



scientific report   
**2011/2015**

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## WELCOME

### Andres Aguilera

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DIRECTOR

It is my pleasure to present the scientific report of CABIMER (Centro Andaluz de Biología Molecular y Medicina Regenerativa / Andalusian Centre of Molecular Biology and Regenerative Medicine) for the period 2011 to 2015. CABIMER is a groundbreaking multidisciplinary biomedical research centre in Andalusia, drawing together basic and applied research with the aim of transforming the results of the scientific work into direct improvements for citizens' health and quality of life. CABIMER has provided a rich intellectual environment to support individual researchers and to foster collaborations among faculty members, postdoctoral fellows, graduate students, technicians, visiting scientists and trainees. A large number of international scientists working at the Centre contribute to a stimulating and international atmosphere.

During this 5-year period there has been real consolidation of CABIMER activities and infrastructural facilities to support the science undertaken by the 20 Principal Investigators (PI's) and their research group members. Even at a time of significant financial pressures, through the collective enterprise of all CABIMER PI's, we have been able to expand and consolidate much needed new core services to diversify and enrich our research programme. Some highlights of the past 5 years are the success of CABIMER researchers in obtaining funding from highly competitive programmes that include 3 ERC grants (Pablo Huertas, Felipe Cortés-Ledesma and Andrés Aguilera) or a H2020 network/project as part of a strong international consortium (Shomi Bhattacharya), the nomination of two of its young PIs as

EMBO Young Investigators (Felipe Cortés and Pablo Huertas), or the recognition of several researchers of highly valuable research prizes and distinctions (Benoit Gauthier, Felipe Cortés-Ledesma, Andrés Aguilera). CABIMER has a 10 fully functional core services including a nationally accredited GMP facility, a state of the art Animal House with a special unit for the generation of genetically modified mice, a Genomic platform for the use of external and internal services, an advanced Imaging unit, or Histology and model organisms services to support the different research activities of the Center. As a result, CABIMER had a significant improvement in high quality publications, grant income and the number of PhD students qualifying from CABIMER by the end of 2015.

CABIMER is now beginning to be noticed as an International Centre of Research of Excellence and a major centre of biomedical research in Spain. To accomplish these goals CABIMER has established an internationally renowned External Scientific Advisory Panel provide highly motivated scientists the opportunity to conduct cutting-edge research and be at the forefront of science. We are proud of the effort and dedication of all PI's and researchers, as well as the support staff who have all contributed so responsibly to the success of CABIMER as a referent in biomedical research in Spain, with an increasing internationally visibility and strength. We still have a long way to go and many objectives to accomplish, but many new exciting discoveries lie ahead of us. I hope the information summarized in our Scientific Report conveys this ambition.





## Cabimer by the Manager

### Luis Casas

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MANAGER

The Scientific Report 11/15 gathers all the research implemented at CABIMER supported by the partnership of the Spanish National Research Council (CSIC), the University of Seville, the University "Pablo de Olavide" and the Andalusian Regional Ministries of Health, and Economy and Knowledge.

An annual running budget on average of 2.2M€ in the last five years, ensures our scientific community to keep their effort on research providing managing and technical services through the 10 Core Services Unit of CABIMER.

The Core Services Units, with technicians highly specialised in Genomics, Biological Resources, Cell Culture, Citometry & Sorter, Microscopy, GMP, Histology, Model Organisms, Biological Safety and Washing and Sterilization provide competitive services to our 20 Research Groups and external users.

Cabimer is proud of promoting the career of young technicians and researchers and it has become a real training Center in a research environment that promotes the gender's equality. In December 2015, women represented the 63% of a total of 195 professional. Cabimer's ability to attract talent is demonstrated not only by the number of PhD Thesis but also for the origin of the students and young research-

ers that come from Andalusia, other regions in Spain and different countries around the world.

Attracting talent along with the joint effort of our partners, the research community and all workers of Cabimer has allowed us to overcome the difficult economic situation that could have compromised the level of excellence reached in science and maintained since the inauguration of Cabimer in 2006.

With an average of 45-50 projects per year developed in our Centre, numerous collaborations with high-level biotechnological companies and international stakeholders have been taken. Since the year 2010, 31 theses have been read and there is an average of 45 postdoctoral students in our groups which makes CABIMER a Center of Excellence in the training of young researchers.

During this period the Center has obtained resources for a total amount of 35.28M including high-competitive grants from international institutions such as The World Wide Cancer, Juvenile Diabetes Research Foundation (JDRF), the European Research Council and the H2020 Programme from EU.

CABIMER has a wide spectrum of possibilities in the near future to fulfil its objective: to improve the citizens' health and quality of life.





## Description of Research Activities

### **Molecular Biology**

The research lines in this department deal with the study of DNA and the effects of its exposure to multiple physical and chemical agents on cell death, mutations and genetic reordering, which becomes evident in view of the number of syndromes and hereditary diseases that often result in cancer or ageing. The department of molecular biology is responsible for the study of mechanisms and factors responsible for the integrity of the genome, its implication in cellular differentiation and the propensity in the creation of tumors and its role in the cell cycle and cellular division.

### **Cell Signalling**

The activity of this department is devoted to the study of mechanisms and proteins that control cell behaviour, both on an individual level and in the context of the organ and tissue of which it forms a part with the aim of advancing in the knowledge of neoplastic, autoimmune and degenerative pathologies. CABIMER, in line with the most important international research centres, includes in its organisation units dedicated to the study of mechanisms of cell signalling and the transmission of biochemical signals from outside the cell to the nucleus.

### **Stem Cells and Cellular Reprogramming**

The research activity in this department is focused on the study of stem cells from adult, foetal and embryonic origins. Self renewal, differentiation as well as their ability to colonise and repopulate tissues, together with drugable and expandable adult progenitors are the biological basis for regenerative medicine. Our Clinical Program includes Research on Diabetes and their Complications, Liver and Rare diseases together with GMP manufacture of Cellular Medicaments. Our aim may be summarized in "Stem Cells and Regenerative Medicine. From DNA Repair to Patient Welfare".

### **Cell Therapy and Regenerative Medicine**

This department applies the results of cellular therapy and regenerative medicine as well as the transfer of knowledge to the health system, with the aim of improving the health of the population. Cellular therapy has as its goal the substitution of damaged cells by new ones. In this sense great importance is given to stem cells (embryo, adult and fetal) and their capacity to develop into cells of whatever type of tissue. Besides this, stem cells may be used for other therapeutic applications such as toxicological and pharmacological assays as well as for the study of the first stages in the appearance of specific and genetic diseases. This department has initially set up lines of research in fields such as pancreatic regeneration, cellular therapy against Diabetes Mellitus, immunology, oncology, molecular pathology, tissue engineering, biomaterials, transplants and regeneration in vertebrates.



## Genome Instability and Cancer

### Dr. Andrés Aguilera

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HEAD OF THE MOLECULAR  
BIOLOGY DEPARTMENT



### Group Members updated

#### Senior Researchers

Rosa Luna  
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Ana G. Rondón

#### Postdoctorals

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José M. Calderon Montaño  
María García-Rubio  
Belén Gómez González  
Emilia Herrera-Moyano  
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Emanuela Tumini

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Juan Carlos Martínez Cañas  
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Carmen Pérez Calero  
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#### Technician

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#### Master Students

Pedro Ortega Moreno

#### Administrative Assistant

Zoë Cooper

### Academic Formation of PI

- 1979: Degree. University of Seville, B.Sc. in Biology
- 1983: PhD. University of Seville, PhD Thesis in Biology

### Present Position

- 2004: Professor of Genetics, University of Seville, Spain
- April 2007-July 2008 & Sept. 2010-Dec. 2012: Scientific Vice-Director of CABIMER, Seville, Spain
- Since July 2006: Chair of the Department of Molecular Biology of CABIMER, Seville, Spain
- Since April 2016: Director of CABIMER, Seville, Spain

### Positions Held

- 1990-2004: Associate Professor of Genetics, University of Seville, Spain
- 1986-1990: Research Associate, NYU Medical Centre, New York, NY, USA
- 1984-1986: Postdoctoral Fellow F. Juan March, DAAD & EMBO. Tech. Universität Darmstadt, Germany

### Research Activity

#### OVERVIEW

The key role of genome instability in tumorigenesis and a number of rare cancer-prone genetic diseases, as well as its potential risks in stem cell-based therapies, has made it a major subject in cancer biology and biomedicine. With this in mind, our research goals are to identify the causes and mechanisms of genome instability, in particular the factors and mechanisms responsible for genome instability associated with replication stress and DNA breaks, including instability caused by transcription and RNA-DNA hybrids. We pursue: 1) to identify the causes of replication failures that cause DNA breaks; 2) to understand repair of replication-born DNA breaks and replication restart as a way to prevent genome instability; and 3) to evaluate the implication of such elements in cancer origin and its potential use in cancer therapy. Our research is performed in human cells and *Saccharomyces* as a model organism, plus the worm *Caenorhabditis*.

#### RESEARCH HIGHLIGHTS

In the last 5 years our work has focused on the identification of new factors and mechanisms responsible for genome instability in eukaryotic genomes, as a hallmark of cancer. The main highlights can be summarized as follows:

**Repair of Replication-born DNA breaks.** We have used a molecular assay, developed by us, to detect and analyze the *in vivo* kinetics of recombination events between sister chromatids (SCE) as a major double strand break repair. We have uncovered that acetylation of lysine 56 of histone H3 determined that chromosomal breaks generated during replication are preferentially repaired via SCE thereby facilitating proper replication restart and avoiding chromosome rearrangements. Analysis of translocations have been extended to a large number of mutants

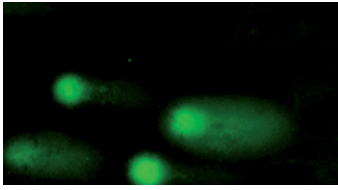


Figure 1. Single-cell electrophoresis (Comet assay) to detect double-strand breaks in tumorigenic HeLa cells

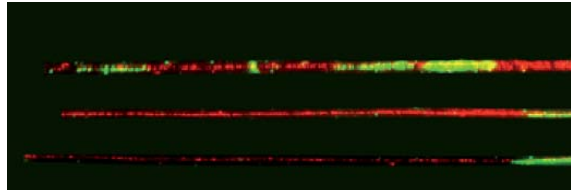


Figure 2. Analysis of DNA replication in human cell by DNA combing

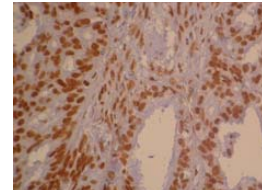


Figure 3. Expression of ALY in ovarian carcinoma determined by immunohistochemistry.

affected in recombination repair, which has permitted us to define the relevance of specific DNA damage response and chromatin functions in channeling repair to the sister to avoid rearrangements. Using similar functional assays we have defined two pathways for the restart of broken replication forks that are dependent on Rad51 and Pol32 proteins. This conclusion was strengthened by the use of specific mutations of the Rad/XPG nucleotide excision repair nuclease that causes the cells to cleave the piece of damaged DNA to be replaced. This new mechanistic connection between nucleotide excision repair and genome instability opens new perspectives to understand the putative role of nucleotide excision repair in cancer cells.

**Transcription-mediated genome-wide replication impairment in RNA biogenesis mutants.** We have previously shown that the molecule of nascent RNA plays a key role in the origin of instability, being able to form DNA-RNA hybrids able to trigger recombination. We have provided genome-wide evidence that the instability associated with transcription is mainly due to the inability of the replication fork to progress through a DNA that is transcribed, which led to the conclusion that genetic instability induced by transcription is caused by obstacles to the progression of the replication fork such as DNA-RNA hybrids or the transcription machinery itself.

**Chromatin compaction as a motor of RNA-mediated genome instability.** Our work with the THO complex and other proteins of RNA metabolism such as THSC/TREX-2 and SETX/SIN1 has revealed the key role of RNA metabolism proteins in maintaining genome integrity in both yeast and human cells is mediated by its regulatory role on chromatin remodeling. Importantly, DNA-RNA hybrids cause chromatin compaction, as identified by phosphorylation of Ser10 and dimethylation of lysine 9 of histone H3, allowing us to propose a model by which we explain the fragility of chromosomes as a consequence of co-transcriptional R loops and changes in chromatin organization caused by RNA-DNA hybrids. Interestingly, we have demonstrated that the chromatin reorganizing FACT complex has a key role in this process.

**RNA-mediated instability in cancer cells.** We have provided data suggesting that hybrids are a major natural source of replication stress found in cancer cells as determined in human cell lines depleted of the BRCA1 and BRCA2 tumor suppressors. This conclusion has been strengthened by the demonstration that the Fanconi Anemia pathway of repair is also involved in preventing RNA-DNA hybrid accumulation and transcription-associated genome instability, provided that BRAC2 and BRCA1 also function in this pathway. These findings have permitted us to propose that RNA-DNA hybrids may be one source of genome instability found in association with cancer. Consequently we believe it is worth to investigate whether RNA-DNA hybrids can be used as a marker of cancer proneness as well as a potential target in cancer therapy and diagnosis.

### Publication Highlights

- Bathia V., Barroso S., García-Rubio M., Tumini E., Herrera-Moyano E., Aguilera A. 2014. BRCA2 prevents R-loop accumulation and associates with TREX-2 mRNA export factor PCID2. *Nature*. 511:362-365
- Herrera-Moyano E., Mergui X., García-Rubio M., Barroso S., Aguilera A. 2014. The yeast and human FACT chromatin reorganizing complexes solve R-loop-mediated transcription–replication conflicts. *Genes Dev*. 28:735-748
- Castellano-Pozo M., Santos-Pereira J.M., Barroso S., Andújar E., Pérez-Alegre M., García-Muse T., Aguilera A. 2013. R Loops Are Linked to Histone H3 S10 Phosphorylation and Chromatin Condensation. *Mol Cell*. 52:583-590
- Santos-Pereira J.M., Herrero A.B., García-Rubio M.L., Marín A., Moreno S., Aguilera A. 2013. The Npl3 hnRNP prevents R-loop-mediated transcription-replication conflicts and genome instability. *Genes Dev*. 27:2445-2458
- Mischo H.E., Gómez-González B., Grzechnik P., Rondon A.G., Wei W., Steinmetz L., Aguilera\* A., Proudfoot\* N.J. 2011. Yeast Sen1 helicase protects the genome from transcription-associated instability. *Mol Cell*. 41:21-32 (\*corresponding authors)

### Grants

2015-2020: ERC2014-0015 Advanced.TARLOOP. European Research Council  
2015-2017: 15/0098. Worldwide Cancer Research (formerly known as AICR)  
2014-2018: P12/BIO-1238. Proyecto de Excelencia, Junta de Andalucía  
2014-2016: BFU2014-51672-REDC. Ministerio de Economía y Competitividad  
2014-2016: BFU2013-42918-P.Ministerio de Economía y Competitividad  
2014-2016: PharmaMar

2013-present: VEC – 001/2014 FVEC-FPS. Fundación Vencer el Cáncer  
2011-2015: Grupo BIO-102. Junta de Andalucía  
2011-2014: BFU2010-16372. Ministerio de Ciencia e Innovación  
2011-2013: (FEDER) UNSE10-1E-433.Ministerio de Ciencia e Innovación  
2007-2012: CONSOLIDER INGENIO 2010, CSD2007-00015.  
Ministerio de Educación y Ciencia



## Epigenetics and Gene Expression

**Dr. Jose C. Reyes**

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GROUP LEADER



### Group Members updated

#### Postdoctorals

Maria Ceballos-Chávez  
Sabrina Rivero Canalejo

#### PhD students

Jose A. Guerrero Martínez  
Macarena Guijo Molero

#### Master Student

Maria Eugenia Soler Oliva

### Academic Formation of PI

- 1990: Degree. University of Seville, B.Sc. in Biology
- 1994: PhD. University of Seville, Biology

### Present Position

- 2009: Scientific Researcher, National Council for Research, CSIC/CABIMER

### Positions Held

- 2006-2009: Research Scientist CSIC/CABIMER, Seville
- 2000-2006: Research Scientist CSIC/Instituto de Bioquímica Vegetal y Fotosíntesis (IBVF), Seville
- 1995-1998: Postdoctoral Research Investigator Institute Pasteur. Paris, France

### Research Activity

#### OVERVIEW

Development and cell differentiation are the consequence of a precise choreography of genes whose expression is controlled in a temporal and spatial manner. Alterations in the process of gene expression are the origin of many congenital malformations and diseases, including cancer. Chromatin – the supramolecular complex formed by DNA and histone proteins – plays a fundamental role in gene expression. Our laboratory is interested in understanding how histones regulate gene expression at several levels, and how alterations in chromatin regulatory proteins affect cell differentiation and proliferation.

#### RESEARCH HIGHLIGHTS

##### **HMG20A and HMG20B, two alternative subunits of the LSD1/CoREST histone demethylase complex**

LSD1 is a histone H3 lysine 4 demethylase that associates with other proteins forming the LSD1/CoREST complex. We have recently demonstrated that this complex is regulated by the alternative association of two high mobility group proteins called HMG20A and HMG20B. HMG20B is modified by sumoylation and this modification is essential for the activity of the LSD1/CoREST complex during repression of neuronal genes in non-neuronal tissue. An increase in the level of HMG20A has three consequences: First, HMG20A forms heterodimers with HMG20B, which inhibits its sumoylation; second, heterodimerization impairs association of HMG20B with the LSD1/CoREST complex and third, HMG20A substitutes HMG20B in the complex. The equilibrium between HMG20A and HMG20B is important for neuronal differentiation and also for the process of epithelium to mesenchymal transition (EMT). Moreover, level of HMG20A mRNA are increased in certain types of tumors and there is a positive correlation between HMG20A expression and that of EMT markers such as ZEB1 or FN1, suggesting that HMG20A may have a role in tumor cell delamination, an early event in metastasis.

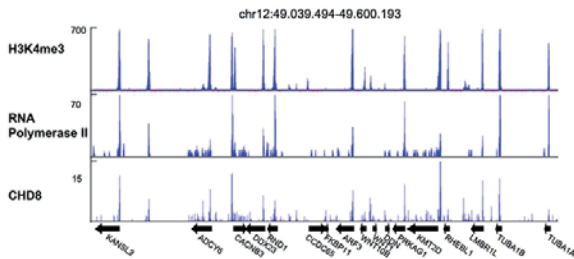


Figure 1

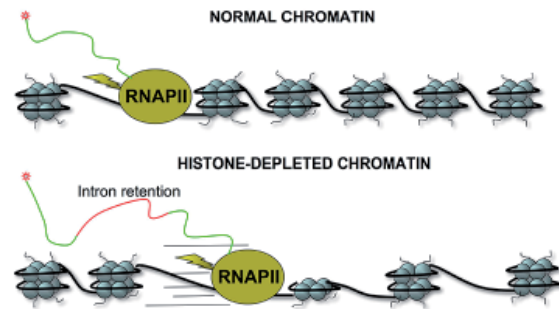


Figure 2

### CHD8, a chromatin remodeler required for activation of promoters and enhancers

CHD8 is an ATPase of the SNF2 family involved in chromatin remodeling. Truncating mutations in CHD8 gene cause a specific type of autism. Alterations in the levels of CHD8 have also been associated with cancer. We have recently shown that under conditions of normal proliferation CHD8 is bound to active promoters also enriched in H3K4me3 and H3K4me2 histone marks (Figure 1). Most of the CHD8 target genes are also bound by the E2F1 transcription factor and encode cell cycle, transcription and RNA processing proteins. In fact, CHD8 interacts with E2F1 and knockdown of CHD8 strongly impairs cell proliferation.

In addition, we have discovered that CHD8 plays also a role in activation of enhancers. In fact, few minutes upon treatment of human breast carcinoma cells T47D with progestin, CHD8 localizes to enhancers also occupied by the Progesterone Receptor. In these enhancers CHD8 is required for normal RNA polymerase II recruitment and synthesis of eRNAs, which are late stages in the activation of the enhancers.

### Alteration of histone levels causes changes in transcriptional elongation and pre-mRNA splicing

How nucleosomal organization of genes affects gene expression is another classical research subject of the group. We have recently reported the transcriptional consequences of reducing the level of canonical histones in the cell. Depletion of canonical histones causes a more accessible chromatin characterized by a lower histone/DNA ratio and increased levels the variant histone H3.3. Under these conditions RNA polymerase II elongates faster but the rate of co-transcriptional splicing is not increased suggesting that splicing is a rate-limiting step for gene expression. Moreover, histone depletion causes strong splicing defects including altered skipping or inclusion of alternative exons and increased intron retentions (Figure 2). These data indicate that a correct chromatin structure is required for normal pre-mRNA processing.

### Publication Highlights

- Jimeno-Gonzalez S., Payán L., Muñoz-Cabello A.M., Guijo M., Gutierrez G., Prado F., Reyes J.C. 2015. Defective histone supply causes changes in RNA polymerase II elongation rate and co-transcriptional pre-mRNA splicing. *Proc Natl Acad Sci USA*. 112:14840-14845
- Ceballos-Chávez M., Subtil-Rodríguez A., Giannopoulou E.G., Soronellas D., Elemento O., Beato M., Reyes J.C. 2015. The chromatin remodeler CHD8 is required for activation of progesterone receptor-dependent enhancers. *PLoS Genet*. 11(4):e1005174
- Rivero S., Ceballos-Chávez M., Bhattacharya S.S., Reyes J.C. 2015. HMG20A is required for SNAI1-mediated Epithelial to Mesenchymal Transition. *Oncogene*. 34:5264-5276
- Subtil-Rodríguez A., Vázquez-Chávez E., Ceballos-Chávez M., Rodríguez-Paredes M., Martín-Subero J.I., Esteller M., Reyes J.C. 2014. The chromatin remodeler CHD8 is required for E2F-dependent transcription activation of S phase genes. *Nucleic Acids Res*. 42:2185-2196
- Ceballos-Chávez M., Rivero S., García-Gutiérrez P., Rodríguez-Paredes M., García-Domínguez M., Bhattacharya S.S., Reyes J.C. 2012. Control of neuronal differentiation by sumoylation of BRAF35, a subunit of the LSD1-CoREST histone demethylase complex. *Proc Natl Acad Sci USA*. 109:8085-8090

### Grants

2015-2017: BFU2014-53543-P. Ministerio de Economía y Competitividad  
 2012-2014: BFU2011-23442. Ministerio de Economía y Competitividad  
 2010-2013: CVI-4844. Proyecto de Excelencia. Junta de Andalucía  
 2010-2013: Fundación Ramón Areces



## Chromatin Integrity and Function

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GROUP LEADER



### Group Members updated

#### Staff Scientist

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#### Postdoctoral

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#### Technician

Elena Gomez Marin

### Academic Formation of PI

- 1992: Degree. University of Seville, B. Sc. in Biology
- 1996: PhD. University of Seville, Molecular and Celular Biology

### Present Position

- Since 2006: Research Scientist CSIC/CABIMER

### Positions Held

- 1997-1999: Postdoctoral fellow. IMT Institute, Phillip University-Marburg, Germany
- 2000-2005: Postdoctoral fellow/Ramón y Cajal Researcher. Biology School, University of Seville

### Research Activity

#### OVERVIEW

Faithful replication of the complete genome is essential for preventing any loss of genetic information. However, this is not an easy task; in fact, the genetic instability that accompanies tumor progression during early stages is associated with replicative stress. Using the yeast *Saccharomyces cerevisiae* as living model, and a wide repertoire of techniques in genetic, biochemistry, genomic, and molecular and cellular biology, we are focused on two different aspects associated with replication dynamics that have a direct impact on genome integrity and cell cycle progression: chromatin assembly and tolerance to replicative DNA damage. Our main goal is to get a deeper insight into their mechanistic and regulation, as well as in the consequences for cell fitness of mutations in the genes encoding their components.

#### RESEARCH HIGHLIGHTS

The assembly of the newly replicated DNA into nucleosomes to form the chromatin fiber is a highly regulated process where genetic and physical interactions between histone chaperones, chromatin assembly factors and components of the replisome ensure a rapid and correct deposition of histones behind the advancing fork. Our studies have shown that defects in chromatin assembly by impairing the pathways of histone deposition or reducing the pool of available histones lead to an accumulation of DNA breaks and genomic rearrangements as a consequence of the breakage of advancing replication forks (Figure 1) (Clemente-Ruiz et al., PLOS Genetics 2011) (Prado and Clemente-Ruiz, Bioarchitecture 2012). The loss of chromatin integrity is also associated with defects in chromosome biorientation and chromatid decatenation that causes the activation of the spindle-assembly checkpoint (Murillo-Pineda et al., NAR 2014). These studies have uncovered a novel connection between the process of chromatin assembly and the activities of DNA topoisomerases, cohesins and condensins, which have led us to try to decipher the genome-wide roles of these major determinants of chromosome architecture in the primary structure of chromatin and the functionality of DNA metabolic processes (Figure 2).

A major source of genetic instability is associated with the encounter of the replication fork with DNA adducts that hinder its advance. In this case, replication fork stability and genome integrity

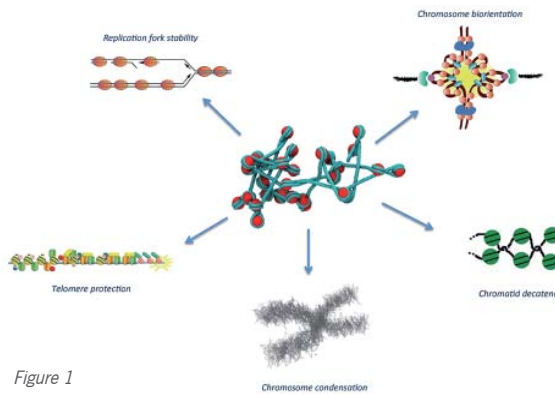


Figure 1

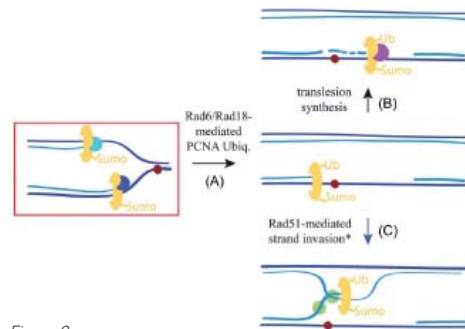


Figure 2

are also maintained by a number of error-free and error-prone mechanisms that help the fork to pass through the lesions and to fill in the gaps of single-stranded DNA (ssDNA) generated during the process of fork blockage and lesion bypass (Figure 3) (Prado, *Mol. Cell. Oncol.* 2014). Consequently, this DNA damage tolerance (DDT) response is essential for cell cycle progression, genome integrity, and cancer avoidance. A major research line in our lab is aimed at understanding the coordination of these mechanisms during the cell cycle, paying particular attention to the role of homologous recombination proteins as master players of the error-free pathways. We have shown that the key recombination proteins Rad52 and Rad51 travel with the fork and, in the presence of replicative blocking lesions, help it to pass through the lesions and fill in the gaps of ssDNA by a mechanism in which, contrary to the recombinational repair of double-strand breaks, their recruitment to the ssDNA replicative lesions has obligatorily to occur during S phase (Gonzalez-Prieto et al., *EMBO J.* 2013). We have also shown that the recombinational repair of the ssDNA lesions is not coupled to the fork but rather prevented until replication is completed, likely to avoid genetic instability through a spatio-temporal separation of replication and DNA repair (Prado, 2014 *Bioessays*). We are currently interested in understanding the regulation of homologous recombination proteins during the cell cycle and their connection with other DDT pathways.

### Publication Highlights

- Murillo-Pineda M., Cabello-Lobato M. J., Clemente-Ruiz M., Monje-Casas F., Prado F. 2014. Defective histone supply causes condensin-dependent chromatin alterations, SAC activation and chromosome decatenation impairment. *Nucleic Acids Res.* 42:12469-12482
- Prado F. 2014. Homologous recombination maintenance of genome integrity during DNA damage tolerance. *Mol Cell Oncol.* e957039
- Prado F. 2014. Genetic instability is prevented by Mrc1-dependent spatio-temporal separation of replicative and repair activities of homologous recombination. *BioEssays.* 36:451-462
- Gonzalez-Prieto R., Muñoz-Cabello A., Cabello-Lobato M.J., Prado F. 2013. Rad51 replication fork recruitment is required for DNA damage tolerance. *EMBO J.* 32:1307-1321
- Clemente-Ruiz M., Gonzalez-Prieto R., Prado F. 2011. Histone H3K56 acetylation, CAF1 and Rtt106 coordinate nucleosome assembly and stability of advancing replication forks. *PLoS Genet.* 7: e1002376

### Grants

2014-2016: P12-CTS-2270. Junta de Andalucía "Proyectos de Excelencia"  
 2013-2015: BFU2012-38171. Ministerio de Economía y Competitividad  
 2010-2012: BFU2009-09036. Ministerio de Ciencia e Innovación  
 2008-2011: P07-CVI-032000. Junta de Andalucía "Proyectos de Excelencia"



## Mitochondrial Plasticity and Replication

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GROUP LEADER



### Group Members updated

#### Postdoctoral

Elisabet Fernández García

#### PhD Student

Hayat Heluani Gahete

### Academic Formation of PI

- 1992 Degree: Diplom Biologe Universitaet Kaiserslautern (D)
- 1996 PhD: Dr. sc. Nat. Eidgenoessische Technische Hochschule Zuerich (ETH, CH)

### Present Position

- Since 2009 Associate Professor at the Department of Genetics,  
University of Seville - CABIMER

### Positions Held

- 1996-2001: Postdoctoral fellow at the ETH Zurich
- 2001-2003: Marie-Curie fellow at the University of Seville
- 2003-2007: Ramón y Cajal fellow at the University of Seville-CABIMER
- 2007-2009: Assistant Professor at the University of Seville-CABIMER

### Research Activity

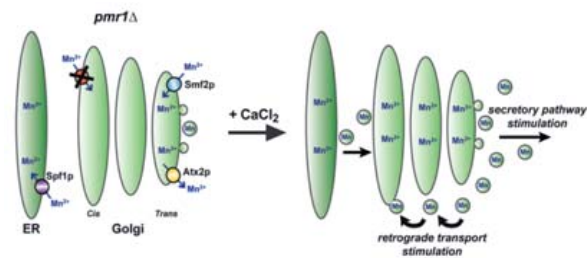
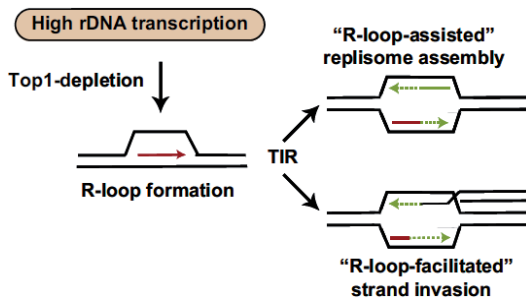
#### OVERVIEW

The genetic material is constantly exposed to endogenous or exogenous stress, such as ROS, leading to DNA damage and disease. Interestingly, oxidative stress is linked to cancer or metabolic disorders such as Hailey-Hailey disease (HHD). Topoisomerase 1 (Top1) is part of the DNA replication machinery and a well-characterized target of cancer cell treatment. Based on nano-technology mediated drug delivery, we develop alternative approaches for improved cancer treatment by Top1-inhibitors connected to ROS. We also use budding yeast to study how the lack of Top1 is connected to origin-independent replication priming and cancer progression. We furthermore investigate how sunlight and metabolic alterations can challenge genome stability. These studies take advantage of budding yeast as model to study the molecular bases of HHD, is a rare hereditary blistering skin disease. The goal of these studies is enhanced and preventative overall skin protection but also to improve the life quality of HHD patients.

#### RESEARCH HIGHLIGHTS

**Origin-independent replication by transcription initiated replication (TIR):** Understanding the process of DNA replication is fundamentally important because of its contribution to genome instability. DNA replication initiates at defined replication origins along eukaryotic chromosomes, ensuring complete genome duplication within a single S-phase. A key feature of replication origins is their ability to control the onset of DNA synthesis mediated by DNA polymerase- $\alpha$  and its intrinsic RNA primase activity. Our recent work describes a novel origin-independent replication process that, similar to mitochondrial DNA replication initiation, is mediated by transcription. We found that RNaseH- and Top1-dependent RNA polymerase I transcription constraints lead to persistent RNA:DNA hybrids (R-loops) that prime replication in the ribosomal DNA locus. Our findings suggest that eukaryotic genomes have developed tools to prevent R-loop-mediated replication events that potentially contribute to copy number variation, particularly relevant to carcinogenesis. Future studies are dedicated to the further characterization of genetic and molecular interactions connected to TIR.





A model for Ca<sup>2+</sup>-mediated suppression of *pmr1Δ*-dependent phenotypes

**Characterization of improved tools for chemotherapy:** In the more immediate term many of the chemotherapeutics in use in the cancer clinics today target the process of DNA replication directly. They inhibit DNA replication, because cancer cells tend to be proliferating much more rapidly than normal cells. We need to understand more about the process of replication and how that process responds to these chemotherapeutic drugs we might be able to intervene in combination therapies, or in better drug design, to prevent some of these side-effects while maintaining cancer killing effects. A draw back in chemotherapy is the limited by the water-solubility of many 'founder' drugs such as the Top1-inhibitor camptothecin (CPT). To overcome this limitation, chemical modifications have been introduced that increase water-solubility at the cost of a strongly reduced therapeutic activity. The research group of Dr. Nouredine Khair (IIQ, Sevilla) developed nanomaterials for the water solubilization and delivery of hydrophobic molecules. We collaborated with the Khair group in order to demonstrate that these nanomaterials are able to improve the sensitivity of human tumor cell lines to CPT. Improved nano-vectors for targeted drug delivery are currently under investigation.

**Intracellular manganese homeostasis and genome instability:** Regulation of intracellular ion homeostasis is essential for eukaryotic cell physiology. An example is provided by loss of ATP2C1 function, which leads to skin ulceration, improper keratinocyte adhesion, and cancer formation in Hailey-Hailey patients. The yeast ATP2C1 orthologue PMR1 codes for a Mn(2+)/Ca(2+) transporter that is crucial for cis-Golgi manganese supply. First we studied the impact of Mn(2+) on cell cycle progression and show that an excess of cytosolic Mn(2+) alters S-phase transit, induces transcriptional up-regulation of cell cycle regulators, bypasses the need for S-phase cell cycle checkpoints and predisposes to genomic instability. On the other hand, we found that depletion of the Golgi Mn(2+) pool requires a functional morphology checkpoint to avoid the formation of polyploid cells. We then presented evidence that calcium overcomes the lack of Pmr1 through vesicle trafficking-stimulated manganese delivery and requires the endoplasmic reticulum Mn(2+) transporter Spf1 and the late endosome/trans-Golgi Nramp metal transporter Smf2. Based on these results, in collaboration with Prof. Dr. Marc Blondel (University of Brest, France) we carried out a chemical screening and isolated FDA-approved compounds that can suppress the *pmr1Δ*-specific phenotypes. It will be interesting to determine the mode-of-action of these compounds, and to evaluate their potential in HHD treatment.

### Publication Highlights

- Stuckey R., García-Rodríguez N., Aguilera A., Wellinger R.E. 2015. Role for RNA:DNA hybrids in origin-independent replication priming in a eukaryotic system. *Proc Natl Acad Sci U S A.* 112:5779-5784
- García-Rodríguez N., Manzano-López J., Muñoz-Bravo M., Fernández-García E., Muñoz M., Wellinger R.E. 2015. Manganese Redistribution by Calcium-stimulated Vesicle Trafficking Bypasses the Need for P-type ATPase Function. *J Biol Chem.* 290:9335-9347
- Assali M., Cid J.J., Pernía-Leal M., Muñoz-Bravo M., Fernández I., Wellinger R.E., Khair N. 2013. Glyconanosomes: disk-shaped nanomaterials for the water solubilization and delivery of hydrophobic molecules. *ACS Nano.* 27:2145-2153
- García-Rodríguez N., Díaz de la Loza M.C., Anderson B., Monje-Casas F., Rothstein R., Wellinger R.E. 2012. Impaired manganese metabolism causes mitotic misregulation. *J Biol Chem.* 287:18717-18729
- de la Loza M.C., Gallardo M., García-Rubio M., Izquierdo A., Herrero E., Aguilera A., Wellinger R.E. 2011. Zim17/Tim15 Links Mitochondrial Iron-Sulfur Cluster Biosynthesis to Nuclear Genome Stability. *Nucleic Acids Res.* 39:6002-6015

### Grants

2015-2018: BFU2015-69183-P. Ministerio de Ciencia e Innovación  
 2013-2016: P08-CTS-04297. Consejería de Economía, Innovación y Ciencia, Junta de Andalucía  
 2011-2013: BFU2010-21339. Ministerio de Ciencia e Innovación



## Chromosome Segregation

**Dr. Fernando Monje**  
*fernando.monje@cabimer.es*  
GROUP LEADER



### Group Members updated

#### Postdoctorals

Javier Manzano López  
Ana María Rincón Romero

#### PhD Students

Inés García De Oya  
Laura Matellán Fernández

#### Technician

Jose Carlos Blanco Mira

#### Master Student

Ernesto López de Alba

### Academic Formation of PI

- 1998: Degree. University of Córdoba, B.Sc. in Biochemistry
- 2003: PhD. University of Córdoba, Biochemistry

### Present Position

- Since 2016: Research Scientist-CSIC/ CABIMER

### Positions Held

- 2013-2016: Researcher. University of Seville, Spain
- 2008-2013: Ramón y Cajal Researcher. University of Seville, Spain
- 2003-2008: Postdoctoral Fellow. MIT, USA

### Research Activity

#### OVERVIEW

The research in our group focuses on the surveillance mechanisms that ensure a proper distribution of the chromosomes during cell division and help maintaining the correct cellular ploidy after the completion of mitosis. We are particularly interested in understanding how these mechanisms specifically regulate mitotic exit. Exit from mitosis is the last cell cycle transition and involves the disassembly of the mitotic spindle, the decondensation of the chromosomes, and the execution of cytokinesis, therefore leading to the final duplication of the cell. Problems with the distribution of the genetic material during mitosis can give rise to aneuploidy, an alteration of the normal number of chromosomes in the cell that is a hallmark of cancer and a number of different genetic diseases. Advances in our knowledge about the regulation of mitotic exit are therefore essential for a better understanding of the mechanisms that underlay these diseases.

#### RESEARCH HIGHLIGHTS

The cells have developed a number of surveillance mechanisms that verify the integrity of the genetic material and the proper distribution of the chromosomes during cell division. We are particularly interested in three of these checkpoints: (i) the DNA damage checkpoint (DDC), which verifies the integrity of the genome; (ii) the spindle assembly checkpoint (SAC), which ensures that every chromosome has been attached to the mitotic spindle; and (iii) the spindle position checkpoint (SPOC), which avoids that cells with a misaligned spindle exit from mitosis. Remarkably, and although the three previous checkpoints are triggered by different signals and in different stages of the cell cycle, all of them promote the inhibition of mitotic exit, which highlights the importance of the regulation of this cell cycle transition. In the budding yeast *Saccharomyces cerevisiae*, exit from mitosis is promoted by the mitotic exit network (MEN), a signalling pathway that is initiated by the Tem1 GTPase. The mitotic checkpoints block MEN signalling by promoting the activity of Bfa1/Bub2, a two-component GTPase-activating protein (GAP) that inhibits Tem1. During the 2011-2015 period, our group has made important contributions into our understanding of MEN regulation, both during a normal cell cycle and after the

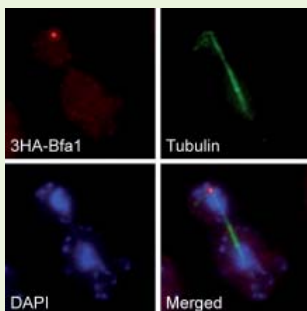


Figure 1: Asymmetric localization of Bfa1 during anaphase.

Immunofluorescence image displaying the localization of a 3HA-tagged version of the MEN inhibitor Bfa1 to the spindle pole body that enters the daughter cell during anaphase. The spindle (tubulin, in green) and the nucleus (DAPI, in blue), as well as a merged image, are also shown as a reference.

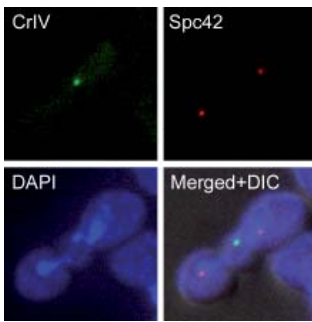


Figure 2: Increased Aurora B activity generates chromosome segregation defects.

The image shows a lagging GFP-tagged chromosome IV (CrIV, in green) that is left behind during chromosome segregation as a consequence of increased expression of the Aurora B homolog in budding yeast (*Ipl1*). The spindle pole body component Spc42 (in red) and the DNA (DAPI, in blue), as well as a merged imaged with DIC, are also shown as a reference.

activation of the mitotic checkpoints. As such, we have demonstrated for the first time that localization of Tem1 onto the spindle pole bodies (SPBs, the equivalent of the centrosomes in yeast) is an essential requirement for MEN signalling. We have further established that Tem1 exclusion from the SPBs is necessary to inhibit mitotic exit after activation of the SPOC, but not after the DDC or the SAC are triggered, since additional mechanisms downstream of Tem1 negatively regulate the MEN under these conditions. Finally, we have demonstrated that although the DDC, the SAC and the SPOC block MEN signalling by impeding the inactivation of Bfa1/Bub2 by the Polo-like kinase Cdc5, each checkpoint uses a different strategy to inhibit this kinase. In this sense, and interestingly, we have recently demonstrated that inhibition of the MEN after activation of the DDC is only specifically required in response to DNA damage to the telomeres, and that it is achieved through the inhibition of Cdc5 by the Rad53-dependent branch of the checkpoint.

Besides our research regarding the regulation of mitotic exit, we have also made key contributions to our understanding of the mechanisms by which Aurora B kinase, an essential protein that repairs erroneous chromosomal attachments that do not lead to the bi-orientation of sister chromatids, regulates chromosome segregation in mitosis. The lack of Aurora B activity leads to severe chromosome segregation defects, aneuploidy and lethality. Interestingly, increased expression of Aurora B also leads to aneuploidy, and it has been linked to different cancer types. We have recently demonstrated that the chromosome segregation defects associated to increased expression of Aurora B are caused by a constitutive disruption of kinetochore-microtubule attachments, which occurs even when these attachments are correct. We have further demonstrated that increased expression of Aurora B also causes premature spindle collapse by promoting instability of the spindle midzone. Besides analysing how alterations in the levels of expression of Aurora B trigger chromosome segregation defects, we have provided new insights into how this kinase and the SAC collaborate to ensure the proper attachment of the chromosomes to the spindle. As such, our research recently helped us to propose that it is the specific time window required for Aurora B to establish chromosome bi-orientation that explains the differential dependence of cells from distinct organisms and different cell types within the same organism on a functional SAC for their viability, an important open question in the field.

### Publication Highlights

- Muñoz-Barrera M., Aguilar I., Monje-Casas F. 2015. Dispensability of the SAC depends on the time window required by Aurora B to ensure chromosome biorientation. *PLoS One*. 10(12): e0144972
- Muñoz-Barrera M., Monje-Casas F. 2014. Increased Aurora B activity causes continuous disruption of kinetochore-microtubule attachments and spindle instability *Proc Natl Acad Sci USA*. 111:3996-4005.
- Murillo-Pineda M., Cabello-Lobato M.J., Clemente-Ruiz M., Monje-Casas F., Prado F. 2014. Defective histone supply causes condensin-dependent chromatin alterations, SAC activation and chromosome decatenation impairment. *Nucleic Acids Res*. 42:12469-12482
- Valerio-Santiago M., de los Santos-Velázquez A.I., Monje-Casas F. 2013. Inhibition of the Mitotic Exit Network in response to damaged telomeres. *PLoS Genet*. 9: e1003859.
- Valerio-Santiago M., Monje-Casas F. 2011. Tem1 localization to the spindle pole bodies is essential for mitotic exit and impairs spindle checkpoint function. *J Cell Biol*. 192:599-614

### Grants

2014-2016: BFU2013-43718-P. Ministerio de Economía y Competitividad  
 2012-2013: BFU2011-23436. Ministerio de Ciencia e Innovación  
 2011-2014: CVI-5806. Consejería de Economía, Educación y Ciencia  
 2010-2013: PIRG04-GA-2008-239416. Marie Curie International Reintegration Grant. 7th Framework Programme  
 2009-2011: BFU2008-00793. Ministerio de Ciencia e Innovación



## Cellular Therapy of the Diabetes Mellitus and its Complications

**Dr. Bernat Soria**

*bernat.soria@cabimer.es*

HEAD OF THE STEM CELLS DEPARTMENT



### Group Members updated

#### Senior Researcher

Karim Hmadcha

#### Postdoctorals

Vivian Capilla González

Christian Lachaud

#### PhD Students

Emilio Javier López Beas

Sandra Pascual Gómez

Mehrdad Vakilian

#### Technicians

Yolanda Aguilera García

Natalia Escacena Acosta

Nuria Mellado-Damas Sanz

### Academic Formation of PI

- 1974: Degree. University of Valencia, Medical Doctor
- 1978: PhD. University of Valencia

### Present Position

- Since 2009. Director of the Department of Stem Cells and Cell Reprogramming of CABIMER
- Scientific Coordinator of GMP-Facilities

### Positions Held

- 1982-1984: Adjunct Professor of Biochemistry and Physiology, School of Medicine, Valencia University, Valencia
- 1984-1985: Adjunct Professor of Biochemistry and Physiology, School of Medicine, Alicante University, Valencia
- 1986-2005: Full Professor of Physiology, Valencia
- 2005-2007: Director of CABIMER, Seville, Spain
- 2005-2007: Extraordinary Professor of Regenerative Medicine, Pablo de Olavide University, Seville, Spain
- 1979-1982: Former positions at Juan March Foundation and Senior Research Associate Dept. of Biophysics.
- 1979-1980: Senior Research Associate Dept. of Biophysics, School of Biological Sciences, University of East Anglia, Norwich

### Research Activity

#### OVERVIEW

The "Cellular Therapy of the Diabetes Mellitus and its Complications" started his activity in CABIMER in January 2006, with a special interests in: i) understanding the molecular and cellular basis of pluripotency and differentiation of stem cells, ii) designing new protocols to expand and differentiate stem cells and iii) promoting clinical trials under European Regulations. During this period this group has published more than 20 papers, filed 9 patents and promoted 4 Clinical Trials. In addition to basic and clinical research the group offers technical and scientific support to boost several clinical trials through the GMP unit of CABIMER is engaged in the scale-up of human cells considered as Advanced Therapeutic Medicinal Products. The Mission of the group consists in improving Stem Cell basic and preclinical research on stem cell biology to foster breakthroughs in Advanced Therapies and Regenerative Medicine.

#### RESEARCH HIGHLIGHTS

**1. Insulin producing cells from human embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC): A.** Describing and patenting a new xeno-free and human components free culture media which may be used both in embryonic and adult stem cells (Patent EP

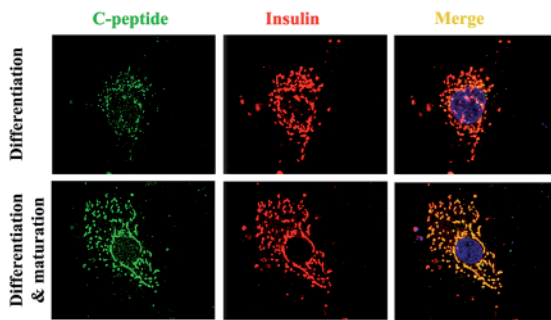


Figure 1. Effect of late maturation on hESCs-derived insulin-secreting cells (Soria B. et al. *Exprt Opin. Biol. Ther.* 2015)

15382417.2 (05-08-2015) ); **B.** New protocols to obtain mature beta cells from embryonic and iPSC cells (*Stem Cells Int.* 2014;379678. *PLoS One.* 2015 Mar 16;10(3):e0119904, Patent PCT/EP2015/070501 (08-09-2015) we have committed ourselves to have a CABIMER-protocol to obtain mature clinical grade pancreatic beta cells that may be used in clinical trials (P2011070165 (20-11-2012)); **C.** Pancreatic islet physiology: *Diabetes.* 2013 Jan;62(1):18-21; *Islets.* 2014;6(5-6):e995997

**2. Basic Research on Stem Cells: Embryonic and induced Pluripotent Stem cells, Adult Progenitors, Mesenchymal Stromal Cells, Liver Stellate cells and Mesothelial Cells.** Most of the effort has been devoted to keep human embryonic stem cell lines, derive new cell lines and generate protocols that provide mature and differentiated beta cells. **A.** New human embryonic stem cell lines have been derived from healthy and monogenetic disease embryos and the molecular basis of pluripotency explored (*Cell Death Dis.* 2013 Apr 4;4:e570); **B.** Role of ionic channels in embryonic stem cell membranes *J Membr Biol.* 2015, 45(8): 2324-34; *J Membr Biol.* 2013 Mar;246(3):215-30; **C.** Lessons from islet development: **i.** In collaboration with the group of Dr Gauthier an expandable Pax-4 positive population has been described (*Sci Rep* 5: 15672, 2015) or **ii.** In collaboration with Dr Rojas it was described the role of GATA4 and GATA6 in beta cell development. (*J Clin Invest* 122(10): 3504-3515, 2012; *Cell Mol Life Sci.* 2014 71(13):2383-402) and more recently the tentative role of GATA 6 in type 2 diabetes is being explored; **D.** Liver Stellate cells. A close correlation between liver stellate cells GATA-decrease and liver fibrosis has been described (*Hepatology* 59(6): 2358-70, 2014; Patent: P201330636 (30-04-2013); **E.** Mesothelial cells. We have explored whether mesothelial cells may produce vesicles (*PLoS One.* 2013;8(2):e55181; *Cell Death Dis.* 5: e1304, 2014) or corneal endothelium (*Invest Ophthalmol Vis Sci.* 55(9): 5967-78, 2014, Patent EP 13382213.0 (05-06-2013). PCT/EP2014/061746(01/08/2014)

**3. GMP Regulations, Clinical Research and Cell therapy. A.** Molecular basis of adverse reactions: describing the safety and efficacy pattern in the use of mesenchymal cells (*Diabetes* 62(12): 4266-9, 2013; Patent EP 13382315.3 (01-08-2013) PCT/EP2014/066600 (01-08-2014); **B.** Use of Cord Blood derivatives, such as cord plasma factors (*Eur J Immunol.* 2015 Aug; 45(8):2324-34 EP 14382348.2 (16/09/2014) or NK cells (*PLoS ONE* 11/2015; 10(10). DOI:10.1371; Patent EP 15382429.2); **C.** Regulatory Framework: *Stem Cells Dev.* 23(10): 1074-83, 2014, *Br Med Bull* 105: 85-105, 2013); **D.** Clinical Trials Our group both expanded mesenchymal stromal cells and coordinated several Clinical Trials (NCT 00872326; NCT01079403; NCT00987363; NCT01056471) using autologous mesenchyma stromal cells to avoid leg amputation in diabetic patients (*Cell Transpl* 20(10): 1329-1639, 2011).

### Publication Highlights

- Lorenzo P.I., Fuente-Martín E., Brun T., Cobo-Vuilleumier N., Jimenez-Moreno C.M., G Herrera Gomez I., López Noriega L., Mellado-Gil J. M., Martín-Montalvo A., Soria B., Gauthier B.R. 2015. PAX4 Defines an Expandable  $\beta$ -Cell Subpopulation in the Adult Pancreatic Islet. *Sci Rep.* 5:15672
- Soria B., Gauthier B.R., Martín F., Tejado J.R., Bedoya F.J., Rojas A., Hmadcha A. 2015. Using stem cells to produce insulin. *Expert Opin Biol Ther.* 15:1469-1489
- Cox S.T., Laza-Briviesca R., Pearson H., Soria B., Gibson D., Gomez S., Madrigal J.A., Saudemont A. 2015. Umbilical cord blood plasma contains soluble NKG2D ligands that mediate loss of natural killer cell function and cytotoxicity. *Eur J Immunol.* 45:2324-2334
- Pezzolla D., López-Beas J., Lachaud C.C., Domínguez-Rodríguez A., Smani T., Hmadcha A., Soria B. 2015. Resveratrol ameliorates the maturation process of  $\beta$ -Cell-like cells obtained from an optimized differentiation protocol of human embryonic stem cells. *PLoS One.* 10(3):e0119904
- Acosta L., Hmadcha A., Escacena N., Pérez-Camacho I., de la Cuesta A., Ruiz-Salmeron R., Gauthier B.R., Soria B. 2013. Adipose mesenchymal stromal cells isolated from type 2 diabetic patients display reduced fibrinolytic activity. *Diabetes.* 62:4266-4269

### Grants

Ministerio de Economía y Competitividad/Ministerio de Sanidad/Consejería de Economía, Innovación y Ciencia y Consejería de Salud (Junta de Andalucía). European Union (BIOREG-SO3/P1/E750/ COST-A FACTT BM 1305)



**Pancreatic Islets  
Pathophysiology Cell  
and Stem Cell**

**Dr. Franz Martín**  
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GROUP LEADER



**Group Members  
updated**

**Postdoctoral**

Lourdes María Varela Pérez

**PhD Students**

Leticia Álvarez Amor

Amparo Luque Sierra

**Technicians**

Raquel Araujo Legido

Antonio M. Cárdenas García

**Academic Formation of PI**

- 1986: Degree. University of Seville, B.Sc. in Medicine and Surgery
- 1994: PhD. University of Seville, PhD in Medicine and Surgery

**Present Position**

- Since 2006: Research Scientist CABIMER/Seville, Spain
- Since 2007: Full Professor at University Pablo de Olavide, Seville, Spain

**Positions Held**

- 1991: Postdoctoral Fellowship, Joslin Diabetes Center, Harvard University
- 1992-1993: Visiting Professor, Department of Physiology, University of Alicante, Valencia
- 1993-1997: Lecturer, Department of Physiology, University of Alicante, Valencia
- 1997-2005: Lecturer, Department of Applied Biology, University Miguel Hernández, Alicante, Valencia
- 2005-2007: Lecturer, Department of Molecular Biology and Biochemistry Engineering, University Pablo Olavide, Seville, Spain

**Research Activity**

**OVERVIEW**

Our main research lines are: i) to study the role of nutrients and diets in the pathogenesis of diabetes, obesity, diabetes, metabolic syndrome and non-alcoholic fatty liver disease and ii) the development of differentiation protocols, from embryonic, induced pluripotent and adult stem cells, to insulin producing cells, as well as, their employment in diabetes cell therapy.

**RESEARCH HIGHLIGHTS**

Our main research highlights are.

1. Intestinal permeability is frequently abnormal in patients with celiac disease. The long-term effect of a gluten-free diet on intestinal permeability and the correlation of intestinal permeability with a gluten-free diet are not known. Thus, it is important to determine the responses of intestinal permeability to gluten free diet and the degree of correlation of these measurements with gluten ingestion. We have developed an ELISA technology to detect antibodies against betalactoglobulin and betalactoglobulin itself, as methodology to quantify intestinal permeability and monitor gluten ingestion. We have observed that gluten ingestion correlates with intestinal permeability measurements using our ELISA. The role of permeability testing in the follow-up of patients with celiac disease, using plasmatic markers, could be an easy and safe clinical approximation.

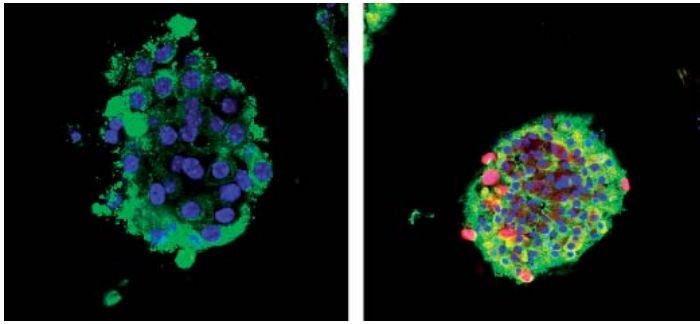


Figure 1. Control and V91L-infected islets showing beta cell replication

2. Excess dietary fat has been implicated in the development and progression of non-alcoholic fatty liver disease (NAFLD) and may be an important modifiable factor involved in the development and progression of NAFLD and NASH. We have found that dietary extra virgin olive oil intake repair HFD-induced hepatic damage, via an anti-inflammatory effect in adipose tissue and modifications in the liver lipid composition and signaling pathways.

3. Edmonton's protocol for the transplantation of pancreatic islets from cadaver donors has proven to be an effective alternative for the treatment of diabetes mellitus. Unfortunately, the number of pancreatic islets that are isolated from cadaver donors is low and this entails the need to have pancreata from 2-3 cadaver donors available in order to guarantee the success of the islet transplantation. The number of donors is clearly insufficient to guarantee islet transplantation for a significant number of diabetes patients. A potential alternative to overcome this problem would be the development of protocols that allow for the *in vitro* proliferation of pancreatic beta cells prior to the transplantation. This would increase the mass of beta cells to be transplanted. We have developed a method for the rapid *in vitro* proliferation of cells derived from tissues of endodermal origin (mainly pancreatic beta cells and hepatocytes). This method allows for a rapid proliferation of endodermal cells *in vitro*, preventing the complete dedifferentiation thereof and, consequently, their loss of functionality.

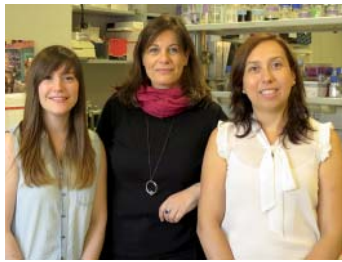
4. Gain-of-function mutations in glucokinase gene (GCK) have also been involved in the pathogenesis of hypoglycemia (GCK-Hypoglycemia) in neonates and infants. GCK encodes for the enzyme glucokinase (GK) which functions as the "glucose sensor" in pancreatic  $\beta$ -cells, regulating glucose-stimulated insulin secretion (GSIS) and setting  $\beta$ -cell physiological threshold for GSIS. Pancreatic tissue from a patient with neonatal GCK-Hypoglycemia due activating GCK mutation V91L (GCK-V91L) revealed enlarged and well formed islets presenting heightened metabolic rate and  $\beta$ -cell both, proliferation and apoptosis. Strikingly, the residual number of islets after 98% pancreatectomy allowed this patient to enjoy a normal life for many years. We have observed that  $\beta$ -cell proliferation from adult human islets can be boosted without altering  $\beta$ -cell function by introducing the activating GCK mutation V91L by means of lentiviral technology, indicating, additionally, the reliability of this system to perform tissue engineering studies in intact adult human islets.

### Publication Highlights

- Soria B., Gauthier B.R., Martín F., Tejedo J.R., Bedoya F.J., Rojas A., Hmadcha A. 2015. Using stem cells to produce insulin. *Expert Opin Biol Ther.* 9:1-21
- Cano D.A., Soria B., Martín F., Rojas A. 2014. Transcriptional control of mammalian pancreas organogenesis. *Cell Mol Life Sci.* 71:2383-2402
- Berná G., Oliveras-López M.J., Jurado-Ruiz E., Tejedo J., Bedoya F., Soria B., Martín F. 2014. Nutrigenetics and nutrigenomics insights into diabetes etiopathogenesis. *Nutrients.* 6:5338-5369
- Oliveras-López M.J., Berná G., Jurado-Ruiz E., López-García H., Martín F. 2014. Consumption of extra-virgin olive oil rich in phenolic compounds has beneficial antioxidant effects in healthy human adults. *J Funct Foods.* 10:475-484
- Carrasco M., Diaz I., Soria B., Martín F., Rojas A. 2012. Gata4 and Gata6 control mouse pancreas organogenesis. *J Clin Invest.* 122:3504-3515

### Grants

2014-2015: AGL-2014-54585-R. Ministerio de Economía y Competitividad  
 2011-2014: IPT-2011-0952-900000. Ministerio de Ciencia e Innovación  
 2011-2014: IPT-20111008. Ministerio de Ciencia e Innovación  
 2011-2013: CTA-10/477. Corporación Tecnológica Andaluza  
 2011-2013: IPT-060000-2010-28. Ministerio de Ciencia e Innovación



## Pancreas and Liver Development and Disease

**Dra. Anabel Rojas**

*anabel.rojas@cabimer.es*

GROUP LEADER



### Group Members updated

#### Postdoctoral

Elisa del Pilar Rodriguez Seguel

#### PhD students

Laura Villamayor Coronado

### Academic Formation of PI

- 1996: Degree. University of Seville, B.Sc. in Biology
- 2001: PhD: University of Seville, Biology

### Present Position

- Since 2015: Research Scientist Ramón y Cajal, CABIMER, Seville, Spain

### Positions Held

- 2002-2007: Postdoctoral position, University of California San Francisco, UCSF
- 2008-2013: Miguel Servet Investigator, CABIMER, Seville, Spain
- 2014-2015: Miguel Servet II Investigator, CABIMER, Seville, Spain

### Research Activity

#### OVERVIEW

Defects in organogenesis or function of liver and pancreas lead to debilitating diseases, including diabetes and cirrhosis. Understanding the processes by which these organs form during development and how cells are regenerated upon injury in adult tissue is critical to further our insights into how disease affecting these organs and how they might be treated in a more efficient manner than currently possible. Indeed, there is an urgent need for generating liver hepatocytes and pancreatic endocrine islets to treat severe liver failure and diabetes by transplantation. To accomplish this goal, it is imperative to fully understand how these organs are formed within the embryo and how they function at adult stages.

#### RESEARCH HIGHLIGHTS

##### 1. Molecular mechanisms of embryonic pancreas formation and adult pancreatic function

The pancreas is an essential organ that serves two vital functions: it makes digestive enzymes that aid in digestion and produce hormones that control blood glucose levels. Dysfunction of this organ might be caused by failures in the genetic program controlling the organogenesis process. Interestingly, many of these pancreatic embryonic pathways are also active in adult pancreas during normal and pathological conditions (diabetes, pancreatitis or pancreas cancer). In our lab, we are interested to understand how transcriptional networks control both pancreas embryonic formation and adult pancreas function, with emphasis on beta cell insulin-producing cells. Recent human genetic studies have identified new the transcription factors GATA4 and GATA6 as new players in pancreas organogenesis. Thus, an association between GATA6 and GATA4 mutations and human congenital pancreas agenesis has recently been reported. Using conditional knockout mouse models, we have elucidated the mechanisms underlying pancreatic agenesis linked to GATA mutations in humans. We have found that GATA4 and GATA6 are

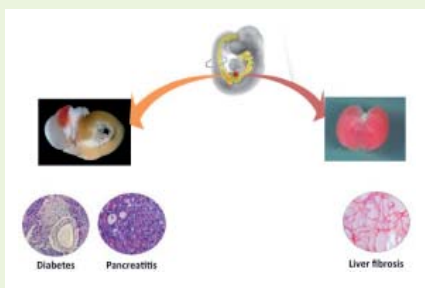


Figure 1: Liver and pancreas;  
from development to disease





Figure 2: *Gata4* and *Gata6* conditional knockout mice in pancreatic progenitors leads to pancreas agenesis in mice

required for the proliferation and differentiation of the pancreatic progenitor cells. Moreover, our data shows that GATA transcription factors are regulators of pancreatic progenitors genes and directly regulates *Pdx1* expression at fetal stages.

GATA factors are also expressed in adult insulin-producing beta cells suggesting that they might also play a role in adult beta cell function and/or glucose homeostasis. Indeed, mutations in *GATA6* or *GATA4* have been associated with adult onset of diabetes in humans. Currently, we are investigating whether deficiency in GATA factors might contribute to develop diabetes in humans.

## 2. Molecular basis for hepatic fibrosis induction and progression

Liver fibrosis is a pathophysiological response to chronic injuries and requires the transformation of quiescent Hepatic Stellate Cells (HSCs) into an active and proliferative myofibroblast phenotype. Our lab is interested in understanding the molecular mechanisms of HSCs activation and in the identification of key players involved of this process. Our group has recently uncovered a critical role for *GATA4* in HSCs function in both mice and human. Loss-of-function experiments in genetically modified mice have shown that *GATA4* is required to maintain the quiescent stage of HSCs. In human, the expression of *GATA4* in HSCs of liver biopsies progressively decreases as the disease progresses and it is dramatically reduced in patients with liver cirrhosis. The use of *GATA4* expression in HSCs as a potential biomarker of liver fibrosis stages is currently patented. The reversion of the HSCs phenotype, from active to quiescent state, is a required step for liver fibrosis regression. The identification of the molecular mechanisms controlling the reversion of HSCs in liver fibrosis is crucial to identify candidates target for liver disease therapies. We have shown that *GATA4* overexpression in human activated hepatic stellate cell line is able to downregulate the expression of fibrogenic genes. We are evaluating the potential of *GATA4* as an anti-fibrogenic agent in liver fibrosis disease.

### Publication Highlights

- Delgado I., Carrasco M., Cano E., Carmona R., García-Carbonero R., Marín-Gómez L., Soria B., Martín F., Cano D., Muñoz-Chápuli R., Rojas A. 2014. *GATA4* loss in the Septum transversum promotes liver fibrosis. *Hepatology*. 59:2358-2370
- Cano D.A., Soria B., Martín F., Rojas A. 2013. Transcriptional control of mammalian pancreas organogenesis. *Cell Mol Life Sci*. 71:2383
- Carrasco M., Delgado I., Soria B., Martín F., Rojas A. 2012. *GATA4* and *GATA6* control mouse pancreas organogenesis. *J Clin Invest*. 122:3504-3515
- Schachterle W., Rojas A., Xu S.M., Black B. 2012. ETS-dependent regulation of a distal *Gata4* cardiac enhancer. *Dev Biol*. 361:439-449

### Grants

2015-2017: PI14/00804. Instituto de Salud Carlos III

2012-2014: PI11/01125. Instituto de Salud Carlos III

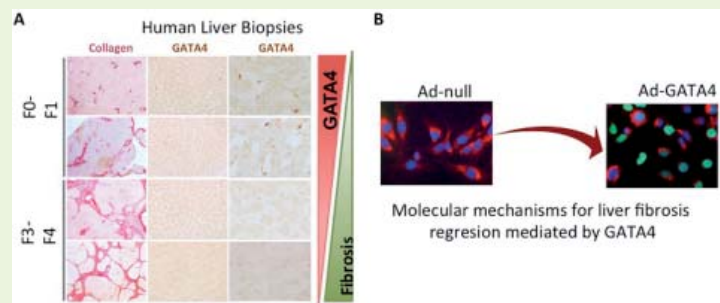


Figure 3: *Gata4* expression in HSCs decreases in advanced stage of liver fibrosis. B: Overexpression of *GATA4* in human LX2 cell line decreases the expression of fibrogenic markers, including laminin.



## Pancreatic Islet Development and Regeneration Unit

**Dr. Benoit R. Gauthier**

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GROUP LEADER



### Group Members updated

#### Senior Researchers

Petra Lorenzo  
Alejandro Martín-Montalvo

#### Postdoctorals

Esther de la Fuente Martín  
José Manuel Mellado Gil

#### PhD Student

Livia López Noriega

#### Technicians

Juan Luis Araujo Garrido  
Nadia Cobo  
Noelia García Rodríguez  
Irene de Gracia Herrera Gomez  
Víctor López Díaz  
Verónica Sanz Serrano

### Academic Formation of PI

- 1987: BSc in Biology. University of Ottawa, Canada
- 1990: MS in Biology. University of Ottawa, Canada
- 1996: PhD in Biochemistry. Queen's University, Canada

### Present Position

- Since 2009: Research Scientist, CABIMER, Seville, Spain

### Positions Held

- 1996-1998: Research Fellow. Ottawa Heart Institute, Canada
- 1999-2000: Postdoctoral Fellow. Geneva University Hospital, Switzerland
- 2001-2007: Research Associate. University of Geneva, Switzerland
- 2007-2009: Assistant Professor. University of Geneva, Switzerland

### Research Activity

#### OVERVIEW

The overall research goal of the Pancreatic Islet Development and Regeneration Unit (PIDRU) focuses on developing innovative therapies for inflammatory/immune related diseases such as Diabetes Mellitus (DM) as well as for promoting healthy aging.

#### RESEARCH HIGHLIGHTS

To this end, the group has developed a research and development (R&D) pipeline that progresses from basic projects to preclinical and clinical studies. Within the basic program our work focuses on: 1) characterizing anti-diabetic targets such as PAX8, PAX4 and HMG20A that foster survival, regeneration and functionality of pancreatic islet insulin-producing beta cells (Figure 1), 2) elucidating the cross talk between brain, immunity and islets in safeguarding glucose homeostasis and 3) exploring whether modulating levels of cytosolic/nuclear Acetyl-Coenzyme A (Ac-CoA) can prevent/revert metabolic diseases and delay aging. Further up the pipeline, our translational program includes: 1) pre-clinical assessment of anti-inflammatory/-diabetic drugs including medicinal chemistry for development of second generation agonist of LRH1 (Figure 2), 2) the medicinal use of mesenchymal stromal cells for Type 1 Diabetes Mellitus (T1DM) therapy, 3) development of a novel viral delivery system for inducing immune tolerance against INUSLIN in T1DM, and 4) genetic screening of HMG20A and PAX8 in patients with Type 2 as well as with gestational diabetes mellitus (T2DM and GDM) (Figure 3). This R&D pipeline is nurtured from a synergistic network comprised of: 1) outstanding basic scientists worldwide and 'in house', 2) National (La Paz) and Regional (Virgen del Rocio, Malaga Regional and Puerta del Mar) hospitals including Clinical units of the Andalusian Health System, 3) National networks such as Red TerCel and CIBERDEM, 4) Biotechnology companies and 4) the infrastructure provided by Fundación Progreso y Salud. Dr. Gauthier was awarded the 2015 Premio Salud Investiga, Investigación Vanguardia from the Andalusia Government for the cutting edge translational research of his group.

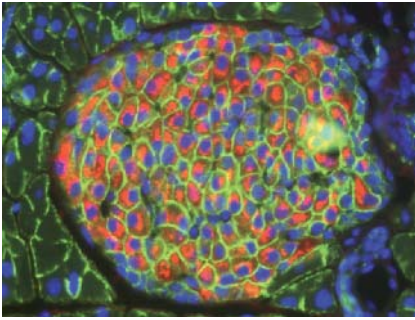


Figure 1: The islet of Langerhans, core unit of blood glucose homeostasis. The hormone insulin (red) and membrane bound E-cadherin (green) are depicted within the islet. Nuclei are stained with DAPI (blue).

### Publication Highlights

- Lorenzo P.I., Fuente-Martin E., Brun T., Cobo-Vuilleumier N., Jimenez-Moreno C.M., de Gracia Herrera Gomez I., Lopez Noriega N., Mellado-Gil J.M., Martin-Montalvo A., Soria B., Gauthier B.R. 2015. Pax4 defines an expandable beta cell subpopulation in the adult pancreatic islet. *Sci. Rep.* 5:15672
- Acosta L., Hmadcha A., Escacena N., Pérez-Camacho I., de la Cuesta A., Ruiz-Salmeron R., Gauthier B.R., Soria B. 2013. Adipose mesenchymal stromal cells isolated from type 2 diabetic patients display reduced fibrinolytic activity. *Diabetes.* 62:4266-4269
- Mellado-Gil J.M., Cobo-Vuilleumier N., Gauthier B.R. 2012. Islet  $\beta$ -cell Mass Preservation and Regeneration in Diabetes Mellitus: Four Factors with Potential Therapeutic Interest. *J Transpl.* ID 230870
- Baquié M., St-Onge L., Kerr-Conte J., Cobo-Vuilleumier N., Lorenzo P.I., Jimenez Moreno C.M., Cederroth C.R., Nef S., Borot S., Bosco D., Wang H., Marchetti P., Pattou F., Wollheim C.B., Gauthier B.R. 2011. The Liver receptor homolog-1 (LRH-1) is expressed in human islets and protects beta cells against stress-induced apoptosis. *Hum Mol Genet.* 20:2823-33
- Hu He K.H., Lorenzo P.I., Brun T., Jimenez Moreno C.M., Aeberhard D., Cornu M., Thorel F., Gjinovci A., Thorens B., Herrera P.L., Meda P., Wollheim C.B., Gauthier B.R. 2011. In vivo conditional Pax4 overexpression in mature islet beta cells prevents stress-induced hyperglycemia in mice. *Diabetes.* 60:1705-1715

### Grants

2015-2020: CP14/00105. Ministerio de Economía y Competitividad, Instituto de Salud Carlos III  
 2015-2017: Fundación Vencer el Cáncer  
 2014-2017: JCI-2012-12491. Ministerio de Ciencia e Innovación  
 2014-2017: PI13/00593. Ministerio de Economía y Competitividad, Instituto de Salud Carlos III  
 2013-2017: Asociación Lucha y Sonríe por la Vida de Pilas (ALUSVI)  
 2013-2016: 17-2013-372. Juvenile Diabetes Research Foundation, USA  
 2013-2016: PI-0085/2013. Consejería de Salud, Junta de Andalucía  
 2011-2014: PI-0727/2010. Consejería de Salud, Junta de Andalucía  
 2011-2014: CTS-6359. Consejería de Economía, Innovación, Ciencia y Empleo, Junta de Andalucía  
 2011-2014: PI10/00871. Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III

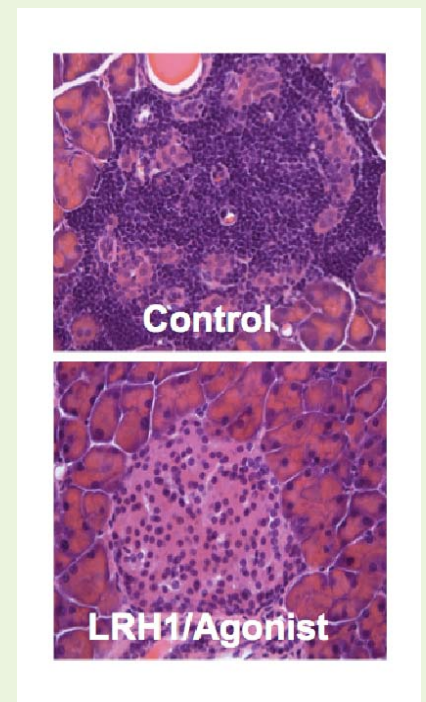


Figure 2: LRH1 agonistic activation reverts insulinitis (compare left to right panels, dense infiltration) and prevents autoimmune-mediated islet cell death.

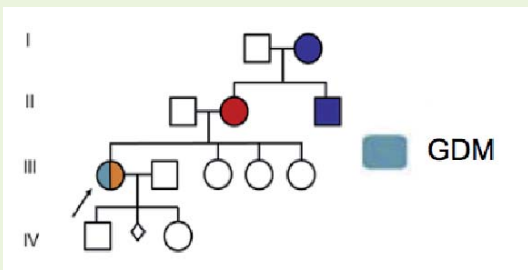
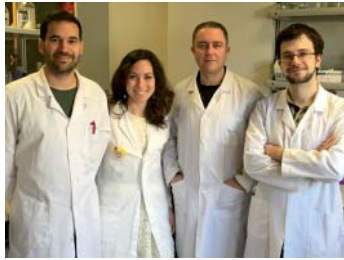


Figure 3: Schematic representation of a pedigree with one family member harbouring a novel gene polymorphism (arrow) linked to Gestational Diabetes Mellitus (GDM).



## Cell Differentiation Laboratory

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GROUP LEADER



### Group Members updated

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Francisco de Paula Juárez Vicente  
Noelia Luna Pelaez

#### Technician

Ignacio Barragán Muñoz

#### Master Students

Luis Miguel Buch Llorente

### Academic Formation of PI

- 1993: Degree. University of Seville, B.Sc. in Biology
- 1999: PhD. University of Seville, Biology

### Present Position

- Since 2009: Research Scientist CSIC/Cabimer, Seville, Spain

### Positions Held

- 2003-2008: Ramón y Cajal Investigator, IBVF and Cabimer, Seville, Spain
- 2001-2003: Marie Curie postdoctoral fellow, Ecole Normale Supérieure, Paris, France
- 1999-2001: FEBS postdoctoral fellow, Ecole Normale Supérieure, Paris, France
- 1994-1997: PhD student, FPU fellowship, IBVF, Seville, Spain

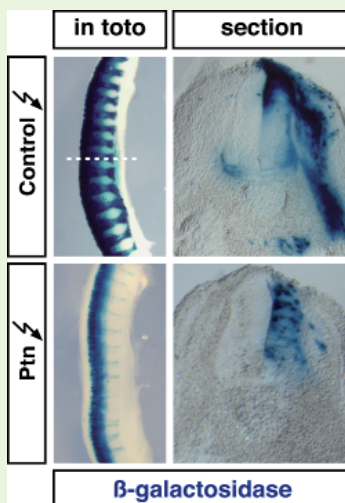
### Research Activity

#### OVERVIEW

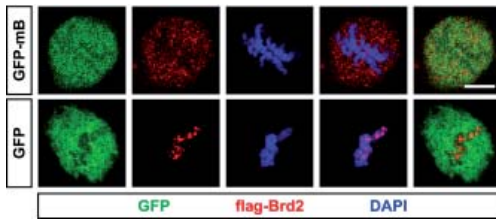
Main objective of our research consists in deciphering the mechanisms involved in neuronal differentiation, especially in the transition from proliferation to differentiation. In the central nervous system, neuronal progenitors exit the cell cycle to differentiate into neurons along development. In this context, we investigate two regulatory systems. One is concerning the cell cycle-associated chromatin adaptors from the BET family, and the other is related to the post-translational modification of proteins by covalent attachment of the Sumo polypeptide. BET proteins (Brd2, Brd3, Brd4 and Brdt in mammals) are bromodomain-containing proteins able to recognize acetylated histones in the chromatin. They are transcriptional activators classically associated to proliferation, although recent reports suggest also a role in differentiation. Sumo attachment to proteins is essential in eukaryotes and is involved in regulating many cellular processes, especially transcription.

#### RESEARCH HIGHLIGHTS

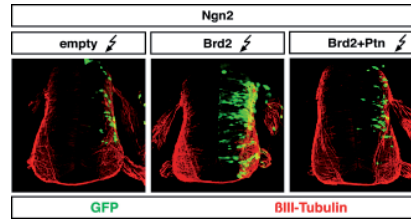
Sumo polypeptide is quite similar to the Ubiquitin and its attachment to proteins has a severe impact in properties of these. The conjugating enzyme Ubc9 is the responsible of the transfer to target proteins. However, the process is usually mediated by a Sumo ligase, which facilitates transfer. In contrast to Ubiquitin, which uses many ligases for target modification, very few Sumo ligases have been described to date. In this context, we demonstrated that the transcription factor Krox20 acts as a Sumo ligase for modification of its co-regulators, the Nab proteins. Krox20 is involved in hindbrain development and Nab1 and Nab2 act as co-repressors of Krox20 during hindbrain development. Thus, Krox20-mediated sumoylation of Nab proteins contributes to repression activity of these co-regulators. On the other hand, we have participated in demonstrating that sumoylation of Braf35, a subunit of the chromatin demethylation complex LSD1, is involved in maintaining the undifferentiated state of neuronal progenitors. Then, overexpression of a sumoylation mutant of Braf35 facilitates neurogenesis. Interestingly, iBraf, a protein highly



*Figure 3. A lacZ reporter construct was electroporated on the dorsal right side of the developing chick spinal cord to monitor migration of the neural crest by β-galactosidase staining (blue). Streams of migrating neural crest were visualized in whole mounts of embryo trunk (in toto) or in sections at the level indicated by a dashed line. It is observed that overexpression of Pleiotrophin (Ptn) severely impairs neural crest migration 30 hours after electroporation.*



**Figure 1.** Expression of the Brd2 motif B (mB) fused to the green fluorescent protein (GFP, green) dissociates Flag-Brd2 (red) from mitotic chromosomes (blue) in P19 cells, while GFP alone has no effect on Brd2 association with chromosomes. Bar 10  $\mu$ m



**Figure 2.** Thirty hours after electroporation of the right side of the spinal cord of the chick embryo with the neurogenic factor Neurogenin 2 (Ngn2), virtually all electroporated cells (green) localize to the margins of the neural tube and express the neuronal marker BIII-Tubulin (red), indicative of neuronal differentiation. Overexpression of the cell cycle stimulator Brd2 impairs Ngn2-induced differentiation, as most cells stay close to the lumen of the neural tube and do not express BIII-Tubulin. However, Pleiotrophin (Ptn) antagonizes Brd2 and restores Ngn2 effects.

homologous to Braf35 and associated to neuronal differentiation, is able, by interacting with Braf35, to antagonize Braf35 sumoylation and its association with the LSD1 complex. Former results indicate that sumoylation is involved in development of the nervous system. However, very little is known about the involvement of Sumo in the initial steps of neurogenesis, so we are interested in identifying proteins whose modification is involved in early steps of neuronal differentiation.

Overexpression of BET proteins is associated to many types of cancers, and antagonizing its binding to the chromatin by drugs mimicking acetylated histones have been successfully used to alleviate a variety of cancers in animal models. Therefore, there is a great interest in unravel the mechanisms accounting for BET protein association to the chromatin. In this regard we have identified a small domain in BET proteins, motif B, mediating dimerization of BET proteins. This domain is essential for chromatin binding and function of BET proteins. Motif B includes a coiled coil domain flanked by acidic and basic regions enabling homo and heterodimerization of BET proteins. Indeed we are able to impair binding of Brd2 to the chromatin by overexpressing a small polypeptide encompassing motif B (Figure 1), which might be of interest for therapies against the cancer. To get insights into the role of BET proteins in the transition from proliferation to differentiation we performed a two-hybrid screening to identify proteins interacting with Brd2. We chose Brd2 because several reports suggest its involvement in differentiation processes. Among the identified proteins interacting with Brd2 we found Pleiotrophin, a secreted growth factor involved in nervous system development and nerve regeneration. Surprisingly, we observed that Pleiotrophin selectively interacts with Brd2 among the different BET members, because of the presence of an exclusive acidic domain in Brd2. Pleiotrophin is expressed following induction of neuronal differentiation and by protein-protein interaction destabilizes attachment of Brd2 to the chromatin, antagonizing its cell cycle-stimulating activity. As a result, the cell is unbalanced towards neuronal differentiation (Figure 2). Epithelial-mesenchymal transition (EMT) is tightly linked to invasiveness of most types of cancers. However, during development, naturally occurring EMT processes are essential. For instance, the neural crest originates from cells in the dorsal part of the neural tube, which delaminate and migrate into the mesoderm, giving rise to different structures. Interestingly, overexpressed Pleiotrophin severely impairs neural crest migration (Figure 3), what might be potentially useful in arresting cancer-associated EMT, especially in those cancers linked to Brd2. Therefore, we currently continue investigating the interaction of Brd2 with different partners, trying to dissect their functions in proliferation and neuronal differentiation.

### Publication Highlights

- García-Gutiérrez P., Juárez-Vicente F., Wolgemuth D.J., García-Domínguez M. 2014. Pleiotrophin antagonizes Bromodomain-containing protein 2 (Brd2) during neuronal differentiation. *J Cell Sci.* 127:2554-2564
- Alfonso-Pérez T., Domínguez-Sánchez M.S., García-Domínguez M., Reyes J.C. 2013. Cytoplasmic interaction of the tumor suppressor protein hSNF5 with dynamin-2 controls endocytosis. *Oncogene.* 33:3064-3074
- Ceballos-Chávez M., Rivero S., García-Gutiérrez P., Rodríguez-Paredes M., García-Domínguez M., Bhattacharya S.S., Reyes J.C. 2012. Control of neuronal differentiation by Braf35 sumoylation. *Proc Natl Acad Sci USA.* 109:8085-8090
- García-Gutiérrez P., Mundi M., García-Domínguez M. 2012. Association of bromodomain BET proteins to the chromatin requires dimerization through the conserved motif B. *J Cell Sci.* 125:3671–3680
- García-Gutiérrez P., Juárez-Vicente F., Gallardo-Chamizo F., Charnay P., García-Domínguez M. 2011. The transcription factor Krox20 is an E3 ligase that sumoylates its Nab coregulators. *EMBO Rep.* 12:1018-1023

### Grants

2014-2017: P12-CTS-2064. Proyectos de Excelencia. Consejería de Economía, Innovación, Ciencia y Empleo, Junta de Andalucía  
 2013-2015: BFU2012-37304/BFI. Ministerio de Economía y Competitividad  
 2010-2012: BFU2009-10986/BMC. Ministerio de Economía y Competitividad



## DNA Damage Response

### Dr. Felipe Cortés-Ledesma

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GROUP LEADER



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María Isabel Ortiz Marchena

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Irene Delgado Sainz  
Carlos Gómez Marín  
Andrés Herrero Ruiz  
Jenna Lieberman  
Marta Moreno Oñate  
Almudena Serrano Benitez

### Academic Formation of PI

- 2000: Degree. University of Seville, B.Sc. in Biology
- 2006: PhD. University of Seville, PhD in Molecular and Cellular Biology

### Present Position

- Since 2014: Research Scientist, CSIC /CABIMER

### Positions Held

- 2006-2007: Postdoctoral Researcher. University of Seville - CABIMER
- 2007-2008: EMBO long-term Fellow. Genome Damage and Stability Centre, University of Sussex (UK)
- 2008-2010: Marie Curie Fellow. Genome Damage and Stability Centre, University of Sussex (UK)
- 2010-2014: Ramón y Cajal Fellow. University of Seville - CABIMER

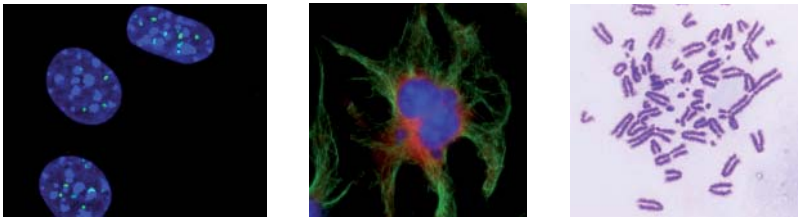
### Research Activity

#### OVERVIEW

The DNA damage response (DDR) ensures efficient and accurate repair of DNA breaks, coordinating it with important cellular functions such as cell cycle progression, chromatin dynamics and gene expression. Deficiencies in the DDR can compromise cell survival, genome integrity and tissue homeostasis, with the consequent implications for human health. This is exemplified by a range of human genetic syndromes with characteristic developmental, degenerative and/or cancer predisposition problems. We apply a comprehensive approach, covering from the detailed molecular analysis of the process to the pathological implications in patients and animal models, in order to understand how DNA breaks are signalled and repaired, and how, if inefficient or aberrant, these processes can impact on human health.

#### RESEARCH HIGHLIGHTS

Our research these years has specifically focused on DNA double-strand breaks (DSBs) arising by the aberrant action of DNA topoisomerase II (TOP2), which, not only constitute an important source of spontaneous DNA damage, but also underlies the clinical efficacy of widely used anticancer agents known as topoisomerase “poisons” (epipodophyllotoxins, anthracyclines, ...). These breaks are characteristic in that the topoisomerase remains covalently bound to DNA termini blocking them for subsequent repair. Tyrosyl DNA phosphodiesterase 2 (TDP2) has the unique capacity to specifically cleave the bond between protein and DNA, eliminating these protein adducts, and facilitating thus the repair of TOP2-induced DSBs. We have characterized the role of this novel DNA repair enzyme in detail, demonstrating its function within an error-free DSB repair mechanism that safeguards cell survival and genome integrity upon the induction



of TOP2-mediated DSBs. Furthermore, we have addressed the physiological relevance of this pathway, first in mice, and then, as part of a multilaboratory collaboration, in human.

Going one step further, and based on the specificity and uniqueness of TDP2 activity, we have developed novel genetic and molecular tools that have allowed us, for the first time, to specifically induce DSBs harbouring either clean or blocked ends in mammalian cells. This overcomes the limitation imposed by the heterogeneity of the lesions generated by traditionally used DNA damaging agents. Using this methodology we demonstrated that ATM, the gene mutated in the human syndrome Ataxia Telangiectasia (AT), is specifically involved in the repair of blocked lesions, but not when they are clean. This solves a long-standing question in the field, as the pivotal role of ATM in DSB signalling is undisputed and well-documented, but, paradoxically, its function in the repair process itself remained controversial. Furthermore, our results put forward blocked DSBs as a possible pathogenic trigger in AT, and maybe other related disorders.

### Publication Highlights

- Caron P., Choudhary J., Clouaire T., Bugler B., Daburon V., Aguirrebengoa M., Mangeat T., Iacovoni J.S., Álvarez-Quilón A., Cortés-Ledesma F., Legube G. 2015. Non-redundant functions of ATM and DNA-PKcs in response to DNA double-strand-breaks. *Cell Rep.* 13:1598-1609
- Gomez-Herreros F., Schuurs-Hoeijmakers J.H.M., McCormack M., Grealley M.T., Rulten S., Romero-Granados R., Counihan T.J., Chaila E., Conroy J., Ennis S., Heinzen E., Goldstein D.B., Delanty N., Cortés-Ledesma F., de Brouwer A.P.M., Cavalleri G.L., El Khamisy S.F., de Vries B.B.A., Caldecott K.W. 2014. TDP2 protects transcription from abortive Topoisomerase 2 activity and maintains normal neural function. *Nat Genet.* 46:516-521
- Álvarez-Quilón A., Serrano-Benítez A., Lieberman J.A., Quintero C., Sánchez-Gutiérrez D., Escudero L.M., Cortés-Ledesma F. 2014. ATM specifically mediates repair of double-strand breaks with blocked DNA ends. *Nat Commun.* 5:3347
- Gómez-Herreros F., Romero-Granados R., Zeng Z., Álvarez-Quilón A., Quintero C., Ju L., Umans L., Vermeire L., Huylebroeck D., Caldecott K.W., Cortés-Ledesma F. 2013. TDP2-dependent non-homologous end-joining protects against topoisomerase II-induced DNA breaks and genome instability in cells and in vivo. *PLoS Genet.* 9:e1003226
- Zeng Z., Cortés-Ledesma F., El Khamisy S. F., Caldecott K. W. 2011. TDP2/TTRAP is the major 5'-tyrosyl DNA phosphodiesterase activity in vertebrate cells and is critical for cellular resistance to topoisomerase II-induced DNA damage. *J Biol Chem.* 286:403-409

### Grants

2015-2020: ERC-CoG-2014-647359.  
 2015-2017: SAF2014-55532-R.  
 2015-2017: Fundación Ramón Areces  
 2014-2015: BFU2013-50400-EXP. Ministerio de Economía y Competitividad  
 2014: SAF2013-47343-P. Proyectos de I+D Excelencia, Ministerio de Economía y Competitividad  
 2013-2016: CVI-7948. Proyecto de Investigación de Excelencia, Consejería de Innovación, Ciencia y Empresa, Junta de Andalucía  
 2011-2013: SAF2010-21017. Ministerio de Ciencia e Innovación  
 2011-2012: BFU2010-11042-E. Ministerio de Ciencia e Innovación

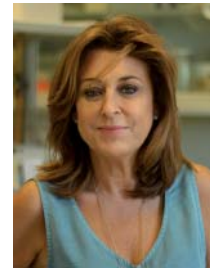


## Membrane Traffic and Cytoskeleton in Cell Dynamics

**Dr. Rosa M. Rios**

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HEAD OF THE CELL SIGNALLING DEPARTMENT



### Group Members updated

#### Postdoctorals

Elena Gavilán  
Fernando Romero Balestra

#### PhD Students

Francisco Arias Aragón  
Marina Arjona Niño  
Pablo Gandolfo Dominguez

#### Technicians

Javier Carmona Cortés  
Loida Pérez García

### Academic Formation of PI

- 1984: Degree. University of Seville, B.Sc. in Biology
- 1988: PhD. University of Seville

### Present Position

- 2006 - Present: Scientific Researcher, Spanish Research Council CSIC/CABIMER

### Positions Held

- 1989-1990: Postdoctoral fellow MEC-EU CGM, CNRS, Gif-sur-Yvette, France
- 1991-1993: Postdoctoral Fellow MEC University of Seville
- 1994: Postdoctoral Fellow U. Seville University of Seville
- 1995: CNRS Investigator Institut Curie, CNRS, France
- 1994-2002: Associated Professor. University of Seville
- 2002-2006: Ramón y Cajal Investigator. University of Seville
- 2006-2011: Research Scientist Spanish Research Council, CSIC
- 2010-2011: Sabbatical leave CRI-CRUK Cambridge, UK

### Research Activity

#### OVERVIEW

A shared feature among all microtubule (MT)-dependent processes is the requirement for MTs to be organised in arrays of defined geometry. This is achieved by precisely controlling the timing and localisation of the nucleation events that give rise to new MTs. MT nucleation relies on gamma-tubulin complexes that are recruited and then activated at specific intracellular locations known as MT-organising centres (MTOCs). In most animal cells, the organization of the MT network results from MT-nucleation activities of two MTOCs, the centrosome (CTR) and the Golgi Apparatus (GA). To preserve proper cell functioning, a balance must be maintained between these two MT subsets. The main focus of my lab is to understand how Golgi- and centrosome-based MT nucleation works in concert to ensure the formation of specialised MT arrays along the cell cycle and during cell differentiation and morphogenesis. We are currently investigating the composition, the activity and the regulation of the MT-nucleating protein complexes that are present at both organelles.

#### RESEARCH HIGHLIGHTS

- Two key aspects of the GA in non-polarized mammalian cells are its organization as a single organelle and its localization to the pericentriolar region. The physiological relevance of these features remained obscure. Our studies have demonstrated that the pericentrosomal organization of the GA is required for establishment of antero-posterior cell polarity, proper cell migration and ciliogenesis (Hurtado et al., JCB 2011). Several years ago, we showed that the GA contains the molecular machinery required for MT nucleation (Rivero et al., EMBO J 2009). Such machinery includes the gamma-tubulin binding protein AKAP450 and the cis-Golgi protein GM130. We further investigated the contribution of the AKAP450/ GM130 complex to the organization of the Golgi/centrosome region in mammalian cells. We identified both a Golgi-binding GM130-interacting domain and a MT-binding p150-glued interacting site at the N-terminus of AKAP450. Expression of AKAP450 fragments containing either the GA-binding motif alone (short fragment)

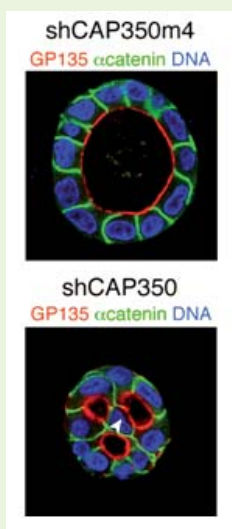
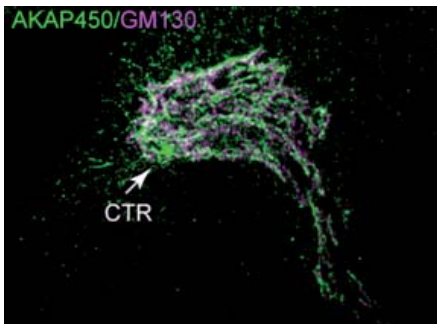
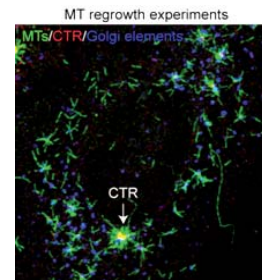


Figure 1: Defective cystogenesis in MDCKII cells lacking Junctional CAP350





Super-resolution microscopy image showing co-localization of AKAP450 and GM130 at the GA.



In most primary mammalian cell lines MT nucleation takes place at both the CTR and the GA

or both GA- and MT-binding motifs (long fragment) had striking different effects on Golgi positioning and integrity. The short fragment induced GA circularization around the centrosome and fragmentation whereas the large construct provoked the separation of an intact Golgi ribbon from the centrosome. By using these mutants and live imaging, we analysed the contribution of GA positioning or integrity to secretion, cell polarization, migration and primary cilium formation. We found that position of the GA is more important than integrity for cell polarity and directional migration whereas both characteristics are essential for primary cilium formation.

- Another particularly relevant issue is how MT nucleation at either the GA or the centrosome contributes to MT remodelling during the establishment of apico-basal cell polarity in epithelial cells. We have demonstrated that the MT-binding Golgi/centrosomal protein CAP350 organizes the apico-basal MT array characteristic of polarized epithelial cells allowing them to acquire a columnar morphology (Gavilan et al PLoS Biol. 2015). CAP350 was previously reported to participate in the stabilization of MTs at both the GA and the CTR. We found that CAP350 also localized at adherens junctions of polarized epithelial cells. CAP350 recruitment to cell-cell contacts was dependent on both E-cadherin-based adhesion and  $\alpha$ catenin. In vitro MT-sedimentation assays revealed binding of  $\alpha$ catenin to MTs mediated by CAP350 suggesting a role of CAP350/ $\alpha$ catenin complexes at the Adherens Junctions-MTs interface. We also identified two in tandem MT-binding sites at the N-terminus of CAP350 that conferred it the ability to bundle MTs. Knocking-down CAP350 inhibited the establishment of an apico-basal array of MTs and the acquisition of columnar shape in MDCKII cells grown as polarised epithelia. MDCKII cystogenesis was also defective in junctional CAP350-depleted cells. Membrane polarity was not affected but cortical microtubule bundles did not properly develop. Furthermore, CAP350 was shown to be required for Medaka embryo epiboly, a morphogenetic movement dependent of cell-cell contacts and MTs. Altogether, our data supported that CAP350 acts as an adaptor between adherens junctions and MTs, and uncovered a central role for  $\alpha$ catenin in global cytoskeleton remodelling by controlling not only actin, but also MT reorganisation during epithelial morphogenesis.

- The major differences between centrosome-nucleated and Golgi-nucleated MTs stem from their geometry and nature. It has been known for long time that MTs emanating from the GA are highly enriched in post-translationally modified tubulins, in particular detyrosinated and acetylated alpha-tubulin. Centrioles and primary cilia are also highly acetylated structures. We have studied the role of the tubulin acetyl-transferase alpha-TAT1 in Golgi and centrosome dynamics. We found that MT acetylation by the acetyl-transferase of alpha-tubulin alpha-TAT1 does not affect Golgi dynamics but, unexpectedly, regulates the size of the pericentrosomal material and, consequently, the MT-nucleation activity of the centrosome.
- Golgi fragmentation and protein aggregates around the centrosome are both frequently observed in nigral neurons of Parkinson's disease patients. By using an in vitro model of PD, we found that vesicular trafficking of dopamine from the GA toward the plasma membrane was impaired what may account for some of the symptoms of the disease (Diaz-Corrales et al. Neurobiol. Aging, 2012).

### Publication Highlights

- Gavilan M.P., Arjona M., Zurbano A., Formstecher E., Martinez-Morales J.R., Bornens M., Rios R.M. 2015. Alpha-catenin dependent recruitment of the centrosomal protein CAP350 to adherens junctions allows epithelial cells to acquire a columnar shape. PLoS Biol. 13(3):e1002087. Comment in PLoS Biol. 13: e1002088.
- Bogdanović O., Delfino-Machín M., Nicolás-Pérez M., Gavilán M.P., Gago-Rodrigues I., Fernández-Miñán A., Lillo C., Rios R.M., Wittbrodt J., Martínez-Morales J.R. 2012. Numb/Numbl-Opo antagonism controls retinal epithelium morphogenesis by regulating integrin endocytosis. Dev Cell. 23:782-795
- Diaz-Corrales F.J., Miyazaki I., Asanuma M., Ruano D., Rios R.M. 2012. Centrosomal aggregates and Golgi fragmentation disrupt vesicular trafficking of DAT. Neurobiol Aging. 33:2462-2477
- Hurtado L., Caballero C., Gavilan M.P., Cardenas J., Bornens M., Rios R.M. 2011. Disconnecting the Golgi ribbon from the centrosome prevents directional migration and ciliogenesis. J Cell Biol. 193:917-933.

### Grants

2014-2016: CTS 2071. Proyecto de Excelencia, Junta de Andalucía  
 2013-2015: BMC2012-36717. Ministerio de Ciencia e Innovación  
 2009-2015: CSD2009-00016. Consolider Ingenio 2010. Ministerio de Ciencia e Innovación  
 2009-2012: BMC2009-07182. Ministerio de Ciencia e Innovación  
 2008-2012: P07-CVI-03199. Proyecto de Excelencia, Junta de Andalucía



## Cell Death Signalling



### Dr. Abelardo López Rivás

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GROUP LEADER

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Marta Mauro Lizcano  
Santiago Serrano Sáenz

**Master Student**  
Rocío Mora Molina

#### Academic Formation of PI

- 1976: Degree. University of Seville, B.Sc. in Biology
- 1980: PhD. University of Madrid, Doctor in Sciences

#### Present Position

- Since 2006, Full Professor CSIC, Andalusian Center for Molecular Biology and Regenerative Medicine-CABIMER, Seville, Spain

#### Positions Held

- 1980-1984: Postdoctoral Fellow, Imperial Cancer Research Fund, London, England
- 1984-1987: Postdoctoral Fellow, Molecular Biology Center Severo Ochoa, CSIC UAM, Madrid, Spain
- 1987-1990: Tenure Scientist CSIC, Institute of Biomedical Research Alberto Sols, Madrid, Spain
- 1990-1992: Research Scientist CSIC, Institute of Biomedical Research Alberto Sols, Madrid, Spain
- 1992-2003: Research Scientist CSIC, Institute of Parasitology and Biomedicine CSIC, Granada, Spain
- 2003-2004: Full Professor CSIC, Institute of Parasitology and Biomedicine CSIC, Granada, Spain
- 2004-2006: Full Professor CSIC, Andalusian Center for Developmental Biology, Seville, Spain

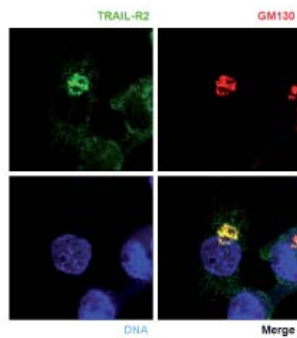
#### Research Activity

##### OVERVIEW

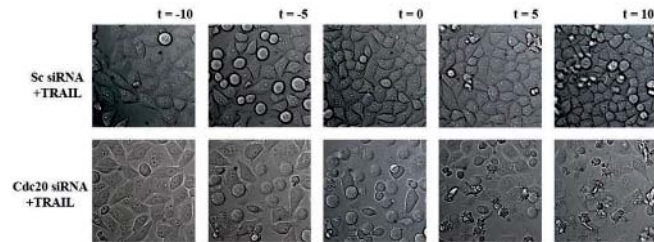
There has been exceptional progress in understanding the signalling involved in the killing of tumor cells by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). In addition, the observation that TRAIL specifically induces cell death in tumor cells without affecting untransformed cells has inspired clinical trials with therapeutic agents designed to activate the apoptosis-inducing TRAIL receptors. However, important questions still remain unresolved regarding the mechanisms underlying the resistance of normal cells to TRAIL. Furthermore, despite early promising results, different tumor cells, like those of the breast, pancreas, melanoma and neuroblastoma are frequently refractory to TRAIL-induced apoptosis. However, a general consensus for resistance to TRAIL has not yet been identified. Lastly, a major goal of our research is to decipher the role of the TRAIL system in the execution of the apoptotic programme in response to environmental and intrinsic stress signals that induces endoplasmic reticulum stress.

##### RESEARCH HIGHLIGHTS

Regarding resistance of normal cells to TRAIL, our data indicate that cFLIP levels are important determinants of the resistance of non-transformed breast epithelial cells to TRAIL-induced apoptosis since a reduction in the cellular levels of cFLIP by RNA interference markedly sensitizes these cells to apoptosis. Interestingly, our data also demonstrate that cFLIPL knockdown in non-transformed breast epithelial cells is sufficient to induce apoptosis in a ligand-independent TRAIL-R2/DR5-dependent manner. This cell death mechanism requires the DISC components FADD and procaspase-8 and is partially inhibited by interfering with the mitochondria-operated apoptotic pathway. Increased activation of the epidermal growth factor receptor (EGFR) is frequently observed in tumors, and inhibition of the signalling pathways originated in the EGFR renders tumor cells more sensitive to apoptotic stimuli. Despite all the available evidences in tumor cells, the regulation of TRAIL sensitivity by EGFR signalling in non-tumor cells remains to be investigated.



**Figure 1:** Co-localization of TRAIL-R2 with Golgi marker GM130 in mutant ErbB2 overexpressing human breast epithelial cells undergoing ER stress.



**Figure 2:** Silencing *Cdc20* expression induces mitotic arrest and sensitization to TRAIL-induced apoptosis independently of mitotic checkpoint activation

We have demonstrated that EGFR activation down-regulates cFLIP expression and enhances the sensitivity of non-transformed human breast epithelial cells to TRAIL-induced apoptosis. Our results also indicate that cFLIP levels and TRAIL sensitivity are both controlled by the EGFR-mediated regulation of the ERK1/2 pathway and c-myc expression. In addition, we have shown that deregulated ERK1/2 activation in human breast epithelial cells transformed with the oncogen Her2/ERBB2 prevents EGF deprivation-induced FLIPL up-regulation and TRAIL resistance, which may explain the increased sensitivity to TRAIL of tumor cells in which the ERK1/2 pathway is frequently deregulated. Tumor microenvironment is characterized by glucose deprivation, acidosis, and severe hypoxia. These combined factors lead to the accumulation of misfolded proteins in the endoplasmic reticulum (ER), triggering the unfolded protein response (UPR) to facilitate tumor survival and growth. Truncated or mutant isoforms of the HER2/ERBB2 receptor tyrosine kinase are found in a number of breast tumors and show increased oncogenicity compared to the wild-type receptor. We have reported that mutant ERBB2 sensitizes human breast epithelial cells to ER stress, altering the unfolded protein response (UPR) of these cells. Deregulation of the ERK, AKT and mTOR activities elicited by mutant ERBB2 were involved in mediating this differential UPR response. Mechanistic investigations in our laboratory revealed that the increased sensitivity of mutant ERBB2-expressing cells to ER stress relied upon an UPR effector signaling involving the PERK-ATF4-CHOP pathway, upregulation of the proapoptotic cell surface receptor TRAIL-R2 and activation of proapoptotic caspase-8 (Figure 1). Collectively, our results offer a rationale for the therapeutic exploration of treatments inducing ER stress against mutant ERBB2-expressing breast tumor cells. Many of the current anti-tumor therapeutic strategies are based on the perturbation of the cell cycle, especially during mitosis. Anti-mitotic drugs trigger mitotic checkpoint activation, mitotic arrest and eventually cell death. However, mitotic slippage is a major mechanism of resistance to these treatments. Our recent results indicate that treatments that induce mitotic checkpoint activation and mitotic arrest down-regulate FLIP levels and sensitize several tumor cell lines to TRAIL-induced apoptosis. Interestingly, our data also demonstrate that in absence of mitotic checkpoint activation (Figure 2), mitotic arrest induced either by *Cdc20* knockdown or over-expression of non-degradable cyclin B is sufficient to induce both FLIP down-regulation and sensitivity to TRAIL. In summary, our data suggest that a combination of anti-mitotic drugs targeting cyclin B degradation and TRAIL might prevent mitotic slippage and allow tumor cells to reach the threshold for apoptosis induction, facilitating tumor suppression.

### Publication Highlights

- Sánchez-Pérez T., Medema R.H., López-Rivas A. 2015. Delaying mitotic exit down-regulates FLIP expression and strongly sensitizes tumor cells to TRAIL. *Oncogene*. 34:661-669
- González-Arzola K., Díaz-Moreno I., Cano-González A., Díaz-Quintana A., Velázquez-Campoy A., Moreno-Beltrán B., López-Rivas A., de la Rosa M.Á. 2015. Structural Basis for Inhibition of the Histone Chaperone Activity of SET/TAF- $\square$  by Cytochrome c. *Proc Natl Acad Sci USA*. 112: 9908-9913
- Martín-Pérez R., Palacios\* C., Yerbes\* R., Cano-González A., Iglesias-Serret D., Gil J., Reginato M.J., López-Rivas A. 2014. (\*equal contribution). Activated ERBB2/HER2 licenses sensitivity to apoptosis upon endoplasmic reticulum stress through a PERK-dependent pathway. *Cancer Res*. 74:1766-1777
- Yerbes R., Palacios C., Reginato M.J., López-Rivas A. 2013. Cellular FLIPL plays a survival role and regulates morphogenesis in breast epithelial cells. *BBA Mol Cell Res*. 1813:168–178
- Yerbes R., López-Rivas\* A., Reginato M.J., Palacios\* C. 2012 (\*corresponding author). Control of FLIPL expression and TRAIL resistance by the extracellular signal-regulated kinase (ERK)1/2 pathway in breast epithelial cells. *Cell Death Differ*. 19:1908-1916

### Grants

2014-2018: BIO 778. Proyecto de Excelencia, Junta de Andalucía  
 2013-2017: RD12/0036/0026. Instituto de Salud Carlos III  
 2013-2015: SAF2012-32824. Ministerio de Economía y Competitividad  
 2010-2013: SAF2009-07163: Ministerio de Ciencia e Innovación  
 2007-2012: RD-06/0020/0068. Instituto de Salud Carlos III

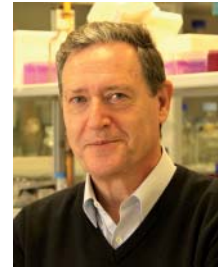


## Cell Cycle and Oncogenesis

**Dr. José A. Pintor Toro**

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GROUP LEADER



### Group Members updated

#### PhD Students

Salvador Polo Generelo  
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#### Technicians

Maria Prieto Corral  
Belén Torres Agrela

### Academic Formation of PI

- 1976: Degree. University of Seville, B.Sc. in Biology
- 1980: PhD. University of Madrid, PhD in Sciences

### Present Position

- Since 1986: Professor CSIC, Andalusian Center for Molecular Biology and Regenerative Medicine-CABIMER, Seville, Spain

### Positions Held

- 1984-1986: Assistant Professor of Biochemistry. Polytechnic University. Madrid, Spain
- 1986-2006: Research Scientist. IRNASE. CSIC. Seville, Spain
- Since 2006: Full Professor. CABIMER/CSIC. Seville, Spain

### Research Activity

#### OVERVIEW

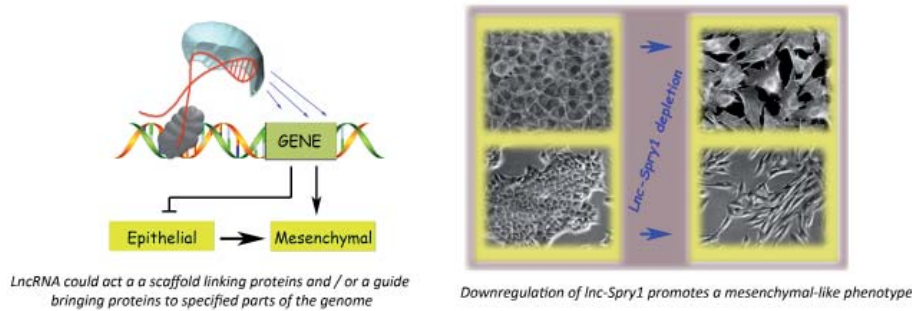
The epithelial-mesenchymal transition (EMT) is a biological process that allows a polarized epithelial cell, which normally interacts with the basement membrane via its basal surface, to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype. A number of distinct molecular processes are engaged in order to initiate an EMT and enable it to reach completion. These include activation of transcription factors, expression of specific cell-surface proteins, reorganization and expression of proteins, production of ECM-degrading enzymes, and changes in the expression of specific microRNAs.

Our work focuses primarily on the analysis of long non-coding RNAs (lncRNAs) that act early (within the first three hours) in the process of epithelial-mesenchymal transition, since they could be master genes that trigger or participate in the start of the process. Our study includes both the analysis of lncRNAs transcriptionally and post-transcriptionally regulated; the second ones through their interaction with the protein AGO2, the catalytic component of the RISC silencing complex. We propose respectively to study the cellular phenotypes acquired by overexpression or depletion of these lncRNAs, dissect the biochemical mechanisms involved in their functions, and investigate, in murine models, the effects of the misregulation of lncRNAs in the tumour growth, development of metastasis and liver fibrosis.

#### RESEARCH HIGHLIGHTS

We demonstrated that PTTG1 protein is associated with the cis face of the Golgi apparatus and that this localization depends on PTTG1 phosphorylation status. PTTG1 forms a complex with proteins involved in microtubule nucleation. In fact, depletion of PTTG1 produces a delay in centrosomal and non-centrosomal microtubule nucleation and severe defects in both cell polarization and migration.

PTTG2, a homologous gene of PTTG1, is expressed at very low levels in various cell lines and



tissues analysed. PTTG2, unlike PTTG1, lacks transactivation activity and does not bind to separase. However, cells with reduced PPTG2 levels assumed a rounded morphology compatible with a defect in cell adhesion and died by apoptosis in a p53- and p21-dependent manner. Knockdown of PTTG2 results in concomitant downregulation of E-cadherin and elevated vimentin levels, consistent with EMT induction.

We have developed a novel methodology to express mature miRNAs and other small RNAs from a double convergent RNA polymerase III promoter. The generated miRNAs function similarly to those processed from primary transcripts or pri-miRNAs. This system allows to produce lentiviral libraries expressing the whole population of small RNAs present in a tissue. This novel methodology provides a powerful and effective way for identifying novel small RNAs involved in a particular biological process.

A functional screening using these novel libraries led to identification of has-miR-30b and has-miR-30c as negative regulators of cell death induced by loss of attachment (anoikis). Acquisition of anoikis resistance via these miRNAs is achieved through down-regulation of caspase 3 expression. Moreover, overexpression of these miRNAs resulted in a decrease of other types of caspase 3-dependent cell death and enhanced the survival of acinar cells, suggesting a putative role as oncomirs.

We have generated a new platform for exploring those small RNAs that act as tumour suppressors. This new approach for generating lentiviral libraries is based on microRNA depletion by sequestration using small RNAs sponges. For this purpose, we used standard procedures for the cloning of small RNAs followed by an amplification step using phi29 DNA polymerase to obtain several targets for a particular small RNA for each sponge.

We identified a long non-coding RNA, lnc-Spry1, as an immediate early regulator of EMT that is downregulated by TGF- $\beta$ . Knockdown of lnc-Spry1 promotes a mesenchymal-like phenotype and results in increased cell migration and invasion. lnc-Spry1 depletion preferentially affects the expression of TGF- $\beta$ -regulated gene targets. Also, lnc-Spry1 associates with U2AF65 and PUF60 splicing factors, suggesting a role in alternative splicing. Depletion of lnc-Spry1 induced, as TGF- $\beta$ , isoform switching of fibroblast growth factor receptors, resulting in FGF-2-sensitive cells. Taken together, these results show that lnc-Spry1 is an early mediator of TGF- $\beta$  signalling and reveal different roles for a lncRNA in modulating transcriptional and post-transcriptional gene expression.

### Publication Highlights

- Méndez-Vidal C., Gámez-Del Estal M.M., Moreno-Mateos M.A., Espina-Zambrano A.G., Torres-Agrela B., Pintor-Toro J.A. 2013. PTTG2 silencing results in induction of epithelial-to-mesenchymal transition and apoptosis. *Cell Death Dis.* 4:e530
- Moreno-Mateos M.A., Barragán V., Torres B., Méndez-Vidal C., Mudduluru G., Allgayer H., Pintor-Toro J. A. 2013. Novel small RNA expression libraries uncover hsa-miR-30b and hsa-miR-30c as key factors in anoikis resistance. *RNA.* 19:1711-1725
- Muñoz-Mayor A., Pineda B., Garcia-Abellán J.O., Antón T., Garcia-Sogo B., Sanchez-Bel P., Flores F.B., Atarés A., Angosto T., Pintor-Toro J.A., Moreno V., Bolari M.C. 2012. Overexpression of dehydrin tas14 gene improves the osmotic stress imposed by drought and salinity in tomato. *J Plant Physiol.* 169:459-468
- Moreno-Mateos M.A., Espina A.G., Torres B., Gámez del Estal M.M., Romero-Franco A., Ríos R.M., Pintor-Toro J.A. 2011. PTTG1/securin modulates microtubule nucleation and cell migration. *Mol Biol Cell.* 22: 4302-4311

### Grants

2015-2017: SAF2014-57632-P. Ministerio de Ciencia e Innovación

2012-2014: SAF2011-22486. Ministerio de Ciencia e Innovación

2010-2013: CVI- 5111. Junta de Andalucía

## Neuronal Plasticity and NeuroDegenerative Disorders

**Dr. Alfredo Rodríguez-Tébar**

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GROUP LEADER



### Academic Formation of PI

- 1971: Degree M.D. University of Granada, Spain
- 1974: PhD. Rocasolano Institute, Autonomus University of Madrid, Spain

### Present Position

- Since 2006: Research Investigator, CABIMER/CSIC, Seville, Spain

### Positions Held

- 1975-1976: Postdoctoral fellow in Biochemistry, Bristol University. UK
- 1977: Postdoctoral fellow in Chemistry USD, San Diego, California. USA
- 1978: Tenure Scientist, Catalisis Institute (CSIC), Madrid, Spain
- 1986-1989: Visiting Scientist in Max-Plank, Neurobiology Institute, Munich, Germany
- 1990-2066: Research Investigator, Cajal Institute/CSIC, Madrid, Spain

### Research Activity

#### RESEARCH HIGHLIGHTS

Adult brain neurons are subject to continuous morphological and synaptic remodelling by which new connections are formed that lead to the establishment of new circuits capable of storing information. These processes are the molecular and cellular basis of the so called, neuronal plasticity, highly necessary for ensuring the individual's adaptation to the environment and survival. Neural plasticity is supported by a series of cellular and molecular processes, whose failure is the beginning of various neurodegenerative processes, like Alzheimer's disease.

We have been studying the role of neurotrophic growth factors (neurotrophins) have on the morphology and connectivity (ie, plasticity) of neurons in the adult central nervous system. Thus, we have found the "Nerve Growth Factor (NGF), by binding to its receptor p75NTR and through the activation of NF-kappa-B controls the expression of homologous of the Enhancer-of-split -1 (Hes-1). This gene controls the shape, number and arborisation of dendrites and GABAergic synaptic input received by the stimulated neuron. Our recent studies indicate that amyloid beta, most likely the main pathogenic agent of Alzheimer's disease, also binds to the receptor but induces p75NTR signalling is completely opposite to that induced by NGF. The result is a loss of neural connectivity, process compatible with the onset of Alzheimer's disease.

On that basis the research lines we are developing, or begin to develop in brief, are:

- Molecular processes linking the activation of NF-Kappa-B to the expression of Hes-1.
- NGF induced signal transduction leading to neurotrophs and neuron survival and the steps at which amyloid beta may interrupt or block NGF signalling.
- To investigate the ultimate basis on which the amyloid beta acts as an antagonist of NGF and to what extent neurotrophic deprivation promotes the presentation and development of Alzheimer's disease.

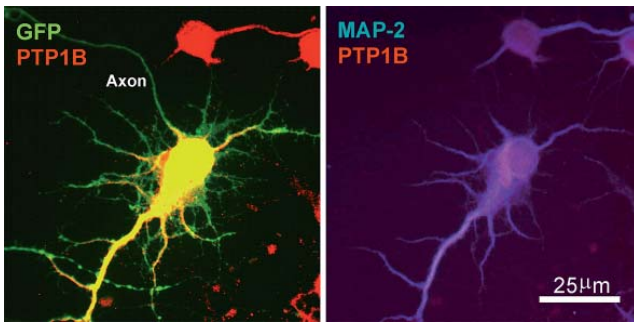


Figure 1: Localization of PTP1B on dendrites of hippocampal neurons.

Hippocampal neuron transfected with EGFP and triple-stained with anti-EGFP, anti-MAP-2 and an anti-PTP1B antibodies. PTP1B immunoreactivity spread on soma and dendrites (MAP-2 positive processes). Lower signal was found in axons.

### Publication Highlights

- Chacón P.J., del Marco Á., Arévalo Á., Domínguez-Giménez P., García-Segura L.M., Rodríguez-Tébar A. 2015. Cerebellin 4, a synaptic protein, enhances inhibitory activity and resistance of neurons to amyloid- $\beta$  toxicity. *Neurobiol Aging*. 36(2):1057-71
- Osório C., Chacón P.J., White M., Kiswa L., Wyatt S., Rodríguez-Tébar A., Davies A.M. 2014. Selective regulation of axonal growth from developing hippocampal neurons by tumor necrosis factor superfamily member APRIL. *Mol Cell Neurosci*. 59:24-36
- Chacón P.J., Rodríguez-Tébar A. 2012. Increased expression of the homologue of enhancer-of-split 1 protects neurons from beta amyloid neurotoxicity and hints at an alternative role for transforming growth factor beta1 as a neuroprotector. *Alzheimers Res Ther*. 4(4):31
- Chacon P.J., Garcia-Mejias R., Rodriguez-Tebar A. 2011. Inhibition of RhoA GTPase and the subsequent activation of PTP1B protects cultured hippocampal neurons against amyloid  $\beta$  toxicity. *Mol Neurodegener*. 6(1):14

### Grants

2010-2011: BFU2010-20995. MICINN. Ministerio de Ciencia e Innovación  
 2010- 2014: P10-CVI-6740. Proyecto de Excelencia, Junta de Andalucía

Figure3: Opposite effects of NGF and amyloid beta on hippocampal neuron morphology and Hes-1 gene expression.

A) Hippocampal neurons were transfected with EGFP and then treated with NGF and/or amyloid beta. Cells were fixed and processed for immunofluorescence. (B) After treatment with NGF and/or amyloid beta total RNA was extracted and Hes-1 expression was analyzed by real-time PCR.

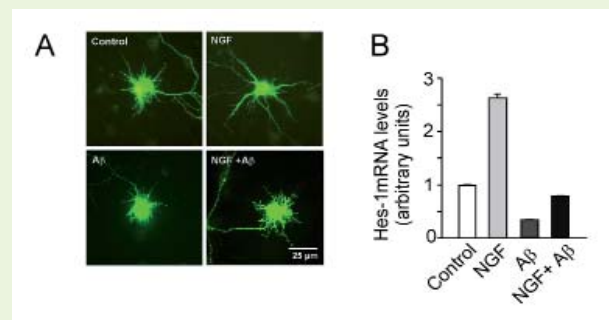
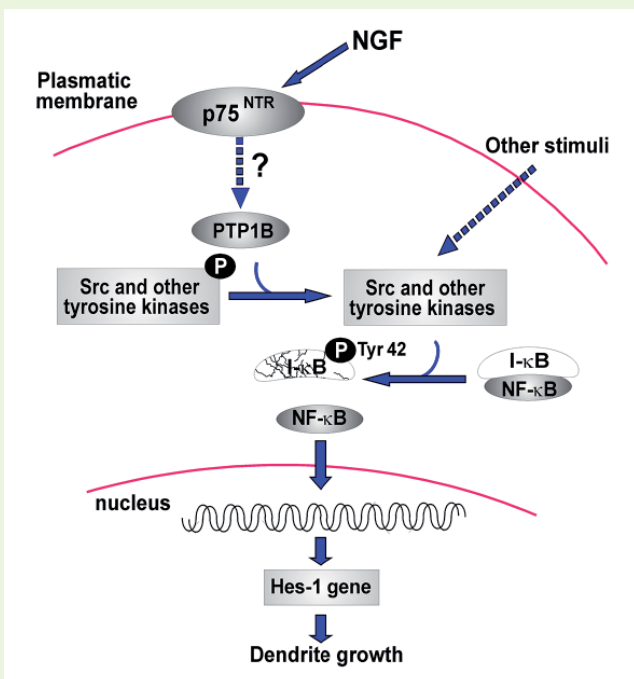


Figure 2: Diagram depicting a mechanism by which NGF may promote dendrite growth.

The binding of NGF to p75NTR activates PTP1B. PTP1B may activate src kinase although other protein tyrosine kinases may also participate. These kinases phosphorylate I-kappa-B, thereby favouring its degradation and activating NF-kappa-B, and subsequently Hes-1.



## Advanced Therapies in Neuroprotection and Immune-Regulation

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GROUP LEADER



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María Magdalena Ieal

Khadija Tayara

### Academic Formation of PI

- 1992: Degree: University of Seville, B.Sc. in Biological Sciences
- 1998: PhD: University of Seville, PhD in Biochemistry & Molecular Biology

### Present Position

- Since 2008: Associate Professor (Professor Titular) of Biochemistry and Molecular Biology, University of Seville, Seville, Spain

### Positions Held

- 2000-2003: University of Cambridge. Division of Immunology. Cambridge, UK. LT-EMBO and Marie Curie postdoctoral fellowships
- 2004: Weizmann Institute of Science. Department of Immunology. Rehovot, Israel. FEBS invited scientist fellowship
- 2006: Short stints as visiting scientist: Weizmann Institute of Science, Israel 2011-2013-2015: Visiting Scientist. Harvard University. Center for Neurologic Diseases
- 2010-2014: Scientific Director. BIONAND (Andalusian Center for Nanomedicine and Biotechnology), Malaga, Spain

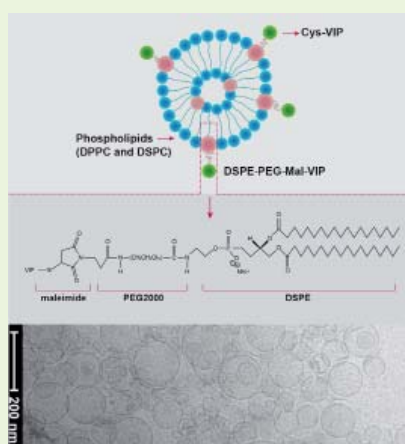
### Research Activity

#### OVERVIEW

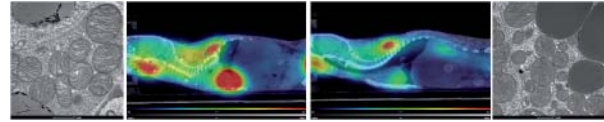
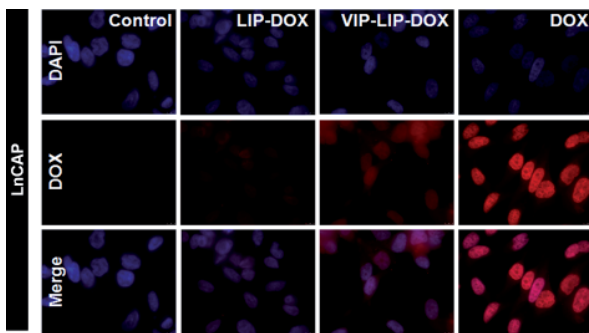
The University of Seville NIR laboratory at CABIMER is focused on understanding molecular and cellular mechanisms that regulate immune homeostasis and contribute to neuronal dysfunction and death, with particular emphasis on the role of key cell populations as microglia, dendritic cells and different T regulatory cell subsets in the development of Parkinson's disease (PD), Multiple Sclerosis (MS), and Amyotrophic Lateral Sclerosis (ALS). The activities at NIR laboratory merge basic disease-oriented research on primary cell cultures and cell line cultures (mouse and human), preclinical studies in mouse models of human diseases (PD, MS, ALS) and patient-driven research in clinical studies in MS and ALS. The active research lines are as follows: a) Immunotherapy and mechanisms of disease-linked protein aggregation in neurodegeneration (PD and MS) b) Modulation of innate and adaptive immunity by endogenous neuropeptides in neurodegeneration c) Nanoparticles for diagnostics and for controlled and targeted drug delivery: improving the drugability of neuropeptides d) Role of immune-mediated mechanisms in Amyotrophic Lateral Sclerosis (ALS).

#### RESEARCH HIGHLIGHTS

Related to basic immune mechanisms and interventional approaches in PD, we found that exogenous, 'native'  $\alpha$ -synuclein primes microglia and determines subsequent response elicited by TLR stimulation, which could help explain association between certain infections and the onset of sporadic Parkinson's disease. In addition, we showed that combination of  $\alpha$ -synuclein with Hsp70, or with certain other chaperones, can induce differential immune responses in vitro and in vivo as a result of immunization of mice. We also identified a variety of other potential 'immunochaperones' by in vitro screening of a set of chaperones with  $\alpha$ -synuclein as an 'amyloid' protein model.







A common feature among several neurodegenerative diseases including PD, MS or ALS is an impairment of neuroprotective mechanisms associated to immune imbalance. In this sense, the characterization of endogenous molecules with both neuroprotective and immunoregulatory properties is of special interest not only in terms of new therapeutic strategies, but particularly taking into consideration the increasing role of immune mediators in central nervous system (CNS) plasticity and homeostasis. The neuropeptide activity-dependent neuroprotective protein (ADNP) was originally cloned from mouse neuroglial cells as a vasoactive intestinal peptide (VIP) responsive gene. ADNP is known to harbour neuroprotective activities that map to the derived sequence peptide NAPVSIQ (termed NAP), which provides potent neuroprotection both, in vitro and in vivo. In this context, we have disclosed for the first time that the neuroprotective peptide NAP regulates neuroinflammatory mediators. Using a model of acute brain inflammation, we reveal that NAP acts as a potent suppressor of inflammation in vivo by inhibiting leukocyte recruitment, microglia activation, and proinflammatory cytokine-chemokine axis. Remarkably, our results in a mouse model of *Adnp* haploinsufficiency demonstrate an emerging role of the activity-dependent neuroprotective protein (ADNP) in brain immune homeostasis. In a pathological context, in the transgenic mouse model of ALS (*SOD1<sup>G93A</sup>*), we characterized a differential profile of VPAC receptors relevant to therapeutic and prophylactic interventions based on NAP and VIP treatments. In this sense, we have delineated for the first time the physiological role of VIP in the progression and disease severity in the ALS mouse model, using *SOD1<sup>G93A</sup>VIP<sup>-/-</sup>* KO mice. The establishment of the *SOD1* colony in the laboratory together with access to samples (CSF and PBMCs) from ALS patients have allowed us to identify the role of innate peripheral immune response and intracellular adaptor molecules as potential biomarkers of early versus established ALS. Peptide-based interventions (immunochaperones or neuropeptides) can be greatly improved in terms of drugability after surface functionalization of noble metal or organic nanoparticles. We have developed smart delivery platforms that enhance the half-life of our bioactive peptides, retaining full biological performance and gaining particular T1/T2 features with extra values as diagnostic tools in MRI.

### Publication Highlights

- Klippstein R., Pozo D. 2015. Vasoactive Intestinal Peptide (VIP) Nanoparticles for Diagnostics and for Controlled and Targeted Drug Delivery. *Adv Protein Chem Struct Biol.* 98:145-68.
- Pernía Leal M., Assali M., Cid J.J., Valdivia V., Franco J.M., Fernández I., Pozo D., Khair N. 2015. Synthesis of 1D-glyconanomaterials by a hybrid noncovalent-covalent functionalization of single wall carbon nanotubes: a study of their selective interactions with lectins and with live cells. *Nanoscale.* 7:19259-72.
- Labrador-Garrido A., Cejudo-Guillén M., Daturpalli S., Leal M.M., Klippstein R., De Genst EJ, Villadiego J., Toledo-Aral J.J., Dobson C.M., Jackson S.E., Pozo D., Roodveldt C. 2015. Chaperome screening leads to identification of Grp94/Gp96 and FKBP4/52 as modulators of the  $\alpha$ -synuclein-elicited immune response. *FASEB J.* 15-275131
- Roodveldt C., Labrador-Garrido A., Gonzalez-Rey E., Lachaud C.C., Williams T., Fernandez-Montesinos R., Benitez-Rondan A., Robledo G., Hmadcha A., Delgado M., Dobson C.M., Pozo D. 2013. Preconditioning of microglia by  $\alpha$ -synuclein strongly affects the response induced by toll-like receptor (TLR) stimulation. *PLoS One.* 8:e79160.
- Cejudo-Guillén M., Ramiro-Gutiérrez ML., Labrador-Garrido A., Díaz-Cuenca A., Pozo D. 2012. Nanoporous silica microparticle interaction with toll-like receptor agonists in macrophages. *Acta Biomater.* 8:4295-4303.

### Grants

2015-2018: RTC-2015-3309-1. Ministerio de Economía y Competitividad  
 2015-2017: PI14-1600. Instituto de Salud Carlos III  
 2014-2016: PI-0575-2013. Consejería de Salud. Junta de Andalucía  
 2013-2017: ALSVac. Amarna Therapeutics. FIUS-Universidad de Sevilla  
 2013-2016: P11-CTS-8161. Proyectos de Excelencia. Consejería de Economía y Conocimiento, Junta de Andalucía  
 2012-2015: SAF 2012-39720. Ministerio de Economía y Competitividad  
 2011-2015: P10-CTS-6928. Consejería de Economía y Conocimiento, Junta de Andalucía  
 2011-2013: CP10-527. Instituto de Salud Carlos III  
 2010-2012: PI09-2252. Instituto de Salud Carlos III  
 2010-2016: Bioibérica. 68/83 US  
 2009-2012: EC08-224. Instituto de Salud Carlos III



## Retinal Degeneration: from Genetics to Therapy

### Dr. Shom Shanker Bhattacharya

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HEAD OF THE CELL THERAPY AND  
REGENERATIVE DEPARTMENT



### Group Members updated

#### Senior Researcher

Fco. Javier Díaz-Corrales

#### Postdoctorals

Vaibhav Bhatia  
Berta De La Cerda Haynes  
Elena Reales Rodríguez

#### PhD Student

Andrea Díez Lloret

#### Technicians

Ana Belen Garcia Delgado  
Abhay Krishan  
Adoración Montero Sánchez  
Eduardo Rodríguez Bocanegra  
Daniel Rodríguez Martínez  
María Lourdes Valdés Sánchez

### Academic Formation of PI

- 1969: Degree: University of Bombay, B.Sc. Upper Second Division with Honors in Chemistry
- 1971: University of Newcastle upon Tyne, U.K, M.Sc. in Clinical Biochemistry
- 1977: PhD. Newcastle University upon Tyne, UK, PhD in Clinical Biochemistry

### Present Position

- Since 2008 Head of Department of Cell Therapy and Regenerative Medicine and Principal Investigator CABIMER

### Positions Held

#### Postdoctoral positions

- 1977-1980: Research Associate in the University Department of Clinical Biochemistry, Royal Victoria Infirmary, Newcastle Upon Tyne, UK
- 1980-1987: Scientific staff and Senior Research Fellow, MRC Human Genetics Unit, Edinburgh and University of Edinburgh
- 1987-1992: Top Grade Scientist (with special responsibilities), and Head of Molecular Genetics Unit, Department of Human Genetics, University of Newcastle upon Tyne, UK

#### Permanent positions

- 1992-onwards: Senior Professor of Experimental Ophthalmology, Institute of Ophthalmology, University College London, UK
- 2008- April 2016: Director of Cabimer, Seville, Spain

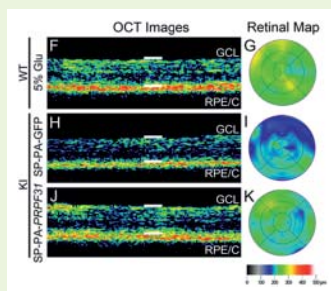
### Research Activity

#### OVERVIEW

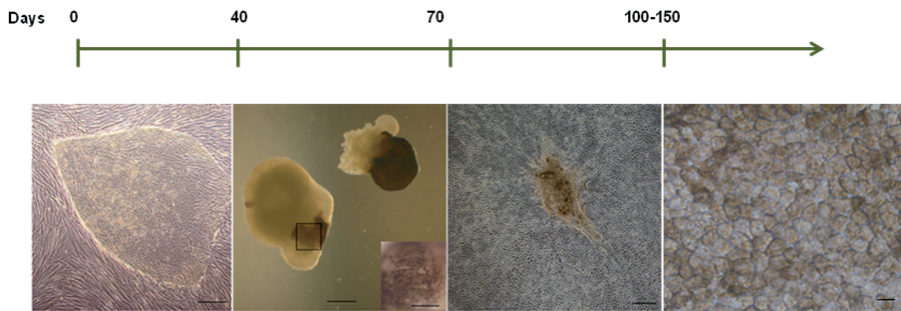
The research lines of the group include the identification of new genes implicated in retinal degeneration, the study of the molecular mechanisms of disease, the development of cellular models of specific retinal cell types and the preclinical test of different therapeutical approaches for hereditary as well as degenerative diseases that affect the retina. We are exploring all the therapeutic possibilities: cell reprogramming technology and cell differentiation to obtain retinal cell types and assay cell therapy in animal models, new vectors and constructions for gene therapy and also new compounds with neuro-protective therapeutic activity.

#### RESEARCH HIGHLIGHTS

The identification of new genes involved in inherited retinal degeneration is currently approached through our participation in the "European Retinal Degeneration Consortium", in which the development of the latest sequencing technology is applied to human genetics. The collaboration of our group with the Ophthalmic Unit of University Hospitals Virgen Macarena and Virgen del Rocío, in Sevilla is the source of patient's samples that are being studied within ERTC consortium. 23 new candidate genes have been identified. Regarding the molecular mechanisms that lead to the death of photoreceptors (PR), we work in different animal models of retinal degeneration. One is Seckel's disease mouse which has a mutation in the cell-cycle checkpoint ATR gene. We have described in detail a total and very early PR degeneration in these animals. Seckel's is a serious and complex syndrome and we have described



Recovery on retinal thickness after nonviral gene therapy replacement for PRPF31 gene in PRPF31 mouse model.



Differentiation protocol for human iPS towards RPE.

for the first time the effect of ATR deficit on the retina. Characterization of cell death of the PR shows a defect in the formation of cilia of these cells during their postnatal development. The description of a new function for a widely studied protein as ATR and the ascription of this retinal degeneration to a type of ciliopathy are the main findings of this first phase of functional characterization. Today, we continue these studies focusing on the molecular interactions of ATR in the cilia. Another animal model of retinitis pigmentosa we have studied is PRPF31, a mouse with a mutation in a splicing factor that we have characterized at the cellular level, finding a functional defect on the retinal pigment epithelium (RPE). Degeneration of RPE causes secondary cell death in PRs in many retinal diseases. PR specific mechanisms to deal with DNA damage and RNA synthesis-related stress are being studied using different animal models to search for a therapeutic target in degenerating PRs. We have used PRPF31 mouse model to assay gene therapy using viral and non-viral vectors, finding a therapeutic effect of the non-viral gene-therapy treatment with recovery of retinal thickness and spatial vision in treated mice. We have a patent on this non-viral approach for gene therapy. Moreover, on the same field of gene therapy, we are currently involved with an international company in a project on the design of vectors for retinal diseases. Regarding cell therapy and cellular modelling of retinal disease, there are several ongoing projects in our group. We have described a cellular model for MERTK-associated retinitis pigmentosa generated from iPS obtained from a patient. We have shown the lack of phagocytosis of the MERTK-RPE cell model as the functional phenotype expected for this genetic defect and currently the project continues to set up the gene correction of the mutation. We have developed CEP290-RPE and PR-AIPL1 cellular models from patients' iPS that will help to dissect the mechanisms of disease and to design therapeutic approaches. On this field of cellular models, we are also participating in the European consortium Eyerisk, devoted to the study of the genetic and non genetic factors that lead to Age-related Macular Degeneration (AMD). We participate in the study of cellular models of RPE derived from iPS of AMD patients. Also on AMD, we have another project focused on therapy in which we are testing different approaches (gene, cell and pharmacological therapy) for the dry type of this degenerative blinding disease that currently has no treatment and affects an increasing number of elder people in our society.

### Publication Highlights

- Lukovic D., Artero Castro A., García Delgado A.B., Martín Bernal M. De los A., Luna Pelaez N., Díez Lloret A., Pérez Espejo R., Kamenarova K., Fernández Sánchez L., Cuenca N., Cortón M., Ávila Fernández A., Sorkio A., Skottman H., Ayuso C., Erceg S., Bhattacharya S.S. 2015. Human iPSC derived disease model of MERTK-associated retinitis pigmentosa. *Sci Rep.* 5:12910
- Garita Hernández M., Díaz Corrales F., Lukovic D., González Guede I., Díez Lloret A., Valdés Sánchez M.L., Massalini S., Erceg S., Bhattacharya S.S. 2013. Hypoxia increases the yield of photoreceptors differentiating from mouse embryonic stem cells and improves the modeling of retinogenesis in vitro. *Stem Cells.* 31:966-978
- Valdés-Sánchez M.L., De la Cerda B., Díaz-Corrales F.J., Massalini S., Chakarova C.F., Wright A., Bhattacharya S.S. 2013. ATR localizes to the photoreceptor connecting cilium and deficiency leads to severe photoreceptor degeneration in mice. *Hum Mol Genet.* 22:1507-1515
- Lukovic D., Valdés-Sánchez M. L., Sanchez-Vera I., Moreno-Manzano V., Stojkovic M., Bhattacharya S.S., Erceg S. 2013. Astrogliosis promotes functional recovery of completely transected spinal cord following transplantation of hESC-derived oligodendrocyte and motoneuron progenitors. *Stem Cells.* 32:594-599
- Kamenarova K., Cherninkova S., Romero Durán M., Prescott D., Valdés Sánchez M.L., Mitev V., Kremensky I., Kaneva R., Bhattacharya S.S., Tournev I., Chakarova C. 2012. A novel locus for autosomal dominant cone-rod dystrophy maps to chromosome 10q. *Eur J Hum Genet.* 21:338-342

### Grants

2015-2019: 634479. EU Horizon 2020  
 2016-2018: CP15/00071. Instituto de Salud Carlos III  
 2013-2015: PI13/01331. Instituto de Salud Carlos III  
 2013-2014: PI-0084-2013. Consejería de Igualdad, Salud y Políticas Sociales de Andalucía. Proyectos de Investigación en Salud 2013  
 2013-2015: PI-0324-2013. Consejería de Igualdad, Salud y Políticas Sociales de Andalucía. Proyectos de Investigación en Salud 2013  
 2013-2013: EF-0571-2013. Consejería de Igualdad, Salud y Políticas Sociales de Andalucía  
 2012-20112: EF-0381-2012. Consejería de Igualdad, Salud y Políticas Sociales de Andalucía



## Laboratory of Beta Cell Regeneration

**Dr. Francisco J. Bedoya**

*francisco.bedoya@cabimer.es*

GROUP LEADER



### Group Members updated

#### Research Associates

Juan Tejado Huamán

#### Postdoctorals

Gladys Cahuana Macedo

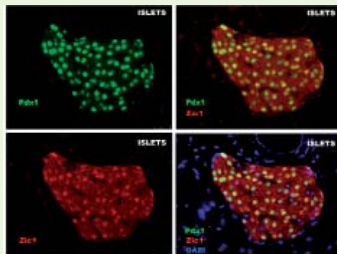
#### PhD Student

Estefania Caballano Infantes

#### Technician

Irene Diaz Contreras

Ana Belen Hitos Prados



### Academic Formation of PI

- 1979: Degree. University of Sevilla, B.Sc. in Medicine and Surgery
- 1982: PhD. University of Sevilla. PhD. In Medicine and Surgery

### Present Position

- Since 2007: Professor in Biochemistry and Molecular Biology, Department of Molecular Biology and Biochemical Engineering. University Pablo de Olavide, Seville, Spain

### Positions Held

- 1980-1983: Hospital Virgen Macarena, Seville Medical Internship in Clinical Biochemistry
- 1985-1985: Teaching Associate. University of Sevilla, Spain
- 1986-2007: Lecturer, University of Sevilla, Spain

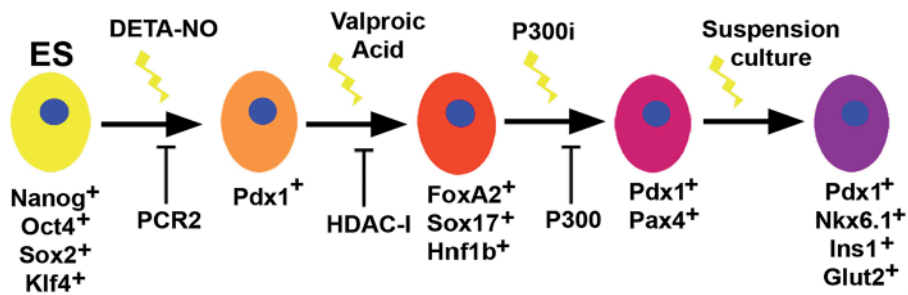
### Research Activity

#### OVERVIEW

Stem cells display unlimited self-renewal capacity and differentiation towards any cell type of the body. Knowledge on the mechanisms that control such processes might be instrumental to direct differentiation towards specific cell types in regenerative medicine. Nitric oxide regulates the differentiation of stem cells to muscle heart cells and insulin producing cells and control also self-renewal. Thus, studies carried out by our group show that low concentrations of this biological messenger preserves human ESC pluripotency, thus being revealed as an efficient tool to control spontaneous differentiation events that occur during 'in vitro' culture of these cells. In addition, this mediator also plays an important role in the start-up of survival responses against environmental stressors in many cell types, including pancreatic beta cells. In this respect our research aims at designing molecular strategies for efficient beta cell protection that might be relevant for protection of residual beta cells in diabetes.

#### RESEARCH HIGHLIGHTS

Nitric oxide (NO) delays mouse embryonic stem cell (mESC) differentiation by regulating genes linked to pluripotency and differentiation. Nevertheless, no profound study on the regulation of essential biological functions for differentiation control by this molecule has been conducted. We sought to demonstrate that NO positively regulates the pluripotency transcriptional core, enforcing changes in the chromatin structure, in addition to regulating cell proliferation and signaling pathways with key roles in stemness. Culturing mESCs with 2 mM of the NO donor diethylenetriamine/NO (DETA/NO) in the absence of leukemia inhibitory factor (LIF) induced significant changes in the expression of 16 genes of the pluripotency transcriptional core. Furthermore, treatment with DETA/NO resulted in a high occupancy of activating H3K4me3 at the Oct4 and Nanog promoters and repressive H3K9me3 and H3k27me3 at the Brachyury promoter. Additionally, the activation of signaling pathways involved in pluripotency, such as Gsk3- $\beta$ / $\beta$ -catenin, was observed, in addition to activation of PI3K/Akt, which is consistent with the protection of mESCs from cell death. Finally, a decrease in cell proliferation coincides with cell cycle arrest in G2/M. Our results provide novel insights into NO-mediated gene regulation



and cell proliferation and suggest that NO is necessary but not sufficient for the maintenance of pluripotency and the prevention of cell differentiation. These results have been published in: *J Cell Biochem.* 2016 Feb 8. doi: 10.1002/jcb.25513. PMID:26853909.

Pancreatic and duodenal homeobox (Pdx1) is a transcription factor that regulates the embryonic development of the pancreas and the differentiation towards beta cells. Previously, we have shown that exposure of mouse embryonic stem cells (mESCs) to high concentrations of NO donor diethylenetriamine nitric oxide adduct (DETA-NO) triggers differentiation events and promotes the expression of Pdx1. Here we report evidence that Pdx1 expression is associated with release of Polycomb Repressive Complex 2 (PRC2) and P300 from its promoter region. These events are accompanied by epigenetic changes in bivalent marks of histone H3K27me3 and H3K4me3, site specific changes in DNA methylation, and no change in H3 acetylation. Based on these findings, we developed a protocol to differentiate mESCs towards insulin producing cells consisting of sequential exposure to DETA-NO, valproic acid, and P300 inhibitor (C646) to enhance Pdx1 expression and a final maturation step of culture in suspension to form cell aggregates. This small molecule-based protocol succeeds in obtaining cells that express pancreatic beta cell markers such as PDX1, INS1, GCK and GLUT2 and respond *in vitro* to high-glucose and KCl. These results have been published in: *Cell Transplant.* 2016 Mar 14. PMID:26980118.

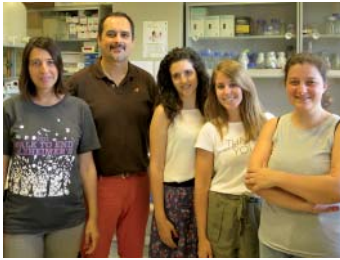
Homeostatic levels of nitric oxide (NO) protect efficiently against apoptotic death in both human and rodent pancreatic beta cells, but the protein profile of this action remains to be determined. We have applied a two dimensional LC-MS-MALDI-TOF/TOF-based analysis to study the impact of protective NO in rat insulin-producing RINm5F cell line and in mouse and human pancreatic islets (HPI) exposed to serum deprivation condition. 24 proteins in RINm5F and 22 in HPI were identified to undergo changes in at least one experimental condition. These include stress response mitochondrial proteins (UQCRC2, VDAC1, ATP5C1, ATP5A1) in RINm5F cells and stress response endoplasmic reticulum proteins (HSPA5, PDIA6, VCP, GANAB) in HPI. In addition, metabolic and structural proteins, oxidoreductases and chaperones related with protein metabolism are also regulated by NO treatment. Network analysis of differentially expressed proteins shows their interaction in glucocorticoid receptor and NRF2-mediated oxidative stress response pathways and eNOS signaling. The results indicate that exposure to exogenous NO counteracts the impact of serum deprivation on pancreatic beta cell proteome. Species differences in the proteins involved are apparent. These results were published in: *Islets.* 2014;6(5-6):e995997. doi: 10.1080/19382014.2014.995997.PMID: 25658244.

### Publication Highlights

- Soria B., Gauthier B.R., Martin F., Tejedo J.R., Bedoya F.J., Rojas A., Hmadcha A. 2015. Using Stem cells to produce insulin. *Expert Opin Biol Ther.* 15:1469-1489
- Beltran-Povea A., Caballano-Infantes E., Salguero-Aranda C., Martin F., Soria B., Bedoya F.J., Tejedo J.R., Cahuana G.M. 2015. Role of nitric oxide in the maintenance of pluripotency and the regulation of the hypoxia response in stem cells. *World J Stem Cells.* 7:605-617
- Tapia-Limonchi R., Diaz I., Cahuana G.M., Bautista M., Martin F., Soria B., Tejedo J.R., Bedoya F.J. 2014. Impact of exposure to low concentrations of nitric oxide on protein profile in murine and human pancreatic islet cells. *Islets.* 6:e995997
- Mora-Castilla S., Tejedo J.R., Tapia-Limonchi R., Diaz I., Hito A.B., Cahuana G.M., Hmadcha A., Martin F., Soria B., Bedoya F.J. 2014. Transient Downregulation of Nanog and Oct4 Induced by DETA/NO Exposure in Mouse Embryonic Stem Cells Leads to Mesodermal/Endodermal Lineage Differentiation. *Stem Cells Int.* 379678
- Horrillo A., Pezzolla D., Fraga M.F., Aguilera Y., Salguero-Aranda C., Tejedo J.R., Martin F., Bedoya F.J., Soria B., Hmadcha A. 2013. Zebularine regulates early stages of mESC differentiation: effect on cardiac commitment. *Cell Death Dis.* 4:e570

### Grants

2013-2017: CTS-7127/2011. Consejería de Economía, Innovación, Ciencia y Empleo  
 2011-2014: PI-0105-2010. Junta de Andalucía Consejería de Salud  
 2011-2014: IPT-2011-1615-900000. Ministerio de Ciencia e Innovación  
 2007-present: RD06/0015/0013. Ministerio de Ciencia e Innovación



## Cell-Based Therapies for Neuropathologies

**Dr. Manuel Alvarez-Dolado**

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GROUP LEADER



### Group Members updated

#### Postdoctoral

María M. Martínez Losa

#### Technicians

María Pérez Fernández

Flora Priego Montes

#### Master Students

Laura del Carmen Galán Pérez

Mónica González Moreno

### Academic Formation of PI

- 1992: Degree. Universidad Autónoma de Madrid, B.Sc. in Biological Sciences
- 1997: PhD. Universidad Autónoma de Madrid, Biological Sciences

### Present Position

- Since 2008 Research Scientist. CSIC/ CABIMER, Seville, Spain

### Positions Held

- 1998-2000: Instituto de Investigaciones Biomédicas, CSIC, Madrid, Spain
- 2000-2003: Investigator, University of California San Francisco
- 2003-2006: FISS Researcher at Hospital General Universitario de Valencia, Spain
- 2006-2008: Group Leader at Centro de Investigación Príncipe Felipe, Valencia, Spain
- 2009-2013: Associated Professor in Cell Biology at UPO, Seville, Spain

### Research Activity

#### OVERVIEW

Our laboratory studies two stem cell types in order to apply them in Regenerative Medicine for the treatment of different neuropathologies. The first type is bone marrow derived stem cells (BMSC), which we apply for the treatment of ataxias and brain injury. We also study GABAergic neuronal progenitors and their effects after transplantation in animal models of epilepsy, infantile encephalopathies, and Alzheimer's disease. Our main goal is the development of new cell-based therapies for the treatment of these important diseases. For this, we study their mechanism of action and effects at the electrophysiological, histological, cellular, molecular, and behavioural levels.

#### RESEARCH HIGHLIGHTS

Many studies have reported the contribution of BMSC to the CNS, raising the possibility of using them as a new source to repair damaged brain tissue or restore neuronal function. This improvement is mediated through three different mechanism of action: 1) Cell replacement; 2) Secretion of trophic factors that promote tissue restoration and neuronal survival; and 3) Cell fusion. We have studied the contribution of BMSC to different neural types in adult brain areas, under both physiological and neurodegenerative/injury conditions, together with the mechanisms of plasticity involved. We grafted bone marrow cells in two animal models of ataxia: a) the PCD (Purkinje Cell Degeneration) mutant mice, suffering a degeneration of specific neuronal populations at different ages, and b) a humanized transgenic mouse line carrying the mutated human gene for frataxin, that recapitulates the symptoms of Friedreich's ataxia (FA). Interestingly, we observed substantial differences in the condition restoration of these models. Whereas the transplant did not avoid the neuronal degeneration in PCD mice, we observed a delay in the onset of the degenerative process in the dorsal root ganglia (DRG) of FA mice, and a partial, but consistent, improvement of their locomotor coordination, measure by the rotarod test. This was positively correlated with an increment in the number of neurons, axons and myelin in the

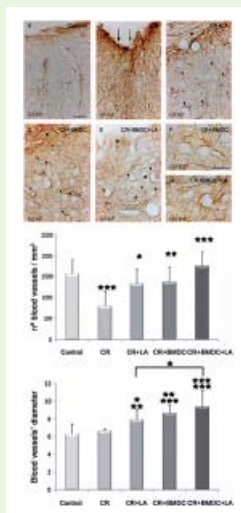
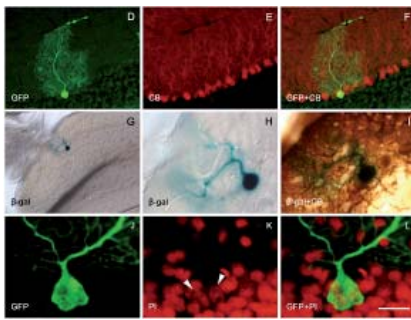
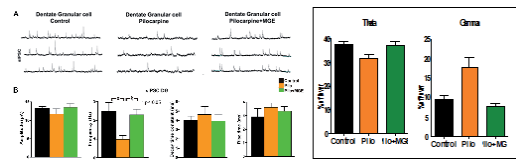


Figure 2. Presence of astrocytes after pharmacological and cellular treatment of the lesioned area, 16 days after injury. (A–E) Micrographs of GFAP+ cells showing consolidation of the glial scar barrier in injured no treated animal (arrows in b) and sprouts of new formed tissue toward the cystic cavity in all three treated groups (asterisk in C–E). On the right, quantification of blood vessel formation, showing an improvement of angiogenesis by BMSC treatment.



**Figure 1.** Fluorescence microscopy images of cerebellum sections from wild-type PCD mice grafted with wild-type bone marrow from CRE-GFP donors showing some examples of Purkinje cells originated from the transplanted bone marrow by the cell fusion mechanism.



**Figure 3.** Restoration of brain activity and rhythms in a model of temporal lobe epilepsy after MGE derived GABAergic precursor transplantation.

DRG of ataxic mice that received the BMSC transplant. The lack of effect of the BMSC in the PCD model may be related with the fast and early beginning of its degeneration, which is already in quick progress at the moment of transplantation. In contrast, the FA model suffers a slow progress in the degeneration, so BMSC transplant may have more time to act. In both model we observed generation of microglial cells, although to a lesser extent a clear formation of neuronal types also exists. We verified that cell fusion contributes to purkinje cell generation in these models (Fig. 1), and also that secretion of neurotrophic factors, together with reduction of oxidative stress may be involved in the improvements observed in the FA model.

There are growing evidences that BMSC promote neuroregeneration and angiogenesis acting as mini-pumps delivering beneficial factors to their microenvironment in an injured brain. We transplanted BMSC in a model of traumatic brain injury, a main cause of disability and death in developed countries, together with Lipoic acid (LA), a potent antioxidant that promotes cell survival, angiogenesis and neuroregeneration, and it is one of the few drugs available for this condition. Our data suggest that transplantation of BMDC is a valid strategy to treat a focal brain injury when LA could not be prescribed due to its secondary effects. We observed increments in cell proliferation, angiogenesis and glial scar formation that improved local injury restoration (Fig. 2).

Finally, the second main research line of the group is to develop a cell therapy with GABAergic neuronal progenitors for the treatment of inter-neuron related diseases. We performed transplants in animal models of temporal lobe epilepsy, west syndrome, and Alzheimer's disease (AD) to show the therapeutic potential of these neuronal precursors. In all this models we observed an anticonvulsant activity of the precursors together with restoration of normal brain rhythms and improvement of behavioural and cognitive deficits (Fig. 3). In the AD model we only observed this improvement when the transplanted progenitors over-expressed the Nav1.1 channel. The results strongly suggest that naïve of genetically-modified GABAergic neuronal precursors are a promising source of cells for regenerative medicine to treat psychiatric conditions.

### Publication Highlights

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### Grants

- 2013-2016: CTS-2563. Proyectos de Excelencia. Consejería de Economía, Innovación Ciencia y Empleo, Junta de Andalucía  
 2013-2015: Alzheimer's Association Research Grants, USA  
 2012-2013: Grupo BIO-237 Junta de Andalucía  
 2012-2015: SAF2012-36853. Ministerio de Educación y Ciencia  
 2012-2015: Fundación Ramón Areces  
 2011-2013: PI-0736-2010. Consejería de Salud, Junta de Andalucía  
 2009-2012: SAF09-07746. Ministerio de Educación y Ciencia



## DNA Double Strand Breaks Repair and Human Disease

**Dr. Pablo Huertas**

*pablo.huertas@cabimer.es*

GROUP LEADER



### Group Members updated

#### Postdoctorals

Cristina Cepeda García  
María S. Domínguez-Sánchez  
Daniel Gómez Cabello  
Sonia Jimeno

#### PhD students

Cintia Checa Rodríguez  
Andres Cruz Garcia  
Ana López Saavedra  
Fernando Mejías Navarro  
María Rosario Prados Carvajal  
Isabel Soria Bretones

#### Technician

María Jesús Fernández Avila

#### Administrative Assistant

Ángeles Garrido Arines

### Academic Formation of PI

- 1998: Degree. University of Seville, B.Sc. in Biology
- 2004: PhD. University of Seville, Ph.D. Thesis in Molecular and Cellular Biology

### Present Position

- 2010: Research Scientist CABIMER
- 2015: Professor of the University of Seville

### Positions Held

- 2004-2010: The Gurdon Institute for Cancer Research and Developmental Biology, University of Cambridge, UK
- Since 2010: Ramón y Cajal, University of Seville/ CABIMER

### Research Activity

#### OVERVIEW

Double strand breaks (DSBs) repair is essential for normal development. Lack of DSBs repair leads to cell death, but mutations that hamper this process cause genetically inherited syndromes and cancer predisposition. There are two ways to repair DSBs. Non-processed breaks can be simply rejoined by the non-homologous end-joining pathway (NHEJ). However, sometimes they are processed to create RPA-coated single stranded DNA, effectively blocking NHEJ and triggering a more complex repair pathway called homologous recombination (HR). Mutations in NHEJ or HR components correlate with several inherited human syndromes or cancer predisposition. Interesting, defects in the repair of DSBs are also commonly exploited for the treatment of cancer. In our laboratory, we are studying how the formation of ssDNA is regulated. This key step controls both the switch between NHEJ and HR. Using a comprehensive list of cellular and molecular biology techniques, we are gaining further insight in this regulatory network.

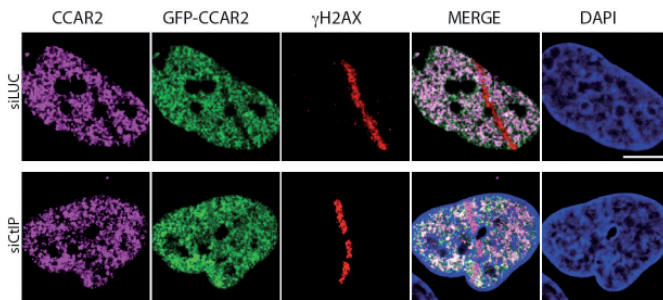
#### RESEARCH HIGHLIGHTS

The 2011-2015 period correspond with the establishment of the laboratory. Although I arrive to CABIMER in mid 2010, my first project grant started in January 2011. Since then, we have been able to establish a solid research line in the laboratory.

Two of our main contributions to the field have come in the development of novel technical tools to study the repair of DSBs and DNA resection. We have created a novel reporter, named the SeeSaw Reporter, specifically designed to study the balance between NHEJ and HR using the accumulation of distinct fluorescent proteins as readout. Moreover, we have developed a high-resolution approach to study DNA resection in which we can measure the actual length of resected DNA in individual DNA fibers.

Using the aforementioned and standard techniques we have been able to publish several papers of great interest. I would like to highlight the resolution of a dilemma in the field: the actual





**Figure 1:** A genome wide screening for factors that control the balance between NHEJ and HR. *a*, Schematic representation of the SeeSaw Reporter (SSR). An I-SceI-induced DSB can be repaired by NHEJ, thus reconstructing an active GFP gene, or by homologous recombination using RFP fragments, thus creating a functional RFP gene. *b*, Workflow of the screening method. *c*, The ratio between green and red cells was established for each individual esiRNA and normalized to an internal control (esiRNA targeted against luciferase) that was included in each plate. The individual NHEJ:HR ratio was then ordered and plotted. *d*, Functional categories enriched among candidates detected with IPA Software.

contribution of BRCA1 to early steps of homologous recombination. In addition, we have been able to link the process of protein neddylation to the regulation of DSB repair.

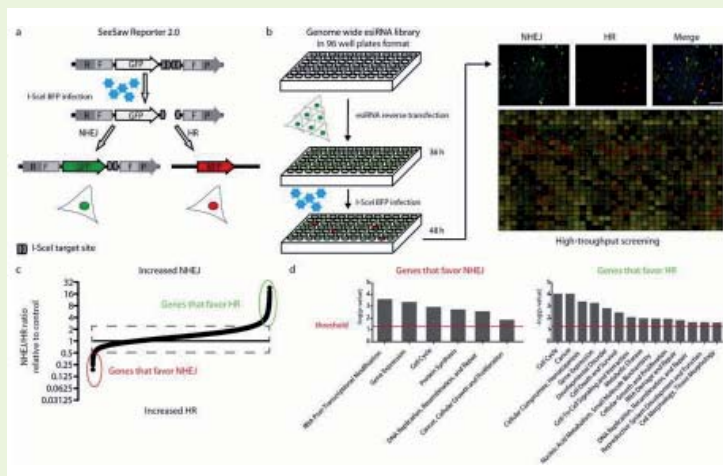
Finally, the long-term goal of our laboratory is to link our basic observations with the appearance and/or treatment of diseases. In that regard, we have uncovered the causal mutation of a variant of the rare disorder Seckel Syndrome and the cause of Jawad Syndrome. Moreover, we have study the contribution of the loss of a specific resection protein, CtIP, with the incidence, prognosis and response to standard treatments of breast cancer patients.

### Publication Highlights

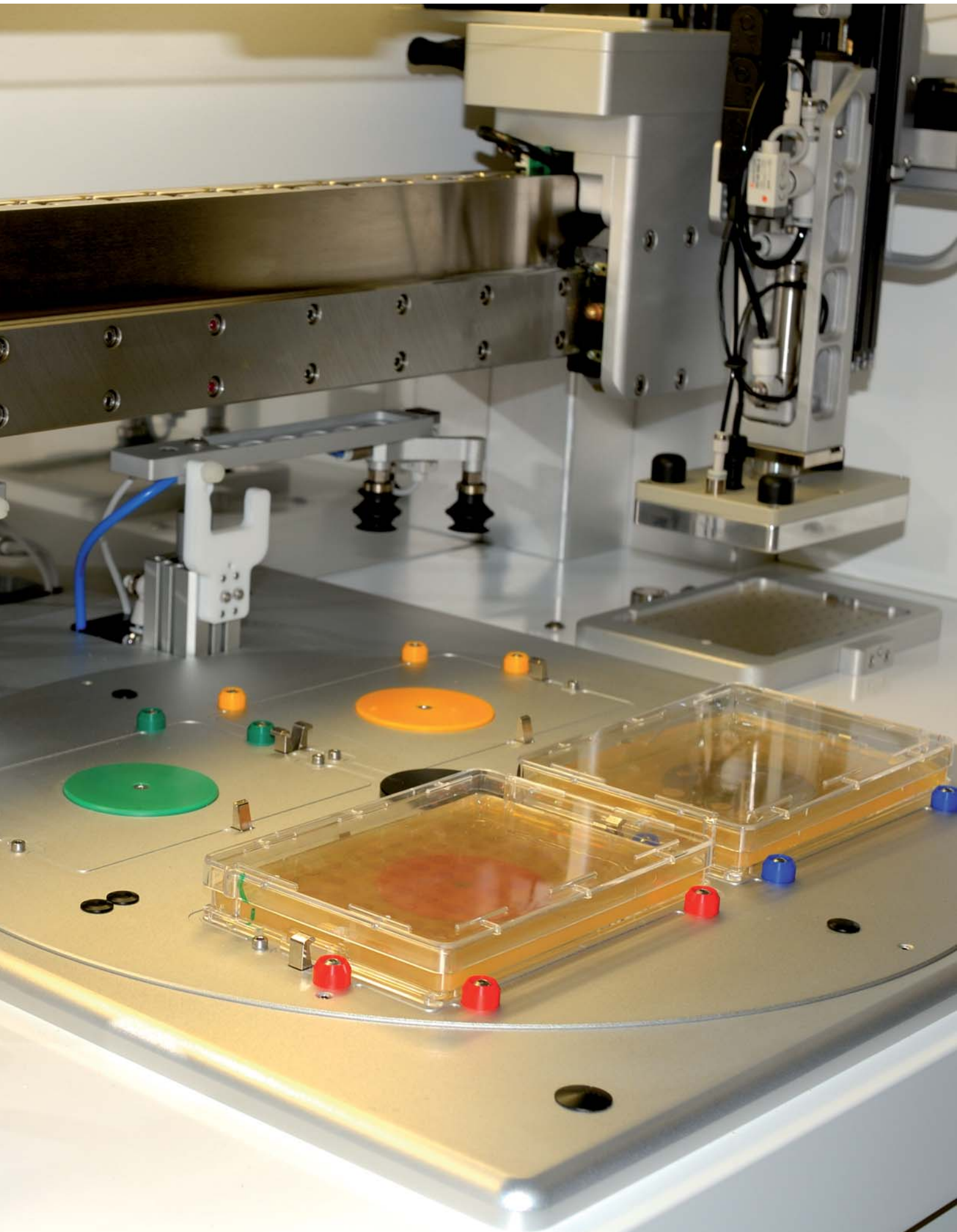
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### Grants

- 2014-2015: SAF2013-43255-P. Ministerio de Economía y Competitividad
- 2014-2017: Fundación Vencer el Cáncer
- 2014-2017: P12-BIO-515 Junta de Andalucía
- 2012-2016: European Research Council-ERC StG
- 2011-2013: SAF2010-14877. Ministerio de Ciencia e Innovación



**Figure 3** CCR2 exclusion from damaged chromatin depends on CtIP. Cells expressing a GFP-CCR2 fusion were transfected with siRNA against CtIP or control and micro-irradiated. CCR2 exclusion from damaged chromatin was determined with GFP signal or an anti-CCR2 antibody (magenta).



## Biological Safety Unit

The Unit of Biological Safety provides guidance and advice on all aspects of biological safety at CABIMER, including protection against biological agents, chemicals and radiations. CABIMER is authorized to work with non-encapsulated as well as with encapsulated radioactivity sources and have two different radioisotopes laboratories equipped with all required means of shielding, containment and detection of ionizing radiation.

The Unit also has a biological irradiator BioBeam 8000 that allows the study, among other applications, of the repair of genetic damage in different experimental models. The Unit is also in charged, together with the Cell Culture Unit, of a Biosafety level 2 laboratory (P2) equipped to work with biological agents of level 2 such as lentiviral or retroviral vectors.

The proper management of biosanitary, toxic and radioactive waste generated in a research center like CABIMER is considered a cornerstone in risks prevention. Improvements in working protocols with chemical or biological agents, information on the risks of each scientific activity, and increase the level to training to researchers, are the main goals of the unit in the last few years. In this context, the continuous incorporation of researcher groups has led to an increase in management and waste generation until reach a production of 12 Tm in 2015.



**José Carlos Reyes Rosa**  
Scientific Coordinator



**Juan Carlos Ostos Vega**  
Technician

## Biological Resources

### Scientific Core Services

Researchers in Cabimer -60% of research groups in 2015- are already using mouse models in a variety of ways, from basic to translational research. The Biological Resources Unit enables animal experimentation in Cabimer providing the necessary resources under conditions required by national and EU legislation (Spanish RD 53/2013 and EU Directive 2010/63) for the protection of animals used for scientific purposes. The unit ensures observance of all legal and ethical standards related to the use of animals for research at Cabimer. The mission is to provide for the care, health and well-being of animals as well as to provide specialized techniques and equipment for research.

The unit has capacity for some 6000 mice maintained in Specific Pathogen Free (SPF) condition, a health status monitored through a comprehensive health surveillance programme. Cages, bedding and water are sterilized by autoclaving and food is irradiated. Equipment and material for research is decontaminated by hydrogen peroxide vapour. Laboratory space and equipment is available for in vivo imaging, stereotaxic surgery and general procedures. A transgenic laboratory provides techniques for the generation and maintenance of transgenic mice including microinjection of DNA into zygotes, microinjection of ES cells into blastocysts and rederivation by embryo transfer.

**Luis Sánchez Palazón**

Director of the Unit and

**Benoit Gauthier**

Scientific Coordinators

**Itziar Benito Latasa de Aranibar**

Veterinarian

**Flora Guerrero Iglesias**

**Laura Canas Calvo**

**Miriam González Fernández**

**Rosario Segarra Bermúdez**

Technicians

## Cell Culture

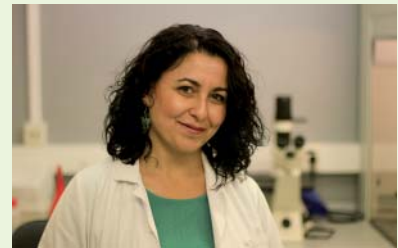
The Cell Culture Core Facility in CABIMER contains different restricted areas where primary and cell lines cultures are carried out. Five rooms are destined to established cell lines, one room to non-human primary cultures, and a biosafety level II room to infecting cells with viruses. The Facility attends to the requirements from the researchers in order to facilitate the use of equipments in the Facility and provides main reagents used in cell cultures as serum, trypsin, antibiotics, glutamine and PBS. In addition, the Facility tests different fetal bovine serum (FBS) batches yearly in order to select one for common use.

The Facility has improved its infrastructure recently. It started up a modular roller bottle system for flexible cell culture scale-up. On the other hand, due to the increasingly cell cultures under hypoxic conditions, the Facility has been equipped with a BioSpherix XVivo Incubation System, an aseptic cell culture and processing workstation that allows the users to work in identical incubation and handling oxygen tensions.

Finally, the Facility acquired the cell analyzer xCELLigence® RTCA DP, which uses noninvasive electrical impedance monitoring to quantify cell proliferation, morphology change, and attachment quality in a real-time manner.



**Mario García Domínguez**  
Scientific Coordinator



**M. Mercedes Dana Jiménez**  
Technician

## Citometry and Sorter

Flow cytometry is a powerful tool that measures functional and structural characteristics of heterogeneous mixtures of cells and particles in suspension. Measurements are performed in liquid suspension of cell samples, which flow one cell at a time, through a stream focused to a laser beam at rates up to several thousand particles per second. Light scattered and fluorescence emitted by the cells is collected, filtered, digitized and sent to a computer for analysis.

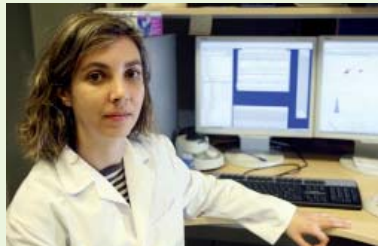
The main applications of flow cytometry include immunophenotyping, measurement of cell cycle progression, apoptosis/necrosis, protein expression, among many others. These assays can also utilize the so-called cell sorting technology, which allows the physical isolation of distinct populations of cell of interest for further downstream applications including cell culture, RNA or protein analysis and single cell cloning.

The Cytometry Core Facility of Cabimer is equipped with two BD FACSCalibur Analyzers and a BD FACSAria Cell Sorter, and provides researchers the capability to analyze and sort cells by differences in physiology, metabolism, morphology and other characteristics. Our facility has also an off-line processing station harbouring data analysis software with the purpose of helping researchers in the analysis and representation of their data. The currently available software includes FACSDiva, WinMDi and ModFit, this later software for specific analysis of cell cycle data.

Currently, researchers from 80% of the groups of Cabimer are common users of the Cytometry Core Facility. Moreover, an average of 150 sorting services are performed annually, which represents a 75% increase of the services we have done the first year the facility started and 40% increase in the last four years. From the total of provided services, about 3% corresponded to external users. This increase is mainly due to the incorporation of new fluorochromes to the analyzers, the development of new applications and an increase in the number of the researcher groups incorporated to Cabimer.



**Abelardo López**  
Scientific Coordinator



**María José Quintero**  
Technician

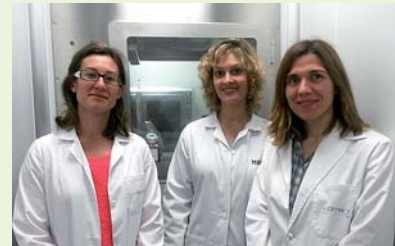
CABIMER's Good Manufacturing Practices (GMP) Core facility is a Unit for ensuring that pharmaceutical products are consistently manufactured and controlled according to quality standards (QC). GMP is designed to minimize the Risk and ensure Safety. The GMP unit of CABIMER is a cell production core facility (UAPC-CABIMER) engaged in the scale-up of human cells considered as Advanced Therapy Medicinal Products (ATMPs) in accordance with article 17 of regulation (EC) n° 1394/2007. The production of ATMPs is carried out in accordance with GMP standards and handled with appropriate controls to ensure their safety, quality, and efficacy as a final medicinal product. UAPC-CABIMER was the first in Andalucía to obtain the Certification from the Spanish Agency of Medicines and Medical Devices (AEMPS, Agencia Española del Medicamento y Productos Sanitarios) to produce cellular medicaments (16 November 2009). On February 2012 and later on April 2015, UAPC-CABIMER passed the inspection of the GMP facilities by AEMPS and got the Accreditation for three more years. So far UAPC-CABIMER has produced approximately 100 doses of Cellular Medicaments under investigation (100 patients treated), contains two Production Units and, in collaboration with University Pablo de Olavide, trained more than 10 experts in Quality Control, Quality Assurance and Cellular Medicaments Production.

#### LINES OF ACTION

The UAPC-CABIMER facility is a fully equipped 57m<sup>2</sup> installation, is part of the Stem Cells Department and a Core facility of CABIMER. The UAPC-CABIMER has 2 production units for manufacturing ATMPs to use in Clinical Trials and Compassive Use and a fully independent Quality Control (QC) Unit. The UAPC-CABIMER follows the strict regulations established by Standard Operating Protocols (SOPs), which cover all issues of ATMPs manufacturing, including recordkeeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling.



**Bernat Soria**  
Scientific Coordinator



**Karim Hmadcha**  
Technical Director

**Natalia Escacena**  
**Maria Galvez**  
Quality Units

**Victoria Jiménez**  
Production Unit

## Genomics

### Scientific Core Services

The main aim of CABIMER Genomics Core Facility, established in 2007, is to provide internal and external researchers resources and services to support their research needs regarding High-throughput Functional Genomics. In recent years, the Microarray and NGS (next generation sequencing) technologies have become some of the most utilized implements in biology to perform studies of transcriptomes and genomes at a global scale. At present, there are several different platforms to carry out these studies.

The Unit is equipped with two platforms for Microarray analyses (Affymetrix and Agilent) able to provide services that include analyses on Molecular Cytogenetics, Expression profiles at the mRNA and Gene/Exon Level, Alternative Splicing, miRNA and Chip-on-Chip. In addition, it handles requests of scientists for Ion-Torrent PGM sequencing. The Unit has set up protocols for whole-genome sequencing, ChipSeq, DRIP-Seq, MNase-Seq, RNA-Seq, AmpliSeq™ RNA/DNA Panels. The Core Facility also offers related services such as High Throughput Screening, data analysis, determination of concentration and integrity of RNA and DNA as well as support for the design of experiments and interpretation of the results.

The manipulation of a vast amount of samples processed in a reduced period of time, with accuracy and high reproducibility, permits in a second phase a wide study of selected genes at an individual level. This is possible due to diverse high performance technologies that have been improved by the use of different robots available in the Core Service.



**Andrés Aguilera López**  
Scientific Coordinator



**Eloísa Andújar**  
**Mónica Pérez**  
Technician

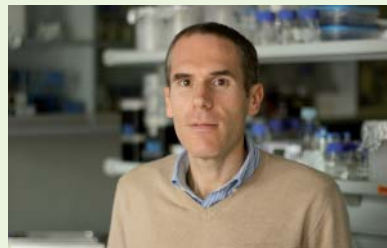


## Microscopy

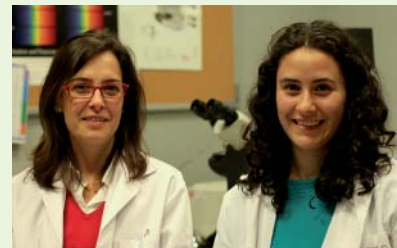
Microscopy is an invaluable tool to directly analyze events that take place in the cell or in a live organism. Its applications, using either fixed samples or live cells, are quite wide and well established in Cell Biology. Moreover, they are considered as extremely powerful to study the function of proteins, its behavior in some structures, and the relationship with other components within a signaling pathway. These studies can be carried out in CABIMER with the support of our Microscopy facility.

The Microscopy unit is one of the most demanded facilities in our center. As such, and in order to provide a better service to all our users, we are continuously making efforts to increase the number of microscopes in the unit, which at the same time allow us to offer additional new techniques that could be useful for the scientists. Specifically, and during this last period, two relevant systems were introduced in the Microscopy unit. One of these systems is designed for the acquisition of large images, or so called mosaic experiments. The benefit in the acquisition of a compound big image is either to show a whole mount/tissue section image at higher detail or to quantify cell phenotypes massively in a single image while maintaining in both cases a high magnification objective and resolution. The other microscope uses a device that projects light in a structured way on the sample at different focal planes, creating several images. These subsequent images are processed in real time using an algorithm, which removes the out-of-focus information before reconstructing them into a final optical section. The resulting image is therefore enhanced in terms of quality and sensitivity. Both systems are now continuously demanded by our researchers, independently of the model system they work in, for resolving and analyzing their results.

The Microscopy facility supports scientists from CABIMER and external entities, (public institutions, hospitals and private companies), throughout the full process of microscopy experiments: designing experiments, teaching techniques, introducing the use of instruments, processing data and analyzing images, and also assists scientists in interpreting and shaping final results. Besides, the facility is responsible for the maintenance of the instruments, in close collaboration with industry partners, to provide non-stop services.



**Fernando Monje-Casas**  
Scientific Coordinator



**Paloma Dominguez Giménez**  
**Ana Cristina Rivas Rivas**  
Technician

## Histology

Histology, as a branch of the morphological sciences, is a very relevant discipline that allows to understand the shape and structure of tissues, and the characterization of abnormalities at the cellular level.

CABIMER has established a very specialized histology service in order to respond the needs of its researches, especially those looking for tumour tissue characterization, developmental histology (embryos), and animal pathology. The samples collected for analysis are treated with the highest quality standards and with the latest technology, providing a full range of histology services to our research community, as well as the neighbor academic and private sectors.

The Histology Core Facility was created in May 2010 as an internal service and since then it has observed an important increment in the demand of the offered services. In last years, we have extended our techniques to insect analysis, becoming an important support for other academic and research institutions.

The histology laboratory offers advice, protocols and equipment allowing fixation techniques, sectioning of tissues and classical staining for easy viewing of samples.

The facility offers methods for the histological analysis of human and animal biological samples. Some of the available methods in this service include the preparation of paraffin embedded samples in the automatic processor of tissue, which simplifies the work of the researches regarding to the manipulation of samples and duration of the protocol. For paraffin blocks and frozen tissues, histological sections can be obtained with an automatic microtome and cryostat, respectively.

For floating samples a vibratome is used. Then, sections can be histological stained or assigned for posterior analysis by immunohistochemistry. The facility is also equipped with a Cytospin for the processing of biological fluids and cell cultures.

The unit is also responsible for new users training and advice in the available equipment. Advanced users have free access to the core facility under internal online booking.



**Manuel Álvarez Dolado**  
Scientific Coordinator



**Cindy Cruz Zambrano**  
Technician

## Model Organism

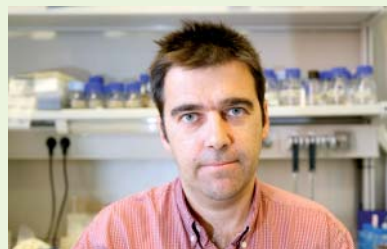
Scientific CABIMER's objectives encompass both the advance in the knowledge of the molecular mechanisms responsible for genetic disorders and cancer and the development of new cellular therapies to address efficiently these diseases. Consistent with these general aims, CABIMER offers a large number of facilities to develop a high quality research based on cell lines and mice. Additionally, CABIMER's research requires the use of different model organisms at two levels:

A. Organisms used as general research tools (required for most research groups). They include the bacteria *Escherichia coli*, which is required for genetic engineering, ectopic expression of recombinant proteins for purification, and in vivo assays of gene expression, the yeast *Saccharomyces cerevisiae*, which is required for in vivo assays for physical interactions between proteins, in vivo assays of gene expression, ectopic expression of recombinant proteins for purification, and vectors for cloning large human and mouse DNA fragments into yeast minichromosomes (YACs), and *Drosophila melanogaster* cell lines infected with baculovirus, which are required for ectopic expression of recombinant proteins for purification.

B. Organisms used as living models by specific research groups to understand the molecular causes of genetic instability and defects in cell cycle progression as two major features of cancer and many genetic disorders. These organisms include the yeast *Saccharomyces cerevisiae*, the worm *Caenorhabditis elegans*, and chicken embryos.

The main objective of this Service is to provide specific facilities for a convenient research with these model organisms. More specifically, this Service is aimed at:

1. Organization, maintenance and handling of specific cell collections
2. Preparation of specific and general solutions and buffers
3. Preparation of media for the growth of different model organisms
4. Growth and collection of high volumes of cell cultures for protein purifications
5. Preparation of competent cells for transformation and electroporation



**Félix Prado**  
Scientific Coordinator



**Cristina Hernández**  
Technician

## Washing and Sterilization

The Washing and Sterilization Unit is a basic and fundamental support service for the dynamics of the Research Center. This Unit is responsible for the collection, processing, washing, sterilization and distribution of all the laboratory material as well as the sterilization of the medium and solutions for the whole Research Center (glassware, plastic and consumables). It also handles the processing of the biological waste generated by the research groups as well as by the different support units, meeting all safety regulations for Biohazardous material.

To carry out this work the Unit is in continuous contact with the different research groups and associated support units, in order to offer them a better service and speed up all new demands that arise.

However, due to the incorporation of new research groups to the Centre, the growth of the existing groups, as well as the generation of new services, the Unit has been adapted to provide a more personalized service mainly focusing on the needs of each research group. We had to increase by more than 50% the ordering of glassware plastic material and consumables, since each group works with different types of materials that have to be processed in different ways. As a consequence of this adaptation, the equipment of the Unit (autoclaves, thermo-disinfector ...) is continuously in service.

All work processes are executed in accordance with the bio-safety regulations, ensuring at all times the quality of the Sterilization Unit, its management and control.



**Francisco Bedoya Bergua**  
Scientific Coordinator



**Mª Jose Figueroa**  
**Mª Dolores Carrión**  
Technician

## General Core Services



### **DIRECTOR**

**Andrés Aguilera**  
Director

### **MANAGEMENT**

**Luis Casas**  
Manager

### **ASSISTANTS**

**Berta Ferrer**  
Executive Assistant  
**Sonia Macías**  
Administration Assistant

### **HUMAN RESOURCES**

**Irene González**  
HHRR Technician

### **ACCOUNTING**

**Carmen Ramos**  
Responsible of Economic Control  
**Inmaculada Uclés**  
Administrative Assistant

### **PURCHASING**

**Francisco J. Dorantes**  
Purchasing Manager

### **STORE HOUSE**

**María Isabel Tovaruela**  
Technician

### **MAINTENANCE**

**Rafael León**  
Technical Maintenance

## Publications

### Publications 2011

- Subtil-Rodríguez A., Reyes J.C. 2011. To cross, or not to cross the nucleosome that is the elongation question. **RNA Biol.** 8:389-393
- Alvarez-Dolado M., Broccoli V. 2011. GABAergic neuronal precursor grafting: implications in brain regeneration and plasticity. **Neural Plast.** 2011:384216
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## Patentes 2011-2015

- Pozo D., R. Klippstein R., González-Campora M.T., de los Monteros V., Trigo I. 2011. "Nanoliposomas funcionalizados con péptidos bioactivos como sistemas para mejorar la citotoxicidad de fármacos antitumorales" P-2011-30185 Universidad de Sevilla, Sistema Sanitario Público Andaluz, Negociaciones con laboratorios Rovi
- Pozo D., Klippstein R., González-Campora M.T., de los Monteros Vargas, Trigo I. 2011. "Nanoliposomas funcionalizados con péptidos" P-2011-30072 Universidad de Sevilla, Sistema Sanitario Público Andaluz, Negociaciones con BioBérica
- Gauthier B.R., St-Onge L., Baquié M., Wollheim C.B. 2011. "Novel methods for preventing or treating diabetes" WO 2011/144725 Fundación Pública Andaluza Progreso and Salud , Luc St-Onge
- Manetsberger J., Gaillard H., Wellinger R., Walzel B. 2012. "Photoresponsive microcapsules and compositions containing same" WO2012104262 A1 Universidad de Sevilla
- Soria B., Martín F. 2012. "Method for the in vitro proliferation of cells derived from tissues of endormal origin" P2011070165. Fundación Progreso y Salud
- Pozo D., Klippstein R. 2012. "Peptide-functionalised nanoliposomes" WO-2012-101309A1. Universidad Sevilla
- Pintor Toro J.A., Moreno Mateos M.A., Rodríguez Mateo C. 2012. "Generacion de genotecas lentivirales de anti-small RNAs" P201231214. CSIC
- Sánchez L. 2012. "Pinza Quirúrgica para la Aproximación y Reducción de fragmentos óseos" P201231694. Fundación Pública Andaluza Progreso y Salud

## Publications

- Rojas González A., Cano González D., Delgado Sainz I., Soria Escoms B., Martín Bermúdez F. 2013. "Método de Obtención de datos útiles para el diagnóstico diferencial de la fibrosis hepática" P201330636. Fundación Pública Andaluza Progreso y Salud, FISEVI, Universidad Pablo de Olavide
- Soria B., Lachaud C., Hmadcha A., Escacena Acosta N., Quesada Fernandez E., Soria F., Alió J., Sanz L. 2013. "Use of Mesothelial Cells in tissue bioengineering and artificial tissues" EP 13382213.0. Fundación Pública Andaluza Progreso y Salud, New Biothechnic, Vissum Corporation
- Soria Escoms B., Hmadcha A., Acosta Lopez M.L., Escacena Acosta N. 2013. "Method for predicting treatment response and test for safe use of mesenchymal stem cells on inflammatory diseases" EP 13382315.3. Fundación Pública Andaluza Progreso y Salud
- Díaz Corrales F.J., Valdés Sánchez M.L., de la Cerda Haynes B, Bhattacharya S.S., Sánchez Barreiro A., Seijo Rey B., Pensado López A. 2014. "Nanoparticulate systems for in vivo transfection" EP14382221.1. Fundación Pública Andaluza Progreso y Salud, Universidad de Santiago de Compostela, CSIC
- Cárdenas J., Ríos R.M. 2014. "Soporte para Inmunofluorescencias" U201330548. CSIC
- Labrador-Garrido A., Pozo D., Roodveldt C. 2014. "Combinaciones de proteínas agregantes y chaperonas moleculares para el tratamiento de proteinopatías o enfermedades conformacionales" PCT-ES2014-070704. Fundación Pública Andaluza Progreso y Salud, Universidad de Sevilla. En negociaciones con VIDIA-HEALTH
- Luis Alió J., Soria B., Lachaud C., Hmadcha A., Escacena N., Quesada E., Soria F. 2014. "Use of mesothelial cells in tissue bioengineering and artificial tissues" PCT/EP2014/061746. Fundación Pública Andaluza Progreso y Salud, Newbiotechnic SA, Vissum Corporación
- Soria B., Hmadcha A., Alejandro Madrigal J., Saudemont A., Cox S. 2014. "Use of cord blood plasma to treat NK cell-mediated diseases and IFN-gamma mediated diseases" EP 14382348.2 / WO2016/042041 A1, Fundación Pública Andaluza Progreso y Salud, Anthony Nolan, Instituto de Salud Carlos III
- Rojas González A., Cano González D., Delgado Sainz I., Soria Escoms B., Martín Bermúdez F. 2014. "Método de obtención de datos útiles para el diagnóstico diferencial de la fibrosis hepática" P201330636. Fundación Pública Andaluza Progreso y Salud, FISEVI, Universidad Pablo de Olavide
- Soria B., Hmadcha A., Tejedó J., Bedoya F.J., Cahuana G.M., Rodríguez-Campins B., Tapia Limonchi R., Beltrán-Poveda A. 2015. "Improved Culture Medium for human Progenitors Cells (hPC)" EP 15382417.2. Fundación Pública Andaluza Progreso y Salud, Universidad Pablo Olavide, NewBiotechnic S.A.
- Saudemont A., Alejandro Madrigal J., Escobedo-Cousin M., Jackson M.N., Luévano M., Laza Briviesca R., Derniame S., Ariza L., Bonnet D., Blundell M., Thrasher A., Cooper N., Soria B., Hmadcha A., Querol S. 2015. "Stem Cell with enhanced clonogenic, migratory and homing capacity" EP 15382429.7. Fundación Pública Andaluza Progreso y Salud, Anthony Nolan, The Francis Crick Institute Limited, UCL Business PLC, Imperial Innovations Limited, Banc de Sangs i Teixits, BTG
- Soria B., Hmadcha A., Salguero-Aranda C., Bedoya F.J., Tejedó J., Martín Bermudo F., Tapia Limonchi R., Cahuana G.M., Rodríguez-Campins B., Beltrán-Poveda A. 2015. "Method for obtaining pancreatic beta cell surrogates by increasing pancreatic and duodenal homeobox 1 (PDX-1) expression" PCT/EP2015/070501. Fundación Pública Andaluza Progreso y Salud, Universidad Pablo de Olavide, Instituto de Salud Carlos III, NewBiotechnic S.A.
- Cobo-Vuilleumier N., Pozo-Perez D., St-Onge L., Gauthier B.R. 2015. "Anti-inflammatory Agents".EP1538216. Fundación Pública Andaluza Progreso y Salud, Universidad de Sevilla
- Cejudo M., Lopez-Enrique S., Roodveldt C., Muñoz-Franco J., Marquez-Infante C., Pozo D. 2015. "Biomarkers for amyotrophic lateral sclerosis (ALS)" P201531271. Servicio Andaluz de Salud, Universidad de Sevilla. En negociaciones con VIDIA-HEALTH
- Soria B., Hmadcha A., Acosta L., Escacena N. 2015. "Method for predicting treatment response and test for safe use of mesenchymal stem cells on inflammatory diseases" PCT/EP2014/066600. Fundación Pública Andaluza Progreso y Salud
- Wellinger R., Khair N., 2015. "Nanoparticles for diagnosis and drug delivery" PCT/EP15382465.1. Universidad de Sevilla, CSIC



## Doctoral Theses

### 2011

• **Ageda Gema Espina Zambrano**

"Función de la proteína pttg1 en la regulación de la expresión del gen dlk1 en procesos de proliferación y diferenciación. Análisis funcional de las isoformas PTTG1, PTTG2 y PTTG3". Thesis Supervisor: Dr. José A. Pintor Toro CSIC/Universidad de Sevilla

• **Angelica Horrillo Ledesma**

"Epigenética de los procesos de autorrenovación, pluripotencialidad y diferenciación de las células troncales" Thesis Supervisor: Dr. Bernat Soria and Abdelkrim Hmadcha. Universidad de Sevilla

• **Sandra Muñoz Galván**

"Factores implicados en la reparación de rotura de doble cadena por recombinación entre cromátidas hermanas" Thesis Supervisor: Dr. Andrés Aguilera. Universidad de Sevilla

• **Maria Salud Dominguez Sanchez**

"Análisis de factores que intervienen en la biogénesis del ARNm y la estabilidad genómica en células de mamíferos" Thesis Supervisor: Dr. Rosa Luna and Dr. Andrés Aguilera. Universidad de Sevilla

• **Ivan Zipancic**

"Estudio del potencial terapéutico de los trasplantes de precursores GABAérgicos en modelos animales de epilepsia" Thesis Supervisor: Dr. Manuel Álvarez Dolado Universidad de Valencia

• **Marta Clemente**

"Papel del Emsablaje de la Cromatina en la Estabilidad Genética" Thesis Supervisor: Dr. Félix Prado. CSIC/Universidad de Sevilla

### 2012

• **Sandra Gavalá Martín**

"Fenómenos de Inestabilidad Genómica Ligados a la Transcripción del DNA en Eucariotas" Thesis Supervisor: Dr. Andrés Aguilera. Universidad de Sevilla

• **Tania Sánchez Pérez**

"Parada mitótica y Sensibilidad a TRAIL en células tumorales de mama" Thesis Supervisor: Dr. Abelardo López Rivas. Universidad de Sevilla/CSIC

• **Juan Luis Herrera Cabello**

"Papel inmunomodulador del péptido neuroprotector NAP derivado de la proteína Activity-dependent Neuroprotective Protein (ADNP)" Thesis Supervisor: Dr. David Pozo Pérez. Universidad de Sevilla/CABIMER

• **Margarita Romero Durán**

"A Novel Locus for Cone-Rod Dystrophy and Evaluation of Fox 12 as a Candidate Gene for Retinal Degeneration" Thesis Supervisor: Dr. Shom S. Bhattacharya and Dr. Kunka Kameranova. Universidad de Sevilla

• **Irene Felipe Abrio**

"Implicación de la Maquinaria de Transcripción en el origen de la Inestabilidad Genética" Thesis Supervisor: Dr. Andrés Aguilera. Universidad de Sevilla

• **Rafael Fernández-Montesinos**

"Efectos inmunomoduladores del péptido bioactivo NAP y evaluación terapéutica en la inflamación" Thesis Supervisor: Dr. David Pozo Perez. Universidad de Sevilla/CABIMER

• **Néstor García Rodríguez**

"Studies on the effect of Manganese on DNA Metabolism and Cell Cycle" Thesis Supervisor: Dr. Ralf E. Wellinger. Universidad de Sevilla

• **Román González Prieto**

"Mecanismos y regulación por ciclo de la reparación de daño replicativo por recombinación Homóloga" Thesis Supervisor: Dr. Felix Prado. CSIC/Universidad de Sevilla

• **Rosa Martín Pérez**

"Regulación de la sensibilidad a TRAIL y activación diferencial de apoptosis en células normales y tumorales por estrés en el retículo endoplásmico" Thesis Supervisor: Dr. Abelardo López Rivas. Universidad de Sevilla/CSIC

### 2013

• **M<sup>a</sup> del Mar Gámez del Estal**

"Caracterización y análisis funcional de los genes homólogos de pttg1/Securina, pttg2 y pttg3" Thesis Supervisor: Dr. José A. Pintor Toro and Dr. Cristina Méndez Vidal. CSIC

• **Alonso Rafael Tapia Limonchi**

"Evaluation of the effect of nitric oxide on gene expression in embryonic stem cells" Thesis Supervisor: Dr. Juan R. Tejado Huamán and Dr. Francisco Bedoya Bergua. CABIMER/Universidad Pablo de Olavide

• **Pablo García Gutierrez**

"Función de Brd2 en la Coordinación entre Proliferación y Diferenciación en el Sistema Nervioso Central de Vertebrados" Thesis Supervisor: Dr. Mario García Dominguez. Universidad de Sevilla

• **Marcela Garita Hernández**

"Influence of oxygen tension on the differentiation of embryonic stem cells towards photoreceptors and other retinal phenotypes" Thesis Supervisor: Dr. Shomi S. Bhattacharya and Dr. Slaven Erceg. Universidad de Sevilla/CABIMER

• **Elena Vázquez Chávez**

"Caracterización de las funciones del factor remodelador de cromatina CHD8 en activación transcripcional y progresión del ciclo celular" Thesis Supervisor: Dr. José C. Reyes Universidad de Sevilla/CABIMER



• **Maikel Castellano Pozo**

“Inestabilidad Genética y Cambios en la Cromatina en Mutantes del Tho Mitosis y Meiosis de Eucariotas Modelo” Thesis Supervisor: Dr. Tatiana García Muse and Dr. Andrés Aguilera. Universidad de Sevilla/CABIMER

## 2014

• **Rebecca Klippstein Martin**

“Nanotechnology approaches for improved vasoactive intestinal peptide based-drug delivery systems” Thesis Supervisor: Dr. David Pozo Pérez. Universidad de Sevilla/CABIMER

• **Daniel Rodríguez Martínez**

“Terapia celular mediante precursores gabaérgicos y su aplicación en encefalopatías infantiles” Thesis Supervisor: Dr. Manuel Álvarez Dolado Universidad de Sevilla/CABIMER

• **Tatiana Alfonso Pérez**

“Función Citoplásmica de la proteína supresora de tumores hSNF5” Thesis Supervisor: Dr. José C. Reyes and Dr. Mario García-Domínguez Universidad de Sevilla/CABIMER

• **Ruth Stuckey**

“Studies on the effects of persistent RNA priming on DNA replication and genomic stability” Thesis Supervisor: Dr. Ralf E. Wellinger and Dr. Andrés Aguilera. Universidad de Sevilla/CABIMER

• **José María Santos Pereira**

“Papel de NPL3, NUP84 y otros factores de transporte de mRNA en el Mantenimiento de la Integridad del Genoma” Thesis Supervisor: Dr. Andrés Aguilera. Universidad de Sevilla/ CABIMER

• **Mauricio Valerio Santiago**

“Mecanismos de Regulación de la Segregación cromosómica y la salida de Mitosis” Thesis Supervisor: Dr. Fernando Monje. Universidad de Sevilla/ CABIMER

• **Emilia Herrera Moyano**

“Implicación de los complejos TFIIF y FACT en el mantenimiento de la integridad del genoma” Thesis Supervisor: Dr. Andres Aguilera. Universidad de Sevilla/CABIMER

## 2015

• **Daniella Pezolla**

“Diferenciación de las células troncales embrionarias humanas hacia un linaje beta-pancreático: estudios enfocados a procesos de maduración” Thesis Supervisor: Dr. Bernat Soria and Dr. Abdelkrim Hmadcha. Universidad de Sevilla/CABIMER

• **Marina Murillo Pineda**

“Dinámica de la Cromatina e Integridad Genómica” Thesis Supervisor: Dr. Felix Prado. Universidad de Sevilla/CABIMER

• **Ada Yeste Bernal**

“Use of gold nanoparticles as a tool for the induction of regulatory T cells in Multiple Sclerosis” Thesis Supervisor: Dr. Francisco J. Quintana and Dr. David Pozo Pérez. Universidad de Sevilla/CABIMER

• **Carmen María Jimenez Moreno**

“Role of PAX4 y PAX8 in Pancreatic Islets Physiology and Patophysiology” Thesis Supervisor: Dr. Benoit Gauthier and Dr. Petra Isabel Lorenzo Ovejero. Universidad de Sevilla/CABIMER

• **Ana María Aramburu del Boz**

“Caracterización Fenotípica y Terapia Génica del ratón PRPF31 A216P” Thesis Supervisor: Dr. Shomi S. Bhattacharya and Dr. Francisco J. Díaz Corrales. Universidad de Sevilla/CABIMER

## Seminar Speakers

### January 2011

"Mechanisms of pluripotency and differentiation in mammalian embryonic stem cells" January, 14th. **Roger Pedersen**. Department of Surgery, University of Cambridge, Cambridge, UK.

"Cancer Epigenetics" January, 28th. **Manel Esteller**. Bellvitge Institute for Biomedical Research. Catalan Institute of Oncology (IDIBELL-ICO), Barcelona, Spain.

### February 2011

"Lipid Metabolism and Function in Model Organisms and Cells" February, 11th. **Howard Riezman**. Department of Biochemistry, University of Geneva, Geneva, Switzerland.

"From pre mRNA splicing to neurodegeneration, a new role for the hnRNP TDP 43" February, 25th. **Prof. Francisco Baralle**. ICGEB, Trieste, Italy.

### March 2011

"Cell cycle exit, cell differentiation and cancer" March, 4th. **Sergio Moreno**. Instituto de Biología Molecular y Celular del Cáncer (CSIC), Salamanca, Spain.

"Controlling recombination" March, 11th. **Simon Boulton**. Clare Hall Laboratories, London Research Institute, Cancer Research UK.

"Ubiquitin and coordination of mRNA biogenesis" March, 18th. **Catherinem Dargemont**. Institut Jacques Monod, Paris, France.

"Sara endosomes and asymmetric cell division" March, 25th. **Prof. Marcos González-Gaitán**. University of Geneva, Switzerland.

### April 2011

"Responses to stress mediated by SAPKs" April, 8th. **Francesc Posas**. Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain.

### October 2011

"The impact of histone modifications and chromatin alterations on gene expression, stem cell differentiation and cancer" October, 7th. **Luciano Di Croce**. Centre de Regulació Genòmica (CRG), Barcelona, Spain.

"Chromatin and transcription regulate alternative splicing" October, 20th. **Alberto R. Kornblihtt**. IFIBYNE-CONICET – Universidad de Buenos Aires, Argentina

"Emerging roles of microRNAs in the control of pancreatic beta cell functions" October, 28th. **Romano Regazzi**. Université de Lausanne, Switzerland.

### November 2011

"Enhancer dynamics during vertebrate development and its influence on the genomic architecture" November, 11th. **Jose L. Gómez Skarmeta**. Universidad Pablo de Olavide, Seville, Spain.

"Interplay between pathways that maintain genome stability" November, 21st. **Andre Nussenzweig**. National Institute of Health/National Cancer Institute (NIH/NCI), USA.

"Nuclear and cytoplasmic regulation of gene expression by the CPEB-family of RNA-binding proteins. From cell cycle to tumor development" November, 25th. **Raúl Méndez**. Institute for Research in Biomedicine (IRB), Barcelona.

### December 2011

"Understanding and Treating Malignant Melanoma" December, 16th. **Marisol Soengas**. Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

### January 2012

"Why do we not understand the impairment of oxidative phosphorylation system" January, 13th. **J. Antonio Enríquez**. Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain.

"Genome stability: impact on cancer, aging and longevity" January, 27th. **Jan H. Hoeijmakers**. Erasmus University, Rotterdam, NL.

### February 2012

"Transcription and its interface with other DNA-related processes" February, 10th. **Jesper Q. Svejstrup**. Cancer Research UK, London Research Institute, UK.

### March 2012

"Cancer-initiating cells in glioblastoma" March, 2nd. **Joan Seoane**. Vall D'Hebron Hospital, Barcelona, Spain.

"From oncogenic viruses to chromatin and cancer" March, 9th. **Moshe Yaniv**. Institut Pasteur, Paris, France.

"Nucleocytoplasmic transport in the midzone membrane domain controls mitotic spindle disassembly" March, 16th. **Juan Jiménez**. CABD, UPO-CSIC, Seville, Spain.

"Cell competition and tumour development in Drosophila" March, 23rd. **Ginés Morata**. Centro de Biología Molecular (CBM), Madrid, Spain.



## April 2012

“Dissecting mechanisms controlling somatic cell reprogramming and tissue regeneration” April, 20th. **M. Pia Cosma**. Centre de Regulació Genòmica (CRG), Barcelona, Spain.

## May 2012

“Neural stem cells: life at home” May, 25th. **Isabel Fariñas**. CIBERNED – Universidad de Valencia, Spain.

## October 2012

“Transcription, replication, chromosomal common fragile site instability and the characterization of the human TREX-2 complex” October, 19th. **Laszlo Tora**. UMR 7104 CNRS, INSERM U964, Université de Strasbourg (UdS), France.

## November 2012

“The mitochondrial H<sup>+</sup>-ATP synthase-gear switch of metabolism in human tumors” November, 9th. **Jose Manuel Cuezva Marcos**. Centro de Biología Molecular “Severo Ochoa”. Universidad Autónoma de Madrid, Madrid, Spain.

“LINE-1 retrotransposition in Fanconi Anemia patients” November, 30th. **Jose Luis García Pérez**. Centro Pfizer - Universidad de Granada - Junta de Andalucía de Genómica e Investigación Oncológica. Granada, Spain.

## December 2012

“Mouse models to investigate cohesin functions” December, 14th. **Ana Losada**. CNIO, Madrid, Spain.

## January 2013

“Controlling genome integrity via post-translational regulation of the eukaryotic replisome” January, 25th. **Karim Labib**. Paterson Institute for Cancer Research, University of Manchester, UK.

## February 2013

“Polycomb proteins in nuclear organisation and developmental regulation in Drosophila” February, 22nd. **Giacomo Cavalli**. Chromatin and Cell Biology lab. Institute of Human Genetics – CNRS. Montpellier, France.

## March 2013

“Symmetry, proportions, and accuracy in size control: role of Drosophila insulin-like peptide 8”. March, 15th. **Maria Domínguez**. Profesora de Investigación del CSIC. Instituto de Neurociencias, CSIC-UMH, Alicante, Valencia, Spain.

## April 2013

“DNA strand break repair, genome instability and cancer” April, 12th. **Stephen West**. London Research Institute, London, UK.

“Treatment of spinal cord injury by transplantation of neural stem cells” April, 29th. **Kinichi Nakashima**. Nara Institute of Science and Technology, Takayama, Ikoma, Nara-cho, Japan.

## May 2013

“Neuroendocrine regulation of the stem cell niche as a therapeutic target” May, 3rd. **Simón Méndez Ferrer**. CNIC, Madrid, Spain.

“Common fragile sites: mechanism of activation and impact on chromosome instability in cancers” May, 17th. **Michelle Debatisse**. Institut Curie, Paris, France.

## October 2013

“Factors Promoting Pancreatic Beta Cell Replication and Regeneration” October, 1st. **Maureen Gannon**. Vanderbilt University medical Center, Nashville, USA.

“Nucleosomal organization and evolution of the eukaryotic genome” October, 18th. **Francisco Antequera**. IbfG-CSIC, Salamanca, Spain.

## November 2013

“Histone demethylases: new regulators of nervous system development” November, 15th. **Marian Martínez-Balbás**. IbmB-CSIC, Barcelona, Spain.

“Exploring the roles of replicative stress in cancer and ageing” November, 29th. **Oskar Fernandez-Capetillo**. CNIO, Madrid, Spain.

“Clustering, conformational changes and cooperativity in the T-cell receptor” December, 13th. **Balbino Alarcón**. CBM Severo Ochoa-CSIC-UAM, Madrid, Spain.

## January 2014

“Cellular responses to spontaneous replication stress” January, 17th. **Philippe Pasero**. Institute of Human genetics-CNRS-Montpellier, France.

“Understanding the Notch pathway during the specification of Hematopoietic Stem Cells in the mouse embryo” January, 24th. **Anna Bigas**. IMIM-Hospital del Mar, Barcelona, Spain.

## February 2014

“Pancreatic cancer: does differentiation set the stage for inflammation and carcinogenesis?” February, 7th. **Francisco Real**. CNIO, Madrid, Spain.

“Acquisition of cell polarity in 3D environments” February, 14th. Fernando Martin-Belmonte. CBM Severo Ochoa-CSIC-UAM, Madrid, Spain.

## Seminar Speakers

### March 2014

"Coordination of chromosome segregation with cell division" March, 7th. **Gislene Pereira**. DKFZ-ZMBH Alliance, Heidelberg, Germany.

"PrimPol, a primitive primase/polymerase involved in damage tolerance and replication restart in human cells" March, 28th. **Luis Blanco**. CBM Severo Ochoa-CSIC-UAM, Madrid, Spain.

### April 2014

"CIN-induced tumorigenesis in Drosophila" April, 11th. **Marco Milán**. IRB-Barcelona, Spain.

### May 2014

"Transcriptional regulation of outflow tract morphogenesis" May, 6th. **Brian Black**. Cardiovascular Research Institute, University of California, USA.

"Mechanisms and consequences of replication fork collapse and restart" May, 16th. **Anthony Carr**. MRC-University of Sussex, England.

"Molecular chaperones: nanomachines in the protein folding pathway" May, 23rd. **José María Valpuesta**. Centro Nacional de Biotecnología (CNB-CSIC) Madrid, Spain.

### June 2014

"Peripheral nervous system stem cells" June, 6th. **Patrick Charnay**. ISERM-Ecole Normale Supérieure, Paris, France.

"Harnessing the regenerative potential of pancreatic islet cells as treatment for Diabetes Mellitus" June, 20th. **Benoit R. Gauthier**. CABIMER, Seville, Spain.

### October 2014

"Competing networks in cell fate decisions: the TRAIL system" October, 3rd. **Abelardo Lopez Rivas**. CABIMER-CSIC Seville, Spain.

"Mechanisms of replication fork monitoring and protection" October, 24th. **Rodrigo Bermejo**. Institute for Functional Biology and Genomics-CSIC. Salamanca, Spain.

### November 2014

"Consequences of ribonucleotides in DNA" November, 6th. **Hannah Klein**. Department of Biochemistry and Molecular Pharmacology. New York University School of Medicine, New York, USA.

"Maintaining genome integrity through mitosis" November, 21st. **Michael Lisby**. Department of Biology, University of Copenhagen, Copenhagen, Denmark.

### December 2014

"Orienting chromosomes in mitosis and meiosis" December, 12th. **Adele Marston**. The Wellcome Trust Centre for Cell Biology, School of Biological Sciences, University of Edinburgh, Edinburgh, UK.

### January 2015

"Inducing alpha-cell-mediated beta-like cell neogenesis" January, 9th. **Patrick Collombat**. Université Nice Sophia Antipolis, Institut de Biologie Valrose, Nice, France.

"The determinants of protein oligomer toxicity" January, 16th. **Fabrizio Chiti**. Experimental and Clinical Sciences, Section of Biochemistry, University of Florence, Italy.

### March 2015

"Single-molecule approaches to study double-stranded DNA break resection" March, 6th. **Fernando Moreno Herrero**. Centro Nacional de Biotecnología, CSIC, Madrid, Spain.

"Functional analysis of the cohesin complexes in mammalian reproduction" March, 13th. **Alberto Pendás**. Instituto de Biología Molecular y Celular del Cáncer, CSIC, Salamanca, Spain.

"Mechanisms underlying somatic reprogramming" March, 27th. **Dr. Natalia Tapia**. Independent Junior Group Leader Heinrich-Heine Universität Düsseldorf, Germany.

### April 2015

"DNA replication and genome stability maintenance: novel molecular insights using a vertebrate cell free system" April, 10th. **Vincenzo Costanzo**. The FIRC Institute of Molecular Oncology (IFOM) Foundation; Milan, Italy.

"Cone Photoreceptor pathogenesis in retinitis pigmentosa" April, 17th. **Hemant Khanna**. UMASS Medical School, Worcester, Massachusetts, USA.

### May 2015

"Chromatin dynamics in epithelial-mesenchymal transition (EMT)" May, 8th. **Sandra Peiró**. Institut Hospital del Mar d'Investigacions Mèdiques-PRBB, Barcelona, Spain. "Molecular and structural understanding of DNA repair using 3D-Electron Microscopy" May, 22nd. Oscar Llorca. Centro de Investigaciones Biológicas, CSIC, Madrid, Spain.

### June 2015

"Chromatin assembly in genome integrity and cell cycle progression" June, 12th. **Félix Prado**. CABIMER, CSIC, Seville, Spain



## October 2015

“GATA factors in pancreas and liver development and disease” October, 9th  
**Anabel Rojas**. CABIMER, Sevilla, Spain.

“Translation and cell-cycle transitions” October, 15th. **Erik Boye**. Institute  
for Cancer Research. Oslo, Norway.

## November 2015

“Functional analysis of the cohesin complexes in mammalian reproduction”  
November, 6th. **Alberto Pendás**. Centro de Investigación del Cáncer.  
Salamanca, Spain.

“Topoisomerase II intertwines sister chromatids post-replication at cohesin  
sites” November, 20th **Luis Aragón**. MRC Clinical Sciences Centre -  
Imperial College. London, UK.

“Gene Regulatory Networks Guiding Photoreceptor Development and  
Disease” November, 27th. **Anand Swaroop**. National Eye Institute – NIH.  
Bethesda, USA.

## Master Students

### 2011-2012

- Francisco P. Juárez Vicente.  
Supervisor: Mario García-Domínguez. Universidad de Sevilla
- Andrés Cruz García. Supervisor: Pablo Huertas. Universidad de Sevilla
- Isabel Soria Bretones. Supervisor: Pablo Huertas. Universidad de Sevilla
- Miguel Muñoz-Bravo. Ralf Wellinger. Universidad de Sevilla
- Maria Zeleznik. Supervisor: Pablo Huertas. Wroclaw University, Polonia
- Alejandro Álvarez Quilón. Supervisor: Felipe Cortés. Universidad de Sevilla
- Emilio Javier López Beas. Supervisors: Bernat Soria and Abdelkrim Hmadcha. Universidad de Granada
- Ángeles Martín Bernal. Supervisor: Dunja Lukovic.  
Universidad Pablo de Olavide
- Irene Salas Armenteros. Supervisor: Andrés Aguilera. Universidad de Sevilla
- Sara Maisanaba. Supervisor: Franz Martín. Universidad Pablo de Olavide
- Manuel Barceló. Supervisor: Franz Martín. Universidad Pablo de Olavide
- Enric Llorens. Supervisor: David Pozo. Universidad de Barcelona

### 2012-2013

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- Giorgia Cerqueni. Supervisor: Franz Martín. Università Carlo Bo Urbino, Italy
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### 2013-2014

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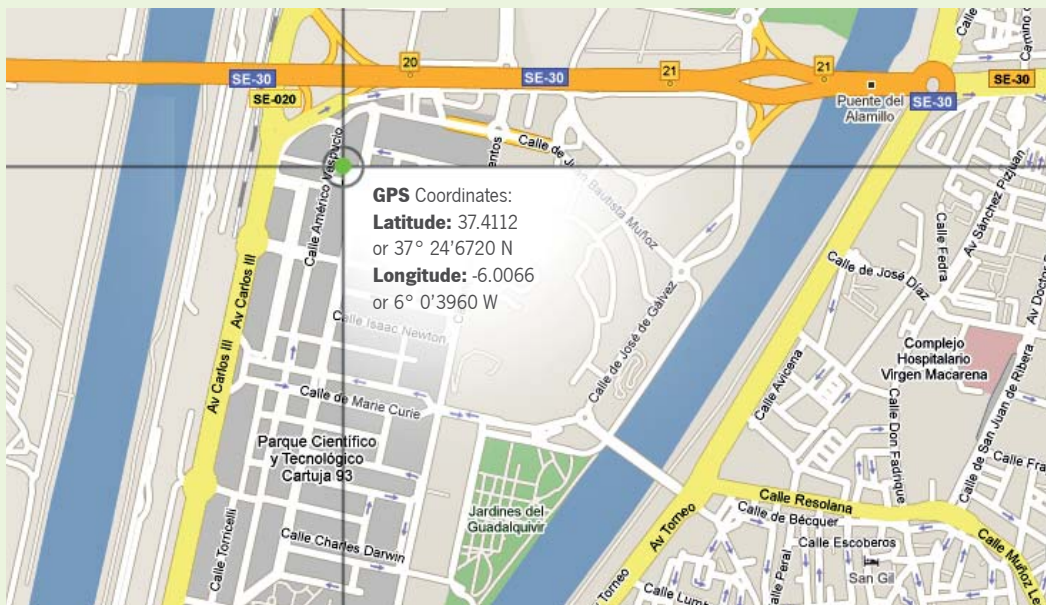
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