel Mayer, Pablo Carbonell, Núria Queralt, Alexia Giannoula, Janet Piñero.
PhD students: Alex Bravo, Alba Gutierrez, Angela Leis.
Technicians: Santiago de la Peña, Emilio Centeno.
Project Manager: Maria Saarela.

Selected publications 2015-16

Queralt-Rosinach N, Piñero J, Bravo A, Sanz F, Furlong LI. (2016) DisGeNET-RDF: Harnessing the Innovative Power of the Semantic Web to Explore the Genetic Basis of Diseases. Bioinformatics, 32(14): 2236-8.

Faner R, Gutiérrez-Sacristán A, Castro-Acosta A, Grosdidier S, Gan W, Sánchez-Mayor M, Lopez-Campos JL, Pozo-Rodriguez F, Sanz F, Mannino D, Furlong LI, Agusti A. (2015) Molecular and clinical disease-some of comorbidities in exacerbated COPD patients. Eur Respir J. 46(4):1001-10.

Piñero J, Queralt-Rosinach N, Bravo À, Deu-Pons J, Bauer-Mehren A, Baron M, Sanz F, Furlong LI. (2015) DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes. Database (Oxford).

Bravo A, Piñero J, Queralt-Rosinach N, Rautschka M, Furlong LI*. (2015) Extraction of relations between genes and diseases from text and large-scale data analysis: implications for translational research. BMC Bioinformatics, 16 (1): 55.

Gutiérrez-Sacristán A, Grosdidier S, Valverde O, Torrens M, Bravo A, Piñero J, Sanz F, Furlong LI. (2015) PsyGeNET: a knowledge platform on psychiatric disorders and their genes. Bioinformatics, 31 (18): 3075-3077.

Other relevant publications from last 10 years

Marti-Solano M, Birney E, Bril A, Della Pasqua O, Kitano H, Mons B, Xenarios I, Sanz F. (2014) Integrative knowledge management to enhance pharmaceutical R&D. Nat Rev Drug Discov, 13(4): 239-40.

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); e1002457.

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.

PharmacoInformatics Group

Manuel Pastor and Jana Selent

Website

http://phi.upf.edu

Research Outline

Our research is related with the application and development of computational methods in the field of pharmaceutical research and development. Regarding the application of computational methods, we make use of highly sophisticated computational simulations applied to G-protein coupled receptors in the context of the schizophrenia treatment, aimed to understand the molecular mechanisms involved and design safer and more effective drugs. Regarding the development of computational methods, we are authors of many novel methodologies, many of which have been implemented in scientific software with direct application in pharmaceutical research, mainly in the areas of preclinical drug safety evaluation.

Current Projects / Research Lines

- **eTOX**

Development of in silico methods for the prediction of in vivo toxicity of novel drug candidates. This project, involving a large consortium of academic groups and pharmaceutical companies, has compiled one of the largest databases available of preclinical repeated dose toxicity, which is being exploited for developing integrated prediction models.

- **EU-ToxRisk**

The project EU-ToxRisk aims to drive a paradigm shift in toxicological testing away from animal testing towards a toxicological assessment based on human cell responses and mechanistic understanding of chemical adverse effects. The ultimate goal is to deliver testing strategies to enable reliable, animal-free hazard and risk assessment of chemicals.

- **Antipsychotic drug action**

The clinical efficacy of antipsychotic drugs has been ascribed to a complex interplay involving multiple targets (particularly G protein-coupled receptors, GPCRs). We use advanced computational methods like molecular dynamics for understanding the molecular mechanisms that are behind the pharmacological effects of antipsychotic drugs.

Team during 2015-16

Senior researchers: Núria B. Centeno, Ismael Zamora.
Postdocs: José Carlos Gómez, Ramón Guixa, Juan Manuel Ramirez.
PhD students: Oriol López, Kevin Pinto, Ismael Rodriguez, Tomek Stępniewski.

Selected publications 2015-16

Carbonell P, Lopez O, Amberg A, Pastor M, Sanz F. (2016) Hepatotoxicity prediction by systems biology modeling of disturbed metabolic pathways using gene expression data. ALTEX-Altern Anim Ex. doi: 10.14573/altex.1602071.

Guixà-González R, Javanainen M, Gómez-Soler M, Cordobilla B, Domingo JC, Sanz F, Pastor M, Ciruela F, Martinez-Seara H, Selent J. (2016) Membrane omega-3 fatty acids modulate the oligomerisation kinetics of adenosine A2A and dopamine D2 receptors. Sci Rep-UK, 6: 19839.

Carrió P, Sanz F, Pastor M. (2015) Toward a unifying strategy for the structure-based prediction of toxicological endpoints Arch Toxicol. 90: 2445-60.

Carrió P, López O, Sanz F, Pastor M. (2015) eTOXlab, an open source modeling framework for implementing predictive models in production environments. J Cheminform. 7: 8.

Martí-Solano M, Iglesias A, de Fabritiis G, Sanz F, Brea J, Loza MI, Pastor M, Selent J. (2015) Detection of New Biased Agonists for the Serotonin 5-HT2A Receptor: Modeling and Experimental Validation. Mol Pharmacol. 87: 740-6.

Other relevant publications from last 10 years

Marti-Solano M, Birney E, Bril A, Della Pasqua O, Kitano H, Mons B, Xenarios I, Sanz F. (2014) Integrative knowledge management to enhance pharmaceutical R&D. Nat Rev Drug Discov. 13: 239-40.

Carrió P, Pinto M, Ecker G, Sanz F, Pastor M. (2014) Applicability Domain Analysis (ADAN): A Robust Method for Assessing the Reliability of Drug Property Predictions. J Chem Inf Model. 54: 1500-11.

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: 483-92.

Structural bioinformatics

Baldomero Oliva

Website

Sbi.upf.edu

Research Outline

Macromolecular 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. We interrogate protein structure to unveil its function, generate the network of interactions and to relate genes/proteins with diseases by exploiting the topology of the network. Simlarly, the regulatory network implies the formation of large macromolecular complex of transcription in which proteins interact with DNA. We also interrogate the structure of these complexes to relate other types of mutations affecting the final network.

Current Projects / Research Lines

- **Development of bioinformatic tools to study the mechanisms of protein-interaction network rewiring: Application in systems medicine**

Development of tools for the analysis of protein interation 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 rewirement produced by mutations or post-transcriptional modifications, such as phosphorylations.

- **Translational quantitative systems toxicology to improve the understanding of the safety of medicines**

Building systemic models of organ/cell exposure to drug and metabolites in a holistic fashion. Development of translational quantitative systems-based toxicological models for different organsl.

- **Research lines:**
  - Characterization of the structural motifs involved in the function and interactions between macromolecules.
  - Development of statistical potentials for interactions between macro-molecules.
  - Prediction of protein-protein and protein-DNA interations and study the mechanisms of interface selection of protein-protein and protein-DNA interactions.

Team during 2015-16

Senior researchers: Narcís Fernández-Fuentes. **PhD students**: Manuel Alejandro Marín, Bernat Antón, Daniel Poglayen, Joaquim Aguirre, Alberto Meseguer.

Selected publications 2015-16

Oliva B, Fernandez-Fuentes N (2015) Knowledge-based modeling of peptides at protein interfaces: PiPreD. Bioinformatics. 31(9):1405-10.

Wright Rh, Lioutas A, Le Dily F, Soronellas D, Pohl A, Bonet J, Nacht As, Samino S, Font-Mateu J, Vicent Gp, Wierer M, Trabado Ma, Schelhorn C, Carolis C, Macias Mj, Yanes O, Oliva B, Beato M (2016) ADP-ribose-derived nuclear ATP synthesis by NUDIX5 is required for chromatin remodeling. Science. 352(6290):1221-5.

Sieberts Sk, Zhu F, García-García J, Stahl E, Pratap A, Pandey G, Pappas D, Aguilar D, Anton B, Bonet J, Eksi R, Fornés O, Guney E, Li H, Marín Ma, Panwar B, Planas-Iglesias J, Poglayen D, Cui J, Falcao Ao, Suver C, Hoff B, Balagurusamy Vs, Dillenberger D, Neto Ec, Norman T, Aittokallio T, Ammad-Ud-Din M, Azencott Ca, Bellón V, Boeva V, Bunte K, Chheda H, Cheng L, Corander J, Dumontier M, Goldenberg A, Gopalacharyulu P, Hajiloo M, Hidru D, Jaiswal A, Kaski S, Khalfaoui B, Khan Sa, Kramer Er, Marttinen P, Mezlini Am, Molparia B, Pirinen M, Saarela J, Samwald M, Stoven V, Tang H, Tang J, Torkamani A, Vert Jp, Wang B, Wang T, Wennerberg K, Wineinger Ne, Xiao G, Xie Y, Yeung R, Zhan X, Zhao C; Members Of The Rheumatoid Arthritis Challenge Consortium, Greenberg J, Kremer J, Michaud K, Barton A, Coenen M, Mariette X, Miceli C, Shadick N, Weinblatt M, De Vries N, Tak Pp, Gerlag D, Huizinga Tw, Kurreeman F, Allaart Cf, Louis Bridges S Jr, Criswell L, Moreland L, Klareskog L, Saevarsdottir S, Padyukov L, Gregersen Pk, Friend S, Plenge R, Stolovitzky G, Oliva B, Guan Y, Mangravite Lm, Bridges Sl, Criswell L, Moreland L, Klareskog L, Saevarsdottir S, Padyukov L, Gregersen Pk, Friend S, Plenge R, Stolovitzky G, Oliva B, Guan Y, Mangravite L.M. (2016) Crowdsourced assessment of common genetic contribution to predicting anti-TNF treatment response in rheumatoid arthritis. Nat Commun 7:12460 .

Gubern A, Joaquin M, Marquès M, Maseres P, Garcia-Garcia J, Amat R, González-Nuñez D, Oliva B, Real Fx, De Nadal E, Posas F (2016) The N-Terminal Phosphorylation of RB by p38 Bypasses Its Inactivation by CDKs and Prevents Proliferation in Cancer Cells. Mol Cell 64(1):25-36.

Wright Rh, Fernandez-Fuentes N, Oliva B, Beato M (2016) Insight into the machinery that oils chromatin dynamics Nucleus 7(6):532-9.

Other relevant publications from last 10 years

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. 1;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(Web Server issue):W147-51.

Gitter A, Siegfried Z, Klutstein M, Fornes 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.

Computational RNA Biology Group

Eduardo Eyras

Selected presentations in 2016-2015 (as invited speaker)

- "Differential splicing across multiple conditions and disease states". Computational RNA Biology conference, Cambridge, October 2016.
- "Alternative splicing drivers of cancer". RNP and disease Conference. Marrakech, Morocco. October 2015.
- "Alternative splicing as drivers of cancer". Advances and Challenges in Protein-RNA: Recognition, Regulation and Prediction. Banff International Research Station. Banff, Alberta. Canada 07-juny-2015.
- "RNA processing alterations as drivers and prognostic markers of cancer" IMPPC Conference, Molecular Targets for Predictive and Personalized Medicine of Cancer Barcelona 8-10 April 2015.

Website http://comprna.upf.edu

Research Outline

We study the mechanisms of RNA regulation and the role of RNA processing alterations in cell differentiation and disease. In particular, we investigate RNA processing alterations in cancer that can be used to inform prognosis and potential therapeutic strategies, with the overall goal of contributing to current approaches in precision cancer medicine. We develop tools to measure differential splicing and RNA processing from RNA sequencing data. We also study the functional impact of differential splicing in physiological process and disease.

Current Projects / Research Lines

- **Characterization and detection of clinically relevant RNA-processing alterations for personalized cancer medicine**

The study of the genome of multiple tumours has been instrumental to identify recurrent alterations in several cancer types, which has facilitated their classification and the development of new therapeutic strategies. However, actionable alterations are frequently absent in patient samples, constituting a major medical problem, as standard therapies will be ineffective. RNA-processing alterations are emerging as important novel signatures to understand tumour formation and to develop new therapies. In this project, we propose to develop a computational platform for the analysis and clinical interpretation of RNA-processing alterations from an individual tumour sample. With this we aim at facilitating the clinical interpretation of the RNA content in tumours, as well as at complementing and improving current strategies of personalized cancer medicine.

Team during 2015-16

Postdocs: Endre Sebestyén.
PhD students: Babita Singh, Juan L. Trincado, Amadís Pagés, Isaac Kremsky.

Selected publications 2015-16

Trincado JL, Sebestyén E, Pagés A, Eyras E. (2016) The prognostic potential of alternative transcript isoforms across human tumors. Genome Med. 8(1):85.

Sebestyén, et al. E., Singh, B., Miñana, B., Pagès, A., Mateo, F., Pujana, M. A., Valcárcel J, & Eyras, E. (2016). Large-scale analysis of genome and transcriptome alterations in multiple tumors unveils novel cancer-relevant splicing networks. Genome Res. 26(6):732-44.

Agirre E, Bellora N, Alló M, PagésA, Bertucci P, Kornblihtt AR, Eyras E (2015). A chromatin code for alternative splicing involving a putative association between CTCF and HP1α proteins. BMC Biology 2;13:31.

Alamancos GP, Pagès A, Trincado JL, Bellora N, Eyras E. (2015). Leveraging transcript quantification for fast computation of alternative splicing profiles. RNA 21(9):1521-31.

Sebestyén E, Zawisza M, Eyras E (2015) Detection of recurrent alternative splicing switches in tumor samples reveals novel signatures of cancer. Nucleic Acids Res. 43(3):1345-56.

Other 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, Hallegger M, Smith CW, Eyras E (2010) Genome-wide association between branch point properties and alternative splicing. PLoS Comput Biol 6(11):e1001016.

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.

Other relevant information 2015-16

Associate editor of BMC Genomics (since 2013) and co-organizer of RNA and alternative splicing workshops at the ISMB Conference (2007- present).

Biomedical Genomics Group

Núria López-Bigas

Website

http://bg.upf.edu/group/index.php

Research Outline

Our group is focused on the study of cancer from a genomics perspective. Our main interest is the development of computational approaches to analyse cancer genomes in order to identify mutations, genes and pathways driving tumorigenesis and the identification of their therapeutic targeting opportunities.

Current Projects / Research Lines

- **Study of mutational processes in tumours**

Using the mutations detected in the whole genomes of hundreds of tumours, we learn some of the features shaping the processes that generate them.

- **Identification of cancer driver elements**

From the somatic alterations detected across cohorts of tumours we develop and apply methods to detect the genomic elements that exhibit signals of positive selection in the pattern of their alterations.

- **Translating cancer genomics findings into the clinic**

We develop resources and methods to help in the interpretation of the alterations detected in tumours with the aim to identify the therapies that may effectively target them.

Team during 2015-16

Other PI: Abel González-Perez.
Postdocs: David Tamborero, Loris Mularoni, Sabarinathan Radhakrishnan.
PhD students: Carlota Rubio-Perez, Joan Frigola, Ferran Muiños, Oriol Pich, Inés Sentís.
Technicians: Jordi Deu-Pons, Fernando Benito, Iker Reyes-Salazar.

Selected publications 2015-16

Rubio-Perez C, Deu-Pons J, Tamborero D, Lopez-Bigas N, Gonzalez-Perez A (2016) Rational design of cancer gene panels with OncoPaD. Genome Medicine 8 (1): 98.

Sabarinathan R, Mularoni L, Deu-Pons J, Gonzalez-Perez A, Lopez-Bigas N (2016) Nucleotide excision repair is impaired by binding of transcription factors to DNA. Nature 532 (7598): 264-7.

Mularoni L, Sabarinathan R, Deu-Pons J, Gonzalez-Perez A, López-Bigas N (2016) OncodriveFML: A general framework to identify coding and non-coding regions with cancer driver mutations. Genome Biology 17:128.

Mutation Consequences and Pathway Analysis working group of the International Cancer Genome Consortium (2015) Pathway and network analysis of cancer genomes. Nat Methods 12(7):615-21.

Rubio-Perez C, Tamborero D, Schroeder MP, Antolín AA, Deu-Pons J, Perez-Llamas C, Mestres J, Gonzalez-Perez A, Lopez-Bigas N (2015) In silico prescription of anticancer drugs to cohorts of 28 tumor types reveals unexploited targeting opportunities. Cancer Cell.

Other relevant publications from last 10 years

Gonzalez-Perez A, Lopez-Bigas N (2012) Functional impact bias reveals cancer drivers. Nucleic Acids Res., 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.

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.

Functional Genomics Group

Robert Castelo

Website

http://functionalgenomics.upf.edu

Research Outline

Our research focus is the development of statistical and computational methods and pipelines for the analysis and comprehension of high-throughput genetics and genomics data, motivated by questions of biological and clinical relevance.

Current Projects / Research Lines

- **Reverse engineering the genotype-phenotype map**

Genes and molecules are activated in a coordinated manner under finely tuned regulatory programs. 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.

- **Variant annotation and filtration**

The increased number of individuals profiled by genomics technologies steadily uncovers an increasing number of cases in which pathogenic mechanisms work conditionally on the cellular context where genetic alterations take place, hindering the interpretation of individual mutations. In collaboration with clinical geneticists, we are trying to approach this problem by developing novel methodologies for the annotation and filtration of genetic variants.

- **Prematurity and fetal immunity**

Intrauterine inflammation and infection increases the risk for perinatal mortality and morbidity and its frequency increases with lower gestational age at birth. In collaboration with paediatricians and obstetricians, we study the transcriptome of extremely preterm newborns (< 28 weeks of gestational age) to try to understand the extent of molecular changes that participate in the fetal inflammatory response to an intrauterine infection and how these changes lead to adverse neonatal outcome.

Team during 2015-16

PhD students: Pau Puigdevall and Daniel Costa.
Technicians: Adrià Closa.

Selected publications 2015-16

Hänzelmann S, Wang J, Güney E, Tang Y, Zhang E, Axelsson AS, Nenonen H, Salehi AS, Wollheim CB, Zetterberg E, Berntorp E, Costa IG, Castelo R and Rosengren AH (2015) Thrombin stimulates insulin secretion via protease-activated receptor-3. Islets, 7(4):e1118195.

Baumstark R, Hänzelmann S, Tsuru S, Schaerli Y, Francesconi M, Mancuso FM, Castelo R and Isalan M (2015) The propagation of perturbations in rewired bacterial gene networks. Nature Communications, 6:10105.

Kannan L, Ramos M, Re A, El-Hachem N, Safikhani Z, Gendoo DMA, Davis S, Gomez-Cabrero D, Castelo R, Hansen KD, Carey VJ, Morgan M, Culhane AC, Haibe-Kains B and Waldron L (2016) Public data and open source tools for multi-assay genomic investigation of disease. Briefings in Bioinformatics, 17(4):603-615.

Costa D and Castelo R (2016) Umbilical cord gene expression reveals the molecular architecture of the fetal inflammatory response in extremely preterm newborns. Pediatric Research, 79:473-481.

Other relevant publications from last 10 years

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.

Hänzelmann S, Castelo R, Guinney J (2013) GSVA: gene set variation analysis for microarray and RNA-Seq data. *BMC Bioinformatics*, 14:7.

Tur, I, Roverato A, Castelo R (2014) Mapping eQTL networks with mixed graphical Markov models. Genetics 198(4):1377-1383.

Computational Biophysics Group

Gianni de Fabritiis

Website

www.multiscalelab.org

Workshop

HTMD workshop 2013, 2015, 2016.

Research Outline

We are particularly active in molecular dynamics simulations, binding prediction, binding kinetics, Markov state models, online sampling methods, and software development (ACEMD, HTMD). The approach is completely computational driven for hypothesis generation and then experimentally validated. We also collaborate with experimental laboratories and industries where we work by rationalizing experimental results.

Another of our interests lies in machine learning. We develop machine learning approaches applied to the biological data that we generate. Specially, we are interested in dimensionality reduction methods, artificial neural networks, unsupervised learning. We also look at new computational intelligence approaches in general.

Current Projects / Research Lines

- **CompBioMed EU**

User-driven Centre of Excellence in Computational Biomedicine aimed to nurture and promote the uptake and exploitation of high performance computing within the biomedical modelling community.

- **Molecular recognition of intrinsically disordered domains**

We apply simulation-based methods to understand and then attempt to modify biologically activity of intrinsically disordered domains.

Team during 2015-16

Postdocs: Silvia Lovera, Joao Damas.
PhD students: Nathaniel Stanley, Gerard Martinez, Noelia Ferruz, Stefan Doess, Pablo Nieto.

Selected publications 2015-16

Ferruz N, Tresadern G, Pineda-Lucena A, De Fabritiis G (2016) Multibody cofactor and substrate molecular recognition in the myo-inositol monophosphatase enzyme, Scientific Reports 6, Article number: 30275.

Doerr S, Harvey MJ, Noé F, De Fabritiis G 2016) HTMD: High-throughput molecular dynamics for molecular discovery, J Chem Theory Comput 12 (4):1845–52.

Stanley N, Pardo L, De Fabritiis G (2016) The pathway of ligand entry from the membrane bilayer to a lipid G protein-coupled receptor. Scientific Reports 6, Article number: 22639.

Ferruz N, Harvey M, Mestres J, De Fabritiis G (2015) Insights from Fragment Hit Binding Assays by Molecular Simulations. J Chem Inf Model 55 (10): 2200–5.

Harvey MJ, De Fabritiis G (2015) Acecloud: Molecular Dynamics Simulations in the Cloud. J Chem Inf Model 55 (5): 909–14.

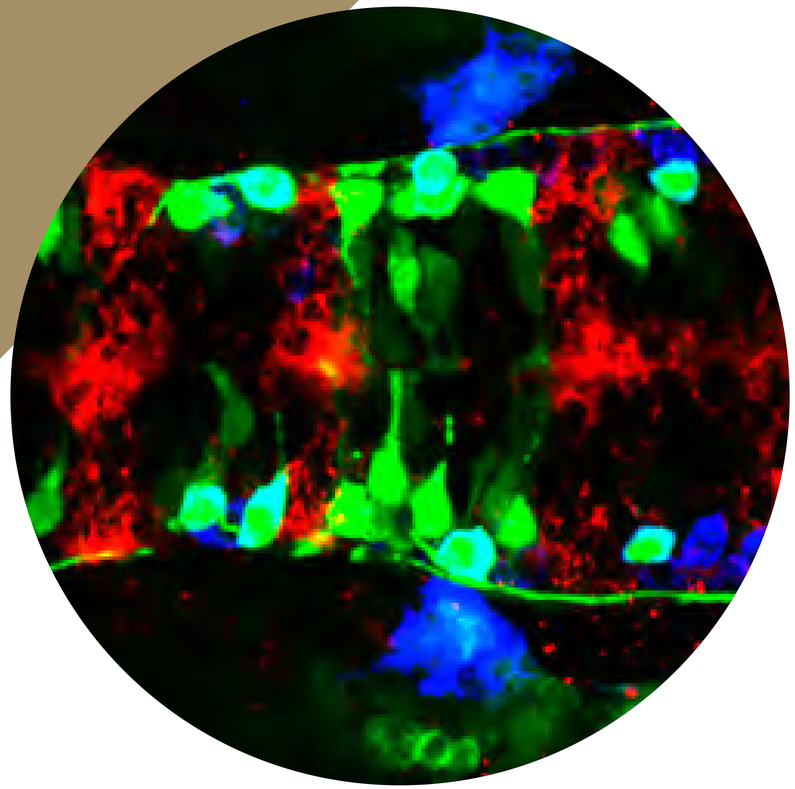
Other relevant publications from last 10 years

Stanley N, Esteban S, De Fabritiis G (2014) Kinetic modulation of a disordered protein domain by phosphorylation. Nat Commun 5:5272.

Buch I, Giorgino T, De Fabritiis G (2011) Complete reconstruction of an enzyme-inhibitor binding process by molecular dynamics simulations. PNAS 108:10184-9.

Harvey M, Giupponi G, De Fabritiis G (2009) ACEMD: Accelerated molecular dynamics simulations in the microseconds timescale. J Chem Theory and Comput 5:1632.

Research groups



Genetics and Neurosciences Programme

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: 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; Genetics of Cognitive Functions, with a special emphasis in two pathologies, Williams-Beuren Syndrome and Autism Spectrum Disorder, and Neuropharmacology, focused on the neurobiological substrate of drug addiction, pain, affective and eating disorders, and 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, including the license of two patents to an external enterprise.

COORDINATOR

Rafael Maldonado

- Laboratory of Neuropharmacology (NeuroPhar)
- Human Genetics
- Morphogenesis and Cell Signaling in Sensory Systems
- Developmental Biology. Ear development
- Developmental Neurobiology

Laboratory of Neuropharmacology (NeuroPhar)

Rafael Maldonado

Website

www.upf.edu/neurophar

Awards

Establishment (November, 2015) of a Mixed Pre-clinical Research Unit between Laboratorios Esteve and the UPF (NeuroPhar), being its director Rafael Maldonado and its research responsible Miquel Martín. The Unit is based at the PRBB, is planned for 10 years, with a budget of 375.000 € per year, and is composed by 5 researchers. Research award of the Antonio Esteve Foundation (2015) for the article Busquets-Garcia et al. Nat Med, 19(5):603-72013. ICREA Acadèmia award from the Generalitat de Catalunya to Rafael Maldonado (2015) and to Andrés Ozaita (2016).

Research Outline

Our main interest is the identification of new therapeutical targets at the nervous system level. We focus our activities in the neurochemical and neuroanatomical bases of the dependence to opioids and cannabinoids employing murine models. We also study the possible use of some of these compounds in the treatment of pain, cognitive, affective and eating disorders. Therefore, we use a classical pharmacological strategy complemented with the use of genetically modified animals, in particular, knockout mice, and biochemichal techniques to quantify in vivo the concentration of several monoamines. We are also interested in the involvement of the endogenous opioid (EOS), cannabinoid (ECS) and hipocretinergic (EHS) systems in the physiopathology of affective disorders and cognitive deficits.

Current Projects / Research Lines

- Involvement of the EOS in addiction (nicotine, cocaine).
- New therapeutic approaches for drug addiction treatment.
- EOS and ECS involvement in palatable food-seeking behaviour.
- EOS, ECS and serotonergic system role in neuropathic, osteoarthritic and inflammatory pain, search for new pharmacological targets and analgesic compounds.
- ECS participation in alcohol consumption vulnerability.
- Evaluation of acylethanolamide-based neuroprotectants in brain hypoxia preclinical models.
- EHS involvement in addiction (nicotine, cannabinoids) and in the mechanisms underlying aversive memories (consolidation and extinction).
- Cognitive deficits associated with nicotine withdrawal.
- Molecular and cellular mechanisms (mTOR) involved in the ECS-controlled cognitive function.
- Targeting the ECS for pharmacological therapies in FXS.
- Brain effects of chronic THC exposure (cognitive and motor coordination deficits).
- Eating disorders and chronic pain mechanisms using RiboTag technology.
- Loss of control of palatable food-seeking behavior using DREADD approach.
- Nursing procedures-associated pain and non-communicative pain bioethics in critical care patients.
- Clinical differences in patients afflicted by vulvodinia using psychometric tools.

Team during 2015-16

Other PIs: Josep-Eladi Baños Díez, Fernando Berrendero Díaz, Andrés Ozaita Mintegui, Elena Martín García, Miquel A. Martín Sánchez. **Postdocs:** David Cabañero Ferri, Antonio Ortega Álvaro, Roberto Cabrera Ortega, Virginia Mela Rivas Aurelijus Burokas and Sueli Mendonça Netto. **PhD students:** Laura Cutando Ruiz, Xavier Viñals Álvarez, Carmen La Porta, Samantha Mancino, África Flores de los Heros, Roger Negrete Buela, Maria Gomis González, Itzel Montserrat, Lara Mayorga, Elk Kossatz de Mello, Míriam Gutiérrez Martos, Victoria Salgado Mendialdúa, Rocío Saravia Santos, Sami Kummer, Alba Navarro Romero, Miriam Martínez Navarro, Mireia Carcolé Estrada, Marina Julià Hernández, Júlia Sala Bayo, Marta Puerto Plasencia, Laura Domingo Rodríguez, Sara Martínez Torres, Ángela Ramírez López, Alejandra Escudero Lara, Lorena Galera López, Sheila Piedra Barrull and Ana M. Gallego Román. **Technicians:** Raquel Martín García, Dulce Real Muñoz, Francisco Porrón López, Alicia Fabra Avilés, Marta Linares López, Mireia Viñas Noguera and Neus Morgui Valls. **Project Manager:** Miquel-Àngel Serra Beltrán.

Selected publications 2015-16

Viñals X, Moreno E, Lanfumey L, Pastor T, de la Torre R, Gasperini P, Lluís C, Canela EI, McCormick P, Maldonado R*, Robledo P* (2015). PLoS Biol, 13(7):e1002194.

Lutz B, Marsicano G, Maldonado R, Hillard CJ (2015). Nat Rev Neurosci, 16(12):705-718.

Flores A, Saravia R, Maldonado R*, Berrendero F* (2015). Orexins and fear: implications for the treatment of anxiety disorders. Trends Neurosci, 38(9):550-559.

Busquets-Garcia A, Gomis-González M, Srivastava RK, Cutando L, Ortega-Alvaro A, Ruehle S, Remmers F, Bindila L, Bellocchio L, Marsicano G, Lutz B*, Maldonado R*, Ozaita A* (2016). Peripheral and central CB1 cannabinoid receptors control stress-induced impairment of memory consolidation. Proc Natl Acad Sci USA, 113(35):9904-9909

Saravia R, Flores A, Plaza-Zabala A, Busquets-García A, Pastor A, de la Torre R, Di Marzo V, Marsicano G, Ozaita A, Maldonado R, Berrendero F (2016). CB1 cannabinoid receptors mediate cognitive deficits and structural plasticity changes during nicotine withdrawal. Biol Psych 81 (7): 625-634.

Other relevant publications from last 10 years

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):1152-8.

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):603-7.

Vallée M, Vitello S, Bellocchio L, Hébert-Chatelain E, Monlezun S, Martin-Garcia E, Kasanetz F, Baillie GL, Panin F, Cathala A, Roullot-Lacarriere V, Fabre S, Hurst DP, Lynch DL, Shore DM, Deroche-Gamonet V, Spampinato U, Revest JM, Maldonado R, Reggio PH, Ross RA, Marsicano G, Piazza PV (2014). Pregnenolone can protect the brain from cannabis intoxication. Science, 343(6166):94-98.

Human Genetics

Luis Alberto Pérez Jurado

Awards

- Direction and Coordination, Master in Genetic Counseling BSM/UPF, accredited as an official training site by the European Board of Genetic Counseling.
- Coordination of the training program. Network Center for Biomedical Research on Rare Diseases (CIBERER).
- Group in the Program in Neurosciences, Hospital del Mar Research Institute (IMIM).
- Direction (and advisory board members), qGenomics laboratory, spin-off participated by the UPF dedicated to the development of genetic and genomic tools for molecular diagnosis of human diseases.
- Consolidated Research Group, AGAUR (since 2005).

Website

upf.edu/genetica - www.qgenomics.com - www.ciberer.es/grupos/grupo-de-investigacion?id=17123

Research Outline

The genetic and genomic disorders affecting human development and the mutational mechanism of the human genome are our main interests. Our multidisciplinary group integrates clinical, molecular and bioinformatic research along with the use of cellular and animal models. We search for biomarkers for early diagnosis of germline and somatic disease, contribute to novel therapeutic strategies, and provide appropriate genetic counseling to families. Translation and transfer of the generated knowledge is achieved through clinical services at the associated hospitals and the Spin-off qGenomics, developing specific tools for clinical diagnosis, prognosis and personalize medicine.

Current Projects / Research Lines

- **Molecular bases of neurodevelopmental disorders and human malformations**

Through the integration of clinical and genomic data, we attempt to unravel the etiologies of several heterogeneous disorders affecting human development.

- **Pathogenic mechanisms and novel therapies in Williams-Beuren and its reciprocal syndrome**

Detailed characterization of patients, identification of genetic modifiers and disease modeling in mice and by cell reprograming are used with the goal to identify novel therapeutic options.

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

A significant proportion of the hidden heritability for human disorders likely lies within complex genomic regions with high genome plasticity but poorly explored so far, including mosaic changes, genomic inversions and gene conversions.

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

We coordinate the Program for Undiagnosed Rare Diseases in Catalonia and the CIBERER. This Program, as well the activities developed by qGenomics, aims to incorporate the genomic and personalized medicine into the Health System.

Team during 2015-16

Postdocs: Victoria Campuzano Uceda (PI), Ivon Cuscó Martí (PI), Lluís Armengol Dulcet (qGenomics director), Benjamín Rodríguez-Santiago (qGenomics), Roser Corominas Castiñeira, Olaya Villa Marcos (qGenomics), Jairo Rodríguez Lumbiarres (qGenomics), Clara Serra Juhé, Maria Segura Puimedon, Sorina Daniela Tatu Boncota. **PhD students:** Marta Codina Solà, Cristina Borralleras Fumaña, Armand Gutiérrez Arumí, Débora Pérez García, Judith Reina Castillón, Marcos López Sánchez, Maria Gabriela Palacios Verdú, Anna Montaner Domènech, Francesc Bou de Pieri, Paula Ortiz Romero. **Technicians:** Raquel Flores Peirats. **Project Manager:** Andrés Medrano.

Selected publications 2015-16

Serra-Juhé C, Cuscó I, Homs A, Flores R, Torán N, Pérez-Jurado LA. DNA methylation abnormalities in congenital heart disease. Epigenetics 10:167-77 (2015).

Dauber A, Muñoz-Calvo MT, Barrios V, Domené HM, Kloverpris S, Serra-Juhé C, Desikan V, Pozo J, Muzumdar R, Martos-Moreno GÁ, Hawkins F, Jasper HG, Conover CA, Frystyk J, Yakar S, Hwa V, Chowen JA, Oxvig C, Rosenfeld RG, Pérez-Jurado LA, Argente J. (2016) Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. EMBO Mol Med 8:363-74.

Zhou W, Machiela MJ, Freedman ND, Rothman N, Malats N, Dagnall C, Caporaso N, Teras LT, Gaudet MM, Gapstur SM, Stevens VL, Jacobs KB, Sampson J, Albanes D, Weinstein S, Virtamo J, Berndt S, Hoover RN, Black A, Silverman D, Figueroa J, Garcia-Closas M, Real FX, Earl J, Marenne G, Rodriguez-Santiago B, Karagas M, Johnson A, Schwenn M, Wu X, Gu J, Ye Y, Hutchinson A, Tucker M, Pérez-Jurado LA, Dean M, Yeager M, Chanock SJ. (2016) Mosaic loss of chromosome Y is associated with common variation near TCL1A. Nat Genet 48:563-8.

Borralleras C, Mato S, Amédée T, Matute C, Mulle C, Pérez-Jurado LA, Campuzano V. (2016) Synaptic plasticity and spatial working memory are impaired in the CD mouse model of Williams-Beuren syndrome. Mol Brain 9:76.

Homs A*, Codina M*, Rodríguez-Santiago B, Villanueva CM, Monk D, Cuscó I*, Pérez-Jurado LA*. (2016) Genetic and epigenetic methylation defects and implication of the ERMN gene in autism spectrum disorders. Translat Psych 6:e855

Other relevant publications from last 10 years

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.

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.

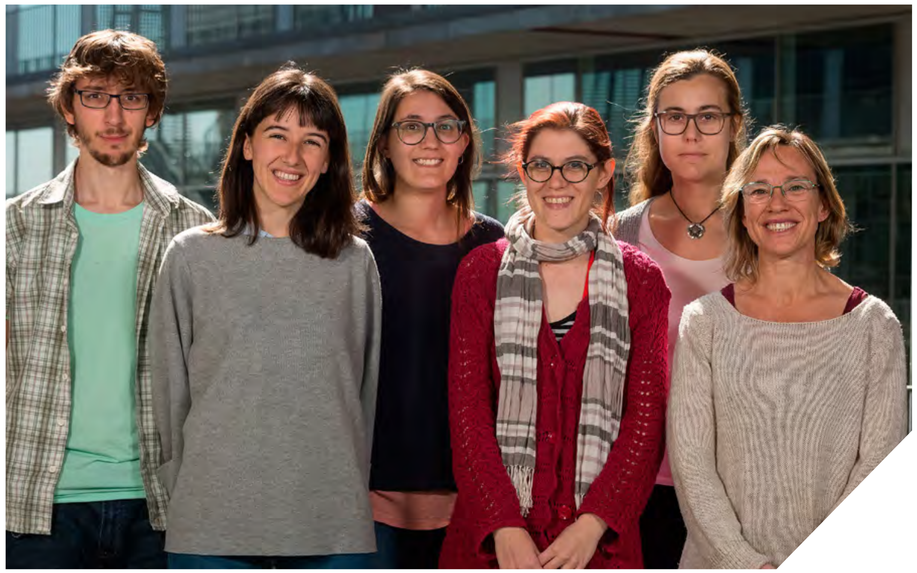
González JR, Cáceres A, Esko T, Cuscó I, Puig M, Esnaola M, Reina J, Siroux V, Bouzigon E, Nadif R, Reinmaa E, Milani L, Bustamante M, Jarvis D, Antó JM, Sunyer J, Demenais F, Kogevinas M, Metspalu A, Cáceres M, Pérez-Jurado LA. (2014) A common 16p11.2 inversion underlies the joint susceptibility to asthma and obesity. Am J Hum Genet 94:361-72.

Morphogenesis and Cell Signaling in Sensory Systems

Berta Alsina

Website

www.upf.edu/web/alsina_lab/research



Research Outline

Our research focuses on the molecular and cellular events underlying the development of the inner ear, a highly sophisticated sensory organ responsible for the senses of hearing and balance. Its dysfunction causes deafness, the most prevalent sensorineural deficit. We address which genes are implicated in the development of sensory neurons and hair cells in order to promote hair cell regeneration and understand deafness mutations. We are also studying the morphogenetic events taking place during inner ear development to understand how cells organize and generate an organ with a precise 3D shape. Our laboratory combines various technologies such as genetic and pharmacological perturbations, high-resolution life imaging, cell ablation and transcriptomic/epigenetic analysis in the zebrafish embryo.

Current Projects / Research Lines

- **Molecular Mechanisms of Hair Cell Regeneration**

Humans cannot regenerate damaged hair cells, which leads to deafness. We have found that retinoic acid signalling has a central role in hair cell regeneration and we are currently studying the epigenetic modifications underlying hair cell regeneration.

- **Epithelial and Neuron Morphogenesis**

Very little is known about how cells acquire their shape, migrate and coordinately organize to a functional organ. We are using the inner ear as a model to investigate in 4D the dynamics of epithelial mesenchymal transition events and neuron migration and the interaction between biomechanics and signaling. These studies will be relevant for organoid techniques.

- **Neurovascular Development**

We are investigating the role of blood vessels in neural stem cell quiescence, neuron differentiation and migration in the inner ear and the brain.

Team during 2015-16

Postdocs: Esteban Hoijman.
PhD students: Davide Rubbini, Laura Fargas, Laura Tabernenr.
Technicians: Marta Linares, Sara Calatayud.

Selected publications 2015-16

Alsina B and Whitfield TT (2016). Sculpting the labyrinth: morphogenesis of the developing inner ear. Seminaris in Cell and Developmental Biology S1084-9521(16) 30311-1.

Rubbini D, Robert-Moreno À, Hoijman E, Alsina B. (2015). Retinoic acid mediates Hair Cell regeneration by prepressing p27kip and sox2 in supporting cells. J Neurosc. 35(47):15752-66 A.

Hoijman E and Alsina B (2015). Cavity morphogenesis: imaging mitotic forces in action. Cell Cycle, DOI: 10.1080/15384101.2015.1076657.

Hoijman E, Rubbini D, Colombelli J and Alsina B (2015). Mitotic cell rounding and epithelial thinning regulate lumen growth and shape. Nature Commun 16;6:7355.

Iturbide A, Pascual-Reguant L, Fargas L, Cebrià JP, Alsina B, García de Herreros A, Peiró S. (2015). LOXL2 Oxidizes Methylated TAF10 and Controls TFIID-Dependent Genes during Neural Progenitor Differentiation. Mol Cell. 58(5):755-66.

Other relevant publications from last 10 years

Maier EC, Saxena A, Alsina B, Bronner ME, Whitfield TT (2014). Sensational placodes: Neurogenesis in the otic and olfactory systems. Dev Biol 126(Pt 1):53-9.

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.

Abelló B, 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.

Developmental Biology. Ear development

Fernando Giraldez

Website

www.upf.edu/web/devbiol

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 development of neurons and hair cells in the inner ear. The study focuses on the genetic networks that specify the onset of hair cells and neurons in the ear and how this is timed during development. This knowledge is crucial for developing new tools for regenerative therapies directed to alleviate hearing impairment.

Current Projects / Research Lines

- **The origin of hair cells in the embryo**

Atonal1 (Atoh1) is a transcription factor that behaves as a master gene for the development of inner ear hair cells. Atoh1 is also able to drive hair cell production also in the adult. The regulation of Atoh1, therefore, is at the heart of hair cell development and regeneration. Our goal is to understand the molecular regulation of Atoh1 in ear precursors. This work is supported by MINECO.

- **Regenerating hair cells**

Tissue regeneration may be improved by reactivating similar genetic programs that operate during embryonic life. This is the value of research on hair cell development as applied to alleviating hearing loss. Our study is focused on finding the conditions that favour the activation of Atoh1 during cell reprogramming, in different cellular contexts. This is done in collaboration with Thomas Schimmang (IBGM, CSIC-UVA) and Marcelo Rivolta (Scheffield University) and supported by Fundació La Marató TV3.

- **Neuroscience and Humanities**

Study of philosophical and aesthetic questions related to the neuroscience of sensory systems.

Team during 2015-16

Postdocs: Gina Abelló.
PhD students: Héctor Gálvez.
Technicians: Sara Calatayud.

Selected publications 2015-16

Vendrell V, López-Hernández I, Durán MB, Abelló G, Gálvez H, Feijó A, Giráldez F, Lamoniere T, Schimmang T (2015) Otx2 is a target of N-myc and acts as suppressor of sensory development in the mammalian cochlea. *Development* 142: 2792-800.

Gálvez H, Abelló G, Giraldez F (2016) Signalling and transcription factors during inner ear development: the generation of hair cells and otic neurons. *Frontiers in Cell and Developmental Biology* 5:21.

Other relevant publications from last 10 years

Neves J, Parada C, Chamizo M, Giráldez F (2011) "Jagged1 regulates the restriction of Sox2 expression in the developing chicken inner ear: a mechanism for sensory organ specification". *Development* 138:735-44.

Petrovic J, Formosa-Jordan J, Luna JC, Abelló G, Ibañes M, Neves J, Giráldez F (2014) Ligand dependent Notch signaling strength orchestrates lateral induction and lateral inhibition in the developing inner ear. *Development* 141(11): 2313-24.

Petrovic J, Abelló G, Gálvez H, Neves J, Giráldez F (2014) Differential regulation of Hes/Hey genes during inner ear development. *Developmental Neurobiology*.

Other relevant information 2015-16

Giraldez (2016) El cerebro y la música: buscando reglas universales. Sonograma Magazine, http://sonograma.org/2016/10/cerebro-musica-reglas-universales/.

Giraldez F (2016) El oído: de las células ciliadas al éxtasis. SEBBM, Acércate a nuestros científicos. http://www.sebbm.es/web/es/divulgacion/acercate-nuestros-cientificos/1634-fernando-giraldez-agosto-2016-el-oido-de-las-celulas-ciliadas-al-extasis.

Giraldez F (2016) La construcción del sabor. Instituto Cervantes, Madrid. La Noche de los Investigadores.

Developmental Neurobiology

Cristina Pujades

Website

pujadeslab.upf.edu/

Research Outline

The Central Nervous System is initially subdivided into regions with distinct identity that underlies the generation of a specific set of cell types, each of which must arise at the right time and place and in the correct proportions for normal development and function. We focus our studies on the embryonic development of the hindbrain, as a model to study how cellular compartments operate during brain development, and how cell diversity is generated. Our goals are to unveil when and how brain progenitors commit to a given fate, how they behave once committed, and how cell fate decisions are regulated to generate the distinct cell lineages. We combine high-resolution imaging with genetics, using the zebrafish embryo as a model system.

Current Projects / Research Lines

- **Deciphering how cell diversity is generated in the developing hindbrain**

Combining high-resolution in vivo imaging and gene transcriptional activation signature analyses, we aim to understand how the neurogenic/gliogenic capacity is allocated to specific territories.

- **Exploring the fate and reconstituting the lineage of the hindbrain boundary cells**

We in vivo track this population –generated at the rhombomere interface - in transgenic fish in which the specific cell populations were targeted by CRISPR-Cas9 genome editing.

- **Studying the impact of morphomechanical changes on tissue subdivision and cell organization** within the hindbrain. We investigate the function of yap/taz-activity as the bridging step between tissue architecture/mechanical forces with cell fate and identity.

- **Developing the digital Z-Hindbrain,** as an open-source platform to integrate cell identity, cell behaviour and tissue growth information over time. This will provide a dynamic morphogenetic map to understand the impact of morphogenesis in cell lineages and cell progenitors behaviour.

Team during 2015-16

Postdocs: Covadonga Fernandez-Hevia, Christian Cortes-Campos.
PhD students: Adrià Voltes, Ivan Belzunce, Carla Belmonte, Sylvia Dyballa (left in 2016).
Technicians: Sara Calatayud.

Selected publications 2015-16

Dyballa S, Savy T, Germann P, Mikula K, Remesikova M, Spir R, Zecca A, Peyrieras N, Pujades C (2016) Distribution of neurosensory progenitor pools during inner ear morphogenesis unveiled by cell lineage reconstruction. eLife 6. pii: e22268.

Terriente J, Pujades C (2015) Cell segregation in the hindbrain: do boundaries matter? Invited review. Cell Mol Life Sci, DOI: 10.1007/s00018-015-1953-8.

Zecca A, Dyballa S, Voltes A, Bradley R, Pujades C (2015) The order and place of neuronal differentiation establish the topography of sensory projections and the entry points within the hindbrain, J Neuroscience 35(19): 7475-86.

Kamaid A, Molina-Villa T, Mendoza V, Pujades C, Maldonado E, Ispizua Belmonte JC, López-Casillas F (2015) Betaglycan knock-down causes embryonic angiogenesis defects in zebrafish. Genesis Jul 15. doi: 10.1002/dvg.22876.

Other relevant publications from last 10 years

Calzolari S, Terriente J, Pujades C (2014) Cell segregation in the vertebrate hindbrain relies on actomyosin cables located at the interhombomeric boundaries. EMBO J Apr 1 33(7): 686-701.

Sapède D, Dyballa S, Pujades C (2012) Cell lineage analysis reveals three different progenitor pools for neurosensory elements in the otic vesicle. J Neurosc 32(46): 16424-34.

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.

Research groups

Transversal Program

The main objective of this programme is to improve the social perspective of health and education in life and health sciences. The Programme has three goals: a scientific objective, which studies how social and economic policies, such as environmental and working conditions, are affecting the health of population; to serve as a bridge between basic research produced in other programmes and hospitals and other public health centres, and 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), the Research Centre Environmental Epidemiology (CREAL) and the Health Service Research Unit in the IMIM-Parc 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. The educational research to improve teaching's quality is carried out by the Research Group in Health Sciences Education.

COORDINATOR

Jordi Pérez

Center for Research in Occupational Health (CiSAL)

Research Group in Health Sciences Education (GRECS)

Center for Research in Occupational Health (CiSAL)

Fernando G. Benavides

Website

www.upf.edu/cisal

Selected presentations in 2016-2015 (as invited speaker)

- **II Ibero-American Meeting on Surveys of Working Conditions and Health** in Minas Gerais (Brazil) on 9 and 10 July 2015.
- **III Ibero-American Meeting on Surveys of Working Conditions and Health** in Lima (Peru) on March 17 and 18, 2016.

Research Outline

We focus a range of contemporary paid work related health problems, including musculoskeletal disorders, workplace injuries, prevention programs, and the determinants of sickness absence and temporary/permanent disability. All of them particularly relevant for the 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.

Current Projects / Research Lines

- **Burden of occupational disease treated in the National Health System (CEPS)**

We contribute to the identification and adequate assessment of the occupational disease burden treated in hospitals of the National Health System to evaluate the assistance and economic impact for such hospitals.

- **Welfare State and health project (EBiSA)**

Analysis of the relationship between labour market trajectories, permanent disability and mortality in a cohort of more than 1 million of workers affiliated to the Social Security System.

- **Evaluation of a multifactorial intervention at the workplace for the prevention of musculoskeletal disorders in workers (INTEVAL_Spain)**

Implementation of an innovative intervention in the workplace that minimizes the adverse impact of disabling MSDs on workers' well-being and the financial cost of sickness absence for employers and social security systems.

- **Surveys of Working Conditions and Occupational Health Indicators**

Evaluation of the employment and working conditions and health indicators in Latin-America and Caribbean countries.

Team during 2015-16

Senior researchers: Consol Serra, Jordi Delclòs, David Gimeno.
Postdocs: José M. Ramada, Laura Serra, Mónica Ubalde, María López.
PhD students: María Andrée López, Pamela Merino, Marianela Rojas, Dinora Bernal, Esther Colell, Rocío Villar, Júlio César Hernando, Mercè Soler.
Technicians: Montserrat Fernández.

Selected publications 2015-16

Colell E, Sánchez-Niubò A, Delclos GL, Benavides FG, Domingo-Salvany A (2015) Economic crisis and changes in drug use in the Spanish economically-active population. Addiction;110(7):1129-37.

Lourenço S, Carnide F, Benavides FG, Lucas R (2015) Psychosocial Work Environment and Musculoskeletal Symptoms among 21-Year-Old Workers: A Population-Based Investigation (2011-2013). PLoS One;10(6):e0130010.

Ruotsalainen JH, Verbeek JH, Mariné A, Serra C (2015) Preventing occupational stress in healthcare workers. Cochrane Database Syst Rev;(4):CD002892. doi: 10.1002/14651858.CD002892.pub5.

Arcas MM, Delclos GL, Torá-Rocamora I, Martínez JM, Benavides FG (2016) Gender differences in the duration of non-work-related sickness absence episodes due to musculoskeletal disorders. J Epidemiol Community Health. 70(11):1065-1073. doi: 10.1136/jech-2014-204331.

Murcia López G, Delclós Clanchet J, Ubalde López M, Calvo Bonacho E, Benavides FG (2016) Has the Spanish economic crisis affected the duration of sickness absence episodes? Soc Sci Med;160:29-34.

Other relevant publications from last 10 years

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.

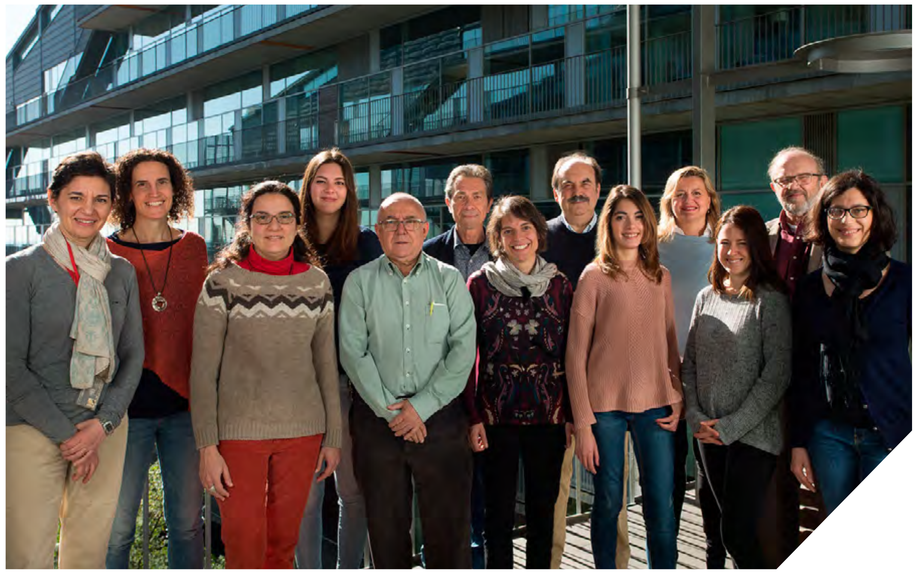
Martínez JM, Benach J, Benavides FG, Muntaner C, Clèries R, Zurriaga O, Martínez-Beneito MA, Yasui Y (2009) Improving multilevel analisys: the integrated epidemiologic design. Epidemiology;20(4):525-32.

Benavides FG, Wesseling C, Delclos GL, Felknor S, Pinilla J, Rodrigo F; on behalf of the research team of the first Central American Survey of Working Conditions and Health (2014) Working conditions and health in Central America: a survey of 12.024 workers in sin six countries. Occup Environ Med;71(7):459-65.

Research Group in Health Sciences Education (GRECS)

Centre of Studies on Science, Communication and Society (CCS)

Josep-Eladi Baños & Jordi Pérez
Gema Revuelta



Research Outline

The education in the field of health sciences is our main interest. We are devoted to improve the educational project of the FCSV of UPF and to enhance the initiatives, which improve the university teaching. We also aim to facilitate the contact with secondary education whit an increase of scientific interest of young students and to bring closer together society and science: we develop actions of scientific communication and citizen participation, assessment and training.

Current Projects / Research Lines

- **Evaluation of teaching and learning strategies in bachelors of the FCSV of UPF**
  - Problem-based learning (PBL) in Human Biology and Medicine degrees
  - Students' mentoring
  - Portfolio for generic competencies development
  - Introduction of multidisciplinary clinical simulation in Medicine degree
  - Pedagogical value of TV medical dramas in medical students (PlaClick 2016).
- **Research on innovation in science education at secondary and higher education**
  - Creaflip: new scenarios to train creative scientist (PlaCLIK 2016-18)
  - IMAX: fostering interactions further classrooms to increase students success
    - (PlaCLIK 2016-17)
  - ABRIC: Learning biology through reflection and collaborative research (PlaClick 2016-18)
  - RESET: reformulating scalable educational ecosystems (PN: 2015-2018) -
  - Project evaluation with new assessment tools Moodle 2.7 and optimizing the
    - organization of internal practices (PlaCLIK 2015-16)
  - Avalua't: a tool for the independent study (PlaCLIK 2016-18).
- **Teachers training and development**
  - Redesigning pre-service science teachers training curricula to foster innovative practices in schools.
  - Implementation of project based learning methodologies at Catalan schools.
- **Science, Communication and Society**
  - HEIRRI: Higher Education Institutions and Responsible Research and Innovation.
  - QUIRAL project: media coverage of health and medical issues.
  - VIDEONLINE: Online video as a tool for science communication.
  - Social perception and participation in the R&D&I process: the role of Civil Society Organizations.

Team during 2015-16

Postdocs & Senior researchers: Education: Laia Agell, Eva Baillés, Mar Carrió, Nuria B. Centeno, Meritxell Girvent, Silvia Lope, Miguel Angel Mayer, Elisabeth Moyano, Mariano Sentí and Vanessa Soria. **Communication**: Vladimir de Semir and Rosario Martínez. **PhD students:** Gemma Rodríguez, Carolina Llorente and Anna Torras. **Technicians:** Pilar Larramona, Emma Cots and Nora Pérez. **Project Manager:** Núria Saladié i Clara Armengou.

Selected publications 2015-16

Landin M, Pérez J (2015) Class attendance and academic achievement of pharmay studens in a European University. Currents in Pharmacy Teaching and Learning, 7:78-83.

Rodriguez G, Baños JE, Carrió M (2016) Fostering creativity through Inquiry Based- Learning in Biomedical Sciences. In: Zhou C, Handbook Research on Creative Problem Solving Skills in Higher Education. International Publisher of Progressive Information Science and Technology Research. IGI Global.

Carrió M, Agell L, Baños JE, Moyano E, Larramona P, Pérez J (2016) Benefits of using a hybrid problem based learning curriculum to improve long term learning acquisition. FEMS Microbiol Lett., 363(15). DOI: 10.1093/femsle/fnw159.

Sentí M, Pérez J, Baños JE (2016) Factores predictores de resultados en la prueba MIR en las universidades públicas. Análisis de la cohorte 2008-2014. FEM 19 (3):155-60.

Nielsen MV, Tauginienė L, Filacek A, Mačiukaitė-Žvinienė S, Revuelta G (2016) RRI at European Universities. In Navigating Towards Shared Responsibility in Research and Innovation. Approach, Process and Results of the Res-AGorA Project, pp 121-125.

Other relevant publications from last 10 years

Revuelta G (2014) Impacts of science communication on publics, cities and actors. Journal of Science Communication, 13, 1.

Gaskell G, Allansdottir A, Allum N, Castro P, Esmer Y, Fischler C, Jackson J, Kronberger N, Hampel J, Mejlgaard N, Quintanilha A, Rammer A, Revuelta G, Stares S, Torgersen H, Wagner W (2011) Eurobarometer on the life sciences. Nature Biotechnology 29, 2: 113-4.

Hernández-Leo D, Moreno P, Carrió M, Chacón J, Blat J (2015) LdShake and the "Biologia en Context" teachers' community across high schools. In: Mor Y, Craft B, Maina M (eds.). The Art and Science of Learning Design. Sense Publisher, Series "Technology Enhanced Learning", pp.195-210.

Research groups

Systems Bioengineering Programme

Research devoted to acquire and interpret quantitative knowledge of biological processes using systems-level approaches, and use this knowledge to control and act upon cells and their environment, with the ultimate goal of producing transferable, diagnostic and/or therapeutic value. To achieve this vision, the program exploits the interdisciplinary expertise existing currently at the DCEXS in cell and molecular systems biology, synthetic biology, computation and mathematical modeling, and complex systems, which is being complemented with new groups working on biomaterials and cell and tissue engineering.

COORDINATOR

Jordi García Ojalvo

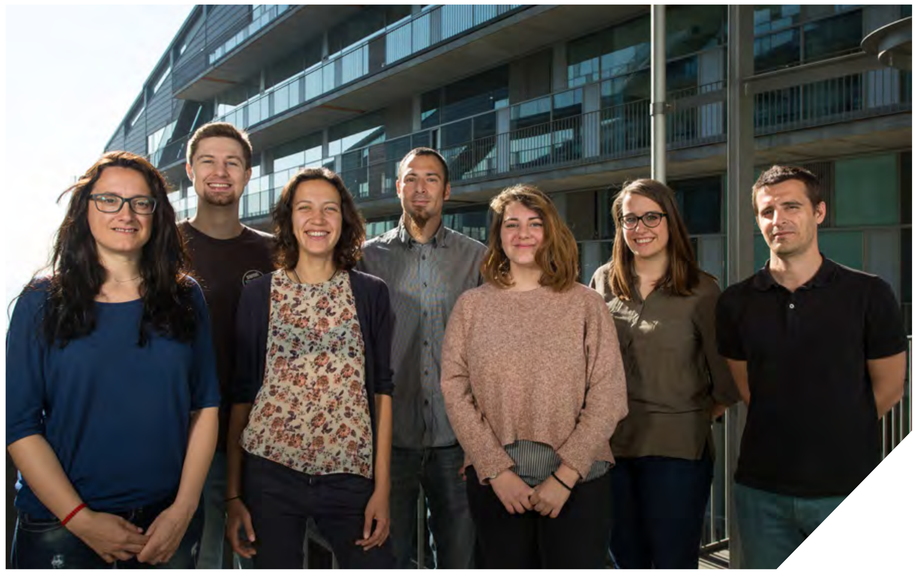
- Single Cell Behavior
- Dynamical Systems Biology
- Biomedical Engineering
- Integrative Biomedical Materials and Nanomedicine Lab

Single Cell Behavior

Lucas Carey

Website

www.upf.edu/web/scb/



Research Outline

We are interested in understanding why individuals within a population look and behave differently from each other, with a focus on both genetic and stochastic (random) differences between individuals.
Single isogenic cells are phenotypically heterogeneous. This is implicit in ideas such as LD50 (the drug concentration that kills 50% of cells): in the absence of variability either 100% would be killed, or none would be. The long-term objective of our research is to determine how brief stochastic events at the molecular level generate heritable phenotypic variability in single cells and in organisms. Non-genetic heterogeneity allows microbes to survive antibiotics, tumor cells to survive chemotherapy, and results in incomplete penetrance of deleterious mutations.

Current Projects / Research Lines

- **How do brief stochastic events lead to heritable phenotypic variation?**

Single cells within an isogenic population display heterogeneity in both proliferation rates and drug resistance. What are the sources of this non-genetic heterogeneity?

- **How common is feedback regulation in gene expression?**

Why do mutations in regulatory elements and copy number variation affect the expression of some genes but not others? The goal of this project is to understand how feedback regulation modifies the relationship between transcription factor activity or gene copy number, and fitness, by modulating gene expression.

- **How do coding sequences regulate expression levels?**

Regulation of gene expression is usually investigated at the level of promoters, enhancers, or other ‘regulatory regions. However, the coding sequence of genes themselves play an important role in determining gene expression. How is this regulation encoded in sequence?

Team during 2015-16

PhD students: Alsu Missarova.
Technicians: Miquel Sas, Marta Badia, Carolina Gonzalez Navasa.

Selected publications 2015-16

van Dijk D, Sharon E, Lotan-Pompan M, Weinberger A, Segal E, Carey LB (2017) Large-scale mapping of gene regulatory logic reveals context-dependent repression by transcriptional activators. *Genome Res* **27**, 87–94.

Schikora-Tamarit M À, Toscano-Ochoa C, Espinós JD, Espinar L, Carey LB (2016) A synthetic gene circuit for measuring autoregulatory feedback control. *Integr Biol* doi:10.1039/C5IB00230C.

Carey LB (2015) RNA polymerase errors cause splicing defects and can be regulated by differential expression of RNA polymerase subunits. *Elife* **4**.

van Dijk D, Dhar R, Missarova AM, Espinar L, Blevins WR, Lehner B, Carey LB (2015) Slow-growing cells within isogenic populations have increased RNA polymerase error rates and DNA damage. *Nat. Commun.* **6**: 7972.

Dynamical Systems Biology

Jordi Garcia Ojalvo

Website

www.upf.edu/web/scb/

Conferences and presentations

- Organization of the B-DEBATE "Synthetic biology: From standard biological parts to artificial life". Caixaforum, Barcelona, Sept. 17-18, 2015.
- Organization of the 17th International Conference on Systems Biology. Fira Montjuïc, Barcelona, Sept. 16-20, 2016.
- Organization of the V DCEXS Symposium, on the topic of Quantitative Biology, PRBB, Barcelona, Sept. 21, 2016

Research Outline

Our laboratory studies the dynamics of living systems, from unicellular organisms to human beings. We use dynamical phenomena to identify the molecular mechanisms of a large variety of biological processes including cellular decision-making, spatial self-organization and tissue homeostasis. Using a combination of theoretical modelling and experimental tools including time-lapse fluorescence microscopy and microfluidics, we investigate dynamical phenomena such as pulses, oscillations and stochasticity in cells and cell populations. At a larger level of organization, we use neurodynamical models to link the structural properties of brain networks with their function.

Current Projects / Research Lines

- **Cellular computation**

We study the architecture of cellular regulatory networks to identify genes and proteins whose location within the network enables them to encode the recent history of the cell and predict future changes in their environment.

- **Stress responses in bacteria**

We investigate how bacterial cells self-organize in space and time when subject to nutrient starvation and antibiotic attacks, and their entry into stationary phase.

- **Dynamics of cellular signaling**

We analyse the temporal organization of signaling processes in organisms ranging from yeast to mammalian cells. We examine the effects of cross-talk between signaling pathways and stochastic variability in signaling processes, particularly in the immune system.

- **Brain dynamics**

We study the dynamics of the brain at different scales, from the microscopic scale of neuronal networks to the macroscopic scale of the full brain, in the context of a variety of pathologies including Down's syndrome and Alzheimer's disease.

Team during 2015-16

Postdocs: Elena Abad.
PhD students: Alessandro Barardi, Lara Escuain de Poole, Marçal Gabaldà Sagarra, Leticia Galera Laporta, David Ibañez Soria, Maciej Jedynak, Daniel Malagarriga Guasch, Rosa Martinez Corral, Carlos Toscano Ochoa.
Technicians: Miquel Sas.

Selected publications 2015-16

Liu J, Prindle A, Humphries J, Gabalda-Sagarra M, Asally M, Lee D, Ly S, Garcia-Ojalvo J, Süel G (2015). Metabolic co-dependence gives rise to collective oscillations within biofilms. Nature 523: 550–54.

Prindle A, Liu J, Asally M, Ly S, Garcia-Ojalvo J, Süel G (2015). Ion channels enable electrical communication in bacterial communities. Nature 527: 59–63.

Valverde S, Ohse S, Turalska M, West BJ, Garcia-Ojalvo J (2015). Structural determinants of criticality in biological networks. Front. Physiol. 6: 127.

Dies M, Galera-Laporta L, Garcia-Ojalvo J (2016). Mutual regulation causes co-entrainment between a synthetic oscillator and the bacterial cell cycle. Integr. Biol. 8: 533.

Sancristóbal B, Rebollo B, Boada P, Sanchez-Vives MV, Garcia-Ojalvo J (2016) Collective stochastic coherence in recurrent neuronal networks. Nature Physics 12: 881–87.

Other relevant publications from last 10 years

Süel, G, Kulkarni R, Dworkin J, Garcia-Ojalvo J, Elowitz M (2007) Tunability and noise dependence in differentiation dynamics. Science 315: 1716–19.

Sprinzak, D, Lakhanpal A, Lebon L, Santat L, Fontes M, Anderson G, Garcia-Ojalvo J, Elowitz M (2010) Cis-interactions between Notch and Delta generate mutually exclusive signalling states. Nature 465: 86–90.

Espinar L, Dies M, Cagatay T, Süel G, Garcia-Ojalvo J (2013) Circuit-level input integration in bacterial gene regulation. Proc. Natl. Acad. Sci. USA 110: 7091–96.

Biomedical Engineering

Javier Macía Santamaría

Research Outline

Our research is divided into three main topics. The first one focuses on the exploration of the fundamental principles governing the behaviour of genetic circuits. In this context we try to define fundamental principles that permit de design of synthetic devices in a predictable manner. Our second topic focuses on the development of cellular computation and reprogrammable cellular devices. Finally, the last topic is more applied and focuses on the design and development of new cellular devices that can be used to regulate the glycaemia in diabetic patients.

Current Projects / Research Lines

- **Systems and synthetic biology approaches to cellular circuit designs for glycaemia homeostasis regulation in diabetics**

Exploration of the application of evolutionary algorithms for designing the architecture of cellular devices that can sense the glucose levels of an organism and induce the secretion of insulin or glucagon in response. This response should be efficient preventing hypoglycaemic periods. The designs obtained are tested in a computational model describing the physiology of a diabetic patient. This project is funded by the MINECO.

- **Encapsulated synthetic cellular circuits to prevent type I diabetes**

Experimental development of a set of genetically modified cells able to regulate glycaemia. These cells will be encapsulated and introduced in mice in order to evaluate their functionality. This project is funded by LA MARATO – TV3.

Team during 2015-16

PhD students: Max Carbonell-Ballesteros, Eva Gonzalez-Flo.

Selected publications 2015-16

Urrios A, Macia J, Manzoni R, Conde N, Bonforti A, de Nadal E, Posas F, Solé R (2016) A synthetic multicellular memory device. ACS Synthetic Biology 5 (8), 862-873.

Macia J, Manzoni R, Conde N, Urrios A, de Nadal E, Solé R, Posas F (2016) Implementation of complex biological logic circuits using spatially distributed multicellular consortia. PLoS Comput Biol 12 (2), e1004685.

Carbonell-Ballestero M, Garcia-Ramallo E, Montañez R, Rodiguez-Caso C, Macia J (2015) Dealing with the genetic load in bacterial synthetic biology circuits: convergences with the Ohm's law. Nucleic acids research 44 (1):496-507.

Sardanyés J, Bonforti A, Conde N, Solé R, Macía J (2015) Computational implementation of a tunable multicellular memory circuit for engineered eukaryotic consortia. Frontiers in physiology.6: 281.

Other relevant publications from last 10 years

Regot S, Macia J, Conde N, Furukawa K, Kjellén J, Peeters T, Hohmann S (2011) Distributed biological computation with multicellular engineered networks. Nature 469 (7329):207-11.

Macía J, Posas F, Solé R (2012) Distributed computation: the new wave of synthetic biology devices. Trends in biotechnology 30 (6): 342-9.

Macia J, Regot S, Peeters T, Conde N, Sole R, Posas F (2009) Dynamic signaling in the Hog1 MAPK pathway relies on high basal signal transduction. Sci Signal 2 (63) ra13-ra13.

Integrative Biomedical Materials and Nanomedicine Lab

Pilar Rivera Gil

Website

www.upf.edu/web/nanomed/home

Other relevant information 2015-16

- WO2015177340 A1: an international licensed patent.

Research Outline

We convert basic research findings on nanobiotechnology into new approaches addressing biomedical challenges. We fabricate multifunctional biomaterials by integrating selected building-blocks into one single system depending on the application's requirements and considering the biophysicochemical properties of the nanomaterial. We target independently two areas: diagnostics and therapeutics of diseases but also simultaneously by creating a theranostic tool towards a more personalized medicinal approach of diseases. We focus on understanding and engineering the nanomaterial-biological system interface. We use state of the art material and biological/molecular characterization methods to find predictive patterns of cellular outcomes after exposure to nanomaterials for translational medicine.

Current Projects / Research Lines

- **Engineering nanomaterials for diagnosis/sensing**

We fabricate optical biosensors based on plasmonic hollow nanocapsules functionalized with sensing molecules and having a surface-enhanced Raman scattering read out. These sensors provide multiplex, unequivocal, ultra-sensitive level analysis.

- **Engineering nanomaterials for controlled release**

We use electromagnetic nanoantennas to trigger the opening of and release from individual nanocarriers on demand.

- **Exploring the therapeutic value of novel nanomaterials**

We use therapeutically active nanomaterials to explore their biomedical uses (i) in chemo-hyperthermia to overcome chemo-resistance by combining physical and chemical approaches; (ii) as anti-oxidant due to ROS scavenging activities.

- **Engineering the nanomaterial-biological interface**

The biological environment critically affects the multiple functionalities of the nanomaterials. This has an impact on the materials' toxicity, internalization, biodistribution, etc. Thus, finally governing functionality. Correlating cellular responses to the physicochemical properties of nanomaterials helps to predict cell behavior towards a more rational design of biomedical materials depending on the requirements of each application.

Team during 2015-16

Postdocs: Marcos Sanles Sobrido. **PhD students:** Paula Zamora Pérez, Weiteng An, Ruixue Xu.

Selected publications 2015-16

Nazarenus M, Abasolo I, García Aranda N, Voccoli V, Rejman J, Cecchini M, Schwartz S, Rivera Gil P*, Parak W* (2015) Polymer Capsules as a Theranostic Tool for a Universal In Vitro Screening Assay - The Case of Lysosomal Storage Diseases. Part Part Syst Charact 32: 991-8.

Qiu J, Zhang R, Li J, Sang Y, Tang W, Rivera Gil P*, and Liu H* (2015) Fluorescent graphene quantum dots as traceable, pH-sensitive drug delivery systems. Int J Nanomedicine 10: 6709–24.

Harimech PK, Hartmann R, Rejman J, del Pino P, Rivera Gil P, Parak W (2015) Encapsulated enzymes with integrated fluorescence-control of enzymatic activity. J Mater Chem B 3:2801-7.

Qiu J, Li D, Mou X, Li J, Guo W, Wang S, Yu X, Ma B, Zhang S, Tang W, Sang Y, Rivera Gil P*, and Liu H* (2016) Effects of Graphene Quantum Dots on the Self-Renewal and Differentiation of Mesenchymal Stem Cells. Adv Healthcare Mater 5: 702–10.

Cabrera I, Abasolo I, Corchero JL, Elizondo E, Rivera Gil P, Moreno E, Faraudo J, Sala S, Bueno D, González-Mira E, Rivas M, Melgarejo M, Pulido D, Albericio F, Royo M, Villaverde A, García-Parajo MF, Schwartz S, Ventosa N, Veciana J (2016) α-Galactosidase-A Loaded-Nanoliposomes with Enhanced Enzymatic Activity and Intracellular Penetration. Adv. Healthcare Mater 5: 829–40.

Other relevant publications from last 10 years

Ganas C, Weiß A, Nazarenus M, Rösler S, Kissel T, Rivera Gil P*, Parak WJ* (2014) Biodegradable capsules as non-viral vectors for in vitro delivery of PEI/siRNA polyplexes for efficient gene silencing. Journal of Controlled Release 196: 132–8.

Kast L, Sasse D, Wulf V, Hartmann R, Mircheski J, Ranke C, Carregal-Romero S, Martínez-López JA, Fernández-Chacón R, Parak WJ, Elsasser HP, Rivera Gil P* (2013) Multiple internalization pathways of polyelectrolyte multilayer capsules into mammalian cells. ACS Nano 7 (8): 6605–18.

Rivera Gil P, Jimenez De Aberasturi D, Wulf V, Pelaz B, del Pino P, Zhao Y, de la Fuente JM, Ruiz de Larramendi I, Rojo T, Liang XJ, Parak WJ (2013) The challenge to relate the physicochemical properties of colloidal nanoparticles to their cytotoxicity. Acc Chem Res 46 (3): 743–9.

Core facilities

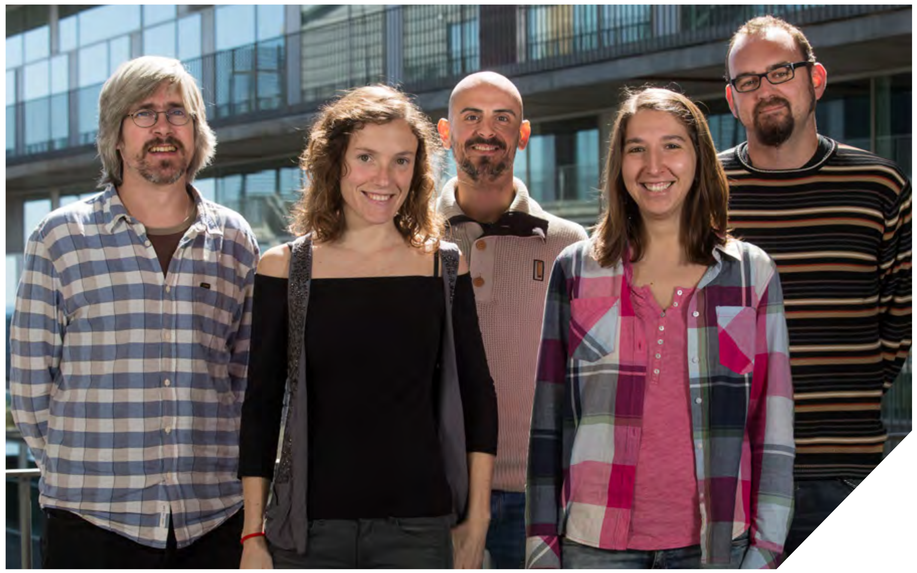
- Genomics Core Facility
- CRG/UPF Advanced Light Microscopy Unit
- UPF/CRG Joint Flow Cytometry Unit
- Proteomics unit
- Peptide Synthesis
- Scientific Information Technologies
- Administrative and Services Staff

Genomics

Ferran Casals

Website

www.upf.edu/web/sct-genomics



Service

We provide a wide variety of methods for DNA and RNA analyses. Available equipment include liquid handling robots to automate pipetting tasks, capillary sequencers for Sanger sequencing and fragment analysis, DNA quantification and quality control with Picogreen and Bioanalyzer, real-time PCR and OpenArray system for absolute and relative quantification of nucleic acids (genotyping and gene expression), and three next-generation sequencing platforms from Illumina: MiSeq, ideal for targeted and small genome sequencing; MiSeqFGx, for population and forensic genetics analyses; and NextSeq, a highly flexible platform performing a broad range of applications, from targeted resequencing to RNA profiling and whole-exome or genome sequencing. Our laboratory also offers the service of library preparation for most of the next-generation sequencing applications. We organize courses and workshops on the new sequencing methodologies and pioneer some of their applications to medical and population genomics research.

Research

One of the missions of the Genomics Core Facility is the development of new technologies and methodologies for genomic analyses. The Genomics Core Facility at the UPF performs collaborative research projects with several labs at the Experimental and Health Sciences Department of the UPF, to develop and implement novel methodological approaches.

Collaborative Projects 2016

Projects	Research Programme
Circular RNA in hepatic cells	Molecular Virology
Methods for genotyping large number oy yeast strains	Single Cell Behavior
Assessing RNA deregulation in synaptopathologies affecting intellectual performance	Laboratory of Neuropharmacology
Single-cell characterization of a cancer transcriptome	Computational RNA Biology
Transcriptomics of dried blood spot samples	Functional Genomics
Isolation of cell size mutants by flow citometry and ultrasequencing	Oxidative Stress and Cell Cycle

Team during 2015-16

PhD students: Guillem de Valles.
Technicians: Roger Anglada, Núria Bonet, Raquel Rasal.

Selected publications 2015-16

Calafell F, Anglada R, Bonet N, González-Ruiz M, Prats-Muñoz G, Rasal R, Lalueza-Fox C, Bertranpetit J, Malgosa A, Casals F (2016) An assessment of a massively parallel sequencing approach for the identification of individuals from mass graves of the Spanish Civil War (1936-1939).Electrophoresis 37(21):2841-7.

Mondal M, Casals F, Xu T, Dall'Olio GM, Pybus M, Netea MG, Comas D, Laayouni H, Li Q, Majumder PP, Bertranpetit J (2016) Genomic analysis of Andamanese provides insights into ancient human migration into Asia and adaptation. Nat Genet 48(9):1066-70.

De Valles-Ibáñez G, Hernandez-Rodriguez J, Prado-Martinez J, Luisi P, Marquès-Bonet T, Casals F (2016) Genetic Load of Loss-of-Function Polymorphic Variants in Great Apes. Genome Biol Evol 8(3):871-7.

E Bosch, Casals F (2016) Next Generation Sequencing for Rare Disease. Book chapter in: Genome-Wide Association Studies: From Polymorphism to Personalized Medicine. Cambridge University Press.

Casals F, Bosch E (2016) Next Generation Sequencing for Complex Disorders. Book chapter in: Genome-Wide Association Studies: From Polymorphism to Personalized Medicine. Cambridge University Press.

Other relevant publications from last 10 years

Cagan A, Theunert C, Laayouni H, Santpere G, Pybus M, Casals F, Prüfer K, Navarro A, Marques-Bonet T, Bertranpetit J, Andrés AM (2016) Natural Selection in the Great Apes. Mol Biol Evol 33(12):3268-83.

Spataro N, Calafell F, Cervera-Carles L, Casals F, Pagonabarraga J, Pascual-Sedano B, Campolongo A, Kulisevsky J, Lleó A, Navarro A, Clarimón J, Bosch E (2015) Mendelian genes for Parkinson's disease contribute to the sporadic forms of the disease. Hum Mol Genet 7:2023-34.

Juyal G, Mondal M, Luisi P, Laayouni H, Sood A, Midha V, Heutink P, Bertranpetit J, Thelma BK, Casals F (2014) Population and genomic lessons from genetic analysis of two Indian populations. Hum Genet 133(10):1273-87.

CRG/UPF Advanced Light Microscopy Unit (ALMU)

Timo Zimmermann (CRG)

Website

www.crg.eu/en/core/programmes-groups/advanced-light-microscopy-unit

Service

Our unit serves as a core facility for high-end light microscopy for PRBB researchers. A range of instruments with unique capabilities fully covers the spectrum of advanced imaging applications. We provide advice in the initial experiment planning, training of the researchers on the instruments and assistance with the subsequent data analysis.

In 2016, the total booked microscope usage time of the unit reached more than 17800 hours in more than 5000 separate bookings. During the year, a total of 224 researchers from PRBB and one company used the unit, as well as projects from external visitors. On average, 88 investigators use the unit every month.

Our technology offer was kept up-to-date by the acquisition of a Leica TCS SP8 confocal microscope by the UPF as well as application-testing a new STED objective for in-vivo imaging together with Leica Microsystems.

Research

All members of the staff are frequently participating as speakers and instructors in master's courses from the CRG and UPF, as well as in many conferences and microscopy courses both at the PRBB as well as at other institutions, nationally and internationally. In May, the unit organized an international course for biological super-resolution microscopy with 12 participants and 4 external speakers and in November an internal image processing course with 20 participants and 2 external speakers.

ALMU hosted together with the super-resolution light nanoscopy facility at ICFO and Leica Microsystems the 6th Leica Super-Resolution User Club with 55 academic and 12 company participants in September.

Team during 2015-16

Technicians: Xavier Sanjuan (UPF), Raquel García (CRG), Arrate Mallabiabarrena (CRG), Raúl Gómez (CRG).
Project Manager: Timo Zimmermann (CRG).

Selected publications 2015-16

Irazoki O, Aranda J, Zimmermann T, Campoy, S, Barbé J (2016) Molecular Interaction and Cellular Location of RecA and CheW Proteins in Salmonella enterica during SOS Response and Their Implication in Swarming Front Microbiol http://dx.doi.org/10.3389/fmicb.2016.01560.

Jelier R, Kruger A, Swoger J, Zimmermann T, Lehner B (2016) Compensatory Cell. Movements Confer Robustness to Mechanical Deformation during Embryonic. Development. Cell Syst 3(2):160-71.

Sage D, Kirshner H, Pengo T, Stuurman N, Min J, Manley S, Unser M (2015) Quantitative evaluation of software packages for single-molecule localization microscopy. Nat Methods 12(8):717-24.

Pérez-Vilaró G, Fernández-Carrillo C, Mensa L, Miquel R, Sanjuan X, Forns X, Pérez-del-Pulgar S, Díez J (2015) Hepatitis C virus infection inhibits P-body granule formation in human livers. J Hepatol. 62(4):785-90.

Pengo T, Holden SJ, Manley S (2015) PALMsiever: a tool to turn raw data into results for single-molecule localization microscopy. Bioinformatics 1;31(5):797-8.

Other relevant publications from last 10 years

Grünberg R, Burnier JV, Ferrar T, Beltran-Sastre V, Stricher F, van der Sloot AM, Garcia-Olivas R, Mallabiabarrena A, Sanjuan X, Zimmermann T, Serrano L (2013) Engineering of weak helper interactions for high-efficiency FRET probes. Nat Methods 10(10):1021-7.

von Blume J, Alleaume AM, Cantero-Recasens G, Curwin A, Carreras-Sureda A, Zimmermann T, van Galen J, Wakana Y, Valverde MA, Malhotra V (2011). ADF/cofilin regulates secretory cargo sorting at the TGN via the Ca2+ ATPase SPCA1. Dev Cell 20(5): 652-62.

Duran JM, Kinseth M, Bossard C, Rose DW, Polishchuk R, Wu CC, Yates J, Zimmermann T, Malhotra V (2008) The role of GRASP55 in Golgi fragmentation and entry of cells into mitosis. Mol Biol Cell. 19(6): 2579-87.

UPF/CRG Joint Flow Cytometry Unit

Òscar Fornas

Website

www.upf.edu/web/sct-flow-cytometry

Service

The Flow Cytometry Unit offers the PRBB researchers technical expertise and training to access the state-of-the-art instrumentation, as well as technical and scientific advice to develop efficient and reliable flow cytometric assays with the highest quality control standards and productivity.

Provided services:

- Unassisted bench-top analysis.
- Assisted bench-top analysis.
- Extensive training on bench-top analysers.
- Extensive training on FACSAria sorter for advanced users.
- Cell sorting: Staff-assisted procedure using two different high-speed sorters.
- Support in project/assay development using Flow Cytometry.
- Application implementation or development under user demand.

The evolution of the usage of the facility can be studied by the hours of instrument usage of around 200 users within 98 research groups, reporting the facility activity. As shown in the following graph, the total activity remains stable since 2012.

Research

The facility is a reference site for single particle/cell sorting as well as for nano-particle detection and sorting. We have developed and established relevant flow cytometry applications for the scientific community. Below the implemented and developed applications that are currently established as research projects of the Unit in collaboration with internal and external researchers:

Flow Karyotyping for chromosome sorting and sequencing

We have established this application in collaboration with Dr. Paul Lizzardi from Yale University, USA (2012-2014). This application has generated new collaborations as new research projects:
Dr. Jordi Surrallés, UAB, Bellaterra, Spain. (2016). Chromosome Flow FISH for diagnostics of Fanconi Anemia.
Dr. Rosa Figueroa, Instituto Español de Oceanografía, Vigo, Spain. (2016). Sorting of chromosomes and “ribosomal chromosomes” in Dinoflagellates and unicellular sea organisms.
Dr. Khaled Hazzour, New York University, Abu Dhabi.(2016). Chromosome sorting of two different fungus that infect a tree crop (date palm).

Single virus sorting for single virus genomics

We have developed this application in collaboration with Dr. Manuel Martínez from Universidad de Alicante, Spain.

Extracellular Vesicles detection and sorting

We have developed this application in collaboration with Dr. Ana Merino from IDIBELL-Erasmus University, Spain-Holland.

Team during 2015-16

Technicians: Eva Julià, Erika Ramírez and Àlex Bote.

Selected publications 2015-16

The publications using data from the facility during the period 2013-2016 are a minimum of 97. At least 35 publications came from 17 UPF groups, 34 publications came from 16 CRG groups and 28 publications came from 11 IMIM groups.

By the other hand, due to the on-going collaborations with external researchers, two papers elaborated in the facility are under revision or in preparation, hopefully will be published before the end of 2017. Those papers are:

- **Single virus sorting for single virus genomics**, 2016 (manuscript under revision at Nature Communications).
- **Extracellular Vesicles detection and sorting**, 2016 (manuscript in preparation).

Proteomics unit

Eduard Sabidó

Website

www.crg.eu/en/core/programmes-groups/crgupf-proteomics-unit

Service

The Proteomics Unit is a joint effort of the Universitat Pompeu Fabra and the Center of Genomic Regulation to create an innovative research infrastructure to support scientists in their research projects and thus, advance in the European science roadmap.

The activities of the Proteomics Unit focus onto the provision of high-quality proteomics services with strong added-value to the research community by i) offering state-of-the-art methods, advise and expertise to support basic and translational researchers; ii) developing new methods and techniques that keep the unit up to date and at the forefront of the proteomics field; and iii) training the community and actively disseminating proteomics science and methods.

Research projects

The Proteomics Unit promotes technology-driven research as an essential task to develop new applications and thus improve the services offered to the users.

In 2016 the Proteomics Unit has significantly advance in internal technology-driven research with the identification of histone modifications (Sebé-Pedrós 2016), the development of targeted proteomics methods to quantify post-translational modifications, and proteins in clinical samples (Cantó 2014, Borràs 2016), and re-annotation of good-quality spectra (Lluch-Senar 2016). Moreover, the Unit was granted with a Plan Nacional EXCELENCIA 2016 and a Plan Nacional RETOS 2016 from the Ministerio de Economía y Competitividad to study protein post-translational modifications and protein-protein interactions in the context of cancer and atherosclerosis.

Finally, the Proteomics Unit has successfully organized in 2016 an EMBO practical course on “Targeted Proteomics”, the “Courses@CRG: Advanced proteomics course for molecular and cellular biologists”, and the Annual Proteomics Symposium 2016.

Team during 2015-16

Scientists: Eva Borràs, Cristina Chiva, Guadalupe Espadas, Roger Olivella Pujol, Mireia Ortega, Olga Pastor, Amanda Solé.

Selected publications 2015-16

1. Sebé-Pedrós A, Peña MI, Capella-Gutiérrez S, Antó M, Gabaldón T, Ruiz-Trillo I, Sabidó E (2016) High-Throughput Proteomics Reveals the Unicellular Roots of Animal Phosphosignaling and Cell Differentiation. Dev Cell 39(2):186-97.
2. Liñeiro E, Chiva C, Cantoral JM, Sabido E, Fernández-Acero FJ (2016) Dataset of the Botrytis cinerea phosphoproteome induced by different plant-based elicitors. Data Brief 7:1447-50.
3. Aebersold R, Bensimon A, Collins BC, Ludwig C, Sabido E. Applications and Developments in Targeted Proteomics: From SRM to DIA/SWATH. Proteomics 16(15-16):2065-7.
4. Guixer B, Arroyo X, Belda I, Sabidó E, Teixidó M, Giralt E (2016) Chemically synthesized peptide libraries as a new source of BBB shuttles. Use of mass spectrometry for peptide identification. J Pept Sci (9):577-91.
5. Liñeiro E, Chiva C, Cantoral JM, Sabidó E, Fernández-Acero FJ (2016) Modifications of fungal membrane proteins profile under pathogenicity induction: A proteomic analysis of Botrytis cinerea membranome. Proteomics 16(17):2363-76.

Peptide Synthesis

David Andreu

Website

www.upf.edu/web/sct-peptide-synthesis

Service

Synthetic peptides are useful in many areas of biomedical research, including well-known applications such as immunogens (anti-peptide antibodies, vaccines), affinity capture and purification ligands, intracellular delivery shuttles or anti-infectives. Our facility performs custom peptide synthesis and downstream operations such as purification to user-defined specifications, conjugation to carrier proteins to generate antibodies, or immobilization on affinity columns.

During 2015-16 the facility has performed over 350 synthesis jobs, 55 conjugations to carrier proteins for antibody production, and related tasks for 60 users, of which 15 are intramural (PRBB) and 45 external (research institutes, biotech and pharma companies). Sizes have ranged from 5 to 60+ residues, with an average of 25. Purities up to >98% (HPLC) are routinely achieved, as well as user-defined modifications such as different end (N- and C-terminal) groups, disulfide formation (intra- or intermolecular), modified (D-amino acid, phosphorylated, acetylated, methylated) amino acids, plus biotinylation, lipidation, fluorescent tags, etc. Average turnover time for most jobs (including synthesis, HPLC purification, analytical documentation) is 1-2 weeks.

Team during 2015-16

Technicians: Javier Valle, Yolanda Tor.

Selected publications 2015-16

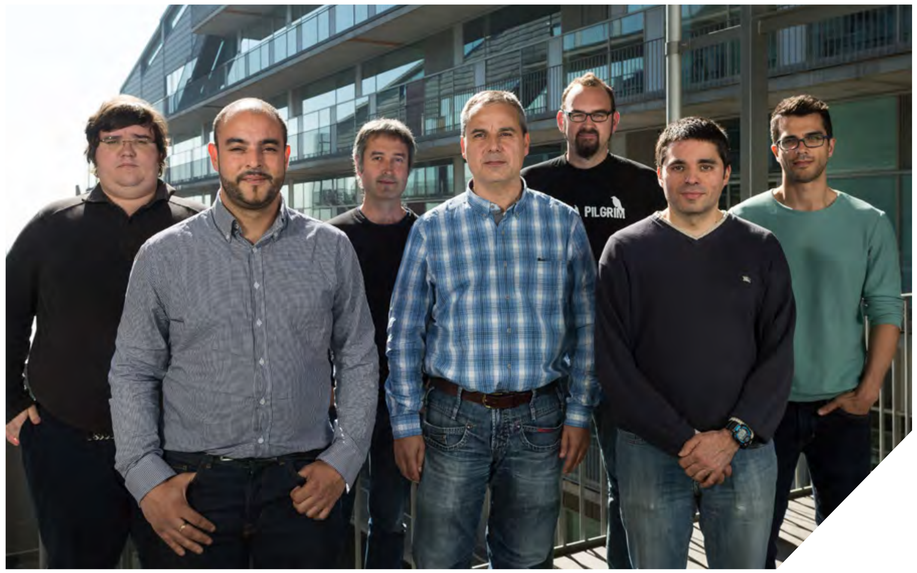
- Guivernau B, Bonet J, Bosch-Morató M, Valls-Comamala V, Godoy JA, Inestrosa NC, Fernández-Busquets J, Andreu D, Oliva B, Muñoz FJ (2016) Amyloid-β peptide nitrotyrosination stabilizes oligomers and enhances NMDAR-mediated toxicity. J Neurosci 36:11693-703.
- González-Magaldi M, Vázquez-Calvo A, De la Torre BG, Valle J, Andreu D, Sobrino F (2015) Peptides interfering 3A protein dimerization decrease FMDV multiplication. PLoS ONE 10:e0141415.

Scientific Information Technologies

Carles Perarnau Sabés

Website

www.upf.edu/sct/sit



Research Outline

We are a recently created internal service (created by DCEXS and IT Service). Our objective is to offer IT resources to DCEXS researchers.

The Department's cluster is a shared high-performance computing environment serving the departmental research community with diverse research requirements. The researchers are provided with high-performance computing cluster for projects in next-generation sequence analysis, molecular dynamics, mathematical modelling, image analysis, proteomics, etc. Also, for data storage, we have two different systems. A traditional NFS for generic use and a high-performance storage system (GPFS) for computing use. These systems are connected with our entire infrastructure. Additionally we offer hosting of additional research systems within a virtual cluster system, as well as data centre server maintenance. Finally, we also provide the installation of scientific machine equipment within our own facilities. This includes the maintenance of equipment as well as its secure storage.

Team during 2015-16

Technicians: Juan Manuel Fuentes, Alfons González, Jose Manuel Linares, Edgar Sánchez, Miguel Ángel Sánchez, Marc Tormo.

Administrative and Services Staff

Campus Director:

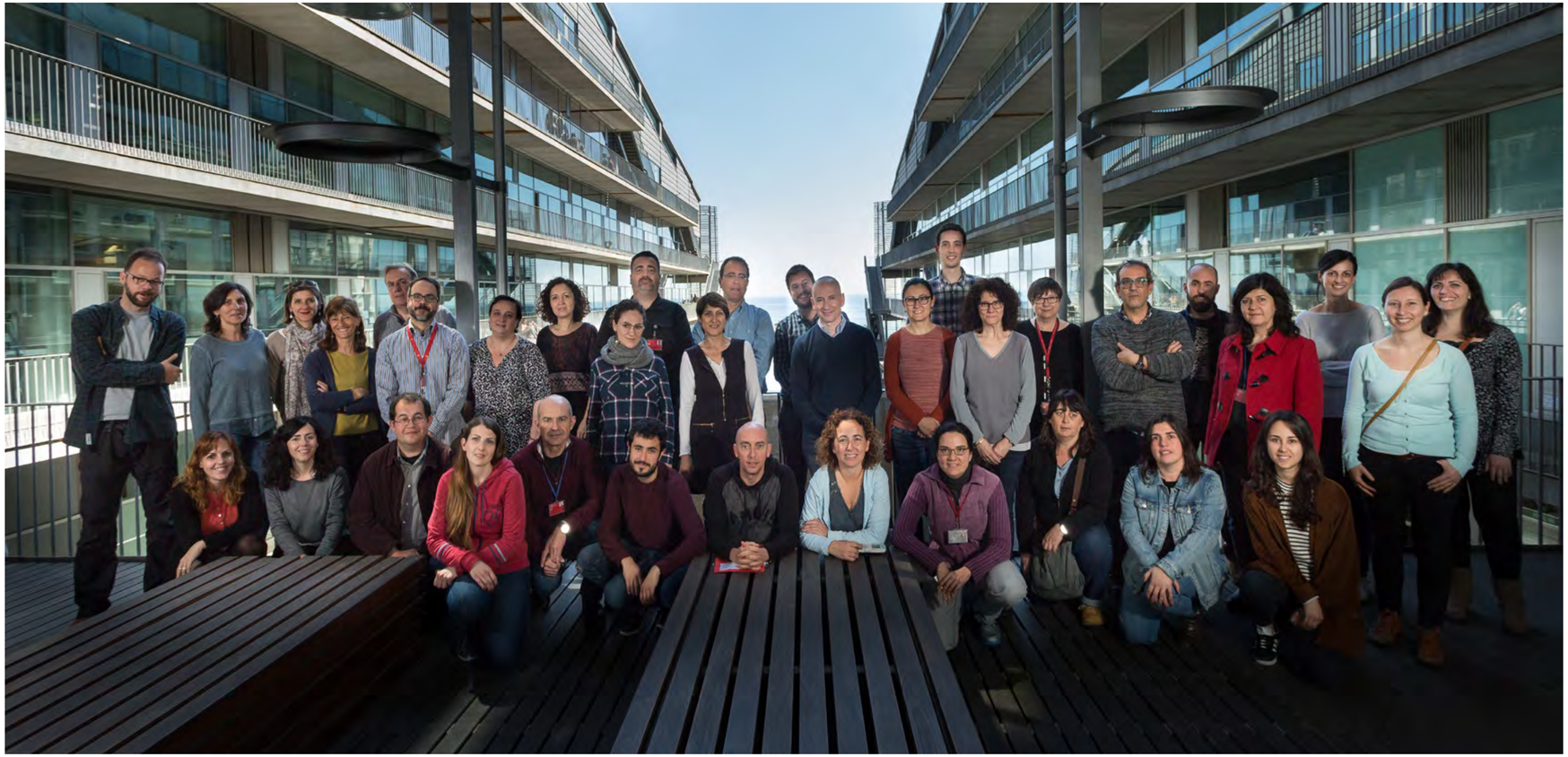
Fina Lorente

Heads:

Rosa Olivé, David Moreso, Mar Garreta, Jordi Solà, Joan Carles Carrión, Sonia Lago, Sílvia Mora, Lluïsa Rojas.

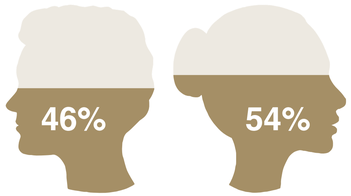
Staff:

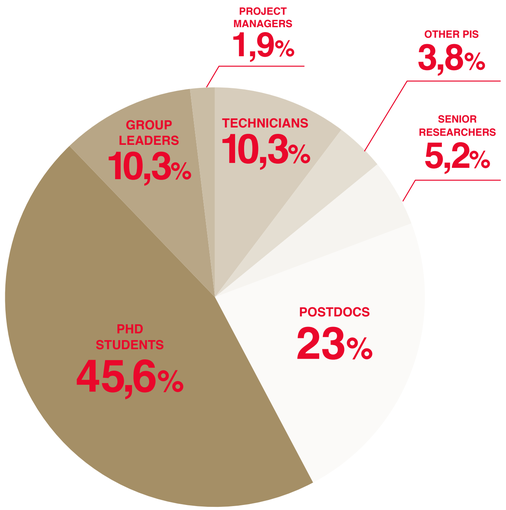
Anna Almor, Alejandro Aparici, Xavier Ardite, Josep Aymami, Marta Bonet, Gemma Burballa, Bianca Cabañero, Mamen Carmona, Neus Cartes, Pilar Cerro, Anna Dieste, Gemma Esparó, Txema Farrona, Lluís Flores, Sònia Gandul, Jordi Garriga, Josep Gibert, Robert González, Cintia Gutiérrez, Sonia Iturrate, Pilar Larramona, Mireia Llimós, Regina López, Núria Margalef, Vanesa Mesquida, Tamara Monrás, Tòfol Moreno, Jordi Palau, Diana Pardo, Susana Pérez, Carolina Pozo, Rafael Puente, Natàlia Ras, Lidia Reichenberg, Núria Reixach, Anna Rivas, Montse Saladrigas, Santa Taberner, Víctor Tomás, Marta Torras, Pedro Vázquez, Alexis Vicioso.



DCEXS in numbers

Personnel

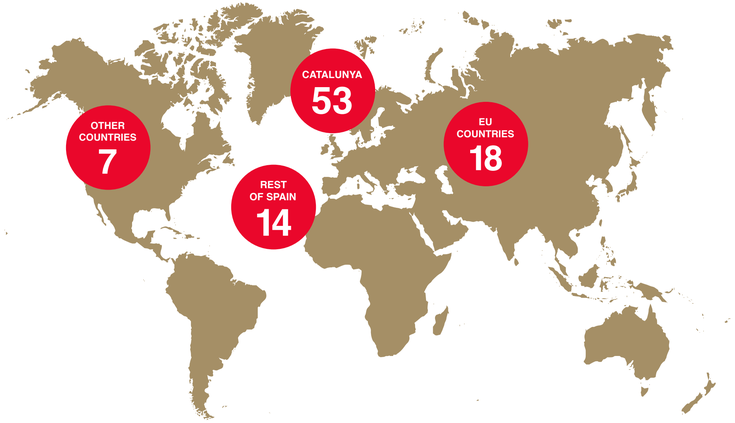




Total PhD students registered

92 New PhD students + 331 Continuing PhD students = **423**

New PhD registrations per home university



Doctoral theses defended

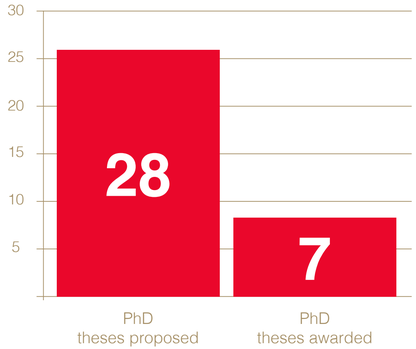
75 Total PhD theses defended

12 PhD theses awarded European/International Mention in Doctoral Diploma

Length average of thesis development

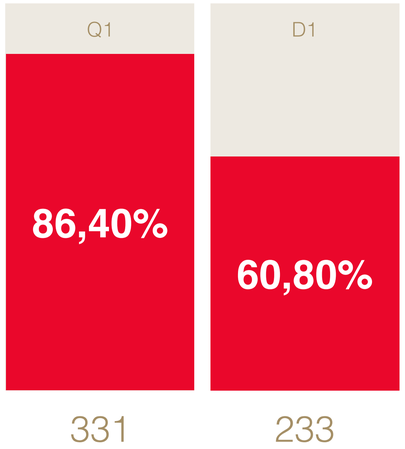
4,65 Academic years

Extraordinary awards 2013/14



DCEXS in numbers

DCEXS Group Leaders



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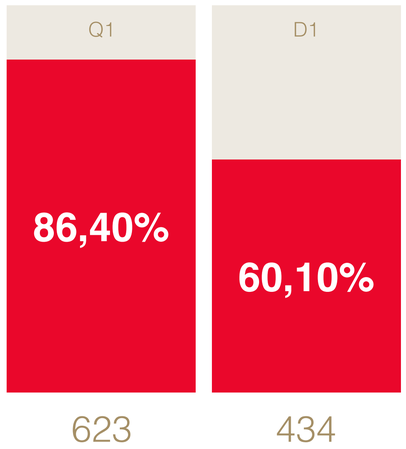
Documents (2015 and 2016)

DCEXS Group Leaders and Affiliated Groups



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Documents (2015 and 2016)

Competitive funding obtained in 2015 & 2016

2015 & 2016		
Funding agencies	N	k€
Autonomical	8	1.262
State	51	11.192
International *(including H2020)*	7	2.533
Companies and institutions	14	1.460
TOTAL	**79**	**16.448**

Nota interna:
DCEXS Group Leaders (and other PIs, 50)
DCEXS Group Leaders and Affiliated Groups (66)

Universitat Pompeu Fabra Barcelona
Department of Experimental and Health Sciences

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