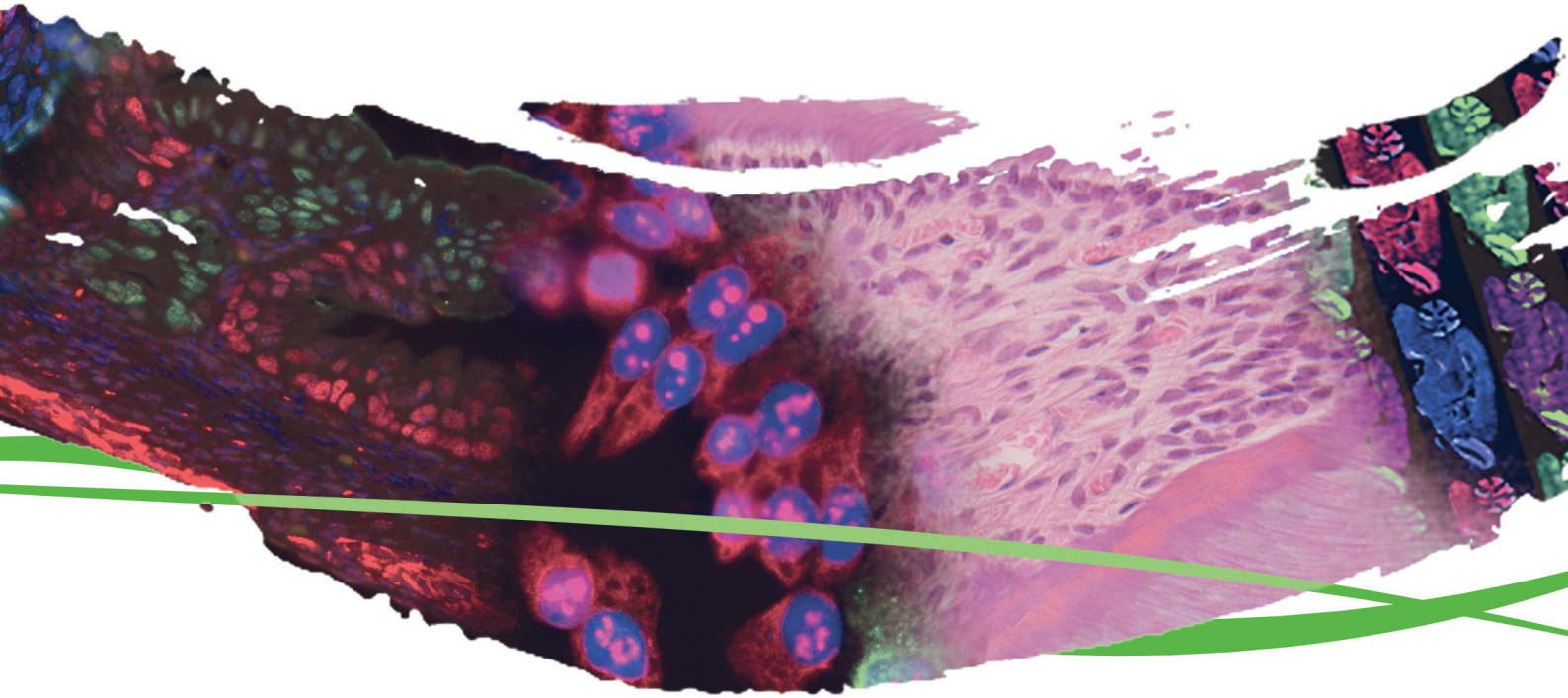
cabimer

Scientific **Report**

2018/2020



Junta de Andalucía

CSIC
Consejo Superior de Investigaciones Científicas

Universidad de Sevilla

Universidad Pablo de Olavide
Sevilla

cabimer

Scientific **Report**

2018/2020

Contents

Scientific Report 2018-2020

Prof. Andrés Aguilera

Director

Welcome

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 2018 to 2020. As a groundbreaking multidisciplinary biomedical research center in Andalusia, CABIMER draws 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 provides 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, and international seminars take place in the Center on a regular frequency all year round, improving the recognition and visibility of its research and researchers.

During this 3-year period there has been a real improvement of CABIMER activities and infrastructural facilities to support the science undertaken by the 23 actual Principal Investigators (PI's), which include 5 new emerging PIs, and their group members. In 2018, CABIMER has partially renovated the Scientific Advisory Board formed by prestigious European Scientists and has stimulated the interaction and collaborations between the research groups of the Center with the celebration of internal scientific workshops and retreats for the young investigators, among other events. Some highlights of the past 3 years are the success of CABIMER researchers in obtaining funding from competitive calls from national and international agencies, such as the European Research Council or the Juvenile Diabetes Research Foundation, or Marie Skłodowska Curie grants, a significant improvement of the quality of its publications and grant incomes, or the number and quality of PhD students and postdoctoral researchers, which has led to the defense of 21 PhD theses during this 3-year period and more than 155 publications, among other achievements. It is worth highlighting the celebration of the First CABIMER International Workshop in February 2020 on "Trends in Genome Integrity and Chromosome Dynamics" with highly recognized invited speakers and attendants from all over the world that had a high international repercussion, and with which CABIMER initiates its series of annual international meetings.

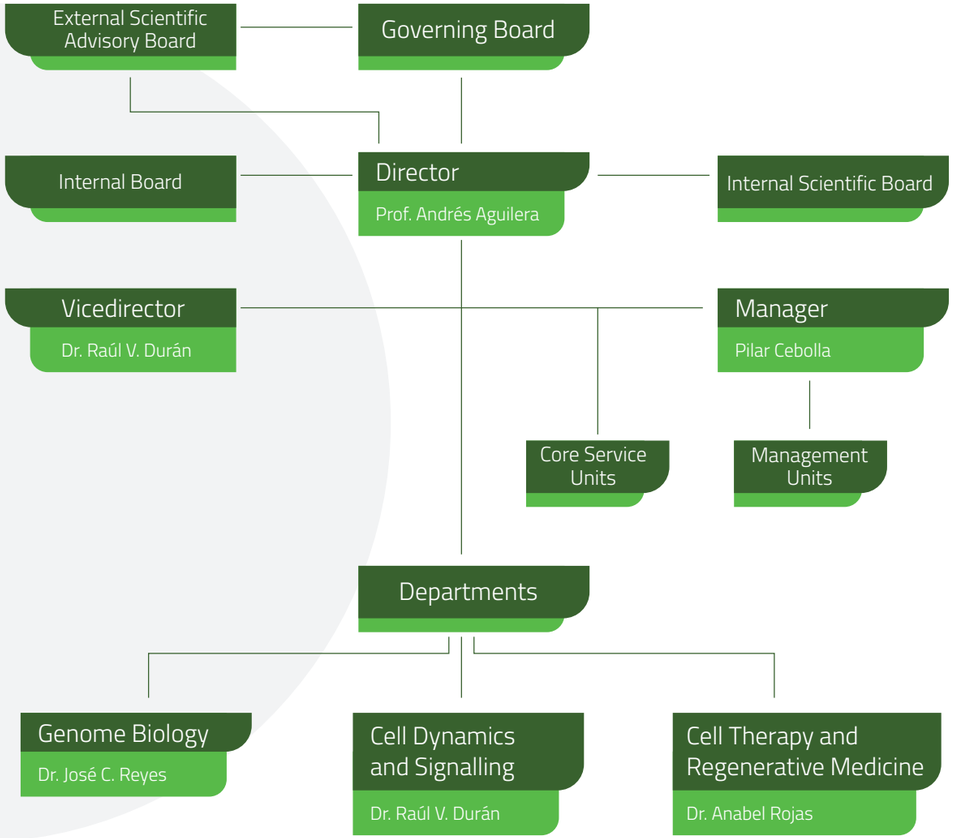
In the 2018-20 period CABIMER has updated and acquired new equipment for its 9 fully-functional core services including the state of the art Biological Research Unit with a special unit for the generation of genetically modified mice, the Genomic platform for the use of external and internal services, the advanced Imaging unit, the nationally accredited GMP facility, as well as Histology and Model organism services to support the different research activities of the Center using the most modern and high-tech molecular and cellular technologies. A strong investment in image analysis and next-generation sequencing has strongly expanded our technical capabilities. CABIMER was included in one of the 2019 Nature lists of top 100 specialized Biomedical Research Centers in the world, and was awarded with the Plaque of Honor of the Province of Seville, given in a public ceremony hosted by the President of Andalusia. CABIMER has been awarded an important grant from Junta de Andalucía to support its research and implement its potential to obtain the recognition of a Research Center of Excellence at the national level.

CABIMER is successfully increasing its reputation as an International Research Center of Excellence and a major centre of biomedical research in Spain. To accomplish these goals and improve its capabilities in the next future CABIMER is preparing a new Strategic Plan for the next 4 years (2021-2024) that aim at expanding the number of research groups and research lines, with special emphasis on young researchers and the incorporation of well-established and successful groups. We are proud of the effort and dedication of all our PI's and researchers, as well as the support staff who have all contributed to the success of CABIMER as a referent in Molecular Biology and Biomedical research in Spain, with an increasing international visibility. I do not want to ignore the negative impact that the SARS-CoV-2 pandemic has had on our day-to-day life and research, but we are optimistic that we will soon be able to adapt to the new post-pandemic era and resume our activity in the best of the conditions. 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.

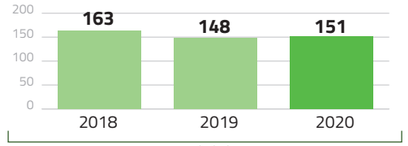
CABIMER is a groundbreaking multidisciplinary biomedical research center in Andalusia.

Scientific Report 2018-2020

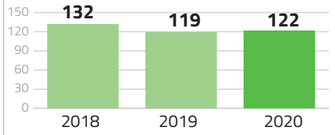
Organization and Outreach



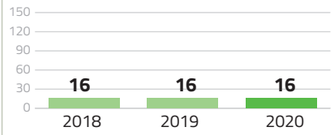
Cabimer staff



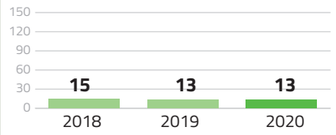
Researchers



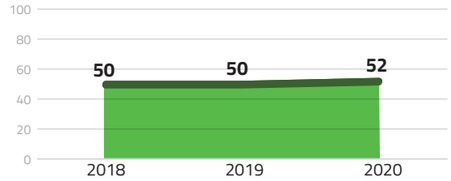
Scientific services



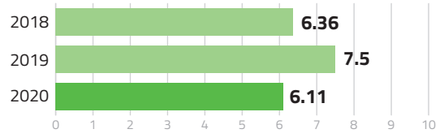
Administration & Technical support



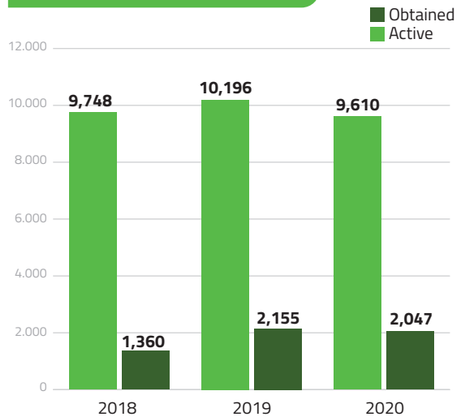
Publications in JCR-Indexed Journals



Average impact factor



Evolution of research funding (K€)



Genome Biology

The department of Genome Biology is focused on the study of fundamental processes that keep genomic homeostasis of the cells, both in normal and pathological conditions. CABIMER research covers different aspects of genome dynamics, including genome instability, DNA recombination, replication and repair, DNA damage response, chromatin integrity, chromosomal segregation, epigenetics and gene expression, with a special focus in Genomics and epigenomics approaches. Genomic instability is the cause of numerous congenital syndromes and rare diseases as well as somatic diseases, specially cancer and aging. Therefore, an important part of our research interest is devoted to understand how different aspects of the genome metabolism are coordinated to avoid genomic instability and the mechanisms and factors involved in genome protection. Other groups study the epigenetic regulation and dynamics during cell cycle and processes of cell differentiation, tissue plasticity and cell signaling and how alteration of this processes causes diseases. The research lines of 9 groups of the Center are included in this area with fruitful collaborations.

HEAD OF DEPARTMENT

Dr. José C Reyes

RESEARCH GROUPS

1. **Epigenetics and gene expression**
   Dr. José C. Reyes
2. **Genome Instability & Cancer**
   Prof. Andrés Aguilera
3. **Chromatin integrity and function**
   Dr. Félix Prado
4. **Mitochondrial plasticity and replication**
   Dr. Ralf E. Wellinger
5. **DNA Double Strand Break Repair**
   Dr. Pablo Huertas
6. **Molecular Oncology and Targeted Therapies**
   Dr. Andrés López-Contreras
7. **DNA Damage Response During Meiosis**
   Dr. Tatiana García-Muse
8. **Transcription and mRNA Processing**
   Dr. Silvia Jimeno-González
9. **Replication and Nuclear Dynamics**
   Dr. Cristina González-Aguilera

FORMER GROUP

DNA-damage response
Dr. Felipe Cortés-Ledesma (finished in 2019)

Dr. José C. Reyes

Epigenetics
and Gene Expression

Group Leader
Head of Department

Genome Biology Department

Current position

- Since 2009: Scientific Researcher, National Council for Research, CSIC/CABIMER
- Since July 2016: Chair of the Genome Biology Department of CABIMER, Seville, Spain

Group Members

Postdocts
- Maria Ceballos-Chávez

PhD Students
- Laura Basurto
- Elena Gómez-Marín
- Elena Sánchez Escabias
- José Antonio Guerrero-Martínez

Technician
- Isabel Pozuelo Sánchez

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. The main goal of our group is to understand how chromatin of regulatory elements and gene bodies change during transcription, how these changes are regulated and inherited and what protein factors are responsible for them. We specially investigate how alterations of these chromatin mechanisms are implicated in human disease, particularly in cancer.

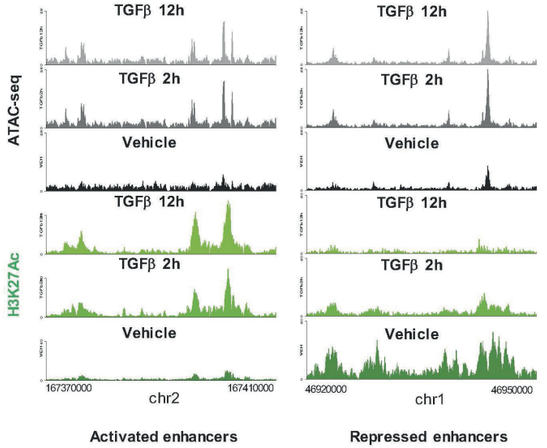
Research Highlights

Chromatin factors involved in Epithelial to Mesenchymal Transition.

Epithelial and mesenchymal cellular phenotypes are the edges of a spectrum of states that can be transitory or stable. The epithelial to mesenchymal transition (EMT) (Figure 1) and its reversion (MET) have attracted considerable interest due to the fact that they are related to tumor cells dissemination and metastasis formation. In our group we investigate epigenetic changes that occurs during EMT and MET and the chromatin factors implicated. During the period 2018-2020 we have studied the role of TBL1 (Rivero et al, 2019), TDRD9 (Guijo et al., 2018) and other chromatin factors in EMT and cancer.

Enhancers regulation by TGFß

Enhancers are DNA sequences that contain multiple binding sites for sequence-specific transcription factors and are classically defined as elements able of activating distant basal promoters regardless of their distance and orientation relative to them. The human genome contains more than 1.000.000 of poorly characterized enhancers which constitute an important part of the non-coding genome. Most of the diseases and predispositions caused by mutations at enhancers are uncharacterized and their study constitutes one of the major challenges of human genetics. Therefore, understanding the mechanisms of enhancer function and regulation is of paramount importance from a basic and also from a biomedical translational point of view. During the period 2018-2020 we have mapped and catalogued all the enhancers in mouse epithelial mammary cells and have characterized their regulation by the growth factor TGFß, a trigger of EMT in epithelial cells. We have recently published that TGFß causes a fast and widespread increase in chromatin accessibility of about 80% of all enhancers, irrespective of whether they are activated, repressed or not regulated by TGFß, thus dissociating the concepts of enhancer accessibility and activity. In addition, we showed that TGFß-regulated genes often are clustered in TGFß regulatory domains (Guerrero-Martínez et al., 2020).



Grants

- 2020-2022: PY18-1962, Junta de Andalucía
- 2018-2020: BFU2017-85420-R, Ministerio de Ciencia, Innovación y Universidades
- 2013-present: VEC – 001/2014 FVEC-FPS. Fundación Vencer el Cáncer

Publication Highlights

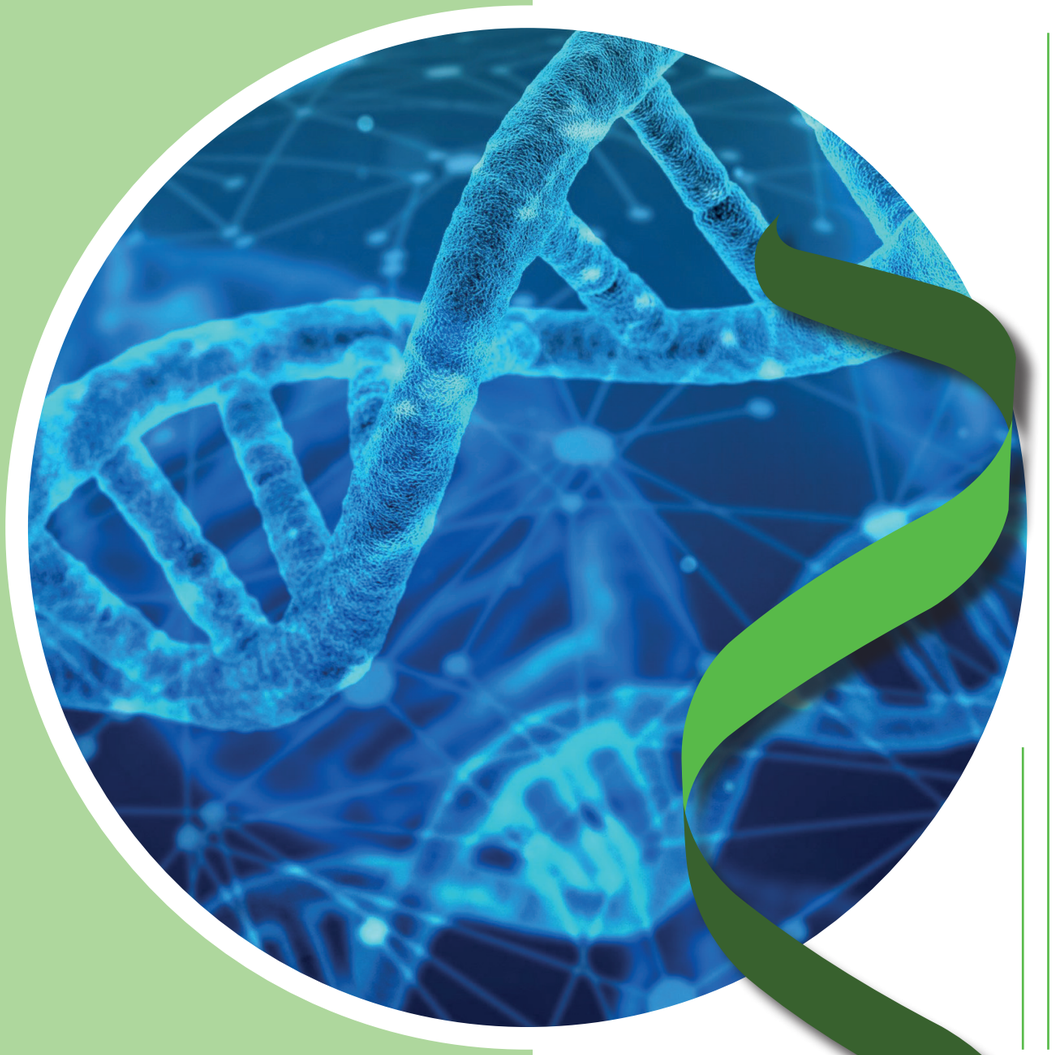
Guerrero-Martínez JA, Ceballos-Chávez M, Koehler F, Peiró S, Reyes JC. **2020.** TGFß Promotes Widespread Enhancer Chromatin Opening and Operates on Genome Regulatory Domains. **Nature Communication.** 11:6196

Rivero S, Gómez-Marín E, Guerrero-Martínez JA, García-Martínez J, Reyes JC. **2019.** TBL1 is required for the mesenchymal phenotype of transformed breast cancer cells. **Cell Death and Disease.** 10(2):95

Guerrero-Martínez JA, Reyes JC. **2018.** High expression of SMARCA4 or SMARCA2 is frequently associated with an opposite prognosis in cancer. **Scientific Report.** 8(1):2043

Guijo M, Ceballos-Chávez M, Gómez-Marín E, Basurto-Cayuela L, Reyes JC. **2018.** Expression of TDRD9 in a subset of lung carcinomas by CpG island hypomethylation protects from DNA damage. **Oncotarget.** 9:9618-9631

Soler-Oliva ME, Guerrero-Martínez JA, Bachetti V, Reyes JC. **2017.** Analysis of the relationship between co-expression domains and chromatin 3D organization. **PLoS Computational Biology.** 13(9):e1005708



Prof. Andrés Aguilera

Genome Instability and Cancer

Group Leader

Current position

- Full Professor of Genetics, University of Seville (US), Spain.
- Director of CABIMER, Seville, Spain.
- Executive Responsible of the Genomics Unit of CABIMER.

Group Members

Senior Researchers

- Belén Gómez-González (Assist. Prof., US)
- Rosa Luna (Assoc. Prof., US)
- Ana G. Rondón (Assoc. Prof., US)
- José F. Ruiz (Assoc. Prof., US)

Postdocs

- María García-Rubio (Assist. Prof., US)
- Sonia Barroso
- Aleix Bayona-Feliu
- José A. Mérida-Cerro
- Gonzalo Millán-Zambrano
- M. Ángeles Ortiz-Bazán
- Sonia P. Silva

PhD Students

- Cristina Guillén-Mendoza
- Pedro Ortega
- Pablo Maraver-Cárdenas
- J Javier Marqueta-Gracia
- Iván Núñez-Martín
- Eugenia Soler-Oliva
- José Terrón-Bautista

Master students

- Mar Bustamante-Sequeiros

Visiting scientists

- Renée Concetta-Duardo (Erasmus+)

Administrative Assistant

- Zoë Cooper

Former Members (2018-2020)

- **Senior researchers:** Tatiana García-Muse; Hélène Gaillard
- **Postdocs:** Sergio Muñoz, Emanuela Tumini, Reyes Babiano, Giovana S Leandro; Lola Pérez-Caminero
- **PhD students:** Francisco García-Benítez; Marta San Martin-Alonso; Carmen Pérez-Calero, Juan CM Cañas; Esther Marchena-Cruz
- **Master students:** Patricia Navarro
- **Erasmus+ PhD students:** Marta Giannini; Alessandro Mozzarelli
- **Sabbatical:** Prof. Ryan Jensen (Yale University, CT, USA)

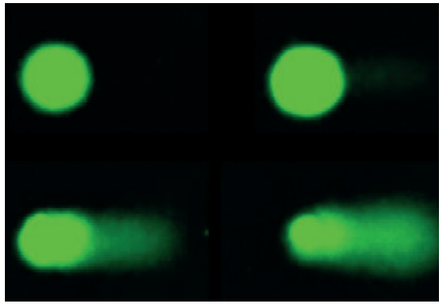
Research Activity

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 basic biological research, cancer biology and biomedicine. Our research is focused on the factors and mechanisms responsible for genome instability associated with replication stress and replication-born DNA breaks, including that caused by transcription-replication conflicts and R-loop accumulation. Our ultimate goals are:

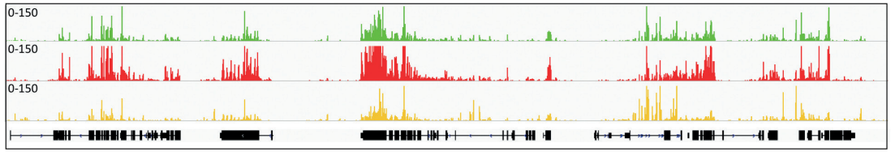
1) to decipher the mechanisms by which cells prevent harmful R loop accumulation and its associated genome instability;

2) to identify the main determinants of replication failures that lead to the stalling or collapse of the replication fork and to DNA breaks;



3) to understand how a replication-born DNA break is repaired to allow replication restart and prevent chromosome rearrangements and genome instability; and

4) to evaluate the implication of such determinants and processes in the origin of cancer and other genetic diseases and its potential use in diagnostic or therapy. Our research is performed in human cells and the model organism *Saccharomyces cerevisiae*.

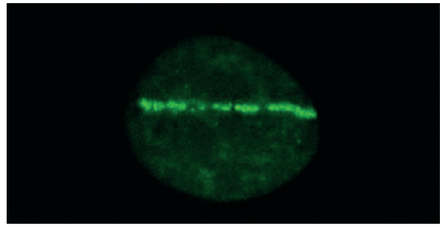


Research Highlights

The main highlights for the period 2018-20 are:

1. Prevention of R loops and R loop-mediated genome instability

After showing that human THO, a complex that links mRNP biogenesis with genome instability, interacts with the Sin3A histone deacetylase to suppress co-transcriptional R loops, we have shown that UAP56/DDX39B, an RNA helicase that interacts with THO, possesses DNA-RNA helicase activity, which supports that transcription uses parallel processes for preventing R loops: i) by protecting the RNA by assembly into a proper mRNP; ii) by transiently closing chromatin by histone deacetylation behind the RNA polymerase, and iii) by removing occasional R loops co-transcriptionally. Interestingly, our results suggest that UAP56 control R loops formed mainly during the G1 phase of the cell cycle (Perez-Calero et al, Genes Dev 2020). In addition, we have shown that the MFAP1/SPP381 splicing factor causes R loop-independent genome instability (Salas-Armentero et al., Cell Reports 2019), and that the Nup84 component of the nuclear pore complex coordinates the response to DNA damage to warrant genome integrity (Gaillard et al., NAR 2019). We have also found a role of the mitochondrial exosome in preventing R loop-mediated instability of the mitochondrial genome, supporting that RNA processing protects from R loops also in organelles (Silva et al, PNAS 2018). Our work has been extended in this field with a high-profile review (García-Muse & Aguilera, Cell 2019).



2. Transcription-replication conflicts

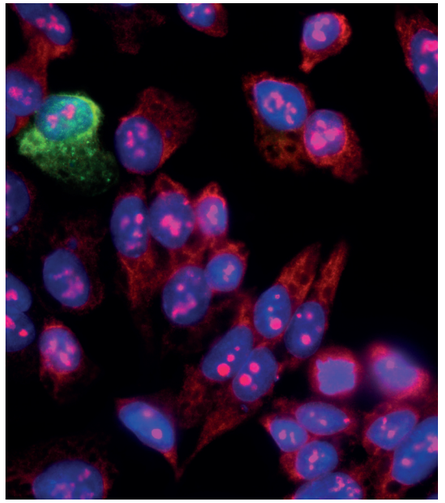
In yeast we have shown that excess of the Yra1 RNA-binding protein stabilizes DNA-RNA hybrids, thus promoting replication fork collapse. Thus, hybrids cause transcription-replication collisions rather than being a consequence (García-Rubio et al, Genes Dev 2018). In human cells, we have shown that DNA-RNA hybrids can be originated before or after DNA replication, triggering a different DNA damage response in each case (Barroso et al, EMBO Rep 2019). In parallel, and in contrast to reports suggesting that R loops form in trans catalyzed by the Rad51 strand exchange protein, we have demonstrated that R loops occur in cis and independently of Rad51 (Lafuente et al, eLife 2020). Our work has been extended in this field with a relevant review (Gómez-González & Aguilera, Genes Dev 2019).

3. Repair of replication-born DNA breaks

We have improved the molecular assay, previously developed by us, to detect recombination events between sister chromatids, the preferred mechanism to repair replication-born double-strand breaks (DSBs). This has permitted to study how breaks are repaired depending on the direction in which the replication fork hits them. We have shown that histone acetylation-deacetylation influences the repair of these replication-born DSBs by the control of cohesin loading (Ortega et al, Nat Comm 2019). Finally, we have shown that a meiotic checkpoint control inter-sister repair in C. elegans (García-Muse et al, Cell Reports 2019).

4. Diagnostic and therapeutic tools in cancer and genetic diseases.

We have shown that the antitumoral drugs trabectedin and lurbinectedin induce transcription-dependent replication stress as a new mechanism to stop cell proliferation (Tumini et al, Mol Cancer Res 2019). In addition, we have reported that the TDP43 RNA processing factor mutated in ALS patients protect cells from R loos,o pening the possibility that R loops may be a key feature associated with cancer and ALS that could be potentially explored in diagnostics and therapies (Giannini et al, PLoS Genet 2020).



Grants

- 2020-2022: P18-FR-655 (PAIDI) Junta de Andalucía
- 2020-2022: US-1258654 Junta de Andalucía-USE
- 2020-2023: PID2019-104270G-100 Ministerio de Ciencia e Innovación
- 2020-2021: RED2018-102372-T Ministerio de Ciencia, Innovación e Universidades
- 2017-2020: BFU2016-75058-P Ministerio de Economía y Competitividad
- 2016-2020: RTC-2016-4611-1 Ministerio de Economía y Competitividad
- 2015-2021: ERC2014-0015 Advanced. TARLOOP. European Research Council
- 2014-2019: P12/BIO-1238. Proyecto de Excelencia, Junta de Andalucía
- 2013-present: VEC – 001/2014 FVEC-FPS. Fundación Vencer el Cáncer

Publication Highlights

Pérez-Calero C, Bayona-Feliu A, Xue X, Barroso SI, Muñoz S, González-Basallote VM, Sung P, Aguilera A. **2020** UAP56/DDX39B is a major cotranscriptional RNA-DNA helicase that unwinds harmful R loops genome-wide. **Genes Dev.** 34:898-912

Ortega P, Gómez-González B, Aguilera A. **2019**. Rpd3L and Hda1 histone deacetylases facilitate repair of broken forks by promoting sister chromatid cohesion. **Nat Commun.** 10:5178

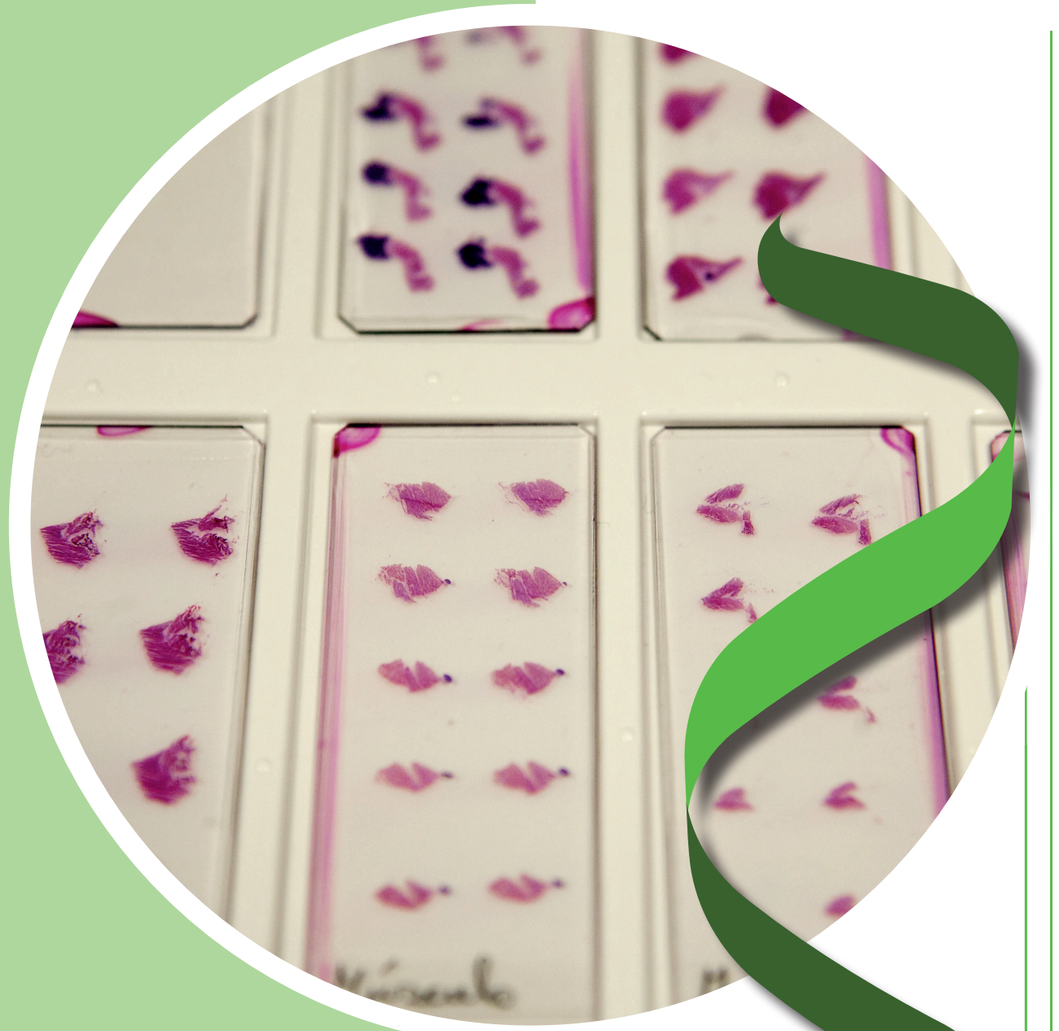
García-Muse T, Aguilera A, **2019**. R Loops: From Physiological to Pathological Roles. **Cell.** 179:604-618

Gómez-González B, Aguilera, A. **2019**. Transcription-mediated replication hindrance: a major driver of genome instability. **Genes Dev.** 33:1008-1026

Barroso S, Herrera-Moyano E, Muñoz S, García-Rubio M, Gómez-González B, Aguilera A. **2019**. The DNA damage response acts as a safeguard against harmful DNA-RNA hybrids of different origins. **EMBO Rep.** 20:e47250

Silva S, Camino LP, Aguilera A. **2018**. Human mitochondrial degradosome prevents harmful mitochondrial R loops and mitochondrial genome instability. **Proc Natl Acad Sci USA.** 115:11024-11029

García-Rubio M, Aguilera P, Lafuente-Barquero J, Ruiz JF, Simon MN, Geli V, Rondón AG, Aguilera A. **2018**. Yra1-bound RNA-DNA hybrids cause orientation-independent transcription-replication collisions and telomere instability. **Genes Dev.** 32(13-14):965-977



Dr. Félix Prado

Chromatin Integrity and Function

Group Leader

Current position

- Since 2006: Research Scientist- CSIC/ CABIMER

Group Members

Postdocts

- Marta Barrientos Moreno

PhD Students

- Aurora Yáñez Vilches
- Cristina González Garrido

Former Members (2018-2020)

- **Scientific staff**: Macarena Morillo Huesca
- **Postdoc:** Douglas Maya Miles
- **PhD students:** María I. Cano Linares, Marta Barrientos Moreno
- **Master students:** Sara Fontalva Ostio, Cristina González Garrido
- **TFG student:** Francisco J. Algaba Sanabria
- **Technician:** Elena Gómez Marín

Genome Biology Department

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

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 are 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. Consequently, this DNA damage tolerance (DDT) response is essential for cell cycle progression, genome integrity, and cancer avoidance. DDT relies on homologous recombination (HR) and translesion synthesis (TLS) mechanisms to fill in the ssDNA gaps generated during passing of the replication fork over DNA lesions in the template. Whereas TLS requires specialized polymerases able to incorporate a dNTP opposite the lesion and is error-prone, HR uses the sister chromatid and is mostly error-free. We have reported that the HR protein Rad52 acts in concert with the TLS machinery to repair MMS and UV light-induced ssDNA gaps through different non-recombinogenic mechanisms. Specifically, Rad52 facilitates the recruitment of the Rad6/Rad18 complex, required for PCNA ubiquitylation and subsequent recruitment of the TLS polymerases (Figure 1). Therefore, Rad52 facilitates the tolerance process not only by HR but also by TLS, providing a novel role for the recombination proteins in maintaining genome integrity.

We have also followed our studies about the roles that chromatin assembly plays in the maintenance of genome integrity. These studies have revealed new functions for the process of histone deposition in genetic instability and transcription. First, we have uncovered an unexpected role for programmed histone depletion in the protection of short telomeres during senescence that is mediated by HR. Interestingly, this mechanism is regulated by the kinase Mec1, the yeast homolog of the tumor suppressor gene ATR, suggesting that this factor prevents genetic instability by

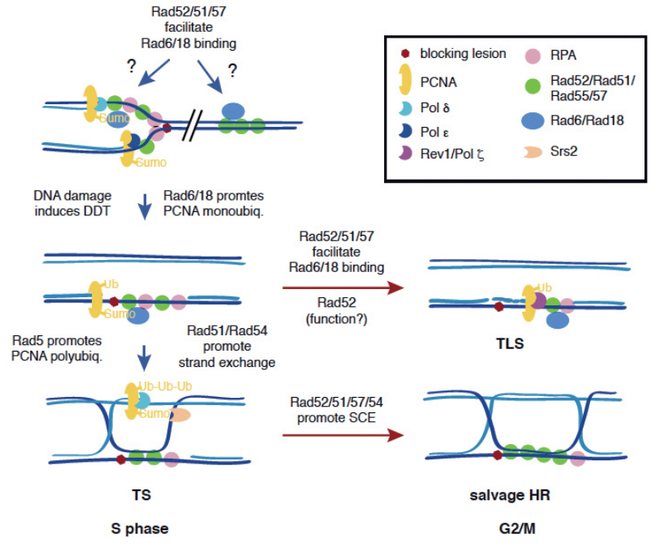


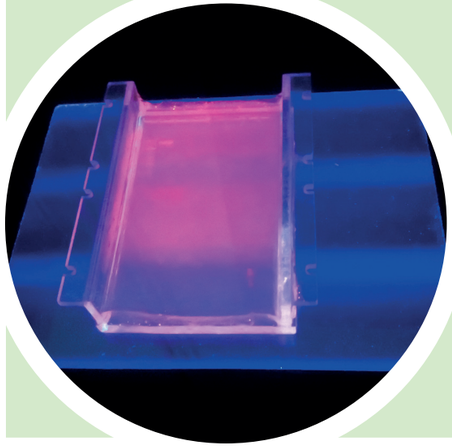
Figure 1. Model for Rad52-mediated tolerance during DDT. The recombination factors Rad52, Rad51 and Rad57 promote efficient Rad6/Rad18 binding to chromatin under unperturbed conditions. In response to blocking lesions that impair replication fork advance the Rad6/Rad18 complex is mobilized to ssDNA lesions where, together with Mms2/Ubc13/Rad5, ubiquitylates PCNA and promotes TS. The ssDNA lesions that escape from this error-free pathway during S phase accumulate in G2/M, where they are filled in by two additional, less accurate mechanisms regulated by Rad52: UbPCNA-independent HR (recombinogenic) and TLS (mutagenic).

controlling histone levels and in turn telomere fusions.

The importance of chromatin in transcription have been long established. Remarkably, we have shown that cohesins regulate transcription by controlling chromatin structure; specifically, they seem to promote transcription activation by helping the RSC chromatin remodeling complex to generate nucleosome free regions at promoters. Finally, we have characterized the accumulation of DNA damage in cells lacking the chromatin assembly factor Swr1, and established a connection between actin-related complexes, the nuclear envelope and genome integrity. These genetic results further support previous observations from our group that support the importance of maintaining strict control over the expression and integrity of chromatin remodeling complexes for genome stability and function.

Grants

- 2019-2021: PGC2018-099182-B-100. Ministerio de Ciencia, Innovación y Universidades
- 2018-2020: BFU2017-90889-REDT. Ministerio de Economía y Competitividad
- 2016-2018: BFU2015-63698-P. Ministerio de Economía y Competitividad



Publication Highlights

Morillo-Huesca M, Murillo-Pineda M, Barrientos-Moreno M, Gómez-Marín E, Clemente-Ruiz M, Prado F. **2019.** Actin and nuclear envelope components influence ectopic recombination in the absence of Swr1. **Genetics** 213:819-834

Maya-Miles D, Andújar E, Pérez-Alegre M, Murillo-Pineda M, Barrientos-Moreno M, Cabello-LobatoMJ, Gómez-Marín E, Morillo-Huesca M, Prado F. **2019**. Crosstalk between chromatin structure, cohesion activity and transcription. **Epigenetics & Chromatin.** 12:47

Prado F. **2018.** Homologous Recombination: To Fork and Beyond. **Genes.** 9:603

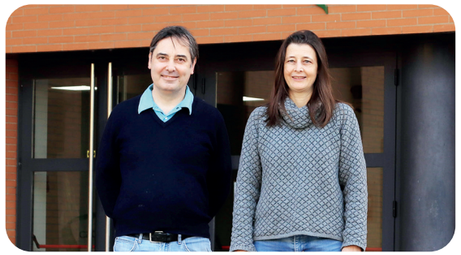
Barrientos-Moreno M, Murillo Pineda M, Muñoz-Cabello AM, Prado F. **2018.** Histone depletion prevents telomere fusions in pre-senescent cells. **PLoS Genetics** 14:e1007407

Prado F, Maya D. **2017.** Regulation of replication fork advance and stability by nucleosome assembly. **Genes.** 8: 49

Dr. Ralf E. Wellinger

Mitochondrial Plasticity and Replication

Group Leader



Genome Biology Department

Current position

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

Group Members

Research Associates
- Helene Gaillard

PhD Students
- Hayat Heluani Gahete

Former Members (2018-2020)

- **Postdoc:** Elisabet Fernández-García, Monica Venegas-Calerón
- **Erasmus + Master students:** Rafael Luis Giner Arroyo, Carlos Ruiz, Lisa Wagenaar, Eugenie Ellen, Christian Ramirez Amarilla

Research Activity

Overview
The genetic material, including mitochondrial, telomeric and nucleolar (ribosomal) DNA, is constantly exposed to endogenous or exogenous stress. We are particularly interested in the factors and molecular pathways causing genome instability, disease and premature aging.

We have two areas of investigation through which we study the interconnection between metabolic response, transcription and replication. Together, these processes regulate and/or interfere with the function of DNA repair pathways.

Research Highlights

DNA replication and genome instability

DNA double strand breaks (DSBs) are a main source of genome instability. DSBs can arise from replication forks that collapse upon the encounter of a DNA nick. We are interested in DNA damaging agents that lead to nicked DNA as well as in the molecular events that promote the conversion of nicked into broken DNA strands. We commented on a recent study that mapped the genome-wide distribution of endogenous DNA nicks suggesting that transcription contributes to the formation and distribution of DNA nicks (see: Mind the nick). R-loops are a byproduct of transcription, and nicked DNA seems to contribute to R-loop formation and vice versa. We therefore discussed the possibility that the 3'OH of nicked DNA at R-loops could trigger unscheduled replication events. Our current projects include genome wide analyses of DNA nicks and their contribution to unscheduled replication events and genome instability.

A collaborative project with the research group of J. Torres-Rosell investigated the function of the Smc5/6 complex in genome integrity (see: Sumoylation of Smc5 Promotes Error-free Bypass at Damaged Replication Forks). The Torres-Rossel group mapped SUMO-targeted lysines to the coiled-coil domain of Smc5 and found that Smc5 is mainly sumoylated in response to replication fork damage. Because Smc5 sumoylation is enhanced by replication fork damage, we analyzed if smc5-KR10 mutant cells could display impairments in fork progression upon encounter with DNA lesions. Forks stalled at DNA lesions are frequently channeled into tolerance pathways to enable DNA synthesis and prevent fork collapse. The error-free branch of the DNA damage tolerance pathway promotes template switch behind the fork, leading to the formation of X-shaped sister chromatid junctions (SCJs). These structures can be detected using 2D gel electrophoresis in cells replicating in the presence of DNA damage (Figure 1).

Surprisingly, we found that the smc5-KR10 allele substantially reduced the amount of SCJs in sgs1Δ mutant cells. Consequently, using SUMO-impaired smc5-KR mutants,

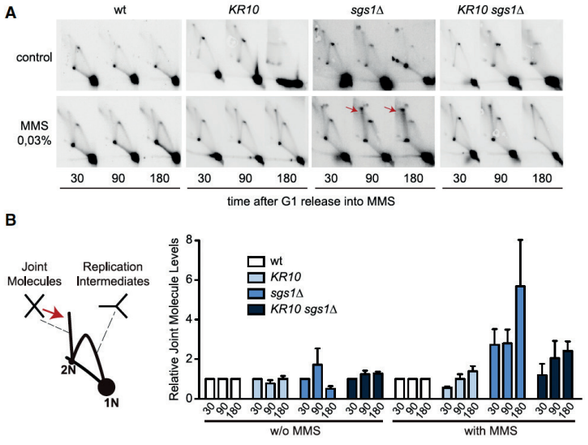


Figure 1: Accumulation of SCJs in smc5-KR10 unsumoylatable mutant cells. (A) 2D gel analysis of WT and indicated mutant cells upon release from G1 into S phase in the presence of MMS. Red arrows indicate joint molecules accumulating in MMS-treated sgs1Δ cells. (B) Quantification of joint molecules shown in (A). For more details see M. Zapatka et al. (2019).

the Torres-Rosell group revealed that this modification promotes DNA damage tolerance though Mph1. In the absence of Smc5 sumoylation, cells upregulate mutagenic TLS and reduce the formation of SCJs indicating that this lesion bypass mechanism is normally backed up by Mms4-Mus81, which allows the completion of chromosome replication and disjunction in the absence of Smc5 sumoylation. Taken together, the results let to a model proposing that sumoylation of Smc5 enhances physical remodeling of damaged forks, avoiding the use of a more mutagenic tolerance pathway

Biometal-metabolism and genome instability

Biometals are essential micronutrients that are needed as cofactor for enzyme function. We initially became interested in biometals because we found that mitochondrial iron–sulphur cluster biosynthesis is important for the maintenance of nuclear genome stability, and that cytosolic excess of manganese predisposes to genomic instability and bypasses the need for S-phase cell cycle checkpoints.

Interestingly, manganese excess is also linked to rapamycin resistance suggesting a link between manganese and the TOR-pathway. To understand how manganese drives rapamycin resistance, we initiated a collaboration with the research group of Prof. Claudio de Virgilio at the University of Fribourg (CH). The results of this collaboration show that manganese serves as a metal-cofactor able to stimulate TORC1 kinase activity in vivo and in vitro (publication pending). Interestingly, TORC1 is transiently activated by a rise in extracellular manganese, or chronically activated by ubiquitin-ligase mutants that fail to degrade NRAMP-type manganese transporters. By complementation assays, we also could show that NRAMP transporters are highly conserved from yeast to mice. These findings could help to improve our understanding of disease phenotypes observed in Hailey-Hailey patients who suffer from impaired manganese/calcium homeostasis, skin ulceration, improper keratinocyte adhesion, and cancer predisposition.

Grants

- 2015-2018: BFU2015-69183-P. Ministerio de Ciencia e Innovación
- 2013-2019: P11-CTS-7962.Consejería de Economía, Innovación y Ciencia, Junta de Andalucía
- 2019: PP2019-1332. Universidad de Sevilla
- 2020: PP2020-VI-IV4. Universidad de Sevilla
- 2020: EST 8685. EMBO Short Term Fellowship

Publication Highlights

Wellinger R E. **2019.** Mind the nick. **Cell Cycle.** 18:115-117

Zapatka M, Pociño Merino I, Bermúdez López M, Tarrés M, Ibars E, et al. **2019.** Sumoylation of the coiled coil domain of Smc5 promotes error-free bypass at damaged replication forks. **Cell Reports** 18

Guintini L, Tremblay M, Toussaint M, D'Amours A, Wellinger RE, Wellinger RJ and Conconi A. **2017.** Repair of UV-induced DNA lesions in natural *Saccharomyces cerevisiae* telomeres is moderated by Sir2 and Sir3, and inhibited by yKu-Sir4 interaction. **Nucleic Acids Res.** 45:4577-4589

Stuckey R, García-Rodríguez N, Aguilera A, Wellinger RE. **2015.** Role for RNA:DNA hybrids in origin-independent replication priming in a eukaroytic system. **Proc Natl Acad Sci U S A.** 112:5779-84

García-Rodríguez N, Manzano-López J, Muñoz-Bravo M, Fernández-García E, Muñiz M, Wellinger RE. **2015.** Manganese Redistribution by Calcium-stimulated Vesicle Trafficking Bypasses the Need for P-type ATPase Function. **J Biol Chem.** 290:9335-47

Dr. Pablo Huertas

DNA double strand breaks repair and human disease

Group Leader

Genome Biology Department

Current position

- Research Scientist CABIMER
- Associate Professor of the University of Seville

Group Members

Senior Researcher
- Sonia Jimeno
- Fernando Romero Balestra

Postdocs
- Néstor García Rodríguez
- Maikel Castellano Pozo

PhD Students
- Rosa Camarillo Daza
- Andrés Domínguez Calvo
- Andrea Moo Bajo
- Amador Romero Franco
- Guillermo Rodríguez Real

Technicians
- Maria del Carmen Domínguez Pérez

Former Members (2018-2020)

- **Postdoc:** Sabrina Rivero Canalejo
- **PhD students:** Cintia Checa Rodríguez, Fernando Mejías Navarro, Mª Rosario Prados Carvajal
- **Master student:** Blanca Lago Solís, Vasily Sorokin
- **Technicians:** Javier Ramón Pasías

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; the simple ligation of both ends, named non-homologous end-joining (NHEJ), or the use of a homologous sequence as a template, 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 can also be exploited for the treatment of cancer. In our laboratory, we are studying how the decision between these two alternative pathways is achieved in concert with the cellular, organismal and environmental situation. Based on previous data from the lab, we are understanding further the molecular cues that govern this choice. Moreover, we are use our gathered knowledge to gain insights on specific hereditary diseases.

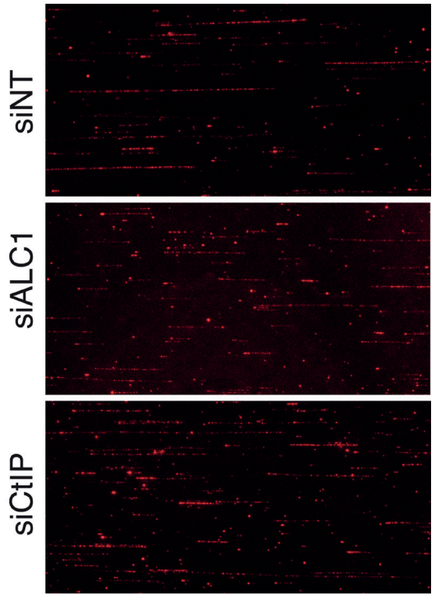


Fig 1: ALC1 is required for DNA end resection. Resection length on individual DNA fibers was calculated using SMART. Briefly, cells depleted for the indicated proteins were incubated for 24 h with BrdU. Cells were then irradiated with 10 Gy, and after 1 h, DNA was extracted. DNA was then stretched on coverslips, and ssDNA was detected using a BrdU antibody.

Research Highlights

The 2018-2020 period has represented the blooming of the productivity of the lab, with many publications and international collaboration in high tier journals. This has helped us to cement our position as a referent in the field at national and international level. Also, we have been able to secure funds from many different sources at all levels, regional to international and public or private.

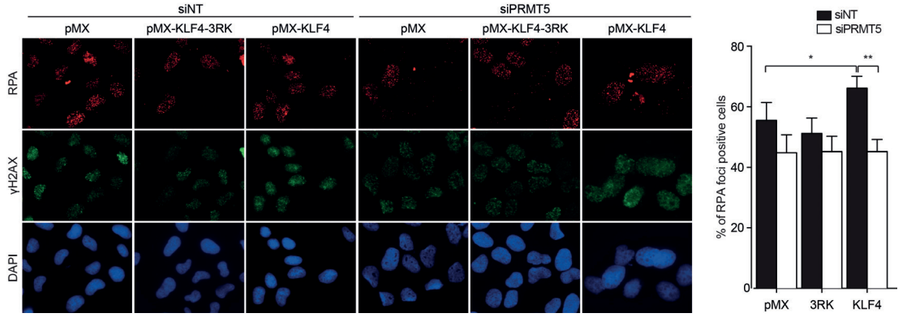


Fig 2: PRMT5-mediated methylation of KLF4 is required for DNA end resection A, Microscopy images of RPA foci in cells transfected with a siRNA against PRMT5 or a control sequence, as indicated, and bearing a plasmid to express the wildtype or non-methylable version of KLF4 (KLF4 and 3RK, respectively) or an empty vector (pMX). A representative image for each condition is shown on the left side. Graph on the right side represents the average and standard deviation of three independent experiments. Statistical significance was calculated using a two-way ANOVA, but only biologically relevant statistical differences are shown for simplicity.

These include funding for understanding fundamental basic elements in cell biology, but also to specifically study a genetic disease. We have also expanded our field of knowledge to stem cell biology, centrosome biology and DNA replication.

Grants

- 2017-2019: SAF2016-74855-P. Ministerio de Economía y Competitividad
- 2019-2022: Fundación Ramón Areces
- 2020-2022: US-1255532. Junta de Andalucía
- 2020-2023: PID2019-104195G9. Ministerio de Ciencia e Innovación
- 2020-2023: P18-RT-1204. Junta de Andalucía

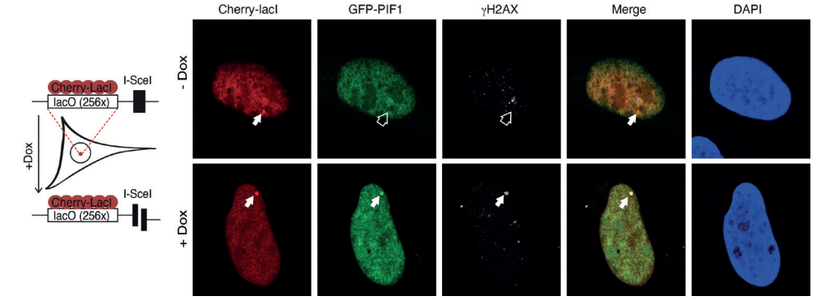


Fig 3: PIF1 recruitment to DNA damaged sites. Left, Schematic representation of a experimental system to measure protein recruitment to DSBs. A single I-SceI target site is located close to 256 copies of the lacO sequence, allowing its visualization using a Cherry-LacI fusion. I-SceI is induced with the addition of doxycycline to induce a break. **Right**, Immuno-FISH representative confocal images of Cherry-lacI in red, γH2AX (white) or GFP-PIF1 in green in cells expressing (+Dox) or not (-Dox) the I-SceI enzyme. An arrow points to the localization of the array in each image. Empty arrow mark where the array is, according to the LacI signal, on those cases in which no protein accumulation is observed (-DOX, without DSB induction).

Publication Highlights

Checa-Rodríguez C, Cepeda-García C, Ramón J, López-Saavedra A, Balestra FR, Domínguez-Sánchez MS, Gómez-Cabello D, Huertas P. **2020.** Methylation of the central transcriptional regulator KLF4 by PRMT5 is required for DNA end resection and recombination. **DNA Repair.** 94:102902

Mejías-Navarro F, Rodríguez-Real G, Ramón J, Camarillo R, Huertas P. **2020.** ALC1/eIF4A1-mediated regulation of CtIP mRNA stability controls DNA end resection. **PLoS Genet.** 16(5):e1008787

Jachimowicz RD, Beleggia F, Isensee J, Bhavana VB, Goergens J, Bustos MA, Doll MA, Shenoy A, Checa-Rodriguez C, Wiederstein JL, Baranes-Bachar K, Bartenhagen C, Hertwig F, Teper N, Nishi T, Schmitt A, Distelmaier F, Lüdecke HJ, Albrecht B, Krüger M, Schumacher B, Geiger T, Hoon DSB, Huertas P, Fischer M, Hucho T, Peifer M, Ziv Y, H Reinhardt HC, Wieczorek D, Shiloh Y. **2018.** UBQLN4 represses homologous recombination and is overexpressed in aggressive tumors. **Cell.** 176(3):505-519.e22

Jimeno S, Camarillo R, Mejías-Navarro F, Fernández-Ávila, MJ, Soria-Bretones I, Prados-Carvajal R, Huertas P. **2018.** The Helicase PIF1 Facilitates Resection over Sequences Prone to Forming G4 Structures. **Cell Rep.** 24(12):3262-3273.e4

Prados-Carvajal R, López-Saavedra A, Cepeda-García C, Jimeno S, Huertas P. **2018.** Multiple roles of the splicing complex SF3B in DNA end resection and homologous recombination **DNA Repair.** 66-67:11-23

Dr. Andrés J. López-Contreras

Molecular Oncology and Targeted Therapies

Group Leader

Current position

- Since 2020: Group Leader at CABIMER

Group Members

Postdocs
- María Castejón Griñán
- Paula Aguilera Aguilera
- Lucía Simón Carrasco

Master students
- Mario Ávila Martínez
- Alba Guillén Benítez

Erasmus+PhD students
- Tristan Escure
- Britt D'hauw

Technicians
- Irene Delgado Sainz
- Adoración Montero Sánchez

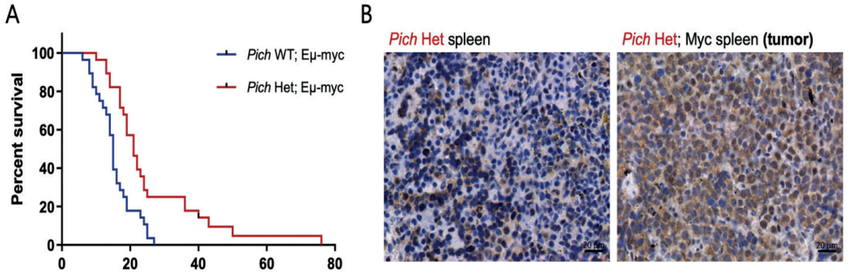
Research Activity

Overview

The focus of our group is the study of genomic instability and the DNA damage Response (DDR) in the context of cancer. The DDR is intimately linked to cancer development and cancer therapy. Indeed, many conventional chemotherapy agents and radiation therapy boost the levels of DNA damage to kill cancer cells. Our final aim is identifying novel therapeutic opportunities to treat cancer. For this, we perform cellular studies including proteomics, CRISPR genetic and drug screens to identify novel factors involved in the DDR. In addition, we use genetically modified mouse models and cellular systems to characterize the relevance of novel factors for cancer development and to develop novel anti-cancer therapies. My group is particularly interested on the study of the biology of Common Fragile Sites, which are conserved chromosomal regions with high propensity to break in conditions of replication stress, and which are therefore frequently altered in cancer.

Research Highlights

The group led by Dr. López-Contreras was established at the end of 2014 at the University of Copenhagen, Denmark, and has recently moved (July 2020) to CABIMER/CSIC. In the past years,we have contributed to the understanding of the effects of replication stress to aging and embryonic stem cell fate potential (Albers E et al., Aging 2020, Atashpaz S et al., eLife 2020) and the impact of dNTP imbalance on genomic instability (López-Contreras et al., Genes and Dev 2015). In addition, we use genetically modified mouse models to characterize the relevance of novel factors for cancer and to develop novel anti-cancer therapies. We have generated a Pich conditional KO mouse, identifying PICH as a potential therapeutic target for cancer (Albers E et al., Cell Reports 2018). We are particularly interested in understanding the biology of Common Fragile Sites (CFS) and their contribution to cancer (funded by the "CFS Modeling" ERC Starting Grant). We have generated the first CFS proteome, identifying the tumor suppressor ATRX to be essential to maintain CFS stability (Pladevall-Morera D et al., Nucleic Acid Research 2018). Finally, we have recently generated the first mouse model with a whole deletion of a CFS that will be used to investigate the impact of FHIT loss in cancer. Of note, Dr. López-Contreras received the prestigious Junior Prize from the Danish Cancer Society in 2020 for his cancer research career.



Role of PICH in Myc-induced lymphoma. A) Survival of Emu-Myc mice in PICH WT and PICH heterozygous (Het) mice. PICHHets show a delayed lethality caused by lymphoma. B) PICH immunohistochemistry showing extensive PICH expression in the Myc-induced lymphomas.

Grants

- 2020-2022: Juan de la Cierva postdoctoral grant (Paula Aguilera)
- 2016-2022: ERC Staring Grant (ERC-2015-STG-679068)
- 2019-2020 Grant from LÊge Sophus Carl Emil Friisoghustru Olga Doris Friis Ï Legat,Denmark
- 2018-2020: KBVU Project from the Danish Cancer Society, Denmark

Publication Highlights

Albers E, Avram A, Sbroggio M, Fernandez-Capetillo O, López-Contreras AJ. **2020.** Supraphysiological protection from replication stress does not extend mammalian lifespan. **Aging.** 12: 5612-5624

Atashpaz S, Shams S, Martin J, Sebestyen E, Arghavanifard N, Gnocchi A, Albers E, Minardi S, Faga G, Soffientini P, Allievi E, Bachi A, Fernandez-Capetillo O, Tripodo C, Ferrari F, López-Contreras AJ, Costanzo V. **2020.** ATR expands embryonic stem cell fate potential in response to replication stress. **eLife.** 9: e54756

Pladevall-Morera D, Munk S, Ingham A, Garribba L, Albers E, Liu Y, Olsen JV, López-Contreras AJ. **2019.** Proteomics characterization of Chromosomal Common Fragile Site (CFS) - associated proteins uncovers ATRX as a regulator of CFS stability. **Nucleic Acid Res.** 47:8004-8018

Albers E, Sbroggiò M, Pladevall-Morera D, Bizard AH, Avram A, Gonzalez P, Martin-Gonzalez J, Hickson ID, López-Contreras AJ. **2018.** Loss of PICH results in chromosomal instability, p53 activation and embryonic lethality. **Cell Reports.** 24: 3274-3284

López-Contreras AJ (*), Specks J, Barlow JH, Ambrogio C, Desler C, Vikingsson S, Rodrigo-Perez S, Green H, Rasmussen LJ, Murga M, Nussenzweig A, Fernandez-CapetilloO(*)(*co-corresponding authors). **2015.** Increased Rrm2 gene dosage reduces fragile site breakage and prolongs survival of ATR mutant mice. **Genes & development.** 29: 690-695

Dr. Tatiana García-Muse

DNA Damage Response During Meiosis

Emerging PI

Current position

- Since 2016: Assistant Professor, University of Seville-Andalusian Center for Molecular Biology and Regenerative Medicine, Seville, Spain

Group Members

Postdocs

- Lola Pérez de Camino Cantos
- Mariola Chacón Rodríguez

Technician

- Nuria Fernández

Research Activity

Overview

Genomic DNA is exposed to both endogenous and exogenous DNA damaging agents. Without proper repair the resulting DNA damages would lead genomic instability thus affecting the faithful transmission of genetic information. In addition, defects during meiosis lead to aneuploidy, an extreme kind of genetic instability associated with fertility problems and syndromes. Since cells undergoing meiosis during oogenesis stay arrested in meiosis I for long periods of time and therefore vulnerable to DNA lesions we speculated if the increase in genome instability inferred from the increase in aneuploidy that correlates with mother age might be related to defects in DDR during meiosis. DNA damage checkpoints kinases ATR and ATM are key regulator of DDR. Our aim is to address how ATR/ATM DNA damage phosphorylations contribute to the regulation of meiosis and different DNA repair pathways to ensure genome stability.

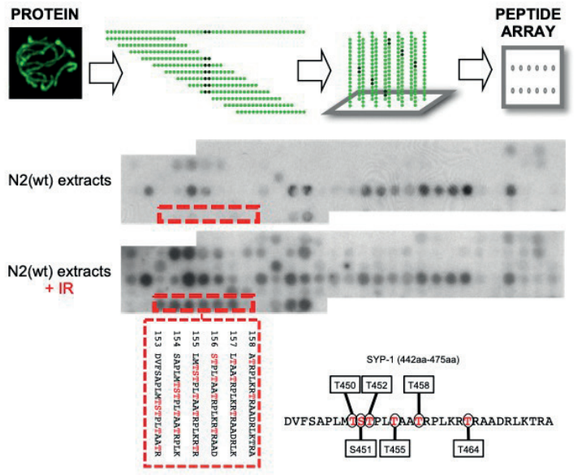


Figure 1: (Top) Scheme of the peptide array. The protein of interest can be scanned across its length by making 18 mer peptides that shifting by three residues. Each peptide is then spotted in a cellulose membrane. (Bottom) In vitro phosphorylation of the SYP-1 peptide array by N2(WT) extracts with/out IR exposition. Positive serial spots (detected by autoradiography) corresponding to DNA damage-phosphorylation are boxed. The peptide sequences with specific DNA damage phosphorylation are shown with the possible phosphorylation residues highlighted in red

Research Highlights

To deal with DNA damage and to prevent genomic instability cells have evolved a set of responses called the DNA damage response (DDR). Phosphorylation is an essential regulator during DDR, and key kinases of DNA damage checkpoints are ATR and ATM. In order to identify residues phsophorylated in response to IR during meiosis, we performed a peptide array screening. We probed withC. elegans extracts, prepared before or after DNA damage, and radio labelled ATP on peptide arrays we identified all in vitroputative phosphorylation sites (Figure 1).

We have uncovered the in vivo relevance of one of this DNA damage-dependent phosphorylation identified by the peptide array, specifically the posttranslational modification of the C. elegans synaptonemal complex (SC) protein, SYP-1 (Figure 1). The SC is the structure that holds together the homolog chromosomes during meiosis, and it is crucial for proper meiotic recombination and chromosome segregation. We generated a phospho-syp-1 complementation allele in which the phosphorylated residues were changed to non-phosphorylable alanine (syp-1(6A)) and characterized the meiosis

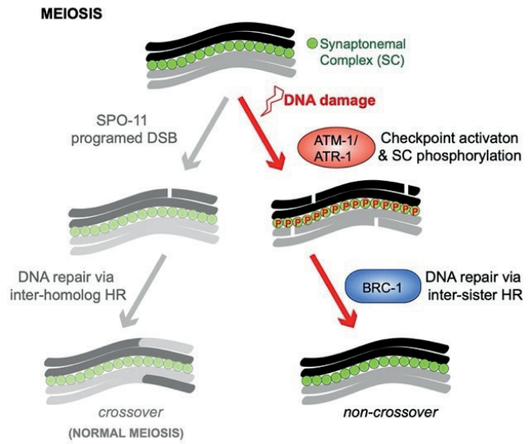


Figure 2: Model. During meiosis, SPO-11 DSBs are repaired by homologous recombination (HR) using the homolog chromatid as template (left)In a context where excessive DSBs are produced, the DNA damage checkpoint is activated and triggers phosphorylation of the SC component SYP-1 to bias repair through the sister chromatid as template that requires BRC-1 activity (right).

progression and the DNA damage response. We first showed that the syp-1(6A) allele rescues the lethality of syp-1 deletion but leads to mild meiotic progression and DSBs repair defects. Strikingly, we observed that the expression of the syp-1(6A) allele is lethal when C. elegans BRCA1 tumour suppressor ortholog, BRC-1, is absent. Since BRC-1 is required exclusively for inter-sister repair in meiosis, these observations have revealed how the phosphorylation of the synaptonemal complex, bias the repair of persistent DSBs towards inter-sister recombination (Figure 2).

Importantly this work has validated our peptide array screening. The long-term goal is to address at the molecular level the biological relevance of the DNA damage-dependent phosphorylations at meiotic proteins to ensure genome stability. Understanding this is of vital importance in order to have a major comprehensive view of the sources of errors that result in dramatically deleterious outcomes including infertility, miscarriages and birth defects such as Down syndrome. This knowledge of DDR regulation during meiosis should, therefore, provide important insights into fertility defects diagnosis and may present opportunities for therapeutic intervention.

Grants

- 2018: 2018/00000498. Plan Propio US
- 2019-2021:PGC2018-101099-B-I00. Ministerio de Ciencia, Innovación y Universidades
- 2019-2021: 2019/00000463. Plan Propio US
- 2020: 2020/00000690. Plan Propio US

Publication Highlights

García-Muse T. **2020**. Detection of DSB in C. elegans meiosis. **Methods Mol. Biol**. 2153:287-293

García-Muse T*, Galindo U, García-Rubio M, Martin JS, Polanowska J, O'Reilly N, Aguilera A*, Boulton SJ*. **2019.** A meiotic checkpoint alters repair partner bias to permit inter-sister repair of persistent DSBs. (*co-corresponding). **Cell Rep.** 26: 775-787

García-Muse T, Aguilera A. **2019.** R Loops from physiological to pathological roles. **Cell.** 179(3): 604-618

García-Muse T, Aguilera A. **2016.** Transcription-replication conflicts: how they occur and how they are resolved. **Nat Rev Mol Cell Biol.** 17(9): 553-563

Gaillard H., García-Muse T, Aguilera A. **2015.** Replication stress and cancer. **Nat Rev Cancer.** 15(5): 276-289

Dr. Silvia Jimeno-González

Transcription and mRNA processing

Emerging PI

Current position

- Since 2016: Ramón y Cajal Researcher, University of Seville, Andalusian Centre for Molecular Biology and Regenerative Medicine, Seville, Spain

Group Members

PhD Students

- Valentina Buglioni

Master Students

- Cristina Peral Pérez

Former members (2018-2020)

- **Postdoctoral Researcher:** María Salud Domínguez Sánchez

Research Activity

Overview

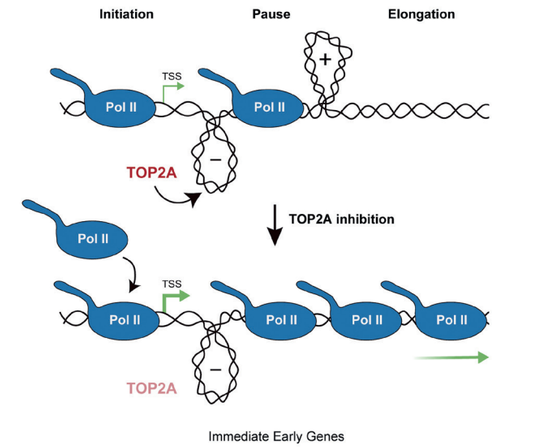
RNAPolymerase II (RNAPII) progression has to be finely coordinated with other processes like the removal of DNA supercoiling, chromatin remodeling and RNA processing. As a matter of fact, RNAPII suffers different pauses through the transcription cycle and those changes in transcription dynamics have been postulated to be related with such coordination.For instance, shortly after starting RNA synthesis, the RNAPII suffers the “so called” promoter-proximal pausing, a mechanism described for approximately 60% of expressed genes in metazoans, in which the main factors involved are well characterized, although its function is still an open question.The main goal of our research is to understand transcriptional mechanisms operatingto regulate gene expression in different physiological contexts. More specifically, we have preliminary data suggesting that promoter-proximal pausing might be important for the transcriptional response after DNA damage and we are currently characterizing such relationship.

Research Highlights

The accumulation of topological stress in the form of DNA supercoiling is inherent to the advance of RNA polymerase II complexes and needs to be resolved to sustain productive transcriptional elongation. DNA topoisomerases are the enzymes that relax this topological stress by transiently gating DNA passage, in a controlled cut-and-reseal mechanism that affects either one (type I DNA topoisomerases; mainly TOP1 in eukaryotes), or simultaneously both (type II topoisomerases; TOP2) DNA strands. Using topoisomerase inhibitors, we have unexpectedly found a rapid and robust induction of highly regulated genes, including a subset of Immediate Early Genes (IEGs), and c-FOS in particular. We have discovered that human topoisomerase IIα(TOP2A), in contrast to the general assumption of topoisomerases as positive transcription regulators, accumulates at gene promoters, where it represses transcription by enforcing promoter-proximal pausing of RNAPII. Indeed, there is a general RNAPII release from pausing under TOP2 catalytic inhibition. As a matter of fact, the function of TOP2A in transcriptional regulation has been found to be tightly interconnected to TOP1 activity and completely independent of double strand breaks (DSB) formation, but instead, relying on the continuous removal of transcription-associated (-) supercoiling at promoter regions. We provide a comprehensive topological framework for the regulation of promoter-proximal pausing that can explain the typical bursting behavior of IEGs, and in more general terms, the tight control of human gene expression by DNA topoisomerases. We therefore describe the control of promoter DNA supercoiling by topoisomerases as a novel layer for the regulation of gene expression, which can act as a molecular switch to rapidly activate transcription.

Because of the connection between promoter-proximal pausing and TOP2 activity at promoters of highly regulated genes, we have decided to study whether promoter-proximal pausing could have a function in the repair of DSB generated by TOP2. Stabilization of the cleavage complexes produced within TOP2 catalytic cycle with TOP2 poisons produces such breaks. We have observed that depletion of pausing factors like NELF or PAF1 complexes decreases the number of TOP2 breaks and the intensity of the $^{\gamma}$-H2AX signal (the histone variant phosphorylated at the site of the break by ATM and ATR) both globally and at specific loci, an effect that is not recapitulated under ionizing radiation treatment. Therefore, pausing seems to be important for the regulation of transcription after DNA damage generated by topoisomerases. Overall, our results show that topoisomerase activity at promoter regions is closely related with the regulation of gene expression at transcription elongation, more specifically, at promoter-proximal pausing level.

Scientific Report 2018-2020



Grants

- 2018: PP. Precompet, Universidad de Sevilla
- 2020-2023: PID2019-104484G, Ministerio de Ciencia e Innovación

Publication Highlights

Álvarez-Quilón A, Terrón-Bautista J, Delgado-Sainz I, Serrano-Benítez A, Romero-Granados R, Martínez-García P, Jimeno-González S, Bernal-Lozano C, Quintero C, García-Quintanilla L, Cortés-Ledesma F. **2020.** Endogenous topoisomerase II-mediated DNA breaks drive thymic cancer predisposition linked to ATM deficiency. **Nature Communications.** 11(1):910

Feng W, Kawauchi D, Körkel-Qu H, Deng H, Serger E, Sieber L, Lieberman JA, Jimeno-González S, Lambo S, Hanna BS, Harim Y, Jansen M, Neuerburg A, Friesen O, Zuckermann M, Rajendran V, Gronych J, Ayrault O, Korshunov A, Jones DT, Kool M, Northcott PA, Lichter P, Cortés-Ledesma F, Pfister SM, Liu HK. **2017.** CHD7 is indispensable for mammalian brain development through activation of a neuronal differentiation programme. **Nature communications.** 8:14758

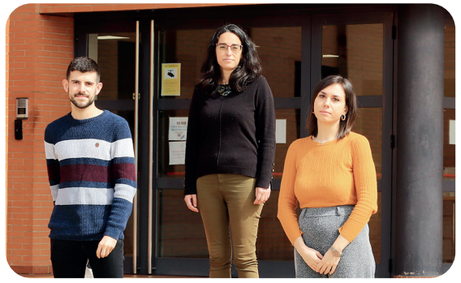
Prado F, Jimeno-González S, Reyes JC. **2017.** Histone availability as a strategy to control gene expression. **RNA Biol.** 21:1-6

Jimeno-González, S* and Reyes JC* (*Corresponding authors). **2016.** Chromatin structure and pre-mRNA processing work together. **Transcription.** 26;7(3):63-8

Dr. Cristina González-Aguilera

Replication and Nuclear Dynamics

Emerging PI



Current position

- Ramón y Cajal Contract (University of Seville, Department of Cellular Biology) at Andalusian Center for Molecular Biology and Regenerative Medicine, Seville, Spain

Group Members

PhD student
- Federica Bruno

Technician
- Cristobal Coronel Guisado

Master student
- Adrián Núñez Sancho

Former Members (2018-2020)

- **Erasmus+ student:** Federica Bruno

Research Activity

Overview

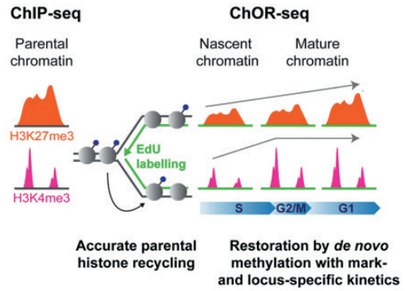
Chromatin replication is a key moment of the cell cycle because the nucleosomes in which the DNA winds and the transcription machinery that operates on it must be released to allow the pass of the replication fork to facilitate the duplication of the genome. Despite the mechanisms of control evolved in the cell to maintain this process as accurate as possible, during the last years, we have learnt that the newly replicated chromatin suffers from transient alterations in the nucleosome positioning and histones' marks abundance and distribution that creates fluctuations of the epigenetics information along the cell cycle. Our goal is to understand the consequences of these epigenetic fluctuations in the nuclear dynamics and its relevance on human diseases.

Research Highlights

During chromatin replication, parental histones have to be evicted from the DNA to allow the pass of the replication fork. Then, parental and newly synthetized histones are mixed together and relocate into the two daughter-strands to restore chromatin structure and nucleosome density. This parental histone recycling and its assembly with the new histones is critical for the maintenance of the cellular identity and functionality due to the presence of post-translational modifications (PTMs) on histones. These modifications together with the methylation in the DNA are called epigenetic information and are responsible of the regulation of all the nuclear processes including transcription, replication and repair of the DNA.

Therefore, the cell has to assure that the epigenetic information is transmitted to the daughter's cells in a reliable way. Despite the great relevance that all these basic cellular activities could have in human diseases, our current knowledge of the regulation of chromatin maintenance after cell division is very limited due to the lack of techniques to study all these processes directly. It was only few years ago that the development of new proteomics techniques, able to analyze the newly replicated chromatin started to enlighten the mechanisms regulating these events. These pioneering studies revealed two important facts: First, that parental histones are recycled preserving their original marks, facilitating the transmission of the epigenetic information to the daughter cells. Second, that the abundance of parental PTMs is reduced by half after replication due to the presence of new histones. More importantly, they observed thattotal restoration of parental PTMs takes time and the kinetics of restoration varies between marks creating a scenario where epigenetic information fluctuates along the cell cycle. However, the proteomic analysis can only provide global quantitative measurements butnot locus-specific information.

To unravel how the histone PTMs restoration occurred in the context of the genome, we developed the ChOR-seq technology (Chromatin Occupancy after Replication and sequencing), a cutting-edge technique able to purify newly replicated chromatin associated to proteins and histone PTMs in mammalian cells. The technique is based on the in vivo labelling of newly replicated DNA with 5-Ethynyl-2´-deoxyuridine (EdU), a thymidine analogue. After DNA labelling, chromatin bound proteins are sequentially purified first, by chromatin immunoprecipitation (ChIP) against the protein of interest and later by streptavidin-capture of biotinylated EdU-labelled DNA. Then, purified DNA is identified by next generation sequencing. With this technology, we have revealed that in human cells, parental histones carrying both active and silent histone PTMs are recycled precisely at their original pre-replicated positions, facilitating the maintenance of parental epigenetic patterns in the two newly replicated strands. However, the restoration of new histone PTM levels is mark and locus specific. Some marks are fast, as H3K4me3, which restoration is completed within 6 hours, before



cell division. However, H3K27me3 restoration is slow and its methylation continues until the next round of chromatin replication in the daughter cell. All these findings confirm the existence of a complex epigenetic changes across the cellcycle whose effects on cellular function will have to be determined.

Grants

- 2020-2023: PID2019-105742GA-100. Ministerio de Ciencia e innovación
- 2020: VIPPIT-2019-IV.2. Atracción de talento. Universidad de Sevilla
- 2020-2024: RYC2018-025485-I. Ayuda Ramón y Cajal. Ministerio de Ciencia e Innovación

Publication Highlights

Gylling HM, González-Aguilera C, Smith MA, Kaczorowski DC, Groth A, Lund AH. **2020.** Repeat RNAs associate with replication forks and post-replicative DNA. **RNA.**26(9):1104-1117

Martín-Broto J.,Cruz J, Penel N, Lecesne A, Hindi N, Luna P, Moura DS, Bernabeu D, de Alava E, López-Guerrero JA, Dopazo J, Peña-Chilet M, Gutierrez A, Collini P,Karajan M, Redondo A, López-Pousa A, Grignani G, Diaz-Martín DM, Fernandez-Serra A, González-Aguilera C, Casali PG, Blay JY, Stachiotti S.**2020.**Pazopanib for treatment of typical solitary fibrous tumour: A multicentre single arm, Phase II trial **The Lancet Oncology.**21(3):456-466

Reverón-Gómez N*,González-Aguilera C*, Stewart-Morgan KR*, Petryk N, Flury V, Graziano S, Johansen JV, Jacobsen JS, Alabert C, Groth A. **2018.** Accurate recycling of parental histones reproduces the histone modification landscape during DNA replication. Mol. **Cell.** 72(2):239-249.e5

Feng Y, Vlassis A, Roques C, Lalonde ME, González-Aguilera C, Lambert JP, ZhaoX, Alabert C, Johansen J, Paquet ER, Yang X, Gingras AC, Côté J, Groth A. **2016.** BRPF3-HBO1 regulates replication origin activation and histone H3K14 acetylation. **EMBO J.** 35(2):176-92

Huang H, Strømme CB, Saredi G, Hödl M, Strandsby A, González-Aguilera C, ChenS, Groth A, Patel DJ. **2015.** A unique binding mode enables MCM2 to chaperonehistones H3-H4 at replication forks. **Nat Struct Mol Biol.** 22(8):618-26

Cell Dynamics and Signalling

The main research objective of the Department of Cell Dynamics and Signaling is the understanding of the molecular mechanisms of basic cellular processes, whose alterations have a high impact in degenerative and metabolic diseases, genetic syndromes, and cancer. The different areas of research cover cell death signaling; cell polarity, adhesion and motility; cell cycle and division; cell differentiation; and cell metabolism. Our research is dedicated to deciphering the mechanisms controlling cell homeostasis and fate, both individually and in the tissue/organ context, with the aim of advancing in the knowledge of neoplasia and metabolic pathologies, as well as of genetic syndromes. It is complementary to the Genome Biology Area of Research, focusing on the impact that genome alterations have on key cellular processes as a possible molecular mechanism to explain disease, with a particular emphasis on the deregulation of cell growth, proliferation, and differentiation. The research of 6 active groups in the Center are included in this Department.

HEAD OF DEPARTMENT

Dr. Raúl V. Durán

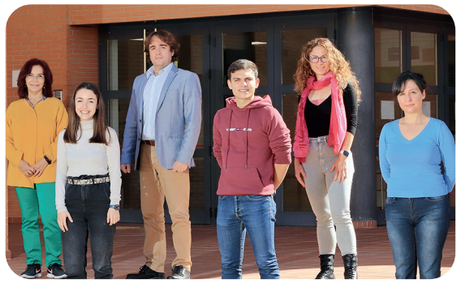
RESEARCH GROUPS

1. **Metabolism and Cell Signaling**
   Dr. Raúl V. Durán
2. **Cell Death Signalling**
   Prof. Abelardo López-Rivas
3. **Cell Cycle and Oncogenesis**
   Prof. José A. Pintor Toro
4. **Microtubule Dynamics in Health and Disease**
   Dr. Rosa M. Ríos
5. **Cell Division Control**
   Dr. Fernando Monje-Casas
6. **Cell Differentation**
   Mario García-Domínguez

Dr. Raúl V. Durán

Metabolism
and cell signalling

Group Leader
Head of Department



Current position

- Since 2018: Senior Research Associate, National Council for Research, CSIC/ CABIMER.
- Since 2019: Head of Department of CABIMER, Seville, Spain.
- Since December 2021: Deputy Director of CABIMER, Seville, Spain.

Current Group Members

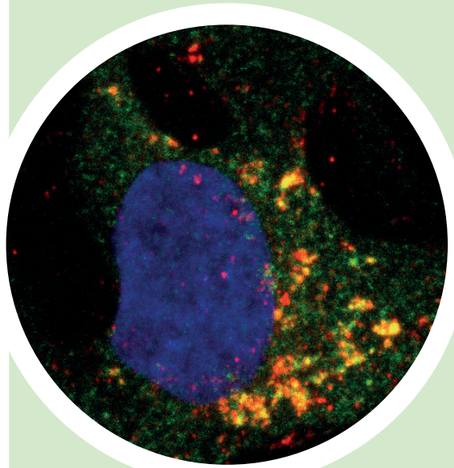
Senior Researcher
- Dr. Socorro Murdoch

Postdoctorals
- Dr. Macarena Morillo Huesca
- Dr. Mercedes Tomé Montesinos

PhD student
- Laura Zarzuela Moncada

Former Members (2018-2020)

- **PhD student:** Clément Bodineau
- **Master student:** Lucia Rebollo López



Research Activity

Overview

My team investigates the crosstalk between the changes in the metabolism of cancer cells and the deregulation of cellular signaling during malignant transformation. Particularly, during last years, we established a mechanistic connection between the metabolism of the important amino acid glutamine and the activation of the mTOR (mammalian target of rapamycin) pathway, a central controller of autophagy and cell growth. Both glutamine and mTOR play a key role in tumor growth and progression. Using both cellular and animal models, our results indicated that interfering with this connection through nutritional imbalance strongly affect the activation of autophagy in cancer cells, leading to a particular type of tumor cell death that we named “glutamoptosis”.

Research Highlights

In August 2018, the Laboratory of Metabolism and Cell Signaling moved from the IECB in Bordeaux (France) to CABIMER. The arrival and installation of the lab at this new emplacement has been as smooth and successful as testified by the fact tha our scientific production has only suffered a minor impact. Indeed, during this 2-year period, we manage to consolidate a team of 5 - 6 people in the lab, to stablish and continue our lines of research, to successfully conclude 1 PhD thesis, 1 Master thesis and 1 TFG, and to publish 2 major authorship publications as corresponding plus several collaborative publications (6 publications in total) with an average IF of 8.4 our investigations continued providing with new insights in the connection between glutamine metabolism and cell growth signaling in cancer cells, detecting new mechanistic players during glutamoptosis, provided with new strategies to specifically kill cancer cells using a new class of mTOR inhibitors, and unravel an unprecedented addiction to glutamine phenotype by Notch1-dirven leukemic cells.

mTOR inhibition via displacement of phosphatidic acid induces enhanced cytotoxicity specifically in cancer cells

The mammalian target of rapamycin (mTOR) is a central regulator of cell growth and is highly activated in cancer cells to allow rapid tumor growth. The use of mTOR inhibitors as anti-cancer therapy has been approved for some types of tumors, albeit with modest results. We recently reported the synthesis of ICSN3250, a halitulin-analogue with enhanced cytotoxicity. Our investigations showed that ICSN3250 is a specific mTOR inhibitor that operates through a mechanism distinct from those described for previous mTOR inhibitors. ICSN3250 competes with and displaces phosphatidic acid from the FRB domain in mTOR, thus preventing mTOR activation and leading to cytotoxicity. Docking and molecular dynamics simulations evidenced not only the high conformational plasticity of the FRB

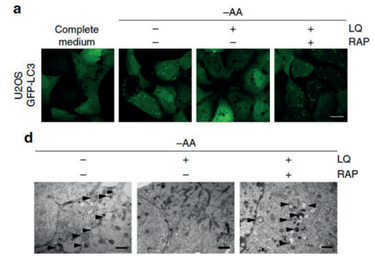


Figure 1. Activation of glutaminolysis using leucine and glutamine (LQ) induces autophagy activation as determine by GFP-LC3 dots using confocal microscopy (top panels) or electron microscopy (lower panel, arrows indicate autophagosome structures). mTORC1 inhibition using rapamycin (RAP) prevents autophagy induction (from Villar *et al.*, 2017 Nature Comms).

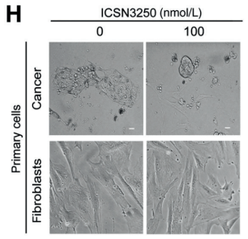


Figure 2. The new class mTOR inhibitor ICSN3250 specifically kills patient colorectal carcinoma cells, with no toxicity to non-cancer fibroblasts from the same patient. This differential toxicity is proves that this mTORC1-inhibitor can be used for cancer therapies with a reduced unspecific toxicity (from Nguyen *et al.*, 2018 Cancer Res).

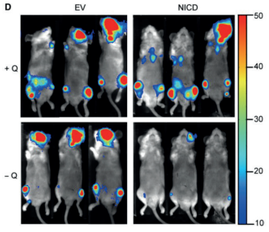


Figure 3. Nutritional imbalance help to reduce Notch-driven leukemia progression in mice. Notch-driven (NICD) and non-Notch-driven leukemia (EV) was induced in mice fed with complete diet (+Q) or with a diet without the amino acid glutamine (-Q). Luminescence analysis of leukemic cells identify a dramatic decrease in Notch-driven leukemia in mice fed with glutamine (from Nguyen *et al.*, 2021 Mol Oncol).

domain, but also the specific interactions of both ICSN3250 and phosphatidic acid with the FRB domain in mTOR. Furthermore, ICSN3250 toxicity acts specifically in cancer cells, as non-cancer cells showed up to 100-fold less sensitivity to ICSN3250, in contrast to other mTOR inhibitors which did not show selectivity. Thus, our results define ICSN3250 as a new-class of mTOR inhibitors that specifically targets cancer cells.

Downregulation of Glutamine Synthetase, not glutaminolysis, is responsible for glutamine addiction in Notch1-driven acute lymphoblastic leukemia

The cellular receptor Notch1 is a central regulator of T-cell development, and as a consequence, Notch1 pathway appears upregulated in >65% of the cases of T-cell acute lymphoblastic leukemia (T-ALL). However, strategies targeting Notch1 signaling render only modest results in the clinic due to treatment resistance and severe side effects. While many investigations reported the different aspects of tumor cell growth and leukemia progression controlled by Notch1, less is known regarding the modifications of cellular metabolism induced by Notch1 upregulation in T-ALL. Previously, glutaminolysis inhibition has been proposed to synergise with anti-Notch therapies in T-ALL models. In our investigations, we have recently demonstrated that Notch1 upregulation in T-ALL induces a change in the metabolism of the important amino acid glutamine, preventing glutamine synthesis through the downregulation of glutamine synthetase. Downregulation of glutamine synthetase is responsible for glutamine addiction in Notch1-driven T-ALL both in vitro and in vivo. Our results also confirm an increase in glutaminolysis mediated by Notch1. Increased glutaminolysis results in the activation of the mTORC1 pathway, a central controller of cell growth. However, glutaminolysis does not play any role in Notch1-induced glutamine addiction. From a clinical perspective, the combined treatment targeting mTORC1 and limiting glutamine availability has a synergistic effect to induce apoptosis and to prevent Notch1-driven leukemia progression. Our results place glutamine limitation and mTORC1 inhibition as a potential therapy against Notch1-driven leukemia.

Grants

- 2019 - 2021: PGC2018-096244-B-I00, Ministerio de Ciencias, Innovación y Universidades.
- 2019 - 2020: 201920E071, *Proyectos Intramurales Especiales, Consejo Superior de Investigaciones Científicas - CSIC*
- 2018 - 2021: PDF20171206689, *Fondation ARC pour la Recherche sur le Cancer.*
- 2018 - 2019: 2018201064, *Proyectos Intramurales, Consejo Superior de Investigaciones Científicas - CSIC.*
- 2018: OPE-2018-0069, *Ligue Contre le Cancer - Nouvelle Aquitaine.*

Publication Highlights

Soulet F, Bodineau C, Hoocks KB, Descarpentrie J, Alves I, Dubreuil M, Mouchard A, Eugenie M, Hoepffner JL, López J, Rosado JA, Soubeyran I, Tomé M, Durán RV, Nikolski M, Villoutreix BO, Evrard S, Siegfried G, and Khatib AM. **2020.** Repression of renal cell carcinoma growth and survival by ELA/Apela through mTORC1 activation, **JCI Insight** 5, e129070.

Chinoy ZS, Bodineau C, Favre C, Moremen K, Durán RV and Friscourt F. **2019.** Selective Engineering of Linkage Specific α2,6-N-Linked Sialoproteins using Sydnone-Modified Sialic Acid Bioorthogonal Reporters. **Angewandte Chem Int** Ed 58, 4281-4285.

Nguyen TL, Nokin MJ, Egorov M, Tomé M, Bodineau C, Di Primo C, Minder L, Wdzieczak-Bakala J, García-Álvarez MC, Bignon J, Thoison O, Delpech B, Surpateanu G, Frapart YM, Peyrot F, Abbas K, Terés S, Evrard S, Khatib AM, Soubeyran P, Iorga B, Durán RV* and Collin P. **2018.** mTOR inhibition via displacement of phosphatidic acid 2 induces enhanced cytotoxicity specifically in cancer cells. **Cancer Research** 78, 5384-5397.

Villar VH, Nguyen TL, Delcroix V, Terés S, Bouchecareilh M, Salin B, Bodineau C, Vacher P, Priault M, Soubeyran P and Durán RV. **2017.** mTORC1 inhibition in cancer cells protects from glutaminolysis-mediated apoptosis during nutrient limitation. **Nature Comms.** 8, 14124

Villar VH, Mehri F, Djavaheri-Mergny M and Durán RV. **2015.** Glutaminolysis and autophagy in cancer. **Autophagy.** 11, 1198-1208

Prof. Abelardo López-Rivas

Cell Death Signalling

Group Leader

Current position

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

Former Members (2018-2020)

- **PhD students:** Marta Mauro Lizcano
- **Master students:** Alejandro Campos Castañeda

Group Members

Research Associates
- Carmen Palacios Casanova

Postdocs
- Rosario Yerbes Cadenas

PhD Students
- Rocío Mora Molina
- Younes El Yousfi El Mourabit

Technicians
- Francisco Javier Fernández Farrán

Research Activity

Overview

Different studies including ours, have implicated proapoptotic TRAIL receptors and caspase-8 in mediating a cell-autonomous apoptosis in response to metabolic and endoplasmic reticulum (ER) stress in oncogene-transformed cells, tumor cell lines and tumor xenografts. However, TRAIL receptor activation does not always kill target cells. Thus, TRAIL-mediated activation of TRAIL receptors on cancer cells has also recently been shown to induce a caspase-8-dependent pro-inflammatory immune response, thereby contributing to tumor growth. These observations point to a dual role of caspase-8 in cancer and suggest the existence of molecular mechanisms that may modulate caspase-8 function switching it from the classical apoptotic roles to other protumoral functions. Our current project is committed to understand the role of the TRAIL-R2/Caspase-8 system in the different outcomes of the stress response in tumor cells and their modulation by extracellular matrix stiffness and the transcriptional regulators YAP/TAZ.

Research Highlights

Glutamine belongs to a group of aminoacids that are conditionally essential, particularly under catabolic stress conditions. Interestingly, the core region of solid tumors displayed glutamine deficiency compared with other amino acids. However, how low glutamine levels in solid tumors affects tumor growth and therapeutic response remains largely unknown. Our recent work demonstrates that treatment with L-asparaginase, through its glutaminase activity, down-regulates FLIP expression and markedly sensitizes triple-negative breast tumor cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Our data also reveal that metabolic stress induced by glutamine starvation activates an apoptotic response in tumor cell lines of different origin by a TRAIL-independent but TRAIL-R2 and caspase-8-dependent mechanism, that is regulated by FLIP levels. Glutamine deprivation may also adversely affect the environment of the endoplasmic reticulum (ER) and impact on the maturation of nascent proteins. The resultant accumulation of unfolded proteins activates a signal transduction pathway, known as the unfolded protein response (UPR), which serves primarily to restore homeostasis to the ER, facilitating tumor growth. However, if the stress is prolonged or there is excessive stimulation of these signalling pathways, irreversible activation of the apoptotic machinery and thereby cell death will take place. Interestingly, our results have implicated proapoptotic TRAIL receptors and caspase-8 in mediating a TRAIL-independent cell-autonomous apoptosis in response to metabolic and endoplasmic reticulum (ER) stress in oncogene-transformed cells, tumor cell lines and tumor xenografts. Moreover, our recent data also have shown that regulation of FLIP expression levels is a key event in the

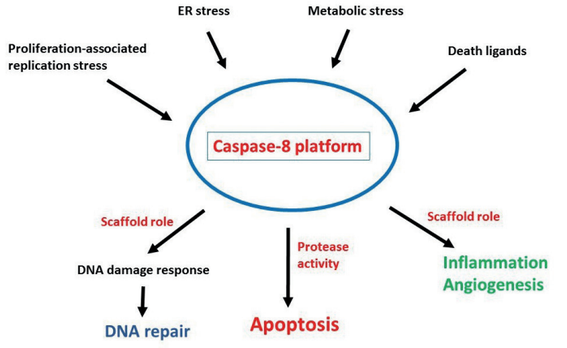


Figure 1. Dual role of Caspase-8 platfom in the control of tumor growth

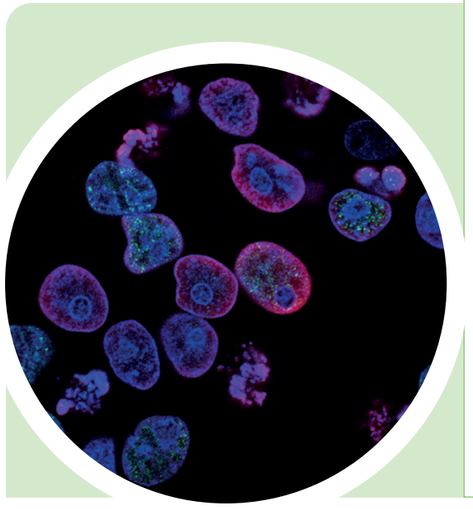
mechanism controlling sensitivity of triple-negative breast tumor cells to ER stress-induced apoptosis.

During angiogenesis blood vessels grow and remodel to ultimately build a hierarchical vascular network. Whether and how cell death signaling molecules contribute to blood vessel formation is still not well understood. Our laboratory has also contributed to define the role of Caspase-8 in angiogenesis in a collaborative work leaded by the group of Dr. C. Ruiz de Almodovar, Heidelberg University. Results from this work have demonstrated that Caspase-8 (Casp-8), a key protease in the extrinsic cell death-signaling pathway, is expressed in endothelial cells (ECs) and is required for proper postnatal angiogenesis. Loss of Casp-8 lead to the hyperactivation of p38 kinase downstream of RIPK3 kinase followed by the destabilization of VE-cadherin in EC junctions which ultimately resulted in reduced EC proliferation, sprouting and migration.

Glioblastoma (GBM) is the most common and aggressive brain tumor and is associated with poor prognosis. GBM cells are frequently resistant to TRAIL and finding new combinatorial therapies to sensitize glioma cells to TRAIL remains an important challenge. PIM kinases are serine/threonine kinases that promote cell survival and proliferation and are highly expressed in different tumors. In collaboration with the group of Dr. F.J. Oliver, Institute of Parasitology and Biomedicine CSIC in Granada, we have demonstrated that PIM inhibition or knockdown facilitated activation by TRAIL of a TRAIL-R2-mediated and mitochondria-operated apoptotic pathway in GBM cells. The sensitizing effect of PIM knockdown on TRAIL-induced apoptosis was mediated by enhanced caspase-8 recruitment to and activation at the Death-Inducing Signaling Complex (DISC). Phospho-proteome profiling revealed a decreased phosphorylation of p62/SQSTM1 after PIM knockdown. Our results also showed that p62/SQSTM1 ablation increased TRAIL-R2/DR5 levels and facilitated TRAIL-induced caspase-8 activation, revealing an inhibitory role of p62/SQSTM1 in TRAIL-mediated apoptosis in GBM. Conversely, up-regulation of TRAIL-R2/DR5 upon PIM inhibition and apoptosis induced by the combination of PIM inhibitor and TRAIL were abrogated by a constitutively phosphorylated p62/SQSTM1^{S332E} mutant. Globally, our data are the first evidence that PIM kinases regulate TRAIL-induced apoptosis in GBM and identify a specific role of p62/SQSTM1^{Ser332} phosphorylation in the regulation of the extrinsic apoptosis pathway activated by TRAIL.

Grants

- 2014-2018: BIO 778. Proyecto de Excelencia de la Junta de Andalucía
- 2016-2018: SAF2015-64383-P. Ministerio de Economía y Competitividad
- 2017-2020: CB16/12/00421. Centro de Investigación Biomédica en Red (CIBERONC), Instituto de Salud Carlos III
- 2019-2021: PGC2018-093960-B-I00. Ministerio de Ciencia, Innovación y Universidades



Publication Highlights

Serrano-Sáenz S, Palacios C, Delgado-Bellido D, López-Jiménez L, García-Diaz A, Yolanda Soto-Serrano, Casal JI, Rubén A, Bartolomé RA, Fernández-Luna JL, López-Rivas A*, Oliver FJ* (*senior and corresponding author). **2019.** PIM kinases mediate resistance of glioblastoma cells to TRAIL by a p62/SQSTM1-dependent mechanism. **Cell Death and Disease** 10(2):51

Tisch N*, Freire-Valls A *, Yerbes R*, et al., López-Rivas A, Schmidt T, Augustin HG, Ruiz de Almodovar C (*equal contribution). **2019.** Caspase-8 modulates physiological and pathological angiogenesis during retina development. **The Journal of Clinical Investigation** 129(12):5092-5107

Mauro-Lizcano M, López-Rivas A. **2018.** Glutamine metabolism regulates FLIP expression and sensitivity to TRAIL in triple-negative breast cancer cells. **Cell Death and Disease** 9(2):205

Cano-González A*, Mauro-Lizcano M*, Iglesias-Serret D, Gil J, López-Rivas A. (*equal contribution). **2018.** Involvement of both caspase-8 and Noxa-activated pathways in ER stress-induced apoptosis in triple-negative breast tumor cells. **Cell Death and Disease** 9(2):134

Martín-Pérez R, Yerbes R, Mora-Molina R, Cano-González A, Arribas J, Mazzone M, López-Rivas A*, Palacios C*. **2017.** (*senior and corresponding author). Oncogenic p95Her2/611CTF primes human breast epithelial cells for metabolic stress-induced activation of TRAIL-R/Caspase-8-dependent apoptosis. **Oncotarget.** 8(55):93688-93703

Prof. José A. Pintor Toro

Cell Cycle and Oncogenesis

Group Leader

Current position

- Since 1986: Professor CSIC, CABIMER, Seville, Spain

Group Members

PhD Students

- Salvador Polo Generelo

Former Members (2018-2020)

- **PhD students:** Salvador Polo Generelo, Cristina Rodríguez-Mateo
- **Postdoc:** Belén Torres Agrela

Research Activity

Overview

The epithelial-mesenchymal transition (EMT) is a basic cellular process in which epithelial cells lose their epithelial characteristics and take on properties of mesenchymal cells. Our interest is focused on studying the immediate-early changes of this process. Two levels of regulation are the object of our study: transcriptional and post-transcriptional levels. Regarding the first level, our interest is identify non-coding RNA molecules (lnc-RNAs) that early regulate this process and act as “master genes”. Regarding the second level, our objective is to determine both coding and non-coding RNA molecules whose primary function is to sequester miRNA molecules that would be blocking the translation of transcripts whose proteins are essential for EMT. Since the appearance of these new proteins would not be correlated with changes in the expression of the corresponding mRNA, these ones would not be included in the transcriptomic profiles corresponding to the expression changes produced. Given the clinical relevance of EMT in tumorigenesis and metastasis, our ultimate interest is to explore the potential use as biomarkers and therapeutic targets of the new identified molecules.

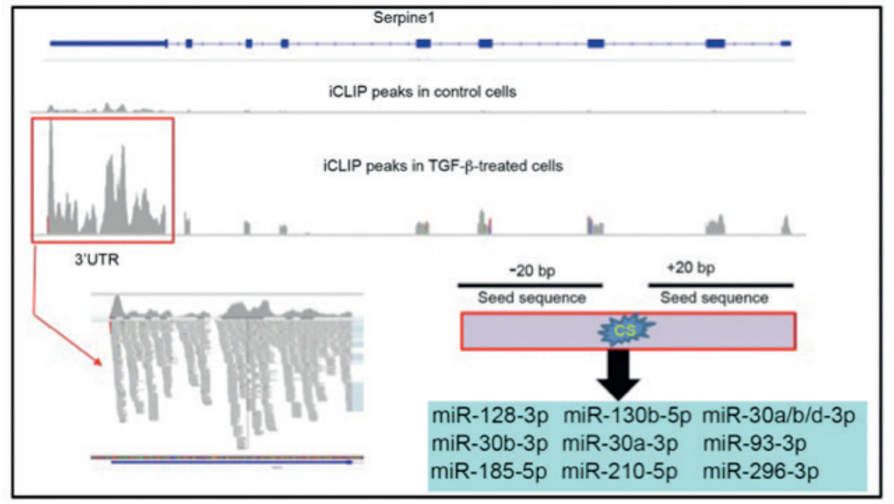
Research Highlights

A TGF-ß up-regulated long non-coding RNA, lnc-Nr6a1, has been identified as an immediate early regulator of EMT. This gene maps on chromosome 2 and is transcribed as a precursor from the third intron of the Nr6a1 gene and in the opposite sense of the Nr6a1 gene. Two isoforms, lnc-Nr6a1-1 and lnc-Nr6a1-2respectively, are early induced at similar levels after TGF-ß treatment. Lnc-Nr6a1-1 isoform is a reservoir of miR-181a-2 and mir-181b-2 genes, located close to the 3’ end of lnc-Nr6a1-1.Lnc-Nr6a1-1 and lnc-Nr6a2 transcripts are direct targets of ERK1/2 and AKT pathways respectively.

Lnc-Nr6a1 gene knockdown resulted in statistically significant changes in the expression levels of 648 genes; among them 298 were down-regulated and 350 were up-regulated. Gene ontology analysis of down-regulated genes showed enrichment in genes involved in cell adhesion. Overexpression of lnc-Nr6a1 isoforms increased significantly cellular motility. Enhanced precursor expression, isoforms plus miR-181, increased anoikis resistance, suggesting that lnc-Nr6a1 precursor expression results in the post-transcriptional downregulation of specific mRNAs during EMT process. Lnc-Nr6a1 isoforms were nuclear-enriched and located mainly in the chromatin fraction. Lnc-Nr6a1-1 isoform associated, in vivo, with lamin A/C.

The iCLIP analysis of the RNA / AGO / miRNA complexes of the epithelium-mesenchymal transition process (EMT) has allowed us to determine RNAs that post-transcriptionally regulate this process early.

Serpine1 mRNA that is abundantly and very rapidly induced during this process is, paradoxically, the most accumulated or enriched mRNA in these complexes, suggesting for this mRNA a function of competing endogenous RNA or sponge of miRNAs. These miRNAs would inhibit the synthesis of certain proteins required for the complete development of the EMT process. The analysis of the proteomic profiles of control cells and cells overexpressing Serpine1 mutated mRNA, showed that expression level of various proteins was affected. TRA2b alternative splicing factor protein level was the most affected by Serpine1 mRNA overexpression. Protein level change was not associated to changes in Tra2b mRNA level, which was not affected. Sequestration of miR-130b by Serpine1 mRNA allowed the Tra2b mRNA translation. In the EMT process, high levels of Serpine1 mRNA and the presence of new isoforms of a large number of mRNAs are detected;



Scheme of the serpine1 gene showing the crosslinking sites of exons and 3'UTR region with AGO2 protein. 3'UTR sequence reads and miRNAs corresponding to crosslinking sites are shown.

likewise, tumors often show high levels of Serpine1 mRNA and also new isoforms of numerous genes. Our data suggest that (a) there is a close relationship between some alternative splicing changes and high levels of Serpine1 mRNA and (b) some of these changes are due to increased levels of TRA2b alternative splicing factor. Also, Serpine1 mRNA function as a natural miRNAs sponge promoting both transcriptional and post-transcriptional expression changes could reveal mRNAs and proteins as new potential therapeutic targets and biomarkers that have not been considered to date.

Grants

- 2018-2020. SAF2017-86189-P. Ministerio de Ciencia e Innovación

Publication Highlights

Moreno-Mateos MA, Barragán V, Torres B, Méndez-Vidal C, Mudduluru G, Allgayer H, Pintor-Toro JA. **2013.** Novel small RNA expression libraries uncover hsa-miR-30b and hsa-miR-30c as key factors in anoikis resistance. **RNA.** 19: 1711-1725

Méndez-Vidal C, Gámez-Del Estal MM, Moreno-Mateos MA,Espina-Zambrano AG, Torres-Agrela B, Pintor-Toro JA. **2013.** PTTG2 silencing results in induction of epithelial-to-mesenchymal transition and apoptosis. **Cell Death Dis.** 4:e530

Rodríguez-Mateo C, Torres B, Gutiérrez G, Pintor-Toro JA. **2017.** Downregulation of Lnc-Spry1 mediates TGF-ß-induced epithelial-mesenchymal transition by transcriptional and posttranscriptional regulatory mechanisms. **Cell Death Differ.** 24(5):785-797

Muñoz MF, Argüelles S, Guzman-Chozas M, Guillén-Sanz R, Franco JM, Pintor-Toro JA, Cano M, Ayala A. **2018.** Cell tracking, survival, and differentiation capacity of adipose-derived stem cells after engraftment in rat tissue. **J Cell Physiol.** 233(10):6317-6328

Dr. Rosa M. Ríos

Microtubule dynamics in health and disease

Group Leader

Current position

- Since 2011: Senior Research Scientist - Spanish National Research Council CSIC-CABIMER
- From 19/02/2019: On temporary leave of absence as Secretary General of University, Research and Technology - Government of Andalucía

Current Group Members

Postdocs
- María P. Gavilán
- Chiara Marcozzi
- Pablo Gandolfo
- Laura Martínez

PhD Students
- Jesús Roca

Technicians
- Loida Pérez García

Former Members (2018-2020)

- **Postdocs:** Elena Gavilán, Eduardo Ródenas
- **Technician:** Casimiro José Baena
- **Master students:** Abel Heredia, Pablo Guerra

Research Activity

Overview

Microtubule (MT) nucleation, the event that initiates de novo formation of MTs, is a highly regulated process that enables cells to acquire specific architectures and to promptly respond to any cellular change. The centrosome and the Golgi Apparatus (GA) are the two major MT-organising centres (MTOCs) in cells, and increasing evidence underpins the idea that there is a high degree of coordination and crosstalk between their activities along the cell cycle and during cell differentiation. The main focus of my lab is to unveil the mechanisms underlying MT nucleation driven by the GA and the centrosome, as well as to explore the existence of alternative pathways relying on other MTOCs such as acentriolar MTOCs. We aim to thoroughly unravel how all these MTOCs work in concert to mediate organelle positioning, intracellular transport, cell polarity, motility, and chromosome segregation during cell division. We are also studying the role of centrosomal proteins in the Wnt/ß-catenin-mediated control of mitotic spindle orientation in cancer progression. Finally, we are investigating how chemokines regulate the spatiotemporal organisation of chemokine receptors, and what are the associated cytoskeletal proteins that orchestrate T lymphocyte migration under shear flow and into the interstitial tissue.

Research Highlights

Interplay between the GA and the centrosome-dependent MT nucleation activities

We have unveiled how cells specifically regulate GA- or centrosome- dependent MT nucleation during interphase and how these MT-nucleating activities are coordinated.

After generating knockout cell lines to disrupt the function of the main $^{\gamma}$-TuRC receptors, namely PCNT, CDK5Rap2, and AKAP450, we dissected their contribution to MT nucleation during interphase either at the GA or at the centrosome. We observed that they all play a major role in MT nucleation at the GA, but surprisingly they contribute minimally to the centrosome-dependent MT nucleating activity. Close examination of other $^{\gamma}$-TuRC receptors revealed that Cep192 has a key role in centrosomal MT nucleation. The combination of $^{\gamma}$-TuRC receptors knockout with Plk4 inhibitor centrinone to induce centrosome loss provided evidence that MT nucleation is a hierarchically regulated process (Fig.1). Centrosome depletion strongly enhances GA-mediated MT nucleation, while inhibition of GA-associated MT nucleation does not affect centrosome activity. Silencing both MTOC nucleation activities prompts the formation of cMTOCs, cytoplasmic complexes containing PCNT, CDK5Rap2 and $^{\gamma}$-tubulin, which are able to nucleate MTs. This work has substantially contributed to the understanding of mechanisms conferring MT formation plasticity in interphase, introducing a completely new role of the centrosome as the leading MTOC exerting tight control on other MTOC sites (Gavilan et al.,2018).

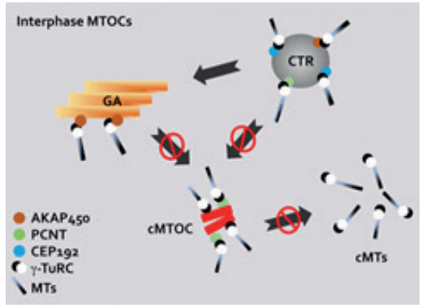


Fig 1. Relationship between the different MTOCs

Dissection of the contribution of ᵞ-tubulin to MT nucleation from different MTOCs

To characterise the dependency of MT nucleation events on ᵞ-tubulin we exploited the auxin degradation system and generated cell lines where the most abundant isoform of ᵞ-tubulin (TUBG1) is tagged with the auxin degron to timely induce its proteolysis. We have found that TUBG1 depletion significantly reduces, but does not fully abolish, MT nucleation from both the centrosome and the GA. Further knock-down experiments on the other ᵞ-tubulin isoform, TUBG2, have revealed an unexpected contribution to the overall MT nucleation process.

Role of Wnt/ß-catenin signalling pathway in controlling oriented cell division

Correct cell division relies on the crosstalk between the centrosomes and the cell cortex. Components of the Wnt/ß-catenin signalling pathway, such as APC, ß-catenin and Axin1, have been found to localise at the centrosome. o understand their role during cancer progression we have fluorescently-tagged these proteins in HCT116 cell line and we are studying their dynamics and contribution to spindle formation and orientation in cell division.

Mechanisms of inhibition of Golgi-associated MT nucleation in mitosis

GA ability to nucleate MTs varies along the cell cycle and is completely inhibited at mitotic onset (Fig. 2). Our previous work identified the large scaffolding protein AKAP450 as responsible for GA-associated MT nucleation activity. To explore how GA-associated MT nucleation is regulated, we have undertaken a proteomic approach in collaboration with the Functional Proteomics Group (ICR-London) to immunopurify AKAP450 protein complexes in interphase and in mitosis. Our interactome analyses have identified previously known and novel AKAP450 interactors such as cytoskeletal associated proteins, centrosomal proteins, protein kinases, and Golgi matrix proteins and uncovered differences in the binding partners-sets between interphase and mitosis. We are currently carrying out functionalstudies of selected interactors and characterizing their potential relevance in GA behaviour regulation.

Functional relevance of spatio-temporal organisation of chemokine receptors during T cell migration

The chemokine receptor CXCR4 and its ligand, the CXCL12 chemokine, form a key pair in lymphocyte trafficking. Using SPT-TIRF microscopy and a T cell line expressing endogenous CXCR4-AcGFP, we are studying the CXCR4 dynamic organisation during T cell migration. We have also identified FLNa as a mechanical regulator of CXCL12-mediated CXCR4 nanoclustering, which orchestrates T cell motility.

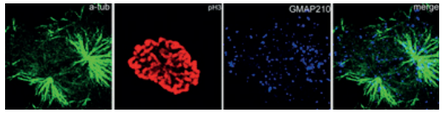


Fig 2. A prophase cell showing a very high MT nucleation activity at the centrosome while no MTs arising from GA elements.

Grants

- 2020-2023: PIE 202080E095. Intramural Project. CSIC
- 2019-2021: PGC2018-095057-B-I00. National Plan for Scientific and Technical Research and Innovation. Ministry of Science and Innovation
- 2019-2022: RTI2018-101789-J-I00. JIN/ Ministry of Science and Innovation
- 2016-2019: BFU2015-65747. National Plan for Scientific and Technical Research and Innovation. MINECO
- 2014-2018: P12-CTS 2071. Excellence Grant from the Junta de Andalucía
- 2017-2018: BFU2016-81912-REDC Consolider Network. MINECO

Publication Highlights

Zucchetti AE, Bataille L, Carpier JM, Dogniaux S, San Roman-Jouve M, Maurin M, Stuck MW, RiosRM, Baldari CT, Pazour GJ, Hivroz C. **2019.** Tethering of vesicles to the Golgi by GMAP210 controls LAT delivery to the immune synapse. **Nat Commun.** Jun 28;10(1):2864

Gavilan MP*, Gandolfo P*, Balestra FR, Arias F, Bornens M and Rios RM. **2018.** The Dual Role of the Centrosome in Organizing the Microtubule Network in Interphase. **EMBORep.** e45942

Moreno-Marín N, Merino JM, Álvarez-Barrientos A, Patel DP, Takahashi S, González-Sancho JM, Gandolfo P, Rios RM, Muñoz A, Gonzalez FJ, Fernández-Salguero PM. **2018.** Aryl Hydrocarbon Receptor Promotes Liver Polyploidization and Inhibits PI3K, ERK, and Wnt/ß-Catenin Signaling. **iScience.** Jun 29;4:44-63

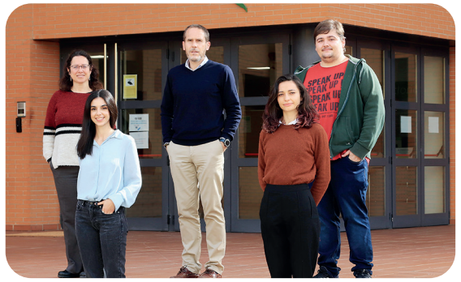
Grant R, Abdelbaki A, Bertoldi A, Gavilan MP, Mansfeld J, Glover DM, Lindon C. **2018.** Constitutive regulation of mitochondrial morphology by Aurora A kinase depends on a predicted cryptic targeting sequence at the N-terminus. **Open Biol.** 8 (6): 170272

Martínez-Muñoz L, Rodríguez-Frade JM, Barroso R, Sorzano CÓS, Torreño-Pina JA, Santiago CA, Manzo C, Lucas P, García-Cuesta EM, Gutierrez E, Barrio L, Vargas J, Cascio G, Carrasco YR, Sánchez-Madrid F, García-Parajo MF, Mellado M. **2018.** Separating Actin-Dependent Chemokine Receptor Nanoclustering from Dimerization Indicates a Role for Clustering in CXCR4 Signaling and Function. **Mol Cell.** Apr 5;70(1):106-119.e10

Dr. Fernando Monje-Casas

Cell division control

Group Leader



Current position

- Since 2016: Staff Scientist. Spanish National Research Council (CSIC)

Current Group Members

Postdocs
- Javier Manzano López
- Ana María Rincón Romero

PhD Students
- Alejandra Álvarez Llamas

Master Students
- Marion Kennel

Former Members (2018-2020)

- **PhD Students:** Laura Matellán Fernández, Inés García de Oya
- **Master Students:** Julia Di Pietro Torres, Javier José Martínez Ruano, Lourdes Arias Salazar
- **Erasmus+ Students:** Eleonora Martinis
- **Technicians:** José Carlos Blanco Mira

Research Activity

Overview

The research in our group aims to shed light on the signalling pathways that orchestrate cell cycle progression, as well as to decipher the molecular mechanisms by which the main cellular checkpoints regulate cell division to ensure the fidelity of chromosome segregation and maintain a correct cellular ploidy. We are also particularly interested in understanding how these processes are coordinated with the establishment of polarity during asymmetric cell divisions. 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. A deeper knowledge about the regulation of cell division is therefore essential to shed light on the mechanisms that underlay these diseases.

Research Highlights

Despite cell division is usually envisioned as a highly symmetric process that involves an equal distribution of the cellular content between the resulting cells, there are multiple examples of asymmetric cell divisions. After an asymmetric division, the duplicated cells differ in size, composition, or in their potential to differentiate into a particular cell type. The establishment of polarity during cell division plays a fundamental role during the proliferation of many microorganisms and in the development and tissue morphogenesis in animals and plants. The budding yeast *Saccharomyces cerevisiae* and the animal stem cells likely represent the most stereotypical models of asymmetric cell divisions among unicellular and pluricellular organisms, respectively. For this type of division to occur, cells must position the mitotic spindle (a bipolar array of microtubules that facilitates the distribution of the chromosomes during mitosis) along a preestablished polarization axis. Hence, in asymmetric cell divisions specific surveillance mechanisms have been developed to control spindle orientation. We are extremely interested in the analysis of the mechanisms that generate polarity during mitosis and the checkpoints that ensure the fidelity of chromosome segregation during asymmetric cell divisions. Our main research achievements during the 2018-2020 period emerged from our scientific incursions in this field.

Spindle microtubules nucleate from microtubule-organizing centers (MTOCs) located at its poles and known as spindle pole bodies (SPBs) in budding yeast and centrosomes in higher eukaryotes. The MTOCs duplicate early in the cell cycle and nucleate both kinetochore microtubules that anchor the chromosomes to facilitate their distribution and astral microtubules that position the spindle. MTOCs are thus essential for proper spindle biogenesis, orientation and elongation. After their duplication, the pre-existent (“old”) and the

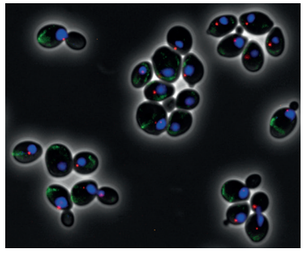


Fig.1. During mitosis, the pre-existent (old) and the newly generated (new) spindle pole bodies (SPBs) are asymmetrically distributed in *S. cerevisiae* cells. Based on the conservative nature of SPB duplication, this phenomenon can be observed by expressing a component of the SPB tagged with a slow-folding version of the red fluorescent protein RFP (in red), so that the old SPB displays a brighter signal than the new one. Also shown in the images are a mitochondrial protein (in green) and the nucleus (in blue).

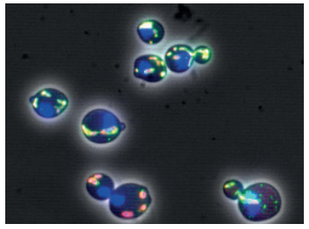


Fig. 2. The most functional and less oxidized mitochondriaare preferentially inherited by daughter cells during yeast cell division, while mother cells retain the damaged mitochondria. To evaluate how the asymmetric inheritance of the spindle pole bodies affects mitochondrial distribution, we have developed a molecular redox probe (yo-mito-rxRFP, in red), which is targeted to mitochondria and displays maximum fluorescent intensity in its most oxidized form. The image also shows a marker for total mitochondria (in green) and the nucleus (in blue).

newly generated ("new") MTOCs differ in composition, size and age. Intriguingly, the old and new MTOCs can be differentially distributed during certain asymmetric divisions. This fascinating phenomenon was originally described in *S. cerevisiae*. During budding yeast division, the old SPB is inherited by the daughter cell, while the new is retained by the mother. Asymmetric centrosome distribution pattern shave been later described in stem cells from different organisms, including humans. Recent research has identified several key regulators of non-random spindle MTOCs inheritance. Interestingly, many of these factors are also important for spindle orientation, highlighting the strong connection between both processes. We are, however, still far from understanding the precise mechanisms that control the differential distribution of MTOCs. Our group has recently contributed to shed new light on this conundrum by unveiling a novel role of Polo-like kinases, a conserved family of key cell cycle regulatory proteins, in the regulation of non-random SPB inheritance in *S. cerevisiae* (Matellán et al. (2020), *eLife*).

Remarkably, despite of its evolutionary conservation, whether the asymmetric inheritance of spindle MTOCs played any biological role was also completely unknown. To answer this question, we generated a *S. cerevisiae* strain in which the old SPB is specifically retained by the mother cell during each division, thus displaying a constitutively reversed pattern of SPB inheritance. Excitingly, our analyses demonstrated that maintenance of the pre-established SPB fate plays a pivotal role in preserving budding yeast replicative lifespan. Specifically, asymmetric SPB inheritance is required to ensure normal levels of the Sir2 sirtuin, a widely conserved lifespan modulator, and to properly distribute functional mitochondria and protein aggregates, which are selectively retained in the mother cell to reset replicative lifespan in the daughter cell, during cell division (Manzano-López et al. (2019), *Nat. Cell Biol.*). Defects during asymmetric cell divisions have been associated with tumorigenesis, neurodegeneration and developmental problems. Unveiling the basic mechanisms that regulate these divisions is therefore of upmost relevance to better understand the causes for these diseases.

Grants

- 2020-2023: PID2019-105609GB-I00. Ministerio de Ciencia e Innovación
- 2020-2022: PY18-3183. Junta de Andalucía
- 2018-2019: BFU2017-92284-EXP Ministerio de Ciencia, Innovación y Universidades
- 2017-2019: BFU2016-76642-P. Ministerio de Economía y Competitividad

Publication Highlights

Matellán L, Manzano-López J, Monje-Casas F. **2020**. Polo-like kinase acts as a molecular timer that safeguards the asymmetric fate of spindle microtubule-organizing centers. **eLife.** 2(9): e61488

Manzano-López J, Monje-Casas F. **2020.** Asymmetric cell division and replicative aging: a new perspective from the spindle poles". **Current Genetics.** 66(4):719-727

Matellán L, Monje-Casas F. **2020.** Regulation of mitotic exit by cell cycle checkpoints: Lessons from *Saccharomyces cerevisiae.* **Genes.** 11(2):e195

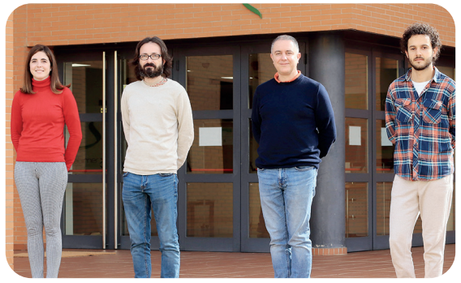
Manzano-López J, Matellán L, Álvarez-Llamas A, Blanco-Mira JC, Monje-Casas F. **2019.** Asymmetric inheritance of spindle microtubule-organizing centers preserves replicative lifespan. **Nature Cell Biology.** 21(8): 952-965

de los Santos-Velázquez AI, de Oya IG, Manzano-López J, Monje-Casas F. **2017.** Late rDNA condensation ensures timely Cdc14 release and coordination of mitotic exit signaling with nucleolar segregation. **Current Biology.** 27(21):3248-3263

Dr. Mario García-Domínguez

Cell Differentiation Laboratory

Group Leader



Current position

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

Current Group Members

PhD Students
- Juan Francisco Correa Vázquez

Postdocs
- Nieves Lara Ureña
- Pablo García Gutiérrez

Master Students
- Olga Fernández Romero

Former Members (2018-2020)

- **Postdocs:** Rosana R. March Díaz, María Ceballos Chávez
- **PhD students:** Noelia Luna Peláez, Francisco de Asís Gallardo Chamizo
- **Master students:** Marta Gil Salvador, Manuel Mora Montesm, Alejandro Flores Acal

Research Activity

Overview

The main objective of our research consists in deciphering the mechanisms involved in neuronal differentiation, in particular in the transition from proliferation to differentiation states. 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 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, while Sumo ligases by enhancing sumoylation of specific targets and Sumo proteases by excising Sumo from targets are the main regulators of the process. In this context, we have observed that the Sumo protease Senp7 is strongly induced under neuronal differentiation conditions, being required for proper progression of neurogenesis. Different 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. Thus, we have performed a SILAC-based proteomic approach to identify more than 300 proteins differentially sumoylated under proliferation versus neuronal differentiation conditions. We have identified new Sumo targets and we have been able to assign a role in proper progression of neurogenesis to the modification by Sumo of specific proteins. Besides this, it has been reported that enhancing sumoylation reduces cell death after ischemia. In this sense, we have also performed a proteomic approach to identify changes in protein sumoylation after simulated ischemia conditions in vitro, what will contribute to select putative targets for therapeutic intervention.

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. To shed light on BET function and its association with human pathologies, we performed a two-hybrid screening to identify

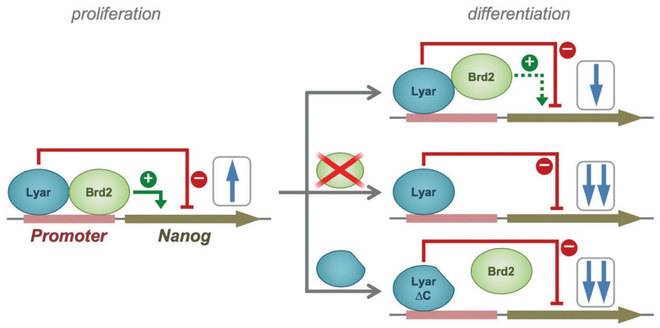


Figure 1. Lyar-mediated recruitment of Brd2 attenuates Nanog downregulation following induction of differentiation. Balanced Lyar-mediated repression and Brd2-mediated activation of Nanog assures proper gene expression under proliferation conditions. Induction of differentiation leads to Brd2 dissociation, but Lyar-mediated retention guarantees progressive downregulation. Absence of Brd2 or interrupted interaction with Lyar results in abrupt downregulation.

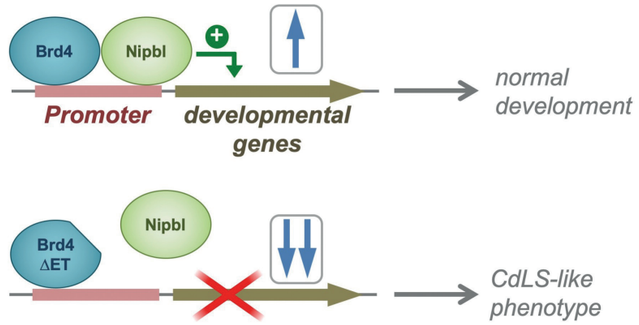


Figure 2. Brd4 cooperates with Nipbl for transcriptional control of developmental genes. Promoter association of Brd4 and Nipbl in a complex, controls expression of a set of developmental genes. Mutations leading to protein degradation, impaired interaction or chromatin displacement of any of these proteins results in deficient transcription of developmental genes, which associates with a CdLS-like phenotype.

new BET partners. On the one hand, we have identified the Brd2 partner Lyar, a transcription factor that participates in recruitment of Brd2 to the chromatin assuring proper downregulation timing of key pluripotency factors, as Nanog, following induction of differentiation. On the other hand, we have identified the Brd4 partner Nipbl, the cohesin loading factor. We have demonstrated that the ET domain of Brd4 is necessary to form a complex with Nipbl, which localizes to promoters and regulate a common set of genes related to different aspects of embryonic development. Mutations in NIPBL are classically linked to the Cornelia de Lange Syndrome (CdLS), a genetic disorder with multiple abnormalities. Recently, mutations in BRD4 have been also linked to a CdLS-like phenotype. Thus, our results mechanistically explain the association of both types of mutations with CdLS.

Grants

- 2020-2021: CV20-93141. Consejería de Economía, Conocimiento, Empresas y Universidades, Junta de Andalucía
- 2019-2021: PGC2018-094232-B-I00. Ministerio de Ciencia e Innovación
- 2016-2019: BFU2015-64721-P/BFI. Ministerio de Economía y Competitividad

Publication Highlights

Moreno-Oñate M, Herrero-Ruiz AM, García-Dominguez M, Cortés-Ledesma F, Ruiz JF. **2020.** RanBP2-mediated SUMOylation promotes human DNA polymerase lambda nuclear localization and DNA repair. **J Mol Biol**. doi: 10.1016/j.jmb.2020.03.020

Luna-Peláez N, March-Díaz R, Ceballos-Chávez M, Guerrero-Martínez JA, Grazioli P, García-Gutiérrez P, Vaccari T, Massa V, Reyes JC, García-Domínguez M. **2019.** The Cornelia de Lange Syndrome-associated factor NIPBL interacts with BRD4 ET domain for transcription control of a common set of genes. **Cell Death Dis.** 10: 548

Luna-Peláez N, García-Domínguez M. **2018.** Lyar-Mediated Recruitment of Brd2 to the Chromatin Attenuates Nanog Downregulation Following Induction of Differentiation. **J Mol Biol.** 430: 1084-1097

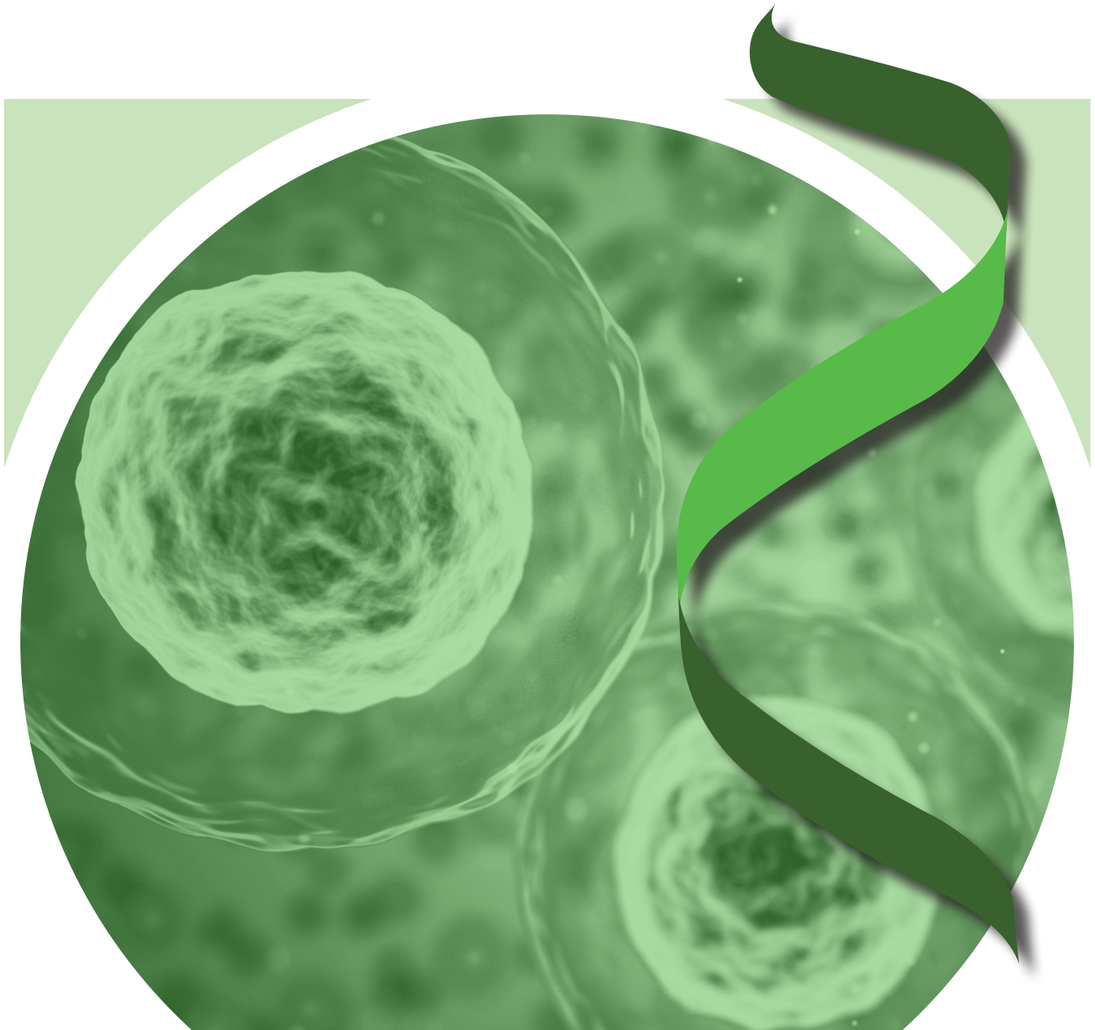
de Frutos CA, Bouvier G, Arai Y, Thion MS, Lokmane L, Keita M, García-Dominguez M, Charnay P, Hirata T, Riethmacher D, Grove EA, Tissir F, Casado M, Pierani A, Garel S. **2016.** Reallocation of olfactory Cajal-Retzius cells shapes neocortex architecture. **Neuron.** 92: 435-448

Juárez-Vicente F, Luna-Peláez N, García-Dominguez M. **2016.** The Sumo protease Senp7 is required for proper neuronal differentiation. **Biochim Biophys Acta.** 1863: 1490-1498

Regeneration and Cell Therapy

The Cell Therapy and Regeneration department houses scientific groups that lead lines of research in different aspects related to tissue regeneration in physiological and pathophysiological circumstances, using both a basic and preclinical approach and patient orientation. Among the objectives of this department is the identification of key factors, mechanisms of action and therapeutic targets focused on the treatment of different diseases related to metabolic stress, neuropathies and other degenerative diseases.

The research activity of this department is aimed to finding drugs and therapeutic targets that promote healthy aging, cell survival, regeneration and the functionality of organs to treat different diseases such as diabetes, liver fibrosis, epilepsy, degenerative diseases that are often associated with aging, such as Alzheimer and amytrophic lateral sclerosis and degenerative pathologies of the retina.



Scientific Report 2018-2020

HEAD OF DEPARTMENT

Dr. Anabel Rojas

RESEARCH GROUPS

1. **Pancreas and Liver Development and Disease**
   Dr. Anabel Rojas
2. **Pancreatic Islets and Stem Cells**
   Prof. Franz Martin
3. **Pancreatic Islet Development & Regeneration**
   Dr. Benoit R. Gauthier
4. **Cell Therapy for Neuropathologies**
   Dr. Manuel Álvarez Dolado
5. **Cellular and Molecular Neuroimmunology**
   Dr. David Pozo
   & Misfolding Proteins and Molecular Chaperones in Immune Dysregulation
   Dr. Cintia Roodveldt
6. **Metabolic Interventions for Successful Aging**
   Dr. Alejandro Martín-Montalvo
7. **Retinal Degeneration: from Genetics to Therapy**
   Dr. Francisco Díaz-Corrales
8. **Stem Cells and Translational Neurology**
   Dr. Vivian Capilla-González

Former Groups

Cell therapy for Diabetes Mellitus and its complications
Dr. Bernat Soria (finished in 2019)
Retinal degeneration: From genetics and epigenetics to therapy
Dr. Shom Shanker Bhattacharya (finished in 2019)

Dr. Anabel Rojas

Pancreas and Liver Development and Disease

Group Leader

Head of Department

Current position

- Since 2020: Profesor at University Pablo de Olavide
- Since 2019: Head of the Regeneration and Cell Therapy Department

Former Members (2018-2020)

- **Postdocs:** Elisa del Pilar Rodríguez Seguel
- **PhD students:** Laura Villamayor Coronado
- **Master students:** Noelia Arroyo del Alba, Ángel Manuel Rodríguez Mata

Group Members updated

PhD Students
- Noelia Arroyo Del Alba

Technicians
- Irene Díaz Contreras

Master student
- Miguel Salazar Martínez

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. To accomplish this goal, the search for key factors, mechanism of action and/or pharmacological agents to restore organ function is imperative for the treatment of these diseases.

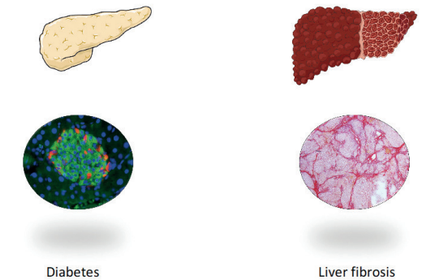


Figure 1: Liver and pancreas; from development to disease.

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 lead to impaired beta cell glucose sensitivity or insulin secretion and ultimately to diabetes. Previous studies form our lab have has uncovered a role of GATA6 transcription factor in the adult beta cell function. Loss of Gata6in mice leads to glucose intolerance as result of dysregulation of key components of insulin synthesis and secretion machinery. Moreover, ultrastructural analysis of Gata6 deficient beta cells revealed swollen mitochondria and endoplasmic reticulum (ER) cisternae appeared disorganized (Villamayor et al., 2018, Diabetes). This data is suggestive of mitochondrial and ER stress in pancreatic beta cells in the absence of GATA6 activity. Currently our group is investigating the contribution of GATA6 to mitochondrial and ER function in adult pancreatic beta cells in physiological conditions as well as in obesity-induced type 2 diabetes and gestational diabetes.

2. Molecular basis for hepatic fibrosis induction and progression

Hepatic Stellate Cells have taken great interest in the field of hepatology in recent years due

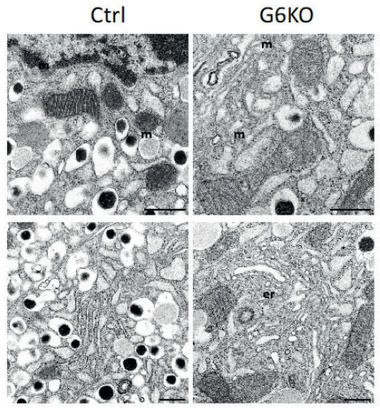


Figure 2: Electron microscopy images of control (Ctrl) and Gata6 KO (G6KO) pancreatic beta cells. (m): Mitochondria; (er): Endoplasmatic reticulum

to their role in the progression of hepatic fibrosis. Chronic liver injury lead to death of parenchymal cells and activation of HSCs, which are the main source of extracellular matrix components (ECM), such as collagen and laminin that form the fibrotic scars. The regression of liver fibrosis implies breakdown of ECM by metalloproteinases and the clearance of activated HSCs, by apoptosis or reversion to an inactive phenotype, thus allowing the hepatocyte to repopulate the damaged hepatic tissue. In recent years, one of the emerging therapies for liver fibrosis focuses in the inhibition of HSCs activation and proliferation. Our previous studies have identified GATA4 as a regulator of HSCs phenotype. GATA4 is required to maintain HSCS quiescence and therefore to inhibt liver fibrosis induction in mice (Delgado et al., 2014, Hepatology). Our studies of lineage tracing show that injured livers displayed a dramatic downregulation of Gata4 expression in HSCs. However, the expression of Gata4 is fully restored in HSCs after the recovery period, suggesting a potential role of GATA4 in the regression of liver fibrosis. Indeed, genetic manipulation of Gata4 overexpression in HSCs, allows the reversion of active HSCs in an in vitro model. More interesting, Gata4 overexpression in HSCs is sufficient to revert

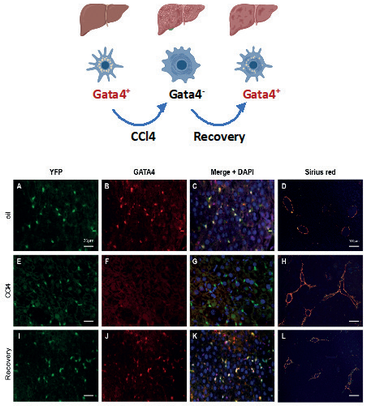
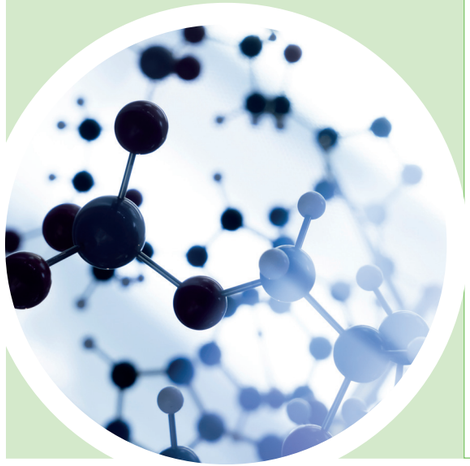


Figure 3: Analysis of Gata4 expression in HSCs (labelled by YFP in G2-Cre; ROSA26RYFP mice) during the course of liver fibrosis (CCl4) and recovery. Accumulation of collagen fibers is visualized by staining with Sirius red in CCl4-treated mice.

liver fibrosis in CCl4-induced liver fibrosis in mice. Our laboratoy goal in this research line is to decipher the molecular mechanism by which GATA4 modulate HSCs phenotype, to identify molecular targets of GATA4 during liver fibrosis regression and to search for pharmacological agents to induce GATA4 expression. Our studies could ultimately help to develop novel therapeutic alternatives to treat hepatic fibrosis regardless the etiology.

Grants

- 2018-2020: BFU2017-82497-P. Programa Estatal de Fomento de la Investigación Científica y Técnica de Excelencia, Subprograma Estatal de Generación de Conocimiento. Ministerio de Ciencia, Innovación y Universidades



Publication Highlights

Rodríguez-Seguel E, Villamayor L, Arroyo N, De Andrés MP, Real FX, Martín F, Cano DA, Rojas A. **2020.** Loss of GATA4 causes ectopic pancreas in the stomach. **J Pathol.** 250(4):362-373

Villamayor L, Cano DA, Rojas A. **2020.** GATA factors in pancreas development and disease. **IUBMB Life.** 72(1):80-88

Ariza L, Rojas A, Muñoz-Chápuli R, Carmona R. **2019.** The Wilms' tumor suppressor gene regulates pancreas homeostasis and repair. **PLoS Genet.** 15(2):e1007971

Villamayor L, Rodríguez-Seguel E, Araujo R, Carrasco M, Bru-Tarí E, Mellado-Gil JM, Gauthier BR, Martinelli P, Quesada I, Soria B, Martín F, Cano DA, Rojas A. **2018.** GATA6 Controls Insulin Biosynthesis and Secretion in Adult ß-Cells. **Diabetes.** 67(3):448-460

Cano E, Carmona R, Ruiz-Villalba A, Rojas A, Chau YY, Wagner KD, Wagner N, Hastie ND, Muñoz-Chápuli R, Pérez-Pomares JM. **2016.** Extracardiac septum transversum/proepicardial endothelial cells pattern embryonic coronary arterio-venous connections. **Proc Natl Acad Sci U S A.** 113(3):656-61

Prof. Franz Martin

Pancreatic Islet Pathophysiology and Stem Cell

Group Leader

Current position

- Since 2006: Research Scientist CABIMER/ Seville, Spain
- Since 2007: Principal Investigator of CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM)
- Since 2007: Full Professor at University Pablo de Olavide, Seville, Spain

Group Members

Postdocs
- Blanca Escudero
- Amparo Luque

PhD Student
- Lucía López

Technician
- Raquel Araujo
- Antonio Cárdenas

Former Members (2018-2020)

- **Research Associate:** Genoveva Berná
- **PhD Student:** Leticia Álvarez Amor

Research Activity

Overview

Our main research lines are: i) to study the role of nutrients and diets in the pathogenesis of diabetes, obesity and non-alcoholic fatty liver disease and ii) the identification of pancreatic adult stem cells and the development of differentiation protocols to obtain insulin producing cells, to be employed in diabetes cell therapy.

Research Highlights

Our main research highlights are:

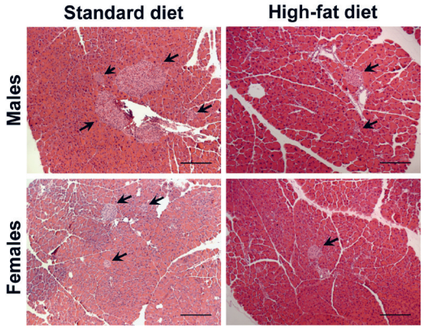
1. Monounsaturated fatty acid consumption has been positively associated with improved insulin sensitivity and ß-cell function. One of the most important dietetic sources of MUFAs, particularly in the Mediterranean diet, is extra virgin olive oil. We found that EVOO intake regulated glucose homeostasis, improving insulin sensitivity and pancreatic ß-cell function. In addition, the intake of an EVOO much richer in phenolic compounds did not increase the beneficial effects of EVOO on insulin sensitivity and ß-cell function.

2. Pancretic beta cells release hexameric Zn^{2+}-insulin into the extracellular space, but monomeric Zn^{2+}-free insulin appears to be the only biologically active form. The mechanisms implicated in dissociation of the hexamer remain unclear, but they seem to be Zn^{2+} concentration-dependent. We have observed that the Zn^{2+}-binding properties of albumin improve the dissociation of Zn^{2+}-insulin into subunits after exocytosis. This is useful in insulin determination, insulin pharmacokinetic assays and islet transplantation.

3. Fat-rich food consumption contributes to the inflammatory state associated with obesity that leads to cardiovascular complications. Animal studies have demonstrated that enrichment of obesogenic HFDs with monounsaturated fatty acids can decrease atherosclerosis lesions and improve insulin sensitivity and reduce NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome activation in adipose tissue. We have demonstrated that consumption of extra virgin olive oil with a natural content of phenolic compounds attenuates adipose tissue hypertrophy and inflammation and exerts antiatherosclerotic effects in mice. A higher phenolic content of olive oil did not provide further benefits in the prevention of atherosclerosis.

4. Dietary fatty acids play a role in the pathogenesis of obesity-associated non-alcoholic fatty liver disease (NAFLD), which is associated with insulin resistance (IR). Fatty acid composition is critical for IR and subsequent NAFLD development. In the past several years, the *Ldlr-/-* background has been frequently used as a model to study diet induced NAFLD in obesity. The *Ldlr-/-*.Leiden substrain develops severe NASH/fibrosis in conjunction with pronounced dyslipidemia and IR, when fed a high fat diet (HFD). In this animal

model, we have found that extra virgin olive oil intake consistently improved BW and insulin sensitivity but aggravated liver inflammation and fibrosis. The potential proposed mechanisms contributing to this extra virgin olive oil effect are the upregulation of genes involved in liver inflammation, fibrosis and oxidative stress, as well as the downregulation of genes critical for liver lipid homeostasis.



Histological images of mouse pancreatic islets from offsprings of mothers fed with control diet (left panels) and high fat diet (right panel)

Grants

- 2017-2019: PC-0111-2016-0111. Consejería de Salud, Junta de Andalucía
- 2017-2019: AGL-2017-86927-R. Ministerio de Economía, Industria y Competitividad

Publication Highlights

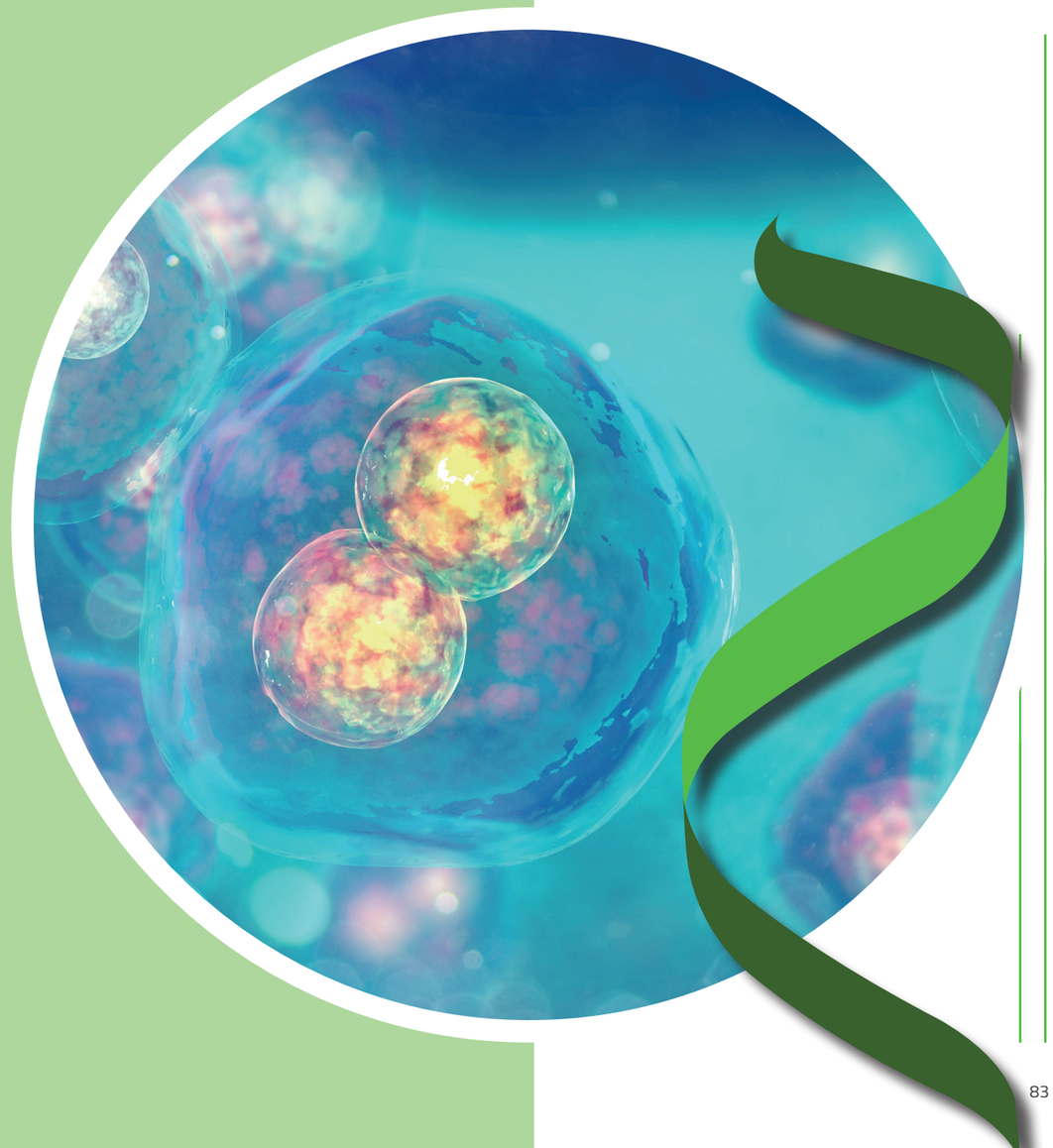
Jurado-Ruiz E, Varela LM, Berná G, Cahuana G, Martinez-Force E, Gallego-Durán R, Soria B, De Roos B, Romero-Gomez M, Martin F. **2017**. Olive oil rich diet intervention ameliorates non-alcoholic steatohepatitis induced by high-fat "western type" diet in mice. **Mol. Nutr. Food Res**. 61(3)

Pertusa JAG, León-quinto T, Berná G, Tejedo JR, Hmadcha A, Bedoya FJ, Martín F, Soria B. **2017**. Zn^{2+} chelation by serum albumin improves hexameric Zn^{2+}-insulin dissociation into monomers after exocytosis. **PloS One**. 2(11):e0187547

Luque-Sierra A, Álvarez-Amor L, Kleemann R, Martín F, Varela LM. **2018.** Extra-Virgin Olive Oil With Natural Phenolic Content Exerts an Anti-Inflammatory Effect in Adipose Tissue and Attenuates the Severity of Atherosclerotic Lesions in Ldlr-/-.Leiden Mice. **Mol. Nutr. Food Res**. 62(13):e1800295

Capilla-Gonzalez V, Lopez-Beas J, Escacena N, Aguilera Y, de la Cuesta A, Ruiz-Salmeron R, Martin F, Hmadcha A, Soria B. **2018.** PDGF restores the defective phenotype of adipose-derived mesenchymal stromal cells from diabetic patients. **Mol. Ther.** 26(11):2696-2709

Jurado-Ruiz E, Álvarez-Amor L, Berna G, Parra-Camacho MS, Oliveras-Lopez MJ, Martinez-Force E, Rojas A, Hmadcha K, Soria B, Martin F. **2019.** Extra virgin olive oil diet intervention improves insulin resistance and islet performance in diet-induced diabetes in mice. **Scientific Reports.** 9(1):11311



Dr. Benoit R. Gauthier

Pancreatic Islet Development and Regeneration Unit

Group Leader

Current position

- Since 2009: Junta de Andalucía-Consejería de Salud y Familias Staff Scientist/Group Leader CABIMER, Seville, Spain

Group Members

Lab Manager
- Nadia Cobo Vuilleumier

Senior Researcher
- Petra Isabel Lorenzo Ovejero

Postdoctoral fellows
- Valentine Comaills
- Christian Lachaud
- Jaime Muños Franco
- Nestor Wenceslao Meza
- Akaitz Dorronsoro González
- Livia López Noriega

PhD student
- María Eugenia Martín Vázquez García

Master student
- Alejandro Andrades Cordero

Erasmus
- Emanuele Nola

Technicians
- Alejandra Crespo Barreda

Former Members (2018-2020)

- **Postdoctoral Fellows:** Alejandro Martín Montalvo, Esther de la Fuente Martín, José Manuel Mellado Gil
- **PhD students:** Irene de Gracia Herrera Gómez, Livia López Noriega
- **Master students:** María Eugenia Martín Vázquez García
- **Technicians:** Noelia García Rodríguez, Adoración Montero Sánchez

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). To this end, the group has developed a research and development pipeline that evolves from basic projects to preclinical and clinical studies. Within the basic program our work focuses on: 1) Identifying ad characterizing novel anti-diabetic targets that foster survival, regeneration and functionality of pancreatic islet insulin-producing beta cells and 2) elucidating the cross talk between immune and islet beta cells as well as brain astrocytes in safeguarding glucose homeostasis. Our translational program includes pre-clinical assessment of: 1) anti-inflammatory/-diabetic drugs, and 2) a novel viral gene therapy for inducing immune tolerance against Type 1 DM and multiple sclerosis. This work is performed in close collaboration with National hospitals and biotechnology companies as well as patients' associations to ensure the best therapeutic outcome.

Research Highlights

Our research efforts for the past two years have focused on delineating the mode of action (MoD) of 3 novel factors implicated in cell survival, plasticity and function in immune cells, pancreatic islets and brain astrocytes. The main highlights can be summarized as follows:

PAX8, a novel candidate gene in gestational diabetes that conveys pro-survival properties to islets specifically during pregnancy: PAX8, which is essential for thyroid development, was reported to be one of the most upregulated genes in mouse islets during gestation while small nucleotide polymorphisms (SNPs) have been associated with diabetes. PAX8, has neither involved in pancreagenesis nor expressed in adult islets. We therefore elucidated the implication of this transcription factor in human islet physiology. We demonstrated that PAX8 expression was increased inhuman islets treated with the pregnancy hormone prolactin. Transcriptome profiling of human islets overexpressing PAX8 revealed enrichment in immune-related pathway, pinpointing to a role in inflammation, an immune process that is induced during pregnancy. Accordingly, PAX8 overexpression protected human islets against cytokine-induced apoptosis. Because of the exclusive expression ofPAX8 during pregnancy that conveys pro-survival properties, we argued that SNPs within the PAX8 gene may be associated with gestational diabetes mellitus (GDM). Accordingly, we identify mutations within the PAX8 gene, in independent families with history of diabetes over 4 generations, in which females harboring one of these mutations developed GDM (Figure 1). In conclusion we have identified PAX8 as the first GDM associated gene in human. PAX8 activation will favor beta cell survival and

stimulating the maintenance of a local anti-inflammatory milieu in the pancreas during pregnancy.

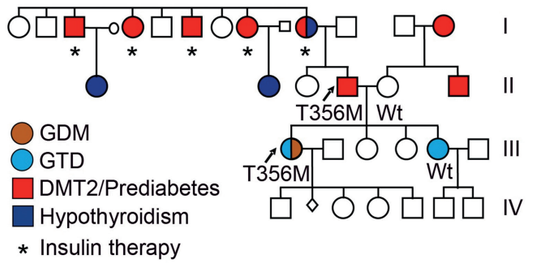


Figure 1: Family pedigree with a PAX8gene mutation (T356M) associated to GDM and type 2 diabetes (DMT2). Family members exhibited T2DM and hypothyroidism in 4 consecutive generations. Circles indicate females, and squares indicate males. GTD: gestational thyroid dysfunction.

HMG20A, a chromatin factor bridging brain and islet response to hyperglycaemia and obesity: We previously demonstrated that the 'Metabesity' factor HMG20A regulates islet beta-cell functional maturity and adaptation to physiological stress such as diabetes. HMG20A also dictates brain development via inhibition of the LSD1/CoREST complex but its expression pattern and function in adult brain remains uncharted. We show that Hmg20a is predominantly expressed in hypothalamic astrocytes, the main nutrient-sensing cells of the brain and that its expression is upregulated in obese pre-diabetic mice, correlating with inflammation and astrogliosis. HMG20A silencing in astrocytes resulted in repression of inflammation, lipid metabolism and epithelial-to-mesenchymal transition pathways (Figure 2) with a concomitant increase in apoptosis. Motoneuron viability was also hindered in HMG20A-depleted astrocyte-derived conditioned media. Astrogliosis was induced using ORY1001, a pharmacological inhibitor of the LSD1/CoREST complex, mimicking the effect of HMG20A.Our results indicate that under physiological pressure such as pre-diabetes or obesity, HMG20A promotes astrocyte reactivity and survival in an attempt to preserve the neuronal network. We identify HMG20A as the first common molecular denominator bridging brain and islet response to diabetes and obesity that could be exploited therapeutically using ORY1001.

Figure 2: Main biological networks regulated by HMG20A in astrocytes. STRING cluster analysis of the down-regulated genes in HMG20A repressed astrocytes.

LRH-1/NR5A2 couples immunity to islet trans-regeneration to revert type 1 diabetes: Type 1 diabetes mellitus (T1DM) is an autoimmune disease that results in the selective destruction of pancreatic islet beta cells by infiltrating immune cells (insulitis). Despite advances in medical device technology and longer-acting insulin as well as strives in generating in vitro insulin-producing cells from various cell sources, there is still no robust therapy to substitute and protect beta cells that are lost in T1DM. Paradoxically, beta cells are still present, in long-standing T1DM patients indicating a disturbed equilibrium between the on-going immune attack and beta cell regeneration reminiscent of unresolved wound healing in which under normal circumstances the anti-inflammatory immune milieu would promote tissue healing/regeneration. The ultimate T1DM therapy should aim on one hand to restore immune self-tolerance and on the other replenish the beta cell mass similar to wound healing. We recently demonstrated that activation of LRH-1/NR5A2 using a small chemical agonist denoted BL001 conveyed such therapeutic properties that induce immune self-tolerance, increase beta cell survival and promote their regeneration through a mechanism of alpha-to-beta cell phenotypic switch reverting T1DM in pre-clinical mouse model. We also demonstrate that this trans-regeneration process is facilitated by an anti-inflammatory environment within the pancreas induced by the LRH-1/NR5A2 signalling cascade (Figure 3). More importantly, BL001 conveys similar anti-inflammatory properties to human immune cells as well as to improve human islet survival after engraftment.

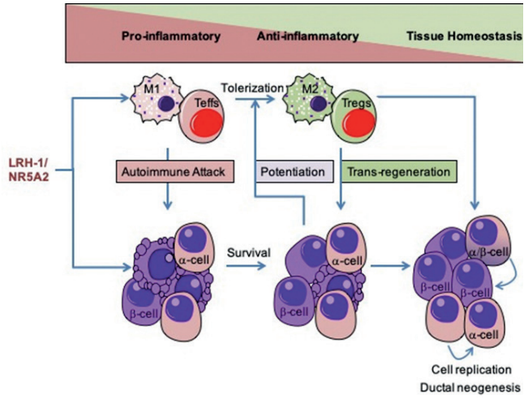


Figure 3: Proposed model of BL001/LRH-1/NR5A2 cellular action. Schematic representation of the cellular modifications induced by LRH-1/NR5A2 activation resulting in immune tolerance coupled to trans-regeneration. The pool of alpha-cell is likely replenished by either cell replication and/or ductal neogenesis.

Grants

- 2019-2021: JDRF, SRA-2019-837-S-B. Juvenile Diabetes Research Foundation
- 2018-2022: PRE2018-084907. Ministerio de Ciencia, Innovación y Universidades
- 2019-2023: AECC, INVES20033COMA. Asociación Española Contra el Cáncer
- 2020-2023: Vencer el Cáncer
- 2019-2021: Amarna Therapeutics S.L.

Publication Highlights

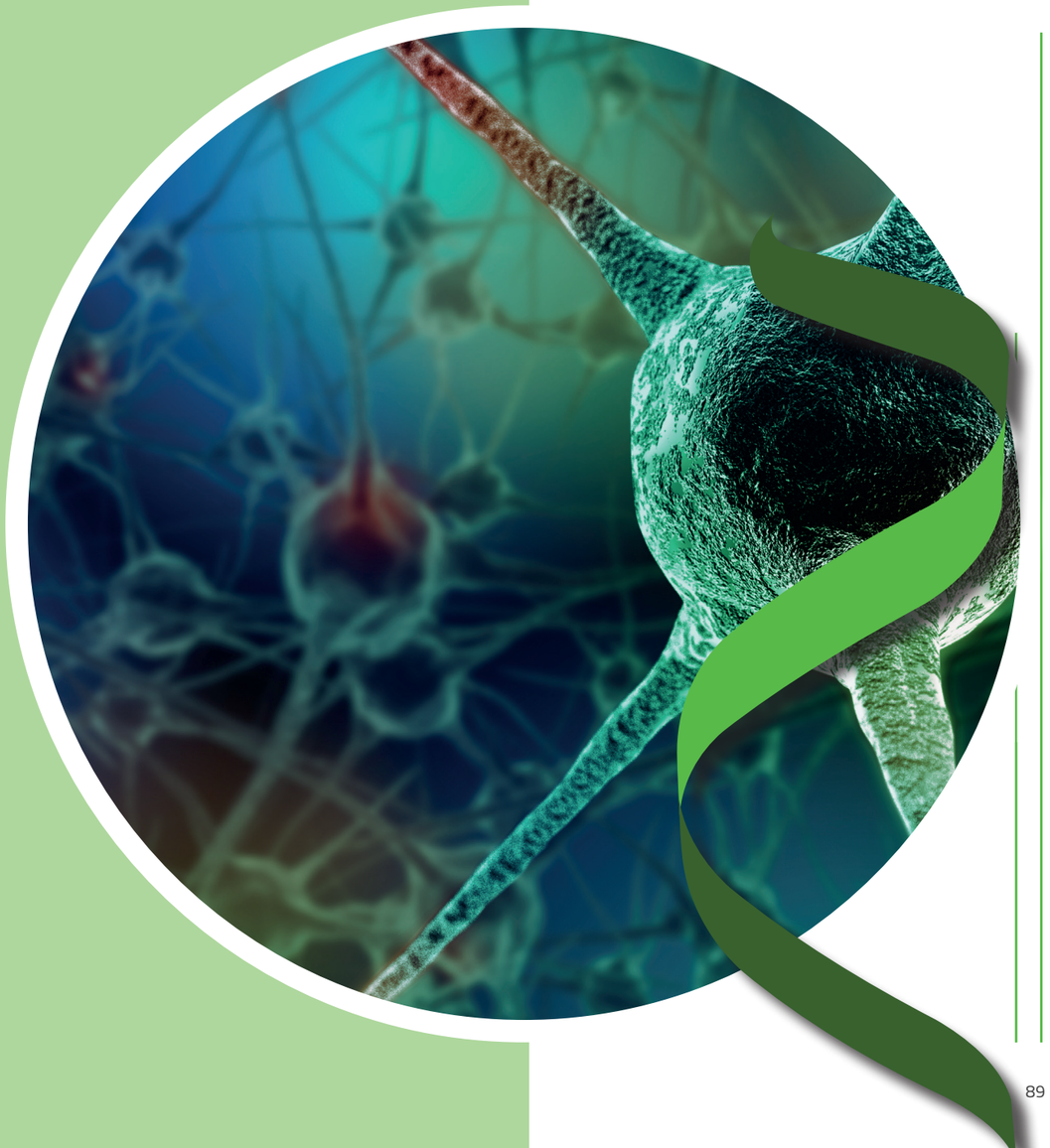
Cobo-Vuilleumier N, Gauthier BR. **2020.** Time for a paradigm shift in treating type 1 diabetes mellitus: coupling inflammation to islet regeneration. **Metabolism** 104:154137

Martín-Montalvo A, López-Noriega L, Jimenez-Moreno C, Herranz A, Lorenzo PI, Cobo-Vuilleumier N, Tamayo A, Gonzalez-Guerrero C, Hosteede JSWR, Lebreton, F, Bosco D, Garcia-Toscano Herranz L, Anselmo J, Moreno JC, Gauthier BR. **2019.** Transient PAX8 expression in islets during pregnancy correlates With ß-cell survival, revealing a novel candidate gene in gestational diabetes mellitus. **Diabetes.** 68:109

Cobo-Vuilleumier N, Lorenzo PI, García-Rodríguez N, Herrera-Gómez I, Fuente-Martin E, López-Noriega L, Mellado-Gil JM, Romero-Zerbo SY, Baquié M, Lachaud C, Stifter K, Perdomo G, Bugliani M, Masini M, Bosco D, Parnaud G, Pozo D., Pérez-Florido J, Toscano M, Haan P, Schoonjans K, Sánchez Palazón L, Marchetti P, Schirmbeck R, Martín-Montalvo A, Meda P, Soria B, Bermúdez-Silva FJ, St-Onge L, Gauthier BR. **2018.** LRH-1 agonism favours an immune-islet dialogue, which protects against diabetes mellitus. **Nature Comms.**16:1488

Mellado-Gil JM, Fuente-Martín E, Lorenzo PI, Cobo-Vuilleumier N, López-Noriega L, Martín-Montalvo A, Herrera-Gómez IG, Ceballos-Chávez M, Gómez-Jaramillo L, Campos-Caro A, Romero-Zerbo SY, Rodriguez-Comas J, Servitja JM, Rojo-Martinez G, Bugliani M, Marchetti P, Bérmudez-Silva FJ, Reyes JC, Aguilar-Diosdado M, Gauthier BR. **2018.** The Type 2 Diabetes-associated HMG20A gene is mandatory for islet beta cell functional maturity. **Cell Death and Dis.** 9:279

Mellado-Gil JM, Jiménez-Moreno CM, Martin-Montalvo A, Álvarez-Mercado AI, Fuente-Martin E, Cobo-Vuilleumier N, Lorenzo PI, Bru-Tari E, Herrera Gómez IG, López Noriega L, Pérez Florido J, Santoyo-López J, Spyrantis A, Meda P, Boehm, BO, Quesada I, Gauthier BR. **2016.** PAX4 preserves endoplasmic reticulum integrity preventing beta cell degeneration in a mouse model of type 1 diabetes mellitus. **Diabetologia**, 59: 755-65



Dr. Manuel Álvarez-Dolado

Cell-Based Therapies for Neuropathologies

Group Leader

Current position

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

Group Members

PhD Students

- Magdalena Martínez-Losa
- Maurizio Riga

Technicians

- Mª Mercedes Pérez Fernández

Former Members (2018-2020)

- **Erasmus+ PhD students:** David Huson

Research Activity

Overview

Our lab is interested in the implementation of different stem cell types to repair the brain function, one of the biggest challenges in Regenerative Medicine. For this, we analyse the effects of stem cell transplants at molecular, histological, behavioural, and electrophysiological functional levels. We develop technical conditions to facilitate the translation of lab discoveries to the clinic. Thus, we develop pre-clinical assays in animal models of so relevant neuropathologies, such as Alzheimer´s disease, epilepsy, and ataxias. We also use this experimental approach to better understand how brain function is disrupted in these conditions. We work with two different stem cell sources: GABAergic neuronal progenitors derived from the medial ganglionic eminence (MGE), which give rise to interneurons and are ideal to restore the inhibitory activity in the brain; and the second type is bone marrow derived stem cells (BMSC), which we apply for the treatment of ataxias.

Research Highlights

Interneuron dysfunction leads to alteration of excitatory/inhibitory balance, which is in the base of severe diseases such as epilepsy, Alzheimer, or different mental disorders. Our main research line is to develop a cell-based therapy with GABAergic interneuron progenitors for the treatment of these diseases. We perform transplants in animal models of infantile epilepsy such as, West, Dravet, or Stxbp1 syndromes, and Alzheimer's disease (AD) as well, to show the therapeutic potential of these neuronal precursors. In general, after transplantation, we have observed an anticonvulsivant activity of the precursors together with restoration of normal brain rhythms, and improvement of behavioural alterations. Especially relevant is the rescue of cognitive deficits, gamma oscillatory activity, and the reduction of network hypersynchronyin a model of familiar AD (Fig. 1), when is transplanted with interneuron progenitors over-expressing the Nav1.1 voltage-gated channel. The results strongly suggest that naïve or genetically-modified GABAergic interneuron precursors are a promising source of cells for regenerative medicine to treat psychiatric conditions. We

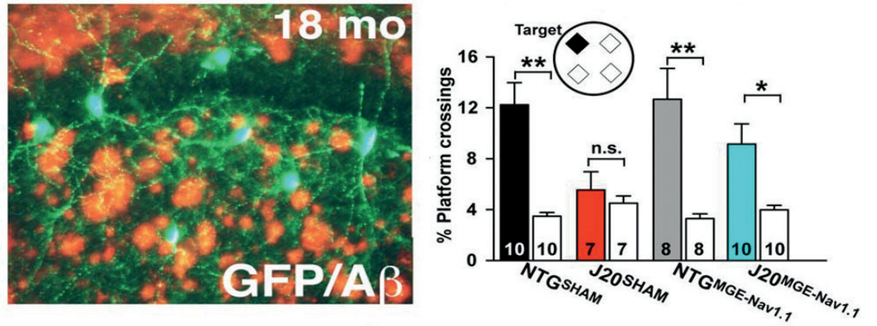


Figure 1. Detection of MGE-derived interneurons precursors by immunohistochemistry against GFP (green) in the hippocampus of 18 months old mice with AD. Note the wide distribution of grafted cells, their normal morphology, and survival despite the presence of important amyloid-beta deposits (red). The graph represents the result of water maze performance of control (black bar), AD (red), control MGE transplanted (grey), and AD MGE transplanted (blue) mice. Observe how transplanted mice remember where the hidden platform was (target) and cross more times the target area (coloured bars). In contrast, AD mice cross a similar percentage of times the target and non-target areas, indicating their lack of memory.

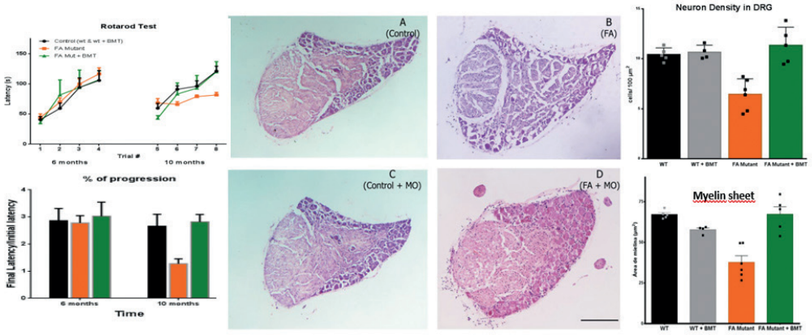


Figure 2. in the left graphsa rotarod analysis showing the locomotor coordination improvement of ataxic mice transplanted with BMSC (10 months old). Photomicrographs show the eosin-hematoxylin histological characterization of dorsal root ganglia from control, ataxic and transplanted mice. Right graph show the quantification of neurons and myelin sheet thickness. Observe the reduction in the myelin and number of neurons in ataxic mice (orange) comparing controls (black/grey), and how the BMSC transplant prevent this degeneration (green). Scale bar: 200 µm

are currently investigating to implement this therapeutic approach into animal models of epileptic syndromes for their future clinical application.

Many studies have reported the contribution of BMSC to tissue homeostasis and modulation of immune response. This has raised the possibility of using them as a new therapeutic tool for brain repair and protection, or neuronal function restoration. In the last years we have collaborated with other CABIMER groups to deliver BMSC intranasally and promote radiation-induced brain injury repair, preserving the neurological function. This intervention confers protection against inflammation, oxidative stress, and neuronal loss. In addition, we are interested in the application of these cells for the treatment of ataxia. This is a locomotor neurodegenerative disorder that unfortunately has no cure, with the current therapies aimed just to reinforce motor re-education or muscular strength. Nevertheless, BMSC is becoming a promising approach to deliver growth factors into the degenerative environment and prevent neuronal death. We have used a model of Friedreich ataxia to study the effect of healthy (wild-type) bone marrow transplantation at early age (P3) on the prevention of defective mobility. Our results show an improvement in locomotor activity, tested by rotarod at 10 months of age, when neurogeneretation has already progressed severely (Fig. 2). Histological analysis revealed an increment in neuronal survival at the dorsal root ganglia and a better preservation of myelin sheet in the transplanted mice. These promising results strongly suggest that early BMSC therapy can be a safe and an effective alternative for dealing with movement disorders such as ataxias.

Grants

- 2014-2018: CTS-2563. Proyectos de Excelencia. Consejería de Economía, Innovación Ciencia y Empleo, Junta de Andalucía
- 2018-2019: Precipita Crowdfunding. Asociación Apoyo Dravet
- 2019-2020: Contrato de Apoyo Tecnológico. Asociación Síndrome Stxbp1
- 2019-2020: Premio Fundación Antonio Guerrero
- 2019-2021: RTI2018-099768-B-I00. Ministerio de Ciencia, Innovación y Universidades

Publication Highlights

Martinez-Losa M, Tracy TE, Ma K, Verret L, Clemente-Perez A, Khan AS, Cobos I, Gan L, Mucke L, Álvarez-Dolado M*, Palop J*. (*Co-Corresponding authors). **2018.** Nav1.1-Overexpressing Interneuron Transplants Restore Brain Rhythms and Cognition in a Mouse Model of Alzheimer's Disease. **Neuron98** (1): 1–15

Díaz D, Piquer-Gil M, Recio JS, Martínez-Losa MM, Alonso JR, Weruaga E, Álvarez-Dolado M. **2018.** Bone marrow transplantation improves motor activity in a mouse model of ataxia. **J Tissue Eng Regen Med.** 12(4): e1950-e1961

Martin-Montalvo A, Aguilera Y, Mellado-Damas N, López-Beas J, Herrera-Herrera I, López E, Barcia JA, Álvarez-Dolado M, Hmadcha A, Capilla-González V. **2019.** Human Mesenchymal Stem Cells Prevent Neurological Complications of Radiotherapy. **Front Cell Neurosci.** 16 (13): 204

Dr. David Pozo

Cellular and Molecular Neuroimmunology

Group Leader

Current position

- Associate Professor of Biochemistry and Molecular Biology. University of Seville (habilitated Full Professor)

Group Members

Postdoctoral
- Zaira González Sánchez
- Aurea Simón Soro

PhD students
- Victoria Areal Quecuty
- Jesús A. Pérez Cabello

Technicians
- Lucía Silvera Carrasco
- Daniel Tejada Moreno

Master students
- Raquel García García
- Laura Martín Herrero

Former Members (2018-2020)

- Jaime Muñoz Franco, María Gómez Lima, M. Magdalena Leal Lasarte, Noemí Solís Palomo, Federico Cannas, Enrico Tebaldi, Rocío Vázquez Lobato

Dr. Cintia Roodveldt

Immune Signalling in Neurodegenerative Proteinopathies

Emerging PI

Current position

- Ramón y Cajal Investigator, University of Seville

Research Activity

Overview

The Cellular and Molecular Neuroimnunology Laboratory (CMNL) of the University of Seville 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, astrocytes, and different T regulatory cell subsets in the development of Amyotrophic Lateral Sclerosis (ALS) and other protein misfolding diseases. The activities at CMNL merge basic disease-oriented research on primary cell cultures and cell line cultures, preclinical studies in mouse models of human ALS and patient-driven research in clinical studies in ALS.

The active research lines are as follows:

a. Modulation of innate and adaptive immunity by endogenous neuropeptides in neurodegeneration.
b. Nanoparticles for controlled and targeted drug delivery: improving the drugability of neuropeptides and smart reprogramming of glia in neurodegenerative diseases.
c. Energy metabolism as modifier of the immune response: tissue crosstalk in Amyotrophic Lateral Sclerosis (ALS) and neurodegeneration.
d. Molecular mechanisms of immune signalling and immune dysregulation in neurodegenerative proteinopathies, including ALS and Parkinson.
e. Role and potential of heat-shock proteins (HSPs) in peripheral immune reshaping in neurodegenerative proteinopathies.

Research Highlights

Research line 1 (D. Pozo): A common feature among several neurodegenerative diseases including ALS is an impairment of neuroprotective mechanisms associated to immune imbalance. In this sense, the characterization of endogenous

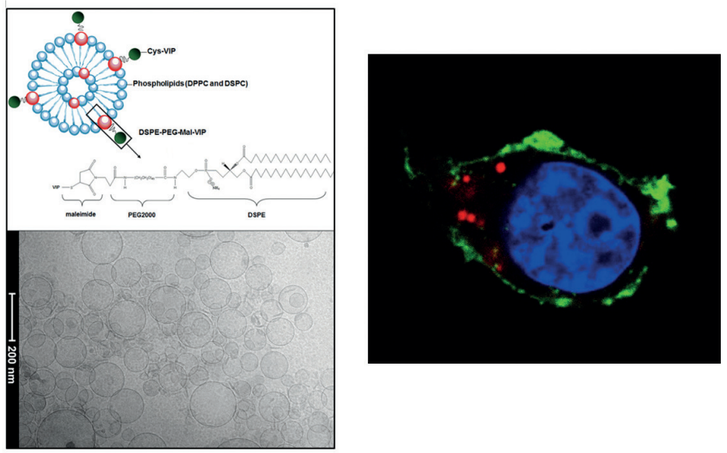


Figure 1. Left. Scheme of the neuropeptide VIP functionalization via DSPE-PEG-Mal and liposome composition and cryo-TEM of VIP-liposomes (Scale bar 200nm). The top figure shows VIP functionalization via its N-terminal cysteine to the maleimide-modified termini of PEG chains located on the external surface of liposomes, forming a stable carbon-sulphur bond. Moreover, the bottom figure shows a microscopy analysis which is in close agreement with the DLS results, displaying an average size of approximately 120 nm for VIP-liposomes. Right. Specific PSMA-micelles targeting microglia. Red (rewiring cargo), Blue (Nucleus), Green (Phalloidin/actin).

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. We identified neuropeptide activity-dependent neuroprotective protein (ADNP) and NAP-derived peptide as new neuroimmunodulators by using different models (acute brain inflammation, septic shock, EAE, ALS and Adnp haploinsuffiency mice) disclosing an emerging role in brain immune homeostasis. Ongoing studies are focused on the unknown molecular mechanisms of ADNP on microglial phenotype based on CRISPR/Cas9 KO cell lines, chromatin remodeling studies and their impact on primary motor neuron function. Limited bioavailability is often a bottleneck

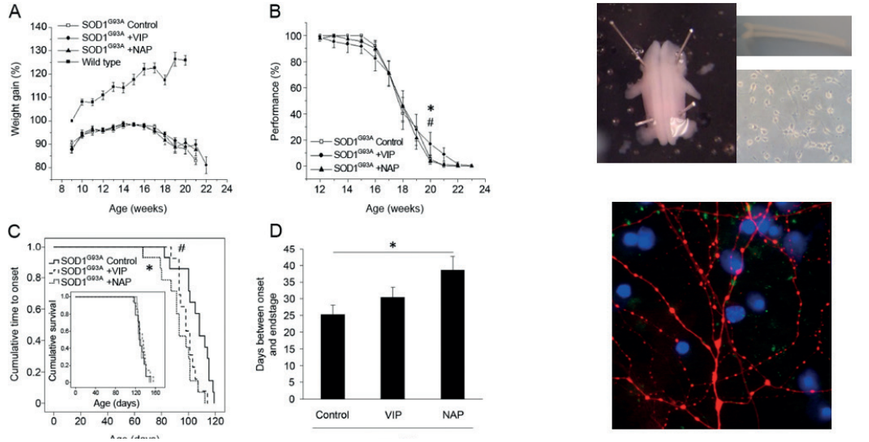


Figure 2. Left. Neuropeptide regulation of ALS onset/disease. Right. Primary motor neurons from mice embryo spinal cord.

for neuropeptide translational research. We have developed new smart delivery platforms to enhance neuropeptide drugability and also to target glial cells for nanoparticle-mediated immune reprogramming. Recently, we have disclosed a new phenotype in the transgenic mouse model of ALS linking energy homeostasis and ALS onset and severity (Franco et al., in preparation). As a follow-up of those findings, we are leading the development of a clinical trial based on drug repurposing as an alternative to the high risk and lengthy procedure of traditional drug development. Clinical and translational studies involve collaborations with S. Martinez (Instituto Neurociencias Alicante, CSIC) and FJ. Quintana (Harvard University, USA).

Research line 2 (C. Roodveldt): A typical characteristic of ALS - apart from de progressive loss of motor neurons - is neuroinflammation. In particular, several studies have shown that microglia, the main immunocompetent cells in the central nervous system (CNS), become activated and neurotoxic, thereby contributing to motor neuron loss and disease duration. The mechanisms driving microglia activation and neurotoxicity in ALS remain incompletely understood. Another key feature of ALS,

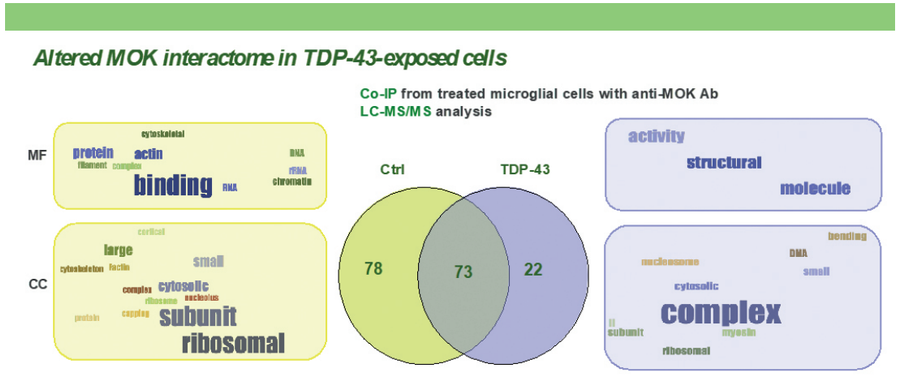


Figure 3. Interactome analysis of MOK binding proteins in primary microglial cells exposed to TDP-43 aggregates vs. control-treated cells. Comparative analysis for enriched molecular functions (MF) and cell compartments (CC) with p<0.05 (GO analysis) from proteins identified by LC-MS/MS in eluted fraction after Co-IP assays, using anti-MOK antibody. The Venn's diagram shows the number of MOK-protein interactors identified for each treatment.

which is considered as a 'protein misfolding disease', is the intracellular accumulation of protein inclusions containing misfolded TDP-43. Recently, as a result of our study with TDP-43 aggregates on microglial responses, we identified a poorly characterized signalling Ser/Thr kinase, MAPK/MAK/MRK overlapping kinase (MOK), as a protein that strongly interacts with internalized TPD-43 aggregates and alters its activation state in primary microglia and organotypic spinal cord cultures (Leal-Lasarte et al., FASEB J. 2017). Up to now, its upstream activating kinase and or its target substrates have not been identified, but MOK has been proposed to have important functions in diverse physiological and pathological processes. As a follow-up of those findings, we have been investigating the possible role of MOK in the neuroinflammatory response of microglia by using a MOK-specific chemical inhibitor, (CRISPR-Cas9) MOK-KO cells, primary microglial and spinal organotypic cultures, and a TDP-43 aggregates-based cellular model. By performing immunofluorescence studies, Co-IP followed by MS/MS analyses to identify MOK interactors, as well as RNA-Seq studies and gene clustering of DEGs, we have made progress in elucidating the participation of MOK in ALS-linked neuroinflammation. Moreover, we have identified phosphorylating substrate candidates for MOK, one of which has been involved in dysregulated immune responses. Finally, we have also been assessing the possible alteration of MOK in spinal cord tissue from ALS mouse models and ALS patients, by immunohistochemistry and with acutely isolated microglia from ALS mice, by flow cytometry. Our results thus far point to a role of MOK in the pathogenic mechanisms of ALS (Gomez et al., in preparation).

Grants

- 2019-2023: RTI2018-098432-B-I00. Programa 'Retos-Investigación' del Plan Nacional, Ministry of Science
- 2019-2021: US-1265227. Programa Operativo FEDER-Junta de Andalucía
- 2019-2022: CIVP19A5938. Proyectos 'Cs. de la Vida', Fundación Ramón Areces
- 2015-2018: RTC-2015-3309-1. Proyectos 'RETOS-Colaboración'. MINECO-Ministerio de Economía y Competitividad
- 2013-2018. P11-CTS-8161. Proyectos de Excelencia. CECI. Junta de Andalucía

Publication Highlights

Caro C, Quaresma P, Pereira E, Franco J, Pernia Leal M, García-Martín ML, Royo JL, Oliva-Montero JM, Merkling PJ, Zaderenko AP, Pozo D, Franco R. **2019.** Synthesis and characterization of elongated-shaped silver nanoparticles as a biocompatible anisotropic SERS probe for intracellular imaging: theoretical modeling and experimental verification. **Nanomaterials.** 9:256-272

Villadiego J, Labrador-Garrido A, Muñoz-Franco J, Leal-Lasarte MM, de Genst EJ, Dobson CM, Pozo D, Toledo-Aral JJ, Roodveldt C. **2018.** Immunization with α-synuclein/Grp94 reshapes peripheral immunity and suppresses microgliosis in a chronic parkinsonism model. **Glia.** 66(1):191-205

Leal-Lasarte MM, Franco JM, Labrador-Garrido A, Pozo D, Roodveldt C. **2017.** Extracellular TDP-43 aggregates target MOK kinase and trigger caspase-3/IL-18 signaling in microglia. **FASEB J.** 31(7):2797-2816

Caballero-Hernandez D, Toscano MG, Cejudo-Guillen M, Garcia-Martin ML, Lopez S, Franco JM, Quintana FJ, Roodveldt C, Pozo D. **2016.** The 'Omics' of Amyotrophic Lateral Sclerosis. **Trends Mol. Med.** 22:53-6

Alcantara D, Lopez S, García-Martin ML, Pozo D. **2016.** Iron oxide nanoparticles as magnetic relaxation switching (MRSw) sensors: Current applications in nanomedicine. **Nanomedicine.** 12:1253-62.

Dr. Alejandro Martín-Montalvo

Metabolic Interventions for Healthy Aging

Group Leader

Current position

- Since 2020: Miguel Servet II investigator of the ISCIII-Fundación Pública Andaluza Progreso y Salud, Andalusian Center for Molecular Biology and Regenerative Medicine, Seville, Spain

Group Members

Postdoctoral
- Isabel Espadas Villanueva

PhD Students
- Alejandro Sola García
- María Ángeles Cáliz Molín

Master Students
- Alejandro Castillo Peña
- Pablo Blanco Carlón

Former Members (2018-2020)

- **PhD students:** Livia López Noriega
- **Master students:** María Ángeles Cáliz Molina, María Eugenia Martín-Vázquez García, Sofía Herrero Valerio, Carmen Cubiles Lozano
- **Technicians:** Leopoldo Pérez Rosendo

Research Activity

Overview

In our current society, more than 50% of elderly humans suffer age-related disabilities that impede optimal quality of life and reduce life expectancy. These disabilities imply important suffering for aging individuals and their families. Currently, the prevalence of age-related metabolic disorders and physical impediments is high and more worryingly, the incidence of this pleiotropic type of diseases/disabilities is rising in parallel. Interventions that delay, or even revert, metabolic disorders could protect other age-related diseases, since epidemiological data indicates that patients suffering metabolic complications have higher likelihood to develop the vast majority of age-related diseases such as cancer, cardiovascular disease and neurodegenerative diseases, later in life. Therefore, there is an urgent need to develop more effective strategies to prevent and treat age-related diseases/disabilities. Our research goal is to identify novel therapeutically promising strategies able to improve the quality of life and life expectancy in humans.

Research Highlights

The use of geroprotectors for healthy aging

We are currently investigating novel approaches to modulate metabolism and aging by targeting the restriction of nuclear/cytosolic Acetyl Coenzyme A (Ac-CoA) levels in mammals. We are evaluating whether a chronic reduction on cytosolic/nuclear Ac-CoA levels using cytosolic Ac-CoA reducing agents, prevent and/or revert metabolic complications, and extend healthspan and lifespan in mammals. We are evaluating the effects of Ac-CoA metabolism in mitochondrial function and processes required to generate endogenous lipids. In order to determine the effects of Ac-CoA metabolism in live organisms

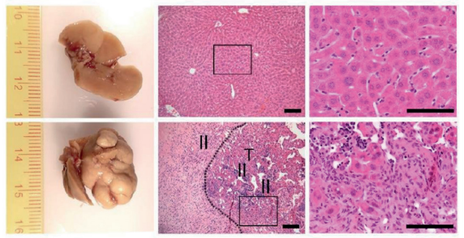


Figure 1. Mild hypothyroidism is associated to increased incidence of liver cancers. Representative photographs and hematoxylin and eosin staining of liver tissue from Wt and Pax8 +/- mice at necropsies. Wt liver exhibits normal hepatic parenchyma with acinar architecture. Pax8 +/- liver displays primary liver epithelial neoplasms (T) with disorganized architecture and inflammatory infiltrate (II). Scale bar 100 um

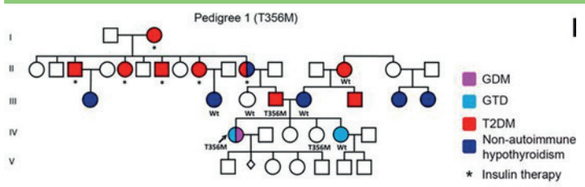


Figure 2. The PAX8-T356M mutation is found in a patient who developed GDM. Family pedigree 1 (T356M) with GDM as well as T2DM and hypothyroidism in consecutive generations. Circles indicate females, and squares indicate males.

we are conducting research on mice focused to determine effects in glucose homeostasis and xenobiotic-induced stress resistance in mice exposed to different interventions that target Ac-CoA levels. Our results indicate that the modulation of Ac-CoA alters genetic and metabolic pathways that control intrinsic processes of aging.

The role of thyroid hormones in mammalian cancer, healthspan and lifespan

Our research on thyroid hormones is focused to determine whether interventions based on the modulation of thyroid hormones affect health and life expectancy. Our results have determined that interventions based on the use of thyroid hormones improve glucose tolerance, blunt the onset and increase survival in two experimental models of autoimmune diabetes mellitus. However, standard healthy mice treated with thyroid hormones develop side effects that

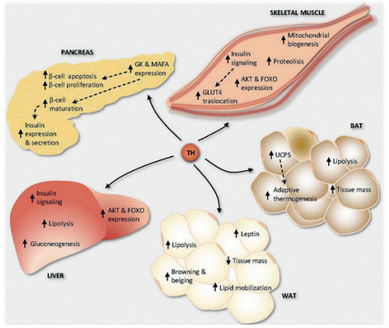


Figure 3. Scheme summarizing the processes regulated by THs in the main metabolic tissues. THs exert profound effects in metabolic tissues. THs enhance GK and MAFA expression in the pancreas favoring a rapid maturation and turnover of ß cells. THs also potentiate insulin expression and secretion in the endocrine pancreas. Insulin-target tissues respond increasing the activity of insulin signaling, which produces increased rates of lipolysis and gluconeogenesis in the liver and proteolysis and mitochondrial biogenesis in the skeletal muscle. Adipose tissues respond to THs increasing lipolysis and lipid mobilization. Browning/beiging of adipocytes occurs in the WAT and increasing thermogenesis via increased UCP expression and subsequent lipolysis occurs in the BAT. AKT, protein kinase B. FOXO: forkhead box O 1. GK: glucokinase. GLUT4: glucose transporter 4. MAFA: MAF bZIP transcription factor A

shorten lifespan. These data suggest that specific thyromimetics targeted to the endocrine pancreas might have therapeutic potential. A separated line of research has been focused to determine whether hypothyroidism could affect the healthspan and lifespan in mice. Our research has determined that mild hypothyroidism has detrimental effects for healthspan without affecting lifespan. Remarkably, our data indicates that mice suffering hypothyroidism exhibit several hallmarks of metabolic syndrome, as well as increased incidence of liver cancers. In parallel, we have performed a genetic screening in a south occidental European population focused to determine whether mutations on PAX8, a gene central in the development and functionality of the thyroid gland, are associated to metabolic deregulations. Our results have revealed that mutations on PAX8 that affect its activity as transcription factor are associated to the development of gestational diabetes and potentially type 2 diabetes. These results indicate that PAX8 should be considered a candidate gene for the study of gestational diabetes.

Grants

- 2020-2021 Young investigator award of the Spanish Diabetes Society
- 2019-2021 PI18/01590. Instituto de Salud Carlos III
- 2016-2018 PI15/00134. Instituto de Salud Carlos III

Publication Highlights

Gauthier BR, Sola-García A, Cáliz-Molina MÁ, Lorenzo PI, Cobo-Vuilleumier N, Capilla-González V, Martin-Montalvo A. **2020.** Thyroid hormones in diabetes, cancer, and aging. **Aging Cell**. e13260

López-Noriega L, Capilla-González V, Cobo-Vuilleumier N, Martin-Vazquez E, Lorenzo PI, Martinez-Force E, Soriano-Navarro M, García-Fernández M, Romero-Zerbo SY, Bermúdez-Silva FJ, Díaz-Contreras I, Sánchez-Cuesta A, Santos-Ocaña C, Hmadcha A, Soria B, Martín F, Gauthier BR, Martin-Montalvo A. **2019.** Inadequate control of thyroid hormones sensitizes to hepatocarcinogenesis and unhealthy aging. **Aging** (Albany NY). 11(18):7746-7779

Martin-Montalvo A, López-Noriega L, Jiménez-Moreno C, Herranz A, Lorenzo PI, Cobo-Vuilleumier N, Tamayo A, González-Guerrero C, Hofsteede JSWR, Lebreton F, Bosco D, García Toscano M, Herranz L, Anselmo J, Moreno JC, Gauthier BR. **2019.** Transient PAX8 Expression in Islets During Pregnancy Correlates With ß-Cell Survival, Revealing a Novel Candidate Gene in Gestational Diabetes Mellitus. **Diabetes.** 68(1):109-118

López-Noriega L, Cobo-Vuilleumier N, Narbona-Pérez ÁJ, Araujo-Garrido JL, Lorenzo PI, Mellado-Gil JM, Moreno JC, Gauthier BR, Martín-Montalvo A. **2017.** Levothyroxine enhances glucose clearance and blunts the onset of experimental type 1 diabetes mellitus in mice. **British Journal Pharmacology**.174(21):3795-3810

Jimenez-Moreno CM, Herrera-Gomez IG, Lopez-Noriega L, Lorenzo PI, Cobo-Vuilleumier N, Fuente-Martin E, Mellado-Gil JM, Parnaud G, Bosco D, Gauthier BR, Martin-Montalvo A. **2015.** A Simple High Efficiency Intra-Islet Transduction Protocol Using Lentiviral Vectors. **Current Gene Therapy**.15(4):436-46

Dr. Francisco Javier Díaz Corrales

Retinal Degeneration: from Genetics to Therapy

Emerging PI

Current position

- Miguel Servet Contract type I and II (03/2016-07/2021)
- Nicolás Monardes Contract (08/2021-06/2025)

Group Members

Postdocs
- Berta De La Cerda Haynes
- Álvaro Plaza Reyes

Technicians
- María Lourdes Valdés Sánchez
- Miriam Ruiz Ballester

Master Students
- Félix Andújar Sánchez

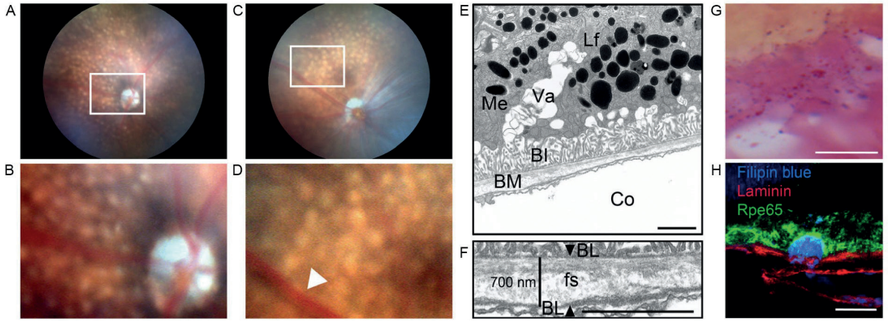
Former Members (2018-2020)

- **Postdocs:** Elena Lucena Padrós
- **PhD students:** Ana Belén García Delgado
- **Technicians:** Adoración Montero Sánchez, Alberto Cañibano Hernández
- **Master students:** Epifanía Arango Isaza, Julia de la Chica Liñan, Laura Vallés Saiz, Inmaculada Izquierdo Simarro, Ana Cristina Almansa García

Research Activity

Overview

Our research focuses on inherited retinal dystrophies such as retinitis pigmentosa (RP) and genetically complex diseases affecting vision like age-related macular degeneration (AMD). Starting from the genetic information, we pursue the study of specific disease mechanisms to explore and test new therapeutics for degenerative retinopathies that are currently incurable. To study retinal degeneration molecular mechanisms, we used both classical in vivo models of retinal degeneration and cellular models by reprogramming induced pluripotent stem cells (iPSCs). The iPSCs are obtained from clinical samples, and then we perform their subsequent differentiation into specific retinal cell types of the retinal organoids. All our experimental tools and human resources are ultimately focused on translational research since our research project's final goal is the development and preclinical evaluation of new therapies to treat retinal degenerative diseases. Our approach includes gene therapy and gene editing using CRISPR/Cas9 technology, cell therapy using iPSCs, development and 3D cultures, and the discovery of new epigenetic drugs to treat RP and AMD. In the frame of translational research, we have created the Spin-off Limnopharma S.L. to boost a future clinical trial for RP. We also work in close collaboration with the Ophthalmology Department of the University Hospital Virgen Macarena and regional and national patient's associations.



Research Highlights

In 2018 we performed the first transplant of retinal pigment epithelium (RPE) in large animals derived from human iPSCs. This study has established the basis for starting the preclinical research to determine the

efficacy and safety of this type of therapeutic approach in AMD. This type of experimental transplantation is currently being carried out in internationally renowned centres such as the Riken Institute in Japan, University College of London in the United Kingdom and the National Eye Institute in the United States. Our innovative approach for RPE cell therapy includes nanotechnology to ensure the polarity of the insert when it is transplanted. Since 2018, we have begun a collaborative research project with the Biological chemistry: molecular recognition and drug design laboratory at the Institute of Parasitology and Biomedicine López-Neyra led by Dr Juan Carlos Morales. This collaboration is based on the study of the neuroprotective effect of several small molecules. One of these new epigenetic drug synthesised at Dr Morales' lab demonstrated a significant delay in retinal degeneration in different autosomal dominant and recessive RP models. For this reason, we decided to patent this discovery. In 2019 we created a Spin-Off responsible for developing more preclinical regulatory studies to promote a clinical trial in RP patients with this new therapeutic alternative. This new molecule's mechanism of action is based on the inhibition of PARP1 and activation of SIRT1. Both proteins play a fundamental role in the degenerative process and maintenance of photoreceptors. Due to this molecule's pharmacochemical properties, its administration can even be topical, which would facilitate its penetration into the retina and avoid side effects.

Grants

- 2017-2020: PI17/01026. Instituto de Salud Carlos III
- 2018-2020: PI-0099-2018. Consejería de Salud y Familia. Junta de Andalucía
- 2016-2019: CP15/00071. Miguel Servet, Instituto Carlos III
- 2017-2019: 113170CELLEX. CELLEX Foundation
- 2015-2019: 634479. EU Horizon 2020

Publication Highlights

Garcia-Delgado AB, Calado SM, Valdes-Sanchez LM, Montero-Sanchez A, Ponte-Zuñiga B, de la Cerda B, Bhattacharya SS, Diaz-Corrales FJ. 2019. Generation of a human iPS cell line (CABi003-A) from a patient with age-related macular degeneration carrying the CFH Y402H polymorphism. Stem Cell Res.38:101473

Valdés-Sánchez L, García-Delgado AB, Montero-Sánchez A, de la Cerda B, Lucas R, Peñalver P, Morales JC, Bhattacharya SS, Díaz-Corrales FJ. 2019. The Resveratrol Prodrug JC19 Delays Retinal Degeneration in rd10 Mice. Adv Exp Med Biol. 1185:457-462

Valdés-Sánchez L, Calado SM, de la Cerda B, Aramburu A, García-Delgado AB, Massalini S, Montero-Sánchez A, Bhatia V, Rodríguez-Bocanegra E, Diez-Lloret A, Rodríguez-Martínez D, Chakarova C, Bhattacharya SS, Díaz-Corrales FJ. 2019. Retinal pigment epithelium degeneration caused by aggregation of PRPF31 and the role of HSP70 family of proteins. Mol Med.26(1):1

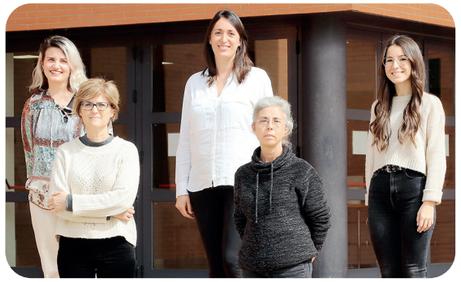
García Delgado AB, de la Cerda B, Alba Amador J, Valdés Sánchez ML, Fernández-Muñoz B, Relimpio López I, Rodríguez de la Rúa E, Díez Lloret A, Calado SM, Sánchez Pernaute R, Bhattacharya SS, Díaz Corrales FJ. 2019. Subretinal Transplant of Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium on Nanostructured Fibrin-Agarose. Tissue Eng Part A. 25(9-10):799-808

de la Cerda B, Díez-Lloret A, Ponte B, Vallés-Saiz L, Calado SM, Rodríguez-Bocanegra E, Garcia-Delgado AB, Moya-Molina M, Bhattacharya SS, Díaz-Corrales FJ. 2019. Generation and characterisation of the human iPSC line CABi001-A from a patient with retinitis pigmentosa caused by a novel mutation in PRPF31 gene. Stem Cell Res. 36:101426

Dr. Vivian Capilla-González

Stem Cells and Translational Neurology

Emerging PI



Current position

- Since 2020: Senior Researcher of the Miguel Servet Program, CABIMER, Seville, Spain

Group Members

PhD Student
- Laura Olmedo Moreno

Technicians
- Yolanda Aguilera García
- Nuria Mellado-Damas

Master student
- Concepción Panadero Morón

Former Members (2018-2020)

- **Technicians:** Víctor López
- **Master student:** Carmen García Sánchez
- **Grade student:** María Marco Aisa

Research Activity

Overview

The number of people that survive cancer is increasing due to the advances in early detection and the development of more effective treatments for cancer. However, the treatments that help these patients survive longer can also cause health problems that limit their quality of life. For this reason, there is an urgent need to develop new regenerative strategies to minimize the sequelae of oncological treatments and to promote a healthy cancer-free life. In this context, cell-based therapy has emerged as a promising alternative in regenerative medicine. Our group brings over 15 years of experience in stem cell research. Currently, we investigate the use of stem cells as strategy to improve cancer treatments from two complementary perspectives; reducing sequelae of cancer treatments and developing new cancer therapeutics.

Research Highlights

Cancer burden raised to 18.1 million new cases and 9.6 million cancer deaths in 2018. However, the number of people that survive cancer is increasing due to advances in early detection and treatments for cancer. For this reason, more attention is being paid to the impact of cancer treatments on patients' health and quality of life. Radiotherapy is one of the most common treatments for cancer. Around 50% of all patients with cancer receive radiation at a given time. Unfortunately, radiotherapy comes with short and long term side effects. In particular, radiation for brain tumors produces neurofunctional sequelae, which may be progressive and permanent. The most frequently described neurological alterations of cranial radiation include learning and memory difficulties, problems in executive functions, reduced processing speed, attention deficits, visual alterations and intellectual decline among others. These neurological sequelae are particularly relevant for pediatric patients because their developing brains are more radiosensitive. Therefore, there is an urgent need to develop new strategies to prevent radiation side effects and promote a healthy cancer-free life.

Our scientific program aims to investigates stem cell-based strategies to improve cancer treatments with the ultimate goal of improving the quality of life of cancer patients. We demonstrated for the first time that intranasally delivered mesenchymal stem cells (MSCs) exhibit therapeutic effect on radiation-related brain damages. In a recent report, we observed that commercial human MSCs migrate from the nasal cavity into the brain of adult mice. In particular, the day after administration, MSCs were observed in the olfactory bulbs and frontal lobes of dissected brains, suggesting efficient grafting. Furthermore, following whole-brain radiation, we found that intranasally delivered MSCs improve motor coordination, odor discrimination

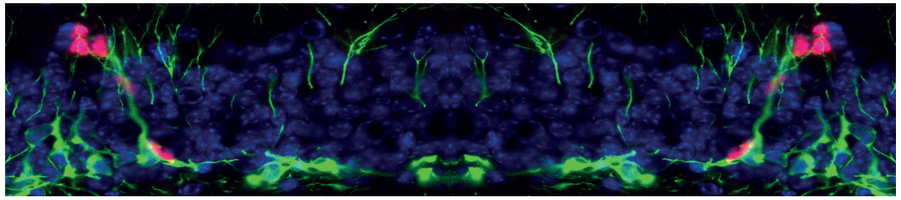


Figure 1. Hippocampus of a whole-brain irradiated mouse. Immunofluorescence against doublecortin (a marker for immature neurons; green) and Ki67 (a marker for proliferating cells; red), and DAPI counterstain in a mouse brain cryosection.

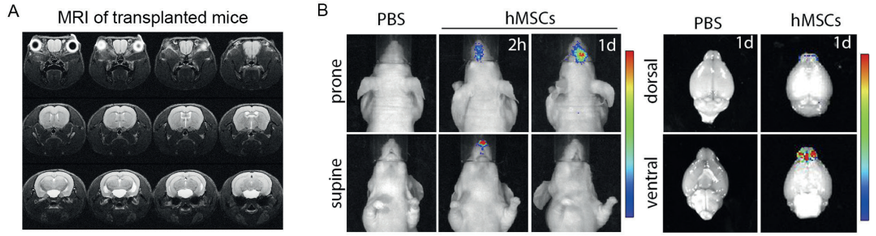


Figure 2. In vivo MRI and biodistribution of transplanted mice. (A) Magnetic resonance images (MRI) of mice that were transplanted with MSCs via the nasal route showing the absence of brain lesions. (B) Images showing the biodistribution of DiR-labelled MSCs that were intranasally administrated in mice.

ability and cognition, as compared to non-transplanted animals. The molecular and cellular study of the brains revealed that MSCs reduce neuroinflammation, protect from oxidative stress and prevent neural cell loss in the irradiated mice, though beneficial effects in neurogenesis were not detected. At mechanistic level, we deciphered molecular pathways involved in neuroregeneration using transcriptomics and conventional western blots, which indicated that MSC administration reduces persistent activation of damage-induced c-AMP response element-binding (CREB) signaling in irradiated brains.

Our previous results uncover an unconventional approach to prevent sequelae of radiation using a non-invasive cell therapy. Now, we have focused on the application of this neuroprotective strategy for pediatric cancer. For this, we are evaluating the safety and efficacy of intranasally delivered patient-derived MSCs in a preclinical model of childhood brain cancer and radiation, which is mandatory before translation to clinical studies with pediatric patients. This line of research is supported by the Asociación Pablo Ugarte (https://www.asociacionpablougarte.es/proyecto-VIDA/). Furthermore, we are investigating new mechanisms to improve the therapeutic potential of MSCs as anti-cancer agent in order to design safer MSC-based therapies for cancer.

Grants

- 2021-2023: PI20/00341. Instituto de Salud Carlos III
- 2020-2022: IDEAS20051CAPI. Asociación Española Contra el Cáncer
- 2020-2023: CP19/00046. Instituto de Salud Carlos III
- 2019-2020: 2018-000237. Precipita - FECYT- Ministerio de Ciencia, Innovación y Universidades
- 2018-2020: PI-0272-2017. Andalusian Regional Ministry of Health
- 2016-2018: PI-0109-2014. Andalusian Regional Ministry of Health

Publication Highlights

Hmadcha A, Martin-Montalvo A, Gauthier BR, Soria B, Capilla-Gonzalez V. **2020.** Therapeutic Potential of Mesenchymal Stem Cells for Cancer Therapy. **Front Bioeng Biotechnol.** 5;8:43

Soria B, Martin-Montalvo A, Aguilera Y, Mellado-Damas N, López-Beas J,Herrera-Herrera I, López E, Barcia JA, Álvarez-Dolado M, Hmadcha A, Capilla-González V. **2019.** Human Mesenchymal Stem Cells Prevent Neurological Complications of Radiotherapy. **Front Cell Neurosci.** 16;13:204

Capilla-González V, López-Beas J, Escacena N, Aguilera Y, de la Cuesta A,Ruiz-Salmerón R, Martín F, Hmadcha A, Soria B. **2018.** PDGF Restores the DefectivePhenotype of Adipose-Derived Mesenchymal Stromal Cells from Diabetic Patients. **Mol Ther.** 7;26(11):2696-2709

Mendivil-Perez M, Soto-Mercado V, Guerra-Librero A, Fernandez-Gil BI, Florido J, Shen YQ, Tejada MA, Capilla-Gonzalez V, Rusanova I, Garcia-Verdugo JM, Acuña-Castroviejo D, López LC, Velez-Pardo C, Jimenez-Del-Rio M, Ferrer JM, Escames G. **2017.** Melatonin enhances neural stem cell differentiation and engraftment byincreasing mitochondrial function. **J Pineal Res.** 63(2)

Guerrero-Cazares H, Lavell E, Chen L, Schiapparelli P, Lara-Velazquez M, Capilla-Gonzalez V, Clements AC, Drummond G, Noiman L, Thaler K, Burke A, Quiñones-Hinojosa A. **2017.** Robo1 Regulates the Migration of Human Subventricular Zone Neural Progenitor Cells During Development. **Stem Cells.** 35(7):1860-1865.

General Core Services

SCIENTIFIC CORE SERVICES

- Genomics
- Biological Resources
- Microscopy
- GMP
- Citometry and Sorter
- Cell Culture
- Model Organism
- Histology
- Lab Material and Sterilization Unit
- Biological Safety

MANAGEMENT UNITS

Scientific Report 2018-2020

Pilar Cebolla

Manager

Cabimer in Numbers

The *raison d'être* of the Management and General Services of a Research Center is to help their scientific community to keep their focus and effort on research.

CABIMER' annual running budget of an average of 2.4 million euros through the period 2018-2020, supported by the partnership of the Spanish National Research Council (CSIC), the University of Seville, the University "Pablo de Olavide", "Consejería de Salud y Familias" and "Consejeria de Transformación Económica, Industria, Conocimiento y Universidad", covers the costs of regular operations (managing, technical services, maintenance, IT, security, etc) to provide support to our researchers.

Additionally, CABIMER has obtained during this period 3.5 million euros that have allowed financing new equipment to expand the science developed at CABIMER and undertaking dissemination activities such as the First CABIMER International Workshop and scientific seminar series, among others.

Concerning the infrastructure, a strong investment has been carried out to improve the technical capabilities of the core services, including a cutting-edge sequencing system.

The valuable commitment of the technical and general services staff has helped to implement new equipment and services, keeping high-quality support for the research, even facing a complicated period due to the SARS-CoV-2 pandemic. In these 3 years, we have strengthened the occupational risk prevention assistance that has been crucial to the preparation and follow-up of the procedure for the prevention of COVID-19 at the workplace.

We have increased our effort to communicate our work to society through our website, actively managing our Twitter account and, improving the media visibility. Many guided visit has been organized in CABIMER and we welcomed an average of 500 visitors a year through this period 2018-2020, mostly high-school students, patients associations and institutional representatives. We have coordinated our participation in 108 outreach events and conferences, and other events with companies such as BioSpain, ASEBIO Investor Day and ASEBIO Health Innovation Forum. We also were very proud of knowing that CABIMER was included in 2019 Nature ranking Top 100 NPO/NGO institutions in biomedical sciences (Nature Index 2019 Biological Science Vol.569 No7756).

By the end of 2020, 158 persons worked at CABIMER, 23 Group Leader (including 5 emerging PIs), 18 senior researchers with stable positions, and a total of 87 PhDs researchers. In addition to the 158 workers, CABIMER has master and last-year bachelor trainee students, which usually constitute a mass of ~17 persons distributed among the different groups.

CABIMER is proud of promoting the career of young researchers and technicians and it has become a training Center in a research environment that promotes gender equality. By mid-year 2020, CABIMER founded the Gender Equality Commission with the main objective of promoting CABIMER's women's career in science and research. By the end of 2020, women represented 62% of total workers but <20% of group leaders are women, so we still need to work harder along this line.

CABIMER's ability to attract talent is demonstrated not only by the number of PhD Thesis (21 during this 3-year period) but also by the origin of the students and young researchers that come from Spain and different countries around the world.

During this period, an average of 45 projects per year are undertaken and we have obtained resources for a total amount of 29.8 million euros including high-competitive grants from international institutions and collaborations with biotechnological companies such as Juvenile Diabetes Research Foundation (JDRF), the European Research Council and the H2020 Programme from EU, Spanish Cancer Association (AECC), Fundación Vencer al Cáncer (VEC), among other entities.

We still have several goals to achieve, for instance, the recognition of National Excellence Research Centre, a new partners agreement to maintain the stable institutional support to the Center, to increase private funding and companies collaborations…but also a wide spectrum of possibilities in the near future to fulfill CABIMER' mission: to transform the results of scientific work into direct improvements of health and quality of life.

I would like to conclude by expressing gratitude and recognition to the Director, Vice-director, and all the scientific, technical and, general services staff whose commitment and great work make it possible to achieve CABIMER's objectives and its enhancement.

A strong investment has been carried out to improve the technical capabilities of the core services, including a cutting-edge sequencing system.

Genomics

Executive Responsible
- Prof. Andrés Aguilera

Scientific Coordinator
- Dr. Cristina González-Aguilera

Technicians
- Dr. Eloísa Andújar
- Dr. Mónica Pérez
- Victoria Jiménez
- Laura Pérez

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 nowadays NGS (next generation sequencing) technologies have become essential 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 Facility 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, CABIMER possess two NGS (Next Generation Sequencing) platforms, Ion-Torrent and Illumina technologies, with three NGS equipments: Ion- Torrent PGM sequencer and Illumina NextSeq500 and Illumina NOVASeq6000 sequencers. Furthermore, a new microfluidics system for partitioning and barcoding single cells (sc) was adquired reciently: the 10xGenomics Chromium Controller. The Core Facility developed and standardized protocols for whole-genome sequencing, ChipSeq, DRIP-Seq, MNase-Seq, RNA-Seq, scRNA-Seq, scATAC-Seq and many others applications for different eukaryotic species using both platforms. The Core Facility also offers advice for experimental design and data analysis.

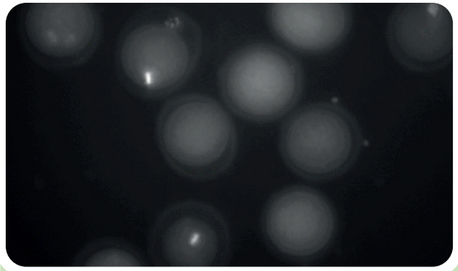
The manipulation of a vast amount of samples processed in a reduced period of time, with accuracy and high reproducibility in the Core Facility, allows the researchers to move to a second phase in their studies on either a wide selection of genes or DNA elements as well as single ones. This is possible due to the diverse high content performance technologies that have been heavily improved in the Core Facility by the use of different robots and high-throughput microscopy.

Biological Resources

Scientific Coordinator
- Dr. Luis Sánchez Palazón

Veterinarian
- Dr. Itziar Benito Latasa de Aranibar

Technicians
- Flora Guerrero Iglesias
- Laura Canas Calvo (until March 2018)
- Miriam González Fernández
- Rosario Segarra Bermúdez



Enucleation of mouse oocytes

Researchers in Cabimer are using mouse models in a variety of ways, from basic research into disease mechanisms 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 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. Animal biosafety level 1 and 2 are available in our facility. During this period, the unit has been successful in competitive calls for research infrastructure which has enhanced our technological capabilities. Laboratory space and equipment is available for metabolic monitoring, behavioural test, in vivo imaging, stereotaxic surgery, electroretinography, optical coherence tomography and transgenesis, including microinjection of DNA into zygotes and rederivation of transgenic lines by embryo transfer. Whenever possible, the unit also collaborates with research groups in Cabimer providing specific technical expertise required in their research projects (1).

(1) Nat Commun 9, 1488 (2018)

Microscopy

Scientific Coordinator

- Dr. Pablo Huertas Sánchez

Technician

- Dr. Paloma Domínguez Giménez

Microscopy is an invaluable tool to directly analyze cellular events. The diverse microscopy techniques facilitate the analysis of the function of proteins, their behavior in some structures, and the relationship among components within a signaling pathway. CABIMER Microscopy Facility provides technical support to scientists from both CABIMER and external entities (public institutions, hospitals and private companies), helping them in all aspects regarding the preparation and development of microscopy experiments: from the experimental design and the use of the instruments to the processing of the data and the analysis of the images. The Microscopy Unit also assists scientists in interpreting and shaping final results. Finally, and in close collaboration with industry partners, the unit is also responsible for the maintenance of the microscopes, to provide the best possible service to our users.

The Microscopy Facility presently counts with state-of-the-art equipment for the development of advanced microscopy techniques. A non comprehensive list of the equipment can be found at http://www.cabimer.es/web3/unidades-apoyo/microscopia/#equipamiento. Being the Microscopy facility an essential core service for CABIMER, the unit is additionally making a constant effort to increase the number of microscopes, thus allowing the implementation of new microscopy methodologies and providing a better service to all our users. This effort has been rewarded during the 2018-2020 period with the concession of a spinning-disc confocal microscope in the context of a call from the Ministry of Economy and Competitiveness. This new equipment will potentiate the capacity of the Microscopy Facility to carry out real time experiments with live cells at higher speed and with high sensitivity, causing less damage and photo-toxicity to the cells. Additionally, this microscope is quite versatile and it helps us to setup novel applications such as TIRF or laser photoablation.

GMP

Technicians

- María Gálvez
- Victoria Jiménez

CABIMER's Good Manufacturing Practices (GMP) core facility is a Unit for ensuring that pharmaceutical products for HUMAN use are CONSISTENTLY manufactured, controlled and documented according to quality standards. GMP is designed to minimize the Risk and ensure the SAFETY of patients enrolled in clinical trials (Regulation (EU) NO 536/2014). The GMP unit of CABIMER is a cell production core facility (UAPC-CABIMER) engaged in the manufacturing of investigational medicinal products "human cells" considered as Advanced Therapy Medicinal Products (ATMPs) in accordance with article 17 of Regulation (EC) nº 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 and later on February 2012 and April 2015).

The UAPC-CABIMER facility is a fully equipped 57m² installation, with 2 Grade B rooms (ISO 14644-1) for manufacturing ATMPs to use in Clinical Trials and Compassive Use and a fully equipped and independent Quality Control Laboratory. The UAPC-CABIMER follows the strict regulations established by Standard Operating Protocols (SOPs), which cover all aspects of ATMPs manufacturing, from the starting material, recordkeeping, premises, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling to the training and personal hygiene of staff.

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L324, 10.12.2007, p.121).

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L158, 27.5.2014, p.1).

Citometry and Sorter

Scientific Coordinator

- Dr. Abelardo López Rivas

Technicians

- Dr. María José Quintero

Flow cytometry is a powerful tool that measures functional and structural characteristics of heterogeneous mixtures of cells 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. Both scattered light and fluorescence emitted by the cells are collected, filtered, digitized and sent to a computer for analysis. The main applications of flow cytometry include immunophenotyping, cell cycle progression, apoptosis/necrosis and protein expression, among many others. Through the cell sorting technology, flow cytometry also allows the physical isolation of distinct populations of cells of interest for further downstream applications including cell culture, RNA or protein analysis and single cell cloning.

The Cytometry Core Facility of Cabimer provides researchers the opportunity to analyze and sort cells of interest. It is equipped with two BD FACSCalibur Analyzers and one BD FACSAriaIIIu Cell Sorter. Recently, a new analytical flow cytometry equipment, BD LSRFortessa X-20, has been incorporated in our Cytometry Core Facility, thanks to the favourable resolution of our application for the acquisition of scientific-technical equipment corresponding to the call from the "Plan Estatal I+D+I 2017-2020", This new flow cytometer has four laser beams that will allow, in addition to the analysis of cell size and complexity, the simultaneous measurement of up to 16 fluorescence parameters. It also includes a loader to automate sample acquisition in 96- and 384-well plates. This loader is quickly and directly interchangeable with the manual socket for tube acquisition. The LSRFortessa X-20 flow cytometer instrument is equipped with the CST module, consisting in a quality control system that automatically allows the complete characterisation of the functional state of the cytometer and the monitoring of its performance. Along with this new acquisition, the two FACSCalibur analyzers have been completely revised and updated to improve their performances and increase their useful working lifetime.

All these actions were undertaken with the aim of maintaining the quality of the services, both internal and external, offered to researchers by our Cytometry Core Facility at Cabimer.

Cell Culture

Scientific Coordinator

- Dr. Raúl V. Durán

Technicians

- Dr. M. Mercedes Dana
- María Galvez

The Cell Culture Core Facility in CABIMER contains different restricted areas where primary and cell line cultures are carried out. Six 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, which also contains a differentiated part to carry out human primary cultures.

The Facility attends to the requirements from the researchers in order to facilitate the use of equipment in the Facility, providing main reagents used in cell cultures such as serum, trypsin, antibiotics, glutamine and PBS. In addition, different foetal bovine serum (FBS) batches are tested yearly in order to select one for common use. Nowadays, the Facility is equipped with numerous normoxic and hypoxic incubators, safety cabinets, centrifuges, electroporation systems and microscopes. As more specific equipment, the Cell Culture Facility has incorporated a BioSpherix XVivo Incubation System (a workstation for hypoxic conditions), a cell analyzer xCELLigence® RTCA DP to quantify cell proliferation and morphology changes in a real-time manner, and an ultracentrifuge for isolation of viral vectors.

Recently, our infrastructure has been improved with the acquisition of two new cryopreservation freezers Custom BioGenic Systems V1500-AB, with patented jacketed technology, which offer safe dry and isothermal storage for samples without liquid nitrogen contact. The Facility has also acquired two automated cell counters CellDrop™ DeNovix, these instruments enable the fastest cell counts, viability assessment, and GFP transfection efficiency measurements across the widest range of cell density, cell type and application.

The Facility makes continuous effort to adapt to the increasing number of users, either by incorporating new areas or by redistributing and optimizing the available space.

Model Organism

Scientific Coordinator
- Dr. Félix Prado

Technician
- Cristina Hernández

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, and 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).

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* and the worm Caenorhabditis elegans.

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.

Histology

Scientific Coordinator
- Dr. Anabel Rojas

Technician
- Dr. Daniel Rodríguez

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 the researches, including tumor tissue characterization, embryo histology, 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 different species, including invertebrates, 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. Specific protocols will be provided on demand and upon availability.

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. Tissues Microarrays (TMA) is also offered by Histology Core Facility, which allow to study a large number of tissue samples assembled on a single histologic slide. The Histology Core also provides different staining protocols for specific cellular structures. The facility is also equipped with a Cytospin for the processing of biological fluids and cell cultures.

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

Lab Material and Sterilization Unit

Scientific Coordinator
- Dr. Ralf Wellinger

Technician
- Mª Jose Figueroa
- Mª Dolores Carrión

The Lab Material and Sterilization Unit is a basic and fundamental support service that serves all research units of CABIMER. This Unit is responsible for the collection, processing, washing, sterilization and distribution of all the laboratory material as well as the sterilization of growth medium and stock solutions (glassware, plastic and consumables). Special trained personnel handles the processing of the biological waste generated by the research groups as well as by other support units, meeting all safety regulations for Biohazaraus 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 an optimal service and to rapidly adapt to newly arising demands.

Due to the incorporation of new and the expansion of existing research groups as well as the generation of new services, the Unit was forced to adapt and to provide a more personalized service mainly focusing on the needs of each research group. Accordingly, the demand for glassware, plastic material and consumables increased by more than 50%, since each research group works with different types of materials that have to be adequately processed. This adaptation required that the equipment of the Unit (autoclaves, thermo-disinfector, etc.) now operates full time to provide maximal service.

To ensure utmost quality of the Sterilization Unit, all management and working procedures undergo regular controls and are executed in accordance with standards outlined in bio-safety regulations.

Biological Safety

Scientific Coordinator
- Dr. José Carlos Reyes

Technician
- Juan Carlos Ostos

The Biosafety unit 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 26 Tm in 2018-2020.

Management Units

Manager
- Pilar Cebolla

Executive Assistants
- Berta Ferrer

Human Resources
- Irene González

Labor Risk Prevention
- Juan Carlos Ostos

Project and economic management
- Carmen Ramos
- Inmaculada Uclés

Purchasing and supplies
- Francisco J. Dorantes
- María Isabel Tovaruela

IT Service
- Arturo Fernández

Maintenance
- Rafael León

Scientific Report 2018-2020

Scientific Publications

2018

- Ariza L, Cañete A, Rojas A, Muñoz-Chápuli R, Carmona R. Role of the Wilms' tumor suppressor gene Wt1 in pancreatic development. **Dev Dyn.** 247(7):924-933
- Bakula D, Aliper AM, Mamoshina P, Petr MA, Teklu A, Baur JA, Campisi J, Ewald CY, Georgievskaya A, Gladyshev VN, Kovalchuk O, Lamming DW, Luijsterburg MS, Martín-Montalvo A, Maudsley S, Mkrtchyan GV, Moskalev A, Olshansky SJ, Ozerov IV, Pickett A, Ristow M, Zhavoronkov A, Scheibye-Knudsen M. Aging and drug discovery. **Aging (Albany NY).** 10(11):3079-3088
- Baranes-Bachar K, Levy-Barda A, Oehler J, Reid DA, Soria-Bretones I, Voss TC, Chung D, Park Y, Liu C, Yoon JB, Li W, Dellaire G, Misteli T, Huertas P, Rothenberg E, Ramadan K, Ziv Y, Shiloh Y. The Ubiquitin E3/E4 Ligase UBE4A Adjusts Protein Ubiquitylation and Accumulation at Sites of DNA Damage, Facilitating Double-Strand Break Repair. **Mol Cell.** 69(5):866-878.e7
- Barrientos-Moreno M, Murillo-Pineda M, Muñoz-Cabello AM, Prado F. Histone depletion prevents telomere fusions in pre-senescent cells. **PLoS Genet.** 14(6):e1007407
- Barroso R, García-Mauriño SM, Tomás-Gallardo L, Andújar E, Pérez-Alegre M, Santero E, Canosa I. The CbrB Regulon: Promoter dissection reveals novel insights into the CbrAB expression network in Pseudomonas putida. **Plos ONE.** 13(12):e0209191
- Bhatia V, Valdés-Sánchez L, Rodriguez-Martinez D, Bhattacharya SS. Formation of 53BP1 foci and ATM activation under oxidative stress is facilitated by RNA:DNA hybrids and loss of ATM-53BP1 expression promotes photoreceptor cell survival in mice. **F1000Research.** 7:1233
- Calado SM, Garcia-Delgado AB, De la Cerda B, Ponte-Zuñiga B, Bhattacharya SS, Díaz-Corrales FJ. Generation of a human iPS cell line from a patient with retinitis pigmentosa due to EYS mutation. **Stem Cells Research.** 33:251-254
- Cano-González A, Mauro-Lizcano M, Iglesias-Serret D, Gil J, López-Rivas A. Involvement of both caspase-8 and Noxa-activated pathways in endoplasmic reticulum stress-induced apoptosis in triple-negative breast tumor cells. **Cell Death Dis.** 9(2):134
- Capilla-González V, López-Beas J, Escacena N, Aguilera Y, de la Cuesta A, Ruiz-Salmerón R, Martín F, Hmadcha A, Soria B. PDGF Restores the Defective Phenotype of Adipose-Derived Mesenchymal Stromal Cells from Diabetic Patients. **Mol Ther.** 26(11):2696-2709
- Carmona-Gutierrez D, Bauer MA, Zimmermann A, Aguilera A et all. Guidelines and recommendations on yeast cell death nomenclature. **Microb Cell.** REVIEW. 5(1):4-31
- Cobo-Vuilleumier N, Lorenzo PI, Rodríguez NG, Herrera Gómez IG, Fuente-Martin E, López-Noriega L, Mellado-Gil JM, Romero-Zerbo SY, Baquié M, Lachaud CC, Stifter K, Perdomo G, Bugliani M, De Tata V, Bosco D, Parnaud G, Pozo D, Hmadcha A, Florido JP, Toscano MG, de Haan P, Schoonjans K, Sánchez Palazón L, Marchetti P, Schirmbeck R, Martín-Montalvo A, Meda P, Soria B, Bermúdez-Silva FJ, St-Onge L, Gauthier BR. LRH-1 agonism favours an immune-islet dialogue which protects against diabetes mellitus. **Nature Commun.** 9(1):1488
- Cubiles MD, Barroso S, Vaquero-Sedas MI, Enguix A, Aguilera A, Vega-Palas MA. Epigenetic features of human telomeres. **Nucleic Acids Research.** 46(5):2347-2355
- De Cárcer G, Huertas P, López-Contreras JA. Chromosome instability: From molecular mechanisms to disease. **DNA Repair (Amst).** 66-67:72-75
- Díaz D, Piquer-Gil M, Recio JS, Martínez-Losa MM, Alonso JR, Weruaga E, Álvarez-Dolado M. Bone marrow transplantation improves motor activity in a mouse model of ataxia. **J Tissue Eng Regen Med.** 12(4):e1950-e1961
- Domínguez-Rodríguez A, Mayoral-Gonzalez I, Avila-Medina J, de Rojas-de Pedro ES, Calderón-Sánchez E, Díaz I, Hmadcha A, Castellano A, Rosado JA, Benitah JP, Gomez AM, Ordoñez A, Smani T. Urocortin-2 Prevents Dysregulation of Ca2+ Homeostasis and Improves Early Cardiac Remodeling After Ischemia and Reperfusion. **Front Physiol.** 9:813
- Duch A, Canal B, Barroso SI, García-Rubio M, Seisenbacher G, Aguilera A, de Nadal E, Posas F. Multiple signaling kinases target Mrc1 to prevent genomic instability triggered by transcription-replication conflicts. **Nature Commun.** 9(1):379
- Elena-Real CA, Díaz-Quintana A, González-Arzola K, Velázquez-Campoy A, Orzáez M, López-Rivas A, Gil-Caballero S, De la Rosa MÁ, Díaz-Moreno I. Cytochrome c speeds up caspase cascade activation by blocking 14-3-3ε-dependent Apaf-1 inhibition. **Cell Death Dis.** 9(3):365

- Fernández O, Izquierdo G, Fernández V, Leyva L, Reyes V, Guerrero M, León A, Arnaiz C, Navarro G, Páramo MD, Cuesta A, Soria B, Hmadcha A, Pozo D, Fernandez-Montesinos R, Leal M, Ochotorena I, Gálvez P, Geniz MA, Barón FJ, Mata R, Medina C, Caparrós-Escudero C, Cardesa A, Cuende N; Research Group Study EudraCT 2008-004015-3. Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: A triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. **PLoS One.** 13(5):e0195891

- Flores-Martínez A, García-Núñez A, Rojas A, Cano DA. Stabilization of HIF-2α impacts pancreas growth. **Sci Rep.** 8(1):13713

- Fueyo R, Iacobucci S, Pappa S, Estarás C, Lois S, Vicioso-Mantis M, Navarro C, Cruz-Molina S, Reyes JC, Rada-Iglesias Á, de la Cruz X, Martínez-Balbás MA. Lineage specific transcription factors and epigenetic regulators mediate TGFß-dependent enhancer activation. **Nucleic Acids Res.** 46(7):3351-3365

- Gaillard H, García-Benítez F, Aguilera A. Gene gating at nuclear pores prevents the formation of R loops. **Mol Cell Oncol.** 5(1):e1405140

- Garcia-Delgado AB, Valdés-Sánchez L, Calado SM, Diaz-Corrales FJ, Bhattacharya SS. Rasagiline delays retinal degeneration in a mouse model of retinitis pigmentosa via modulation of Bax/Bcl-2 expression. **CNS Neurosci Ther.** 24: 448-455

- García-Rubio M, Aguilera P, Lafuente-Barquero J, Ruiz JF, Simon MN, Geli V, Rondón AG, Aguilera A. Yra1-bound RNA-DNA hybrids cause orientation-independent transcription-replication collisions and telomere instability. **Genes Dev.** 32(13-14):965-977

- Gavilan MP, Gandolfo P, Balestra FR, Arias F, Bornens M, Rios RM. The dual role of the centrosome in organizing the microtubule network in interphase. **Embo reports.** 19(11). pii: e45942

- Gavish-Izakson M, Velpula BB, Elkon R, Prados-Carvajal R, Barnabas GD, Ugalde AP, Agami R, Geiger T, Huertas P, Ziv Y, Shiloh Y. Nuclear poly(A)-binding protein 1 is an ATM target and essential for DNA double-strand break repair. **Nucleic Acids Res.** 46(2):730-747

- González-Arranz S, Cavero S, Morillo-Huesca M, Andújar E, Pérez-Alegre M, Prado F, and San-Segundo P. Functional impact of the H2A.Z histone variant during meiosis in *saccharomyces cerevisiae*. **Genetics.** 209: 997-1015

- Guerrero-Martínez JA, Reyes JC. High expression of SMARCA4 or SMARCA2 is frequently associated with an opposite prognosis in cancer. **Sci Rep.** 8(1):2043

- Hernández G, Ramírez MJ, Minguillón J, Quiles P, Ruiz de Garibay G, Aza-Carmona M, Bogliolo M, Pujol R, Prados-Carvajal R, Fernández J, García N, López A, Gutiérrez-Enríquez S, Diez O, Benítez J, Salinas M, Teulé A, Brunet J, Radice P, Peterlongo P, Schindler D, Huertas P, Puente XS, Lázaro C, Pujana MÀ, Surrallés J. Decapping protein EDC4 regulates DNA repair and phenocopies BRCA1. **Nature Commun.** 9(1):967

- Jimeno S, Camarillo R, Mejías-Navarro F, Fernández-Ávila MJ, Soria-Bretones I, Prados-Carvajal R, Huertas P. The Helicase PIF1 Facilitates Resection over Sequences Prone to Forming G4 Structures. **Cell Rep.** 24(12):3262-3273.e4

- López S, García-Serrano S, Gutierrez-Repiso C, Rodríguez-Pacheco F, Ho-Plagaro A, Santiago-Fernandez C, Alba G, Cejudo-Guillen M, Rodríguez-Cañete A, Valdes S, Garrido-Sanchez L, Pozo D, García-Fuentes E. Tissue-Specific Phenotype and Activation of iNKT Cells in Morbidly Obese Subjects: Interaction with Adipocytes and Effect of Bariatric Surgery. **Obes Surg.** 28(9):2774-2782

- López-Beas J, Capilla-González V, Aguilera Y, Mellado N, Lachaud CC, Martín F, Smani T, Soria B, Hmadcha A. miR-7 Modulates hESC Differentiation into Insulin-Producing Beta-like Cells and Contributes to Cell Maturation. **Mol Ther Nucleic Acids.** 2:463-477. doi: 10.1016/j.omtn.2018.06.002

- López-López M, López-Cornejo P, Martín VI, Ostos FJ, Checa-Rodríguez C, Prados-Carvajal R, Lebrón JA, Huertas P, Moyá ML. Importance of hydrophobic interactions in the single-chained cationic surfactant-DNA complexation. **J Colloid Interface Sci.** 521:197-205

- Lorenzo PI, Cobo-Vuilleumier N, Gauthier BR. Therapeutic potential of pancreatic PAX4-regulated pathways in treating diabetes mellitus. **Curr Opin Pharmacol (REW).** 43:1-10

- Luna-Peláez N, García-Domínguez M. Lyar-mediated recruitment of Brd2 to the chromatin attenuates Nanog downregulation following induction of differentiation. **J Mol Biol.** 430(8):1084-1097

- Luque-Sierra A, Álvarez-Amor L, Kleemann R, Martín F, Varela LM. Extra-Virgin Olive Oil With Natural Phenolic Content Exerts an Anti-Inflammatory Effect in Adipose Tissue and Attenuates the Severity of Atherosclerotic Lesions in Ldlr-/-.Leiden Mice. **Mol Nutr Food Res.** 62(13):e1800295

- Martinez-Losa M, Tracy TE, Ma K, Verret L, Clemente-Perez A, Khan AS, Cobos I, Ho K, Gan L, Mucke L, Álvarez-Dolado M, Palop JJ. Nav1.1-Overexpressing Interneuron Transplants Restore Brain Rhythms and Cognition in a Mouse Model of Alzheimer's Disease. **Neuron.** 98(1):75-89.e5

- Martínez-Muñoz L, Rodríguez-Frade JM, Barroso R, Sorzano CÓS, Torreño-Pina JA, Santiago CA, Manzo C, Lucas P, García-Cuesta EM, Gutierrez E, Barrio L, Vargas J, Cascio G, Carrasco YR, Sánchez-Madrid F, García-Parajo MF, Mellado M. Separating Actin-Dependent Chemokine Receptor Nanoclustering from Dimerization Indicates a Role for Clustering in CXCR4 Signaling and Function. **Mol Cell.** 70(1):106-119.e10

- Martínez-Muñoz L, Villares R, Rodríguez-Fernández JL, Rodríguez-Frade JM, Mellado M. Remodeling our concept of chemokine receptor function: From monomers to oligomers. **J Leukoc Biol.** 104(2):323-331

- Mauro-Lizcano M, López-Rivas A. Glutamine metabolism regulates FLIP expression and sensitivity to TRAIL in triple-negative breast cancer cells. **Cell Death Dis.** 9(2):205

- Mellado-Gil Jose M, Fuente-Martín Esther, Lorenzo Petra I., Cobo-Vuilleumier Nadia, López-Noriega Livia, Martín-Montalvo Alejandro, de Gracia Herrera Gómez Irene, Ceballos-Chávez Maria,Gómez-Jaramillo Laura, Campos-Caro Antonio, Romero-Zerbo Silvana Y., Rodríguez-Comas Júlia, Servitja Joan-Marc,Rojo-Martinez G., Hmadcha K., Soria B., Bugliani M., Marchetti P.,Bérmudez-Silva F.J., Reyes J.C., Aguilar-Diosdado M. and Gauthier B. The type 2 diabetes-associated HMG20A gene is mandatory for islet beta cell functional maturity. **Cell Death & Disease.** 9(279)

- Moreno-Marín N, Merino JM, Álvarez-Barrientos A, Patel DP, Takahashi S, González-Sancho JM, Gandolfo P, Rios RM, Muñoz A, Gonzalez FJ, Fernández-Salguero PM. Aryl Hydrocarbon Receptor Promotes Liver Polyploidization and Inhibits PI3K, ERK, and Wnt/ß-Catenin Signaling. **iScience.** 4:44-63

- Muñoz MF, Argüelles S, Guzman-Chozas M, Guillén-Sanz R, Franco JM, Pintor-Toro JA, Cano M, Ayala A. Cell Tracking, survival and differentiation capacity of adipose-derived stem cells after engraftment in rat tissue. **J Cell Physiol.** 233(10):6317-6328

- Muñoz-Pinedo C, López-Rivas A. A role for caspase-8 and TRAIL-R2/DR5 in ER-stress-induced apoptosis. **Cell Death Differ.** 25(1):226

- Prado F. Homologous Recombination: To Fork and Beyond. **Genes (Basel).** 9(12).603

- Prados-Carvajal R, López-Saavedra A, Cepeda-García C, Jimeno S, Huertas P. Multiple roles of the splicing complex SF3B in DNA end resection and homologous recombination. **DNA Repair (Amst).** 66-67:11-23

- Reverón-Gómez N, González-Aguilera C, Stewart-Morgan KR, Petryk N, Flury V, Graziano S, Johansen JV, Jacobsen JS, Alabert C and Groth A. Accurate recycling of parental histones reproduces the histone modification landscape during DNA replication. **Mol Cell.** 72(2):239-249.e5

- Rose AM, Krishan A, Chakarova CF, Moya L, Chambers S, Hollands M, Illingworth JC, Williams SMG, James HE, Shah AZ, Palmer CNA, Chakravarti A, Berg JN, Batra J, Bhattacharya SS. MSR1 repeats modulate gene expression and affect risk of breast and prostate cancer. **Ann Oncol.** 29(5):1292-1303

- Silva S, Camino LP, Aguilera A. Human mitochondrial degradosome prevents harmful mitochondrial R loops and mitochondrial genome instability. **PNAS.** 115(43):11024-11029

- Villadiego J, Labrador-Garrido A, Franco JM, Leal-Lasarte M, De Genst EJ, Dobson CM, Pozo D, Toledo-Aral JJ, Roodveldt C. Immunization with α-synuclein/Grp94 reshapes peripheral immunity and suppresses microgliosis in a chronic Parkinsonism model. **Glia.** 66(1):191-205

- Villamayor L, Rodríguez-Seguel E, Araujo R, Carrasco M, Bru-Tarí E, Mellado-Gil JM, Gauthier BR, Martinelli P, Quesada I, Soria B, Martín F, Cano DA, Rojas A. GATA6 Controls Insulin Biosynthesis and Secretion in Adult ß cell. **Diabetes.** 67:448-460

2019

- Ariza L, Rojas A, Muñoz-Cápuli R, Carmona R. The Wilms' tumor suppressor gene regulates pancreas homeostasis and repair. **Plos Genetics.** 15(2):e1007971

- Barroso S, Herrera-Moyano E, Muñoz S, García-Rubio M, Gómez-González B, Aguilera A. The DNA damage response acts as a safeguard against harmful DNA-RNA hybrids of different origins. **EMBO reports.** 20(9):e47250

- Bru-Tari E, Cobo-Vuilleumier N, Alonso-Magdalena P, Dos Santos RS, Marroqui L, Nadal A, Gauthier BR, Quesada I. Pancreatic alpha-cell mass in the early-onset and advanced stage of a mouse model of experimental autoimmune diabetes. **Sci Rep.** 9(1):9515

- Cabello M, Mozo M, De la Cerda B, Aracil C, Diaz-Corrales FJ, Perdigones F, Valdes-Sanchez L, Relimpio I, Bhattacharya SS, Quero JM. Electrostimulation in an autonomous culture lab-on-chip provides neuroprotection of a retinal explant from a retinitis pigmentosa mouse-model. **Sensors and Actuators B: Chemical.** 288: 337-346

- Caro C, Quaresma P, Pereira E, Franco J, Pernia Leal M, García-Martín ML, Royo JL, Oliva-Montero JM, Merkling PJ, Zaderenko AP, Pozo D, Franco R. Synthesis and Characterization of Elongated-Shaped Silver Nanoparticles as a Biocompatible Anisotropic SERS Probe for Intracellular Imaging: Theoretical Modeling and Experimental Verification. **Nanomaterials (Basel).** 9(2). 256

- Cobo-Vuilleumier N, Lorenzo PI, Gauthier BR. Targeting LRH-1/NR5A2 to treat type 1 diabetes mellitus. **Cell Stress.** 2(6):141-143

- De la Cerda B, Díez-Lloret A, Ponte B, Vallés-Saiz L, Calado SM, Rodríguez-Bocanegra E, Garcia-Delgado AB, Moya-Molina M, Bhattacharya SS, Díaz-Corrales FJ. Generation and characterization of the human iPSC line CABi001-A from a patient with retinitis pigmentosa caused by a novel mutation in PRPF31 gene. **Stem Cell Res.** 36:101426

- Domingo-Prim J, Endara-Coll M, Bonath F, Jimeno S, Prados-Carvajal R, Friedländer MR, Huertas P, Visa N. EXOSC10 is required for RPA assembly and controlled DNA end resection at DNA double-strand breaks. **Nature Commun.** 10(1):2135

- Falcón D, Galeano-Otero I, Calderón-Sánchez E, Del Toro R, Martín-Bórnez M, Rosado JA, Hmadcha A, Smani T. TRP Channels: Current Perspectives in the Adverse Cardiac Remodeling. **Front Physiol.** 10:159

- Fuente-Martín E, Mellado-Gil JM, Cobo-Vuilleumier N, Martín-Montalvo A, Romero-Zerbo SY, Diaz Contreras I, Hmadcha A, Soria B, Martin Bermudo F, Reyes JC, Bermúdez-Silva FJ, Lorenzo PI, Gauthier BR. Dissecting the Brain/Islet Axis in Metabesity. **Genes (Basel).** 10(5). 350

- Gaillard H, Santos-Pereira JM, Aguilera A. The Nup84 complex coordinates the DNA damage response to warrant genome integrity. **Nucleic Acids Res.** 47(8):4054-4067

- Gallego-Durán R, Álvarez-Amor L, Gil-Gómez A, Rojas Á, Muñoz-Hernández R, Cádernas-García A, Maya-Miles D, Montero-Vallejo R, Gato S, Sánchez Torrijos Y, Ampuero J, Martín F, Romero-Gómez M. Metabolic characterization of two different non-alcoholic fatty liver disease pre-clinical mouse models. **Rev Esp Enferm Dig.** 111(4):301-307

- García Delgado AB, de la Cerda B, Alba Amador J, Valdés Sánchez ML, Fernández-Muñoz B, Relimpio López I, Rodríguez de la Rúa E, Díez Lloret A, Calado SM, Sánchez Pernaute R, Bhattacharya SS, Díaz Corrales FJ. Subretinal transplant of iPSC-derived retinal pigment epithelium on nanostructured fibrin-agarose. **Tissue Eng Part A.** 25(9-10)

- Garcia-Delgado AB, Calado SM, Valdes-Sanchez LM, Montero-Sanchez A, Ponte-Zuñiga B, de la Cerda B, Bhattacharya SS, Diaz-Corrales FJ. Generation of a human iPS cell line (CABi003-A) from a patient with age-related macular degeneration carrying the CFH Y402H polymorphism. **Stem Cell Res.** 38:101473

- Garcia-Muse T, Galindo-Diaz U, Garcia-Rubio M, Martin JS, Polanowska J, O'Reilly N, Aguilera A, Boulton SJ. A Meiotic Checkpoint Alters Repair Partner Bias to Permit Inter-sister Repair of Persistent DSBs. **Cell Rep.** 26(3):775-787

- García-Muse T, Aguilera A. R Loops: From Physiological to Pathological Roles. **CELL.** 179(3):604-618

- García-Rodríguez N, Ulrich Hellen D. A dual system to manipulate protein levels for DNA replication-and cell cycle related studies. **Methods in Enzymology.** 619:121-143

- Gauthier BR, Bermúdez-Silva FJ. Advances in Genetics of Regeneration in Metabesity. **Genes (Basel).** 10(5). 383

- Gómez-González B, Aguilera A. Transcription-mediated replication hindrance: a major driver of genome instability. **Genes Dev.** 33(15-16)

- Guadix JA, López-Beas J, Clares B, Soriano-Ruiz JL, Zugaza JL, Gálvez-Martín P. Principal Criteria for Evaluating the Quality, Safety and Efficacy of hMSC-Based Products in Clinical Practice: Current Approaches and Challenges. **Pharmaceutics.** 11(11).552

- Jachimowicz RD, Beleggia F, Isensee J, Velpula BB, Goergens J, Bustos MA, Doll MA, Shenoy A, Checa-Rodriguez C, Wiederstein JL, Baranes-Bachar K, Bartenhagen C, Hertwig F, Teper N, Nishi T, Schmitt A, Distelmaier F, Lüdecke HJ, Albrecht B, Krüger M, Schumacher B, Geiger T, Hoon DSB, Huertas P, Fischer M, Hucho T, Peifer M, Ziv Y, Reinhardt HC, Wieczorek D, Shiloh Y. UBQLN4 Represses Homologous Recombination and Is Overexpressed in Aggressive Tumors. **Cell.** 176(3):505-519

- Jimeno S, Mejías-Navarro F, Prados-Carvajal R, Huertas P. Controlling the balance between chromosome break repair pathways. **Adv Protein Chem Struct Biol.** 115:95-134

- Jimeno S, Prados-Carvajal R, Huertas P.The role of RNA and RNA-related proteins in the regulation of DNA double strand break repair pathway choice. **DNA Repair (Amst).** 81:102662

- Jurado-Ruiz E, Álvarez-Amor L, Varela LM, Berná G, Parra-Camacho MS, Oliveras-Lopez MJ, Martínez-Force E, Rojas A, Hmadcha A, Soria B, Martín F. Extra virgin olive oil diet intervention improves insulin resistance and islet performance in diet-induced diabetes in mice. **Sci Rep.** 9(1):11311

- Klein HL, Bačinskaja G, Che J, Cheblal A, Elango R, Epshtein A, Fitzgerald DM, Gómez-González B, Khan SR, Kumar S, Leland BA, Marie L, Mei Q, Miné-Hattab J, Piotrowska A, Polleys EJ, Putnam CD, Radchenko EA, Saada AA, Sakofsky CJ, Shim EY, Stracy M, Xia J, Yan Z, Yin Y, Aguilera A, Argueso JL, Freudenreich CH, Gasser SM, Gordenin DA, Haber JE, Ira G, Jinks-Robertson S, King MC, Kolodner RD, Kuzminov A, Lambert SA, Lee SE, Miller KM, Mirkin SM, Petes TD, Rosenberg SM, Rothstein R, Symington LS, Zawadzki P, Kim N, Lisby M, Malkova A. Guidelines for DNA recombination and repair studies: Cellular assays of DNA repair pathways. **Microb Cell.** 6(1):1-64

- Koveitypour Z, Panahi F, Vakilian M, Peymani M, Seyed Forootan F, Nasr Esfahani MH, Ghaedi K. Signaling pathways involved in colorectal cancer progression. **Cell Biosci.** 9.97

- López-Noriega L, Capilla-González V, Cobo-Vuilleumier N, Martin-Vazquez E, Lorenzo PI, Martinez-Force E, Soriano-Navarro M, García-Fernández M, Romero-Zerbo SY, Bermúdez-Silva FJ, Díaz-Contreras I, Sánchez-Cuesta A, Santos-Ocaña C, Hmadcha A, Soria B, Martín F, Gauthier BR, Martin-Montalvo A. Inadequate control of thyroid hormones sensitizes to hepatocarcinogenesis and unhealthy aging. **Aging (Albany NY).** 11(18):7746-7779

- Luna-Peláez N, March-Díaz R, Ceballos-Chávez M, Guerrero-Martínez JA, Grazioli P, García-Gutiérrez P, Vaccari T, Massa V, Reyes JC, García-Domínguez M. The Cornelia de Lange Syndrome-associated factor NIPBL interacts with BRD4 ET domain for transcription control of a common set of genes. **Cell Death Dis.** 10(8):548

- Mannini B, Vecchi G, Labrador-Garrido A, Fabre B, Fani G, Franco JM, Lilley K, Pozo D, Vendruscolo M, Chiti F, Dobson CM, Roodveldt C. Differential Interactome and Innate Immune Response Activation of Two Structurally Distinct Misfolded Protein Oligomers. **ACS Chem Neurosci.** 10(8):3464-3478

- Manzano-López, J., Matellán, L., Álvarez-Llamas, A., Blanco-Mira, J.C., Monje-Casas, F. Asymmetric inheritance of spindle microtubule-organizing centres preserves replicative lifespan. **Nature Cell Biology.** 21(8):952-965

- Marín-Aguilar F, Castejón-Vega B, Alcocer-Gómez E, Lendines-Cordero D, Cooper MA, de la Cruz P, Andújar-Pulido E, Pérez-Alegre M, Muntané J, Pérez-Pulido AJ, Ryffel B, Robertson AAB, Ruiz-Cabello J, Bullón P, Cordero MD. NLRP3 inflammasome inhibition by MCC950 in aged mice improves health via enhanced autophagy and PPARα activity. **J Gerontol A Biol Sci Med Sci.** 75(8):1457-1464

- Martin-Montalvo A, López-Noriega L, Jiménez-Moreno C, Herranz A, Lorenzo PI, Cobo-Vuilleumier N, Tamayo A, González-Guerrero C, Hofsteede JSWR, Lebreton F, Bosco D, Toscano MG, Herranz L, Anselmo J, Moreno JC, Gauthier BR. Transient PAX8 Expression in Islets During Pregnancy Correlates With Beta Cell Survival Revealing a Novel Candidate Gene in Gestational Diabetes Mellitus. **Diabetes.** 68(1):109-11

- Martinez-Pinna J, Marroqui L, Hmadcha A, Lopez-Beas J, Soriano S, Villar-Pazos S, Alonso-Magdalena P, Dos Santos RS, Quesada I, Martin F, Soria B, Gustafsson JÅ, Nadal A. Oestrogen receptor ß mediates the actions of bisphenol-A on ion channel expression in mouse pancreatic beta cells. **Diabetologia.** 62(9):1667-1680

- Maya-Miles D, Andújar E, Pérez-Alegre M, Murillo-Pineda M, Barrientos-Moreno M, Cabello-Lobato MJ, Gómez-Marín E, Morillo-Huesca M, Prado F. Crosstalk between chromatin structure, cohesin activity and transcription. **Epigenetics Chromatin.** 12(1):47

- Merle BMJ, Colijn JM, Cougnard-Grégoire A, de Koning-Backus APM, Delyfer MN, Kiefte-de Jong JC, Meester-Smoor M, Féart C, Verzijden T, Samieri C, Franco OH, Korobelnik JF, Klaver CCW, Delcourt C; EYE-RISK Consortium. Mediterranean Diet and Incidence of Advanced Age-Related Macular Degeneration: The EYE-RISK Consortium. **Ophtalmology.** 126(3):381-390

- Morillo-Huesca M, Murillo-Pineda M, Barrientos-Moreno M, Gómez-Marín E, Clemente-Ruiz M, Prado F. Actin and Nuclear Envelope Components Influence Ectopic Recombination in the Absence of Swr1. **Genetics.** 213(3):819-834.

- Ortega P. Gómez-González Belén, Aguilera A. Rpd3L and Hda1 histone deacetylases facilitate repair of broken forks by promoting sister chromatid cohesion. **Nature Commun.** 10(1):5178

- Petra I L, Martín-Montalvo A, Cobo Vuilleumier N, Gauthier BR. Molecular Modelling of Islet ß-Cell Adaptation to Inflammation in Pregnancy and Gestational Diabetes Mellitus. **Int J Mol Sci.** 20(24)

- Pintado-Berninches L, Fernandez-Varas B, Benitez-Buelga C, Manguan-Garcia C, Serrano-Benitez A, Iarriccio L, Carrillo J, Guenechea G, Egusquiaguirre SP, Pedraz JL, Hernández RM, Igartua M, Arias-Salgado EG, Cortés-Ledesma F, Sastre L, Perona R. GSE4 peptide suppresses oxidative and telomere deficiencies in ataxia telangiectasia patient cells. **Cell Death Diffe.** 26(10):1998-2014

- Rivero S, Gómez-Marín E, Guerrero-Martínez JA, García-Martínez J, Reyes JC. TBL1 is required for the mesenchymal phenotype of transformed breast cancer cells. **Cell Death Dis.** 10(2): 95

- Romero-Ben E, Cid JJ, Assali M, Fernández-García E, Wellinger RE, Khiar N. Surface modulation of single-walled carbon nanotubes for selective bacterial cell agglutination. **Cell Reports.** 14:3245-3263

- Rondón AG, Aguilera A. What causes an RNA-DNA hybrid to compromise genome integrity?. **DNA Repair (Amst).** 81:102660

- Rondón AG, Aguilera A. R-Loops as Promoters of Antisense Transcription. **Mol Cell.** 76(4):529-530

- Salas-Armenteros I, Barroso SI, Rondón AG, Pérez M, Andújar E, Luna R, Aguilera A. Depletion of the MFAP1/SPP381 Splicing Factor Causes R-Loop-Independent Genome Instability. **Cell Reports.** 28(6):1551-1563

- Serrano-Saenz S, Palacios C, Delgado-Bellido D, López-Jiménez L, Garcia-Diaz A, Soto-Serrano Y, Casal JI, Bartolomé RA, Fernández-Luna JL, López-Rivas A, Oliver FJ. PIM kinases mediate resistance of glioblastoma cells to TRAIL by a p62/SQSTM1-dependent mechanism. **Cell Death Dis.** 10(2):51

- Soria B, Martin-Montalvo A, Aguilera Y, Mellado-Damas N, López-Beas J, Herrera-Herrera I, López E, Barcia JA, Álvarez-Dolado M, Hmadcha A, Capilla-González V.Human Mesenchymal Stem Cells Prevent Neurological Complications of Radiotherapy. **Front Cell Neurosci.** 13:204

- Soria-Juan B, Escacena N, Capilla-González V, Aguilera Y, Llanos L, Tejedo JR, Bedoya FJ, Juan V, De la Cuesta A, Ruiz-Salmerón R, Andreu E, Grochowicz L, Prósper F, Sánchez-Guijo F, Lozano FS, Miralles M, Del Río-Solá L, Castellanos G, Moraleda JM, Sackstein R, García-Arranz M, García-Olmo D, Martín F, Hmadcha A, Soria B 2019 Cost-Effective, Safe, and Personalized Cell Therapy for Critical Limb Ischemia in Type 2 Diabetes Mellitus. **Front Immunol.** 10:1151

- Tisch N, Freire-Valls A, Yerbes R, Paredes I, La Porta S, Wang X, Martín-Pérez R, Castro L, Wong WW, Coultas L, Strilic B, Gröne HJ, Hielscher T, Mogler C, Adams R, Heiduschka P, Claesson-Welsh L, Mazzone M, López-Rivas A, Schmidt T, Augustin HG, Ruiz de Almodovar C. Caspase-8 modulates physiological and pathological angiogenesis during retina development. **J Clin Invest.** 129(12):5092-5107

- Tumini E, Herrera-Moyano E, San Martín-Alonso M, Barroso S, Galmarini CM, Aguilera A. The Antitumor Drugs Trabectedin and Lurbinectedin Induce Transcription-Dependent Replication Stress and Genome Instability. **Mol Cancer Res.** 17(3):773-782

- Vakilian M, Tahamtani Y, Ghaedi K. A review on insulin trafficking and exocytosis. **Gene.** 706:52-61

- Valdés-Sánchez L, Calado SM, de la Cerda B, Aramburu A, García-Delgado AB, Massalini S, Montero-Sánchez A, Bhatia V, Rodríguez-Bocanegra E, Diez-Lloret A, Rodríguez-Martínez D, Chakarova C, Bhattacharya SS, Díaz-Corrales FJ. Retinal pigment epithelium degeneration caused by aggregation of PRPF31 and the role of HSP70 family of proteins. **Mol Med.** 26(1):1

- Valdés-Sánchez L, García-Delgado AB, Montero-Sánchez A, de la Cerda B, Lucas R, Peñalver P, Morales JC, Bhattacharya SS, Díaz-Corrales FJ. The Resveratrol Prodrug JC19 Delays Retinal Degeneration in rd10 Mice. **Adv Exp Med Biol.** 1185:457-462

- Villamayor L, Cano DA, Rojas A. GATA factors in pancreas development and disease **IUBMB Life.** 72(1):80-88

- Zapatka M, Pociño-Merino I, Heluani-Gahete H, Bermúdez-López M, Tarrés M, Ibars E, Solé-Soler R, Gutiérrez-Escribano P, Apostolova S, Casas C, Aragon L, Wellinger R, Colomina N, Torres-Rosell J. Sumoylation of Smc5 Promotes Error-free Bypass at Damaged Replication Forks. **Cell Reports.** 9(10):3160-3172

- Zatreanu D, Han Z, Mitter R, Tumini E, Williams H, Gregersen L, Dirac-Svejstrup AB, Roma S, Stewart A, Aguilera A, Svejstrup JQ. Elongation Factor TFIIS Prevents Transcription Stress and R-Loop Accumulation to Maintain Genome Stability. **Mol Cell.** 76(1):57-69.e9

- Zoeisha S. Chinoy, Clément Bodineau, CamiLLE Favre, Kelley W. Moremen, Raúl V. Durán, Frédéric Friscourt. Selective Engineering of Linkage Specific α2,6-N-Linked Sialoproteins using Sydnone-Modified Sialic Acid Bioorthogonal Reporters. **Angewandte Chemie International Edition.** 58(13):4281-4285

- Zucchetti AE, Bataille L, Carpier JM, Dogniaux S, San Roman-Jouve M, Maurin M, Stuck MW, Rios RM, Baldari CT, Pazour GJ, Hivroz C. Tethering of vesicles to the Golgi by GMAP210 controls LAT delivery to the immune synapse. **Nature Commun.** 10(1):2864

2020

- Alba G, Martínez R, Postigo-Corrales F, López S, Santa-María C, Jiménez J, Cahuana GM, Soria B, Bedoya FJ, Tejedo JR. AICAR Stimulates the Pluripotency Transcriptional Complex in Embryonic Stem Cells Mediated by PI3K, GSK3-beta, and beta-Catenin. **ACS Omega.** 5(32):20270-20282

- Alonso-de Vega I, Paz-Cabrera MC, Rother MB, Wiegant WW, Checa-Rodríguez C, Hernández-Fernaud JR, Huertas P, Freire R, van Attikum H, Smits VAJ. PHF2 regulates homology-directed DNA repair by controlling the resection of DNA double strand breaks. **Nucleic Acids Res.** 48(9):4915-4927

- Alonso-de Vega I, Paz-Cabrera MC, Rother MB, Wiegant WW, Checa-Rodríguez C, Hernández-Fernaud JR, Huertas P, Freire R, van Attikum H, Smits VAJ. PHF2 Regulates Homology-Directed DNA Repair by Controlling the Resection of DNA Double Strand Breaks. **Nucleic Acids Res.** 8(9):4915-4927

- Álvarez-Quilón A, Terrón-Bautista J, Delgado-Sainz I, Serrano-Benítez A, Romero-Granados R, Martínez-García PM, Jimeno-González S, Bernal-Lozano C, Quintero C, García-Quintanilla L, Cortés-Ledesma F. Endogenous topoisomerase II-mediated DNA breaks drive thymic cancer predisposition linked to ATM deficiency. **Nature Commun.** 11(1):910

- Baghi M, Rostamian Delavar M, Yadegari E, Peymani M, Pozo D, Hossein Nasr-Esfahani M, Ghaedi K. Modified level of miR-376a is associated with Parkinson's disease. **J Cell Mol Med.** 24(4):2622-2634

- Baratto-Roldán A, Jiménez-Ramos MDC, Jimeno S, Huertas P, García-López J, Gallardo MI, Cortés-Giraldo MA, Espino JM. Preparation of a radiobiology beam line at the 18 MeV proton cyclotron facility at CAN. **Phys Med.** 74:19-29

- Berná G, Romero-Gomez M. The role of nutrition in non-alcoholic fatty liver disease: Pathophysiology and management. **Liver Int** 40 Suppl 1:102-108

- Carmona R, Barrena S, López Gambero AJ, Rojas A, Muñoz-Chápuli R. Epicardial cell lineages and the origin of the coronary endothelium. **FASEB J.** 34(4):5223-5239

- Courtois S, Haykal M, Bodineau C, Sifré E, Azzi-Martin L, Ménard A, Mégraud F, Lehours P, Durán RV, Varon C, Bessède E. Autophagy induced by Helicobacter pylori infection is necessary for gastric cancer stem cell emergence. **Gastric Cancer.** 24(1):133-144

- Checa-Rodríguez C, Cepeda-García C, Ramón J, López-Saavedra A, Balestra FR, Domínguez-Sánchez MS, Gómez-Cabello D, Huertas P. Methylation of the central transcriptional regulator KLF4 by PRMT5 is required for DNA end resection and recombination. **DNA Repair (Amst).** 94:102902

- De Breuk A, Acar IE, Kersten E, Schijvenaars MMVAP, Colijn JM, Haer-Wigman L, Bakker B, de Jong S, Meester-Smoor MA, Verzijden T, Missotten TOAR, Monés J, Biarnés M, Pauleikhoff D, Hense HW, Silva R, Nunes S, Melo JB, Fauser S, Hoyng CB, Ueffing M, Coenen MJH, Klaver CCW, den Hollander AI; EYE-RISK Consortium. Development of a Genotype Assay for Age-Related Macular Degeneration: The EYE-RISK Consortium. **Ophthalmology.** S0161-6420(20)30725-9

- Esmaeili M, Keshani M, Vakilian M, Esmaeili M, Peymani M, Seyed Forootan F, Lan Chau T, Ismail Göktuna S, Rasoul Zaker S, Hossein Nasr Esfahani M, Ghaedi K. Role of Non-Coding RNAs as Novel Biomarkers for Detection of Colorectal Cancer Progression Through Interaction With the Cell Signaling Pathways. **GENE.** 44796. 753:144796

- Gauthier BR, Sola-García A, Cáliz-Molina MÁ, Lorenzo PI, Cobo-Vuilleumier N, Capilla-González V, Martin-Montalvo A. Thyroid hormones in diabetes, cancer, and aging. **Aging Cell.** 2020 Nov; 19(11):e13260

- Gómez-González B, Aguilera A. Looping the (R) Loop in DSB Repair via RNA Methylation. **Mol Cell.** 79(3):361-362

- Gómez-González B, Barroso S, Herrera-Moyano E, Aguilera A. Spontaneous DNA-RNA hybrids: differential impacts throughout the cell cycle. **Cell Cycle.** 19(5):525-531

- Gómez-González B, Ortega P, Aguilera A. Histone deacetylases facilitate the accurate repair of broken forks. **Mol Cel Oncology.** 7(2):1705731

- Gonzalez-Moro I, Olazagoitia-Garmendia A, Colli ML, Cobo-Vuilleumier N, Postler TS, Marselli L, Marchetti P, Ghosh S, Gauthier BR, Eizirik DL, Castellanos-Rubio A, Santin I. The T1D-associated lncRNA Lnc13 modulates human pancreatic ß cell inflammation by allele-specific stabilization of STAT1 mRNA. **Proc Natl Acad Sci USA.** 117(16):9022-9031

- Guerrero-Martínez JA, Ceballos-Chávez M, Koehler F, Peiró S, Reyes JC. TGFß Promotes Widespread Enhancer Chromatin Opening and Operates on Genome Regulatory Domains. **Nature Commun.** 11:6196

- Hmadcha A, Martin-Montalvo A, Gauthier BR, Soria B, Capilla-Gonzalez V. Therapeutic Potential of Mesenchymal Stem Cells for Cancer Therapy. **Front Bioeng Biotechnol.** 8:43

- Lafuente-Barquero J, García-Rubio ML, Martin-Alonso MS, Gómez-González B, Aguilera A. Harmful DNA:RNA hybrids are formed in cis and in a Rad51-independent manner. **Elife.** 9:e56674

- López-Beas J, Guadix JA, Clares B, Soriano-Ruiz JL, Zugaza JL, Gálvez-Martín P. An overview of international regulatory frameworks for mesenchymal stromal cell-based medicinal products: From laboratory to patient. **Med Res Rev.** 40(4):1315-1334

- Luna R, Rondón AG, Pérez-Calero C, Salas-Armenteros I, Aguilera A. The THO Complex as a Paradigm for the Prevention of Cotranscriptional R-Loops. **Cold Spring Harb Symp Quant Biol.** 84:105-114

- Mahmud MRA, Ishii K, Lozano CB, Sainz ID, Toi M, Akamatsu S, Fukumoto M, Watanabe M, Takeda S, Ledesma FC, Sasanuma H. TDP2 suppresses genomic instability induced by androgens in the epithelial cells of prostate glands. **Genes Cells.** 25(7):450-465

- Manzano-López J, Monje-Casas F. The Multiple Roles of the Cdc14 Phosphatase in Cell Cycle Control. **Int J Mol Sci.** 21(3). 709
- Manzano-López J, Monje-Casas F. Asymmetric cell division and replicative aging: a new perspective from the spindle poles. **Curr Genet.** 66(4):719-727
- Matellán L, Monje-Casas F. Regulation of Mitotic Exit by Cell Cycle Checkpoints: Lessons From *Saccharomyces cerevisiae*. **GENES.** 11(2). 195
- Matellán L, Manzano-López J, Monje-Casas F. 2020. Polo-like kinase acts as a molecular timer that safeguards the asymmetric fate of spindle microtubule-organizing centers. **Elife.** 9:e61488
- Mejías-Navarro F, Rodríguez-Real G, Ramón J, Camarillo R, Huertas P. ALC1/eIF4A1-mediated regulation of CtIP mRNA stability controls DNA end resection. **PLoS Genet.** 16(5):e1008787
- Moreno-Oñate M, Herrero-Ruiz AM, García-Dominguez M, Cortés-Ledesma F, Ruiz JF. RanBP2-Mediated SUMOylation Promotes Human DNA Polymerase Lambda Nuclear Localization and DNA Repair. **J Mol Biol.** 432(13):3965-3979
- Olivieri M, Cho T, Álvarez-Quilón A, Li K, Schellenberg MJ, Zimmermann M, Hustedt N, Rossi SE, Adam S, Melo H, Heijink AM, Sastre-Moreno G, Moatti N, Szilard RK, McEwan A, Ling AK, Serrano-Benitez A, Ubhi T, Feng S, Pawling J, Delgado-Sainz I, Ferguson MW, Dennis JW, Brown GW, Cortés-Ledesma F, Williams RS, Martin A, Xu D, Durocher D. A Genetic Map of the Response to DNA Damage in Human Cells. **CELL.** 182(2):481-496
- Ortega P, García-Pichardo D, San Martin-Alonso M, Rondón AG, Gómez-González B, Aguilera A. Histone H3E73Q and H4E53A mutations cause recombinogenic DNA damage. **Microb Cell.** 7(7):190-198
- Pardo, Benjamin; Moriel-Carretero, Maria; Vicat, Thibaud; Aguilera, Andres; Pasero, Philippe. Homologous recombination and Mus81 promote replication completion in response to replication fork blockage. **EMBO reports.** 21(7):e49367
- Peña-Gómez MJ, Rosado IV, Balestra FR, Huertas P, López-Cornejo P. Metallo-Liposomes of Ruthenium Used as Promising Vectors of Genetic Material. **Pharmaceutics.** 12(5):482

- Peñate X, Praena-Fernández JM, Romero Pareja P, Enguix-Riego MDV, Payán-Bravo L, Vieites B, Gomez-Izquierdo L, Jaen Olasolo J, Rivin Del Campo E, Reyes JC, Chávez S, Lopez Guerra JL. Overexpression of Canonical Prefoldin Associates with the Risk of Mortality and Metastasis in Non-Small Cell Lung Cancer. **Cancers (Basel).** 12(4). 1052
- Pérez-Calero C, Bayona-Feliu A, Xue X, Barroso SI, Muñoz S, González-Basallote VM, Sung P, Aguilera A. UAP56/DDX39B is a major cotranscriptional RNA-DNA helicase that unwinds harmful R loops genome-wide. **Genes Dev.** 34(13-14):898-912
- Ronald P. Wong, Néstor Garcıa-Rodríguez, Nicola Zilio, María Hanulová, Helle D. Ulrich. Processing of DNA Polymerase-Blocking Lesions during Genome replication in spatially and temporally segregated from replication forks. **Molecular Cell.** 77(1):3-16. e4
- Rincón AM, Monje-Casas F. A guiding torch at the poles: the multiple roles of spindle microtubule-organizing centers during cell division. **Cell Cycle.** 19(12):1405-1421
- Rodríguez-Seguel E, Villamayor L, Arroyo N, De Andrés MP, Real FX, Martín F, Cano DA, Rojas A. Loss of GATA4 causes ectopic pancreas in the stomach. **J Pathol.** 26(1):1
- Romero-Zerbo SY, García-Fernández M, Espinosa-Jiménez V, Pozo-Morales M, Escamilla-Sánchez A, Sánchez-Salido L, Lara E, Cobo-Vuilleumier N, Rafacho A, Olveira G, Rojo-Martínez G, Gauthier BR, González-Mariscal I, Bermúdez-Silva FJ. The Atypical Cannabinoid Abn-CBD Reduces Inflammation and Protects Liver, Pancreas, and Adipose Tissue in a Mouse Model of Prediabetes and Non-alcoholic Fatty Liver Disease. **Front Endocrinol (Lausanne).** 11:103
- Salto R, Girón MD, Manzano M, Martín MJ, Vílchez JD, Bueno-Vargas P, Cabrera E, Pérez-Alegre M, Andujar E, Rueda R, Lopez-Pedrosa JM. Programming Skeletal Muscle Metabolic Flexibility in Offspring of Male Rats in Response to Maternal Consumption of Slow Digesting Carbohydrates during Pregnancy. **Nutrients.** 12(2):528
- Schellenberg MJ, Appel CD, Riccio AA, Butler LR, Krahn JM, Liebermann JA, Cortés-Ledesma F, Williams RS. Ubiquitin stimulated reversal of topoisomerase 2 DNA-protein crosslinks by TDP2. **Nucleic Acids Res.** 48(11):6310-6325
- Serrano-Benítez A, Cortés-Ledesma F, Ruiz JF. An End to a Means: How DNA-End Structure Shapes the Double-Strand Break Repair Process. **Front Mol Biosci.** 6:153

- Smani T, Mayoral-Gonzalez I, Galeano-Otero I, Gallardo-Castillo I, Rosado JA, Ordoñez A, Hmadcha A. Non-coding RNAs and Ischemic Cardiovascular Diseases. **Adv Exp Med Biol.** 1229:259-271

- Soulet F, Bodineau C, Hooks KB, Descarpentrie J, Alves I, Dubreuil M, Mouchard A, Eugenie M, Hoepffner JL, López JJ, Rosado JA, Soubeyran I, Tomé M, Durán RV, Nikolski M, Villoutreix BO, Evrard S, Siegfried G, Khatib AM. ELA/APELA precursor cleaved by furin displays tumor suppressor function in renal cell carcinoma through mTORC1 activation. **JCI Insight.** 5(14):129070

- Vanhaeren T, Divina F, García-Torres M, Gómez-Vela F, Vanhoof W, Martínez-García PM. A Comparative Study of Supervised Machine Learning Algorithms for the Prediction of Long-Range Chromatin Interactions. **Genes (BASEL).** 11(9). pii: E985

- Vítor AC, Huertas P, Legube G, de Almeida SF. Studying DNA Double-Strand Break Repair: An Ever-Growing Toolbox¡. **Front Mol Biosci.** 7:24

- Vuilleumier NC, Gauthier BR. Time for a paradigm shift in treating type 1 diabetes mellitus: coupling inflammation to islet Regeneration. **Metabolism.** 104:154137

- Wagner T, Pérez-Martínez L, Schellhaas R, Barrientos-Moreno M, Öztürk M, Prado F, Butter F, Luke B. Chromatin modifiers and recombination factors promote a telomere fold-back structure, that is lost during replicative senescence. **Plos Genetics.** 16(12):e1008603

Book Chapters

2018

- García-Rubio, M., Barroso, S.I., Aguilera, A. Detection of DNA-RNA hybrids in vivo.2018. Methods in Molecular Biology

- Huertas, P., Cruz-García, A. Single molecule analysis of resection tracks. 2018. Methods in Molecular Biology

2019

- Benítez, T., Rincón, A.M., Codón, A.C. Yeasts associated with biological ageing of fortified wines.2019. Yeasts in the Production of Wine

- García-Rodríguez, N., Ulrich, H.D. A dual system to manipulate protein levels for DNA replication- and cell cycle-related studies.2019. Methods in Enzymology. 619:121-143

- Jimeno, S., Mejías-Navarro, F., Prados-Carvajal, R., Huertas, P.2019. Controlling the balance between chromosome break repair pathways. Advances in Protein Chemistry and Structural Biology

- Valdés-Sánchez, L., García-Delgado, A.B., Montero-Sánchez, A., (...), Bhattacharya, S.S., Díaz-Corrales, F.J.2019. The Resveratrol Prodrug JC19 Delays Retinal Degeneration in rd10 Mice. Advances in Experimental Medicine and Biology. pp 457-462

- Escacena-Acosta N, Lopez-Beas J, Claude Lachaud C, Vakilian M, Tejedo JR, Capilla-González V, Bedoya FJ, Martin F, Hmadcha A, Soria B. Stem Cells: Concept, Properties, and Characterization. Corneal Regeneration: Therapy and Surgery. Springer. pp. 41 - 55

2020

- Marente J, Ortega P, Pardo-Medina J, Avalos J, Limón MC. Modulation of Activity of a Carotenoid Pathway Through the Use of the TeT-on Regulatory System: Application in the Fungus Fusarium Fujikuroi. Methods Mol Biol. 343-360

- González-Prieto R, Cabello-Lobato MJ, Prado F. In Vivo Binding of Recombination Proteins to Non-DSB DNA Lesions and to Replication Forks. Methods Mol Biol. 2153:447-458

- Tumini E, Aguilera A. The Sister-Chromatid Exchange Assay in Human Cells. Methods Mol Biol. 2153:383-393

- García-Muse T. Detection of DSBs in C. elegans Meiosis. Methods Mol Biol. 2153:287-293

- Barroso SI, Aguilera A. Detection of DNA Double-Strand Breaks by $^{\gamma}$-H2AX Immunodetection. Methods Mol Biol. 2153:1-8

Patents

2018

- Roodveldt C, Leal-Lasarte María M, Muñoz Franco J, Pozo D. Agentes moduladores de MOK para el tratamiento de enfermedades con componente inflamatorio, enfermedades neurodegenerativas, enfermedades inflamatorias y cáncer.2018. PCT/ES2018/070216

- Soria B, Capilla-Gonzalez V, Hmadcha A, Lopez-Beas J, Aguilera Y. Mesenchymal stem cells for use in a method of treatment of radiation-induced brain injury. 2018. PCT/EP2018/074962

2019

- De la Cerda Haynes, B, Díaz Corrales FJ, García Delgado A, Díaz Cuenca A, Borrego González S. Matriz de composición definida útil para cultivo de células pluripotentes inducidas y epitelio pigmentario humanos. 2019. CABIMER-19001

- Diaz Corrales FJ, de la Cerda Haynes B, Borrego González S, Valdés Sánchez L, Montero Sánchez A, Díaz Cuenca A. Vectores no virales a partir de nanopartículas mesoporosas para su aplicación en terapia génica para el tratamiento de patologías degenerativas de la retina. CABIMER-19002. OTRI FPS: 04/02/2019

- Gauthier B, Lorenzo PI, Fuente-Martín E, Cobo-Vuilleumier N, Mellado-Gil JM, Bérmudez-Silva FJ, Rojo-Martinez G, Reyes JC. LSD1 Inhibitors for use in the treatment of type 2 Diabetes.2019. EP19382051.1

Doctoral Theses

2018

Francisco García Benítez
"Inestabilidad genética Asociada a R loops" Thesis Supervisors: Dr. Andrés Aguilera and Dr. Hélène Gaillard. Universidad de Sevilla.

Francisco de Asís Gallardo Chamizo
"Estudio del proceso de modificación postraduccional de proteínas por unión del polipéptido Sumo en condiciones simuladas de isquemia."Thesis Supervisors: Dr. Mario García. Universidad de Sevilla

Livia del Rocío Lopez Noriega
"Role of PAX8 and Thyroid hormones in metabolic homeostasis". Thesis Supervisors: Dr. Benoit Gauthier and Dr. Alejandro Martín-Montalvo. Universidad Pablo de Olavide.

2019

Irene Herrera Gómez
"Two Nobel Therapies for the Treatment of type 1 Diabetes mellitus". Thesis Supervisor: Dr. Benoit Gauthier. Universidad de Sevilla

Marta Mauro Lizcano
"Papel del Metabolismo de la glutamina en el control de la sensibilidad a TRAIL." Thesis Supervisor: Dr. Abelardo López. Universidad de Sevilla

María Magdalena Leal-Lasarte
"Novel Molecular Mechanisms and Signalling pathways of Microgrial responses in Amyotrophic lateral sclerosis (ALS)". Thesis Supervisors: Dr. Cintia Roodveldt and Dr. David Pozo. Universidad de Sevilla

Fernando Mejías
"Regulation of Resection by chromatin associated proteins". Thesis Supervisor: Dr. Pablo Huertas. Universidad de Sevilla

Marta San Martín
"New Cellular elements associated with DNA: RNA hybrid homeostasis in Eukaryotes". Thesis Supervisors: Dr. Andrés Aguilera and Dr. Tatiana García Muse. Universidad de Sevilla

Noelia Luna
"Función de las interacciones de las proteínas con bromodominios BRD2 y BRD4 con las proteínas Lyar y NIPBL". Thesis Supervisors: Dr. Mario García and Dr. Jose Carlos Reyes. Universidad de Sevilla

María Isabel Cano
"Regulación de las Rutas de tolerancia a daños replicativos dependientes de RAD6, RAD5 y RAD52 durante el ciclo celular de *Saccharomyces cerevisiae*". Thesis Supervisor: Dr. Félix Prado. Universidad de Sevilla

José Antonio Mérida Cerro
"New factors involved in transcription-associated genome instability". Thesis supervisors: Dr. Andrés Aguilera and Dr. Ana García Rondón. Universidad de Sevilla

Almudena Serrano Benítez
"Regulation of blocked-DSB repair by DNA-Pkes and ATM Kinases". Thesis supervisor: Dr. Felipe Cortés. Universidad de Sevilla

Laura Villamayor Coronado
"Papel de los factores GATA en la función de las células pancreáticas y en el mantenimiento de la identidad del epitelio gástrico" Thesis supervisor: Dr. Anabel Rojas. Universidad Pablo de Olavide

2020

Cintia Checa Rodríguez
"Regulation of DNA endresection by cell stemness". Thesis supervisor: Dr. Pablo Huertas. Universidad de Sevilla

Laura Matellán Fernández
"Estudio de Asimetrías Asociadas al huso mitótico de *saccharomyces cerevisiae*: nuevos regladores de posicionamiento del huso y a herencia no aleatoria de los centros organizadores de microtúbulos". Thesis supervisor: Dr. Fernando Monje. Universidad de Sevilla

María del Rosario Prados Carvajal
"Crosstalk between DNA endresection and RNA metabolism". Thesis Supervisor: Dr. Pablo Huertas. Universidad de Sevilla

Marta Barrientos Moreno
"Papel de la Reducción de Histonas en la protección de los telómeros durante la pre-senescencia". Thesis Supervisor: Dr. Félix Prado. Universidad de Sevilla

Carmen Pérez Calero
"Papel de la Helicasa UAP56/DDX39B y otros factores asociados al metabolismo del ARN en la integridad del Genoma. Thesis Supervisor: Dr. Andrés Aguilera. Universidad de Sevilla

Andrés Manuel Herrero Ruiz
"Regulación Transcripcional mediada por la DNA Topoisomerasa 2. Thesis supervisors: Dr. Felipe Cortés and Silvia Jimeno. Universidad de Sevilla

Pablo Gandolfo Domínguez
"Estudios de los mecanismos que coordinan la actividad de los centros organizadores de microtúbulos de las células animales". Thesis Supervisors: Dr. Rosa M Ríos and Dr. Mari Paz Gavilán. Universidad de Sevilla

Juan Carlos Martínez Cañas
"The influence of chromatin in DNA-RNA hybrid metabolism". Thesis supervisors: Dr. Andrés Aguilera and Dr. Belén Gómez González. Universidad de Sevilla

Seminar Speakers

2018

January 2018

"Role of Vavoncoproteins in cancer: from mice to humans and viceversa" January 19th. **Xosé J. Bustelo.** Centro de Investigación del Cáncer, CIC, Salamanca, Spain

"Chromatin architecture in development and disease" January 26th. Max Planck Institute for Molecular Biomedicine, Münster. Germany

February 2018

"The genetics and epigenetics of intellectual disability" February 2nd. **Ángel Blanco.** Instituto de Neurociencias, Alicante, Spain

"BRCA1 ensures genome integrity by eliminating estrogen-induced pathological topoisomerase II-DNA complexes". February 5th. **Hiroyuki Sasanuma.** Kyoto University, Japan

"RASSF tumor suppressors: from epigenetic inactivation to functional characterization". February 9th. Justus-Liebig-Universität, Giesen, Germany

"Reciprocal regulatory links between transcription and DNA repair". February 16th. **Sergio Fernandes de Almeida.** Instituto de Medicina Molecular, Universidade de Lisboa, Portugal

"The many roles of Elg1 in the maintenance of genome stability". February 19th. **Martín Kupiec.** Tel Aviv University, Israel

March 2018

"A histone variant links chromatin architecture and metabolism" March 9th. **Marcus Bushbeck.** Josep Carreras Leukaemia Research Institute, Barcelona, Spain

"Pathways regulating recombination during chromosome replication". March 16th. **Dana Branzei.** The FIRC Institute of Molecular Oncology, IFOM, Milán, Italy

"News on double strand DNA break processing and repair from yeast to man". March 23rd. **Achille Pellicioli.** University of Milan, Italy

April 2018

"Mitochondrial homeostasis importance for brain function". April 6th. **Vanessa Morais.** Instituto de Medicina Molecular, Lisboa, Portugal

"Pathway activity models as precision diagnostic and prognostic biomarker linked to cell function that uncover disease mechanism". April 13th. **Marco Muzi-Falconi.** University of Milan, Italy

"Cellular Therapy in ALS: experience after clinical trials in Spain" April 27th. **Salvador Martinez.** Instituto Neurociencias, Alicante, Spain

May 2018

"Dealing with DNA damage during replication" May 11th. **Helle Ulrich.** Institute of Molecular Biology, IBM, Mainz, Germany

"Identification of novel replication proteins mutated in patients with microcephalic dwarfism" May 18th. **Grant S. Stewart**. Institute of Cancer and Genomic Sciences, University of Birmingham, England, United Kingdom

"Deciphering tumor HSP70-exosomes as cancer dissemination markers: ExoDiag Clinical study". May 25th. **Carmen Garrido.** InstitutNational de la Santé et de la Recherche Médicale, INSERM, Univ. Bourgogne, Dijon, France

June 2018

"Is brain AMPK a realistic target against obesity?"June 1st. **Miguel López.** Universidad de Santiago de Compostela, Spain

"Endoplasmic reticulum stress: the Achilles heel of pancreatic beta cells" June 8th. **Miriam Cnop.** Universite Libre de Bruxelles, Belgium

"Autophagy as protective mechanism of pancreatic beta cells survival: The aggression of amylin" June 15th.**Manuel R. Benito de las Heras.** Universidad Complutense de Madrid, Spain

October 2018

"Eating corpses: microglial phagocytosis from neurodegeneration to neurogenesis" October 5th. **Amanda Sierra.** Vizcaya Achucarro Basque Center for Neuroscience Ikerbasque Foundation University of the Basque Country EHU/UPV

"Epigenetic mechanisms and bio-mechanical effectors controlling cell fate". October 19th. **Tiziana A.L. Brevini.** IMI (Milán)

"Sensing the matrix: transducing mechanical signals from integrins to the nucleus" October 26th. **Pere Roca-Cusachs.** Institute for Bioengineering of Catalonia (IBEC), Barcelona

"The sting of WASp is chromatin-deep: new mechanism of immunodeficiency and genomic instability in Wiskott-Aldrich syndrome" October 29th. **Vyas, Yatin M.** University of IOWA Health Care

2019

January 2019

"Tissue-specific and time-dependent mechanisms of metastasis" January 18th. **Roger Gomis.** Institute for Research in Biomedicine (IRB). Barcelona.

February 2019

"Regulation of TORC1 by Amino Acids: A central Role for Rag GTPases within the EGO Complex" February 1st. **Claudio de Virgilio.** Universität Freiburg, Freiburg, Switzerland

"Reference epigenomes and 3D genomes in normal and neoplastic B cells" February 6th. **José Ignacio Martí Subero.** Institut d'investigacions Biomèdiques August Pi i Sunyerand Universitat de Barcelona

"DNA replication stress and cancer" February 15th. **Thanos Halazonetis.** University of Geneva Department of Molecular Biology

"The enemies within-regions of the genome that are inherently difficult to replicate" February 15th. **Ian Hickson.** University of Copenhagen,Copenhagen, Denmark

"Zooming in on neurodegeneration: from protein aggregation to neuronal dysfunction" February 22nd. **Tiago F. Outeiro**. University of Göttingen, Göttingen, Germany

March 2019

"Implication of deregulated phase separation in neurodegenerative and neuromuscular diseases" March 1st. **Serena Carra.** Università degli Studi di Modena e Reggio Emilia, Modena, Italy

"Treatment and management of endocrine tumors: new mechanisms and targets" March 8th. **Raúl M. Luque.** Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)-Universidad de Córdoba, Córdoba, Spain

"Pervasive transcription, gene regulation and replication in yeast" March 15th. **Françoise Stutz.** University of Geneve, Geneve, Switzerland

April 2019

"Transcription-replication conflicts beyond R-loops" April 5th. Matthias Altmeyer. University of Zürich, Zürich, Switzerland

May 2019

June 2019

"Mechanisms of DNA repair in eukaryotic cells" June 7th. **Tanya Paull.** University of Texas at Austin, Texas, EEUU

"Mitochondrial DNA: In the Loop" June 14th. **Ian J. Holt.** Iberbasque Research Professor, Biodonostia Research Institute, San Sebastián, Spain

October 2019

"Illuminating the Molecular Functions of BRCA2" October 4th. **Ryan Jensen.** Dept. of Therapeutic Radiology Yale School of Medicine New Haven, CT, USA

"Signalling and metabolic alterations at the core of cancer biology" October 25th. **Arkaitz Carracedo**. CIC bioGUNE, Derio (Spain).

"Recombination and Genomic Instability" October 30th. **Wolf Heyer.** Dept. Microbiology & Molecular Genetics University of California Davis, CA, USA

November 2019

"Epithelial morphogenesis: a story based on real-life events" November 15th. **Luis María Escudero.** Universidad de Sevilla Instituto de Biomedicina de Sevilla Sevilla, Spain

December 2019

"Compatability between genes and enhancers in development and congenital disease" December 13th. **Álvaro Rada Iglesias**. IBBTEC (Santander, SPAIN) / University of Cologne (COLOGNE, Germany)

2020

January 2020

"Nanomedicines for the treatment of chronic inflammation". January 17th. **Pere Santamaría.** Snyder Institute for Chronic Diseases, Calgary (Canada); Institut D'Investigacions Biomediques August Pi i Sunyer, Barcelona (Spain)

"Transcriptional response to proteotoxic stress in mammalian cells" January 31st. **Ritwick Sawarkar.** University of Cambridge/ Medical Research Council (MRC), Cambridge, UK

February 2020

"Inheritance of the effects of exercise on the brain" February 7th. **José Luis Trejo.** Department of Translational Neuroscience, Cajal Institute, CSIC. Madrid (Spain)

"Dysfunctional microglia in the pathogenesis of neurodegeneration" February 14th. **Rosa C. Paolicelli.** Department of Physiology. University of Lausanne (Switzerland)

March 2020

"Control of chromosome structure and function during meiosis" March 6th. **Enrique Martinez Pérez.** MRC London Institute of Medical Sciences, London (UK)

December 2020

"The Eukaryotic Replisome: Structure and Mechanism" December 4th. **Joseph Yeeles.** Protein & Nucleic Acid Chemistry Division. MRC Laboratory of Molecular Biology, Cambridge (UK)

Workshops, Retreats & Seminars

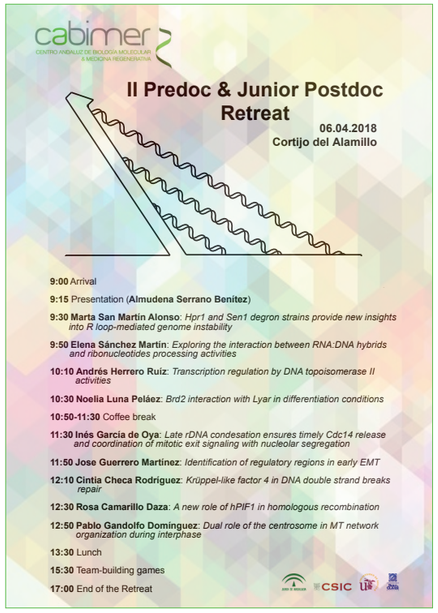
International Workshops

Institutional Visits

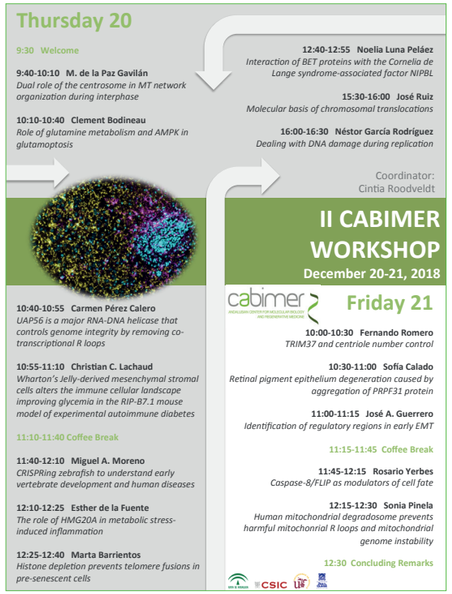
Visit from the Andalusian Minister of Economy, Industry, Research and Universities, Rogelio Velasco and Meeting with all the Directors of the Andalusian CSIC Research Institutes. March 2019

Visit of the President of CSIC, Rosa Menéndez. April 2019

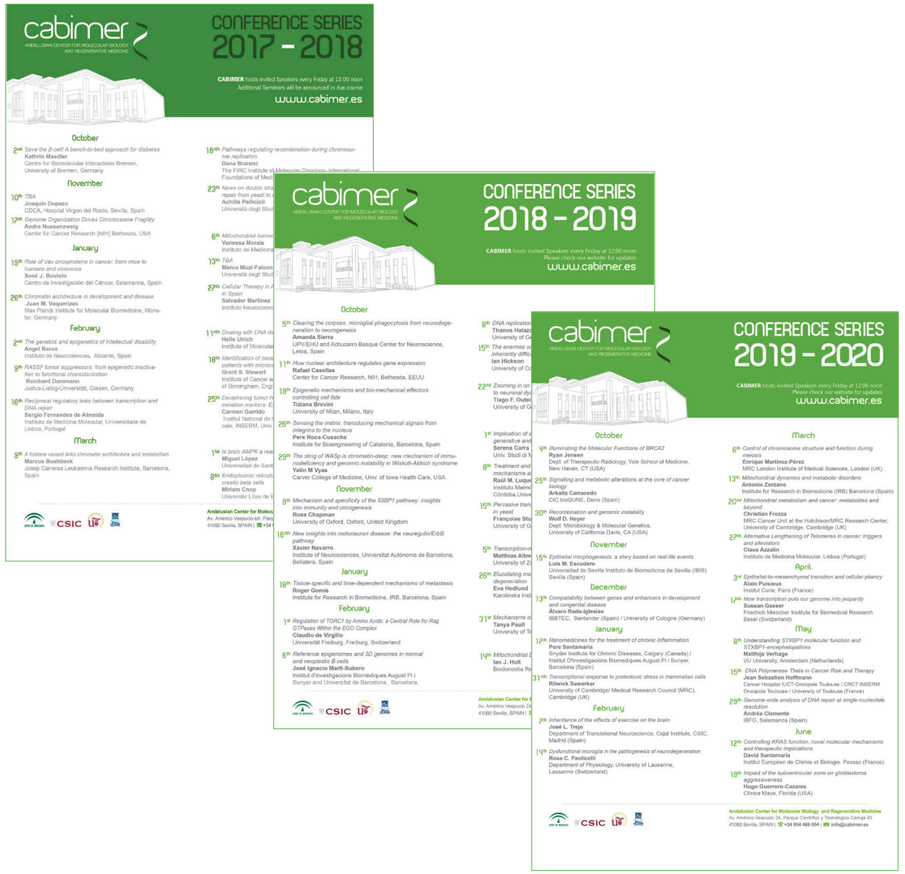
Predoc and Postdoc Retreats



Internal Workshops



Conference Series



Scientific Advisory Board

Dr. Pier Paolo Di Fiore
IFOM- FIRC Institute of Molecular Oncology. Milan (Italy)

Dr. Susan M. Gasser
Friedrich Miescher Institute for Biomedical Research. Basel (Switzerland)

Dr. Simon Boulton
The Francis Crick Institute.
London (UK)

Dr. Jose Manuel García Verdugo (ended 2019)
University of Valencia (Spain)

Dr. Manuel Serrano
Institute for Research in Biomedicine (IRB), Barcelona, Spain

Dr. Juan Valcárcel
ICREA Research Professor at the Centre de Regulació Genòmica-CRG Barcelona (Spain)

Dr. Vivek Malhotra
Centre de Regulació Genòmica-CRG Barcelona (Spain)

Dr. Purificación Muñoz
ICREA and Pompeu Fabra University (UPF) Barcelona (Spain)

Dr. Ramón Gomis
The August Pi i Sunyer Biomedical Research Institute (IDIBAPS). Barcelona (Spain)

Dr. Jiri Lukas (ended 2020)
Novo Nordisk Foundation Center for Protein Research. University of Copenhagen (Denmark)

Where we are

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Longitude: -6.0066 or 6° 0'3960 W


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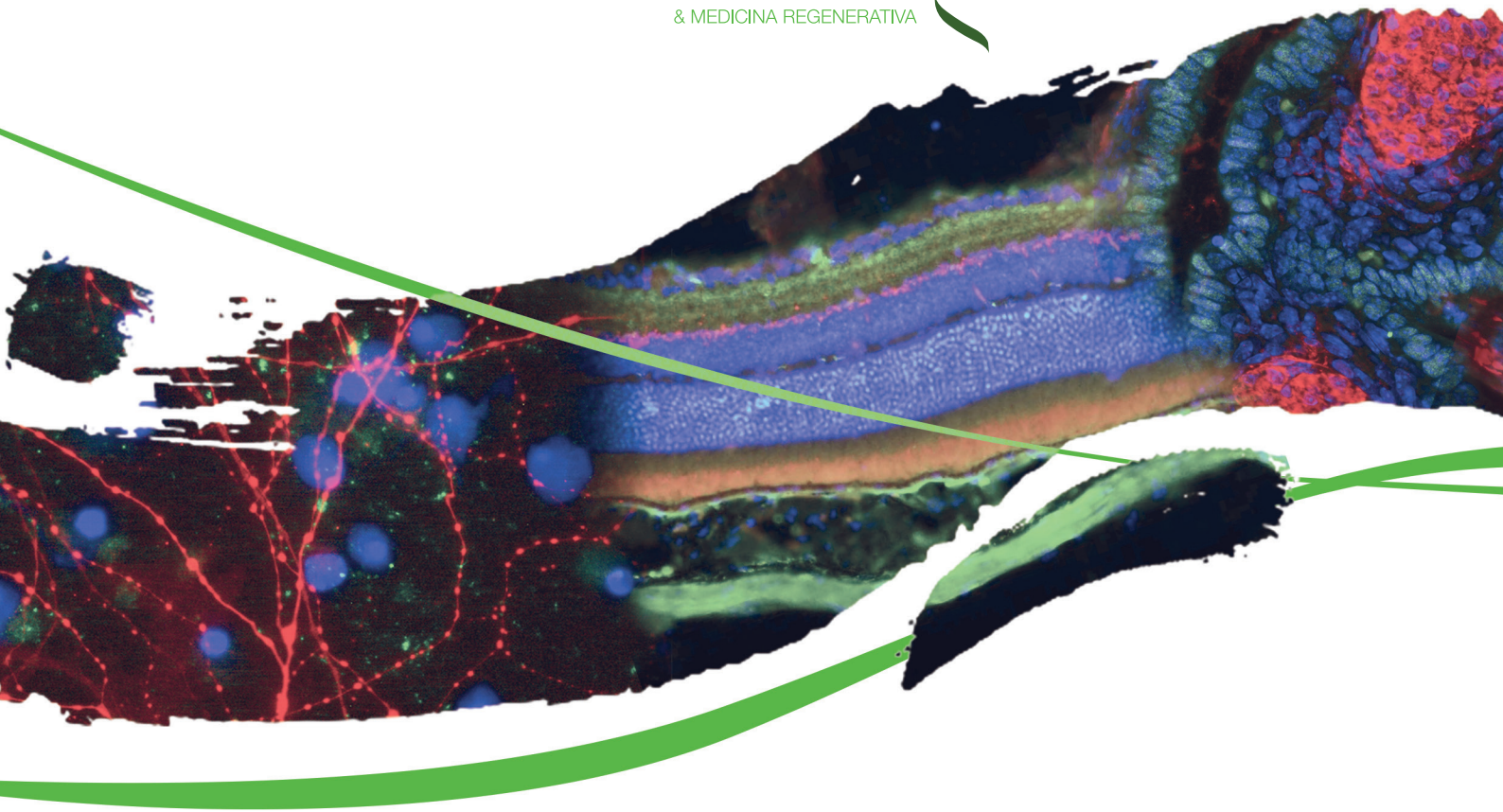

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