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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 2021 to 2022. 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 and technicians of 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 2-year period there has been an important improvement of CABIMER activities and facilities to support the science undertaken by the 28 actual Principal Investigators (PIs), including 7 new emerging PIs, and their group members. In 2022, CABIMER has partially renovated the Scientific Advisory Board formed by prestigious international 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 2 years are the success of CABIMER researchers in obtaining funding from competitive calls from national and international agencies, such as the Caixa Research Foundation or the Juvenile Diabetes Research Foundation, as well as 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 12 PhD theses during this 2-year period and more than 119 publications, among other achievements. It is worth highlighting the celebration of the Second CABIMER International Workshop in February 2020 on “Trends in Cancer Biology and Advanced Therapies” 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. This represents an important achievement towards regularizing a scientific activity that not only stimulates collaborative science but helps place CABIMER in the international map of high standard research centers in Molecular Biology and Biomedicine. As a result of its scientific achievements in the last years, CABIMER has been distinguished as a Center of Excellence of Andalusia under the program QUALIFICA with a 689,000€ grant from the Andalusian Ministry of University, Research and Innovation.

In the 2021-22 period CABIMER has updated the 9 fully-functional core services with technologies including the state of the art Biological Research Unit with a special service for the generation of genetically modified mice, the Genomic platform for the use of external and internal services, the advanced Imaging unit as well as Histology and Model organisms service to support the different research activities of the Center using the most modern and high-tech molecular and cellular technologies in addition to genome-wide studies. A strong investment in image analysis and next-generation sequencing has strongly expanded our technical capabilities but also that of many external laboratories all over Andalusia and beyond to which we provide high-standard NGS services.

CABIMER is successfully increasing its reputation as an International Research Center and a major center of biomedical research in Spain. To accomplish these goals and improve its capabilities in the next future CABIMER has a new Strategic Plan for the next 4 years (2023-2026) 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 PIs 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. We still have a long way to go and many objectives to accomplish, many of which pass through the ampliation of the lab space in the center to be able to incorporate new groups and technologies that allow us to work on the most actual problems in modern Biology and Biomedicine, and many new exciting discoveries lie ahead of us. I hope the information summarized in our Scientific Report conveys this ambition.
The department of Genome Biology is dedicated to studying the processes involved in the expression and homeostasis of the genome, and how the alteration of these processes causes diseases. CABIMER’s research covers various aspects of genome dynamics, including genome instability, DNA recombination, replication and repair, DNA damage response, chromatin integrity, epigenetics, and gene expression, with a special focus on genomics and epigenomics approaches analyzed using computational biology tools. Genomic instability is the cause of numerous congenital syndromes, rare diseases, as well as somatic diseases, especially cancer and aging. Therefore, an important part of our research interests is devoted to understanding how different aspects of genome metabolism are coordinated to avoid genomic instability, as well as the mechanisms and factors involved in genome protection. Other groups study the transcriptional and epigenetic regulation during cell differentiation, tissue plasticity, and cell signaling, and how alterations in these processes cause diseases. The department exhibits great thematic coherence, which enhances opportunities for collaboration among groups as they frequently utilize similar techniques, equipment, and molecular tools. Moreover, the extensive interrelationships between nuclear processes make it convenient to integrate various perspectives for a molecular understanding of the mechanisms of genome dynamics, which also increases cooperation between groups. Eleven groups are included in this area.

HEAD OF DEPARTMENT
Dr. José C. Reyes

RESEARCH GROUPS
1. Genome Instability & Cancer
   Prof. Andrés Aguilera
2. Epigenetics and Gene Expression
   Dr. José C. Reyes
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
10. Replication and Endogenous DNA Damage
    Dr. Iván V. Rosado
11. Chromatin Modifications
    Dr. G. Millán-Zambrano
mesenchymal properties. This process occurs during embryonic development, tissue remodeling, wound healing, and it is the origin of cancer metastasis. During EMT, the epithelial cells lose their cell-cell junctions and become more motile. They also undergo changes in their cytoskeleton and extracellular matrix, which allow them to move through tissues and invade other areas of the body. EMT is a consequence of an intense transcriptomic and epigenomic reorganization that we have been studying during the last years.

Research Highlights

The main highlights for the period 2021-2022 are:

1.- RNA and protein factors involved in EMT.

In collaboration with different groups we have investigated the role of several protein and RNA factors in EMT. In collaboration with the group of José A. Pintor-Toro (CABIMER, Sevilla) we have shown that a long non coding RNA called lnc-Nr6a1 acts as a reservoir of miR-181 (a miRNA involved in EMT) and mediates assembly of a glycolytic complex (Polo-Generelo et al., Noncoding RNA 2022).

In collaboration with Mario García-Domínguez (CABIMER, Sevilla) we showed that SENP7 overexpression protects cancer cells from oxygen and glucose deprivation and associates with poor prognosis in colon cancer (Gallardo-Chamizo et al., Genes & Diseases 2022).

Finally, in collaboration with S. Chavez (IBIS, Sevilla) we have contributed to demonstrate that Prefoldin complex, another factor that has been also involved in EMT, modulates co-transcriptional pre-mRNA splicing (Payán-Bravo et al., Nucleic Acid Research 2021).

2.- Co-transcriptional splicing efficiency is a gene-specific characteristic.

It is well-known that alternative splicing dramatically increases protein diversity. Now we have investigated whether splicing...
efficiency of introns within the same gene is coordinated and eventually regulated as a mechanism to control mature mRNA levels. We have shown that co-transcriptional splicing (CTS) tends to be similar between the different introns of a gene. We have established that there are two strategies for CTS efficiency at the extremes of a gradient: short genes that produce high levels of pre-mRNA undergo inefficient splicing, while long genes with relatively low levels of pre-mRNA have an efficient splicing. We found that genes with efficient CTS displayed a relatively higher level of mature mRNA. TGFβ is the best known inductor of EMT. We showed that TGFβ regulates the general CTS efficiency, causing changes in mature mRNA levels (Sánchez-Escabias et al., Communications Biology 2022).

3.- Roles of HMG20A and PHF14 in EMT and disease. HMG20A is a high mobility group protein that binds structured DNA without sequence specificity. Previously, we demonstrated that HMG20A regulates the LSD1/CoREST histone demethylase complex and is crucial for neuronal differentiation (Ceballos-Chávez et al., PNAS 2012). In collaboration with Dr. Gauthier (CABIMER, Seville), we have now discovered that HMG20A is also expressed in astrocytes and plays a crucial role in their function. Silencing HMG20A resulted in the repression of inflammatory, cholesterol biogenesis, and epithelial-to-mesenchymal transition pathways, which are hallmarks of reactive astrogliosis (Lorenzo et al., Theranostics 2021). Furthermore, we have found that HMG20A interacts with the histone reader PHF14 through the formation of a two-stranded alpha-helical coiled-coil structure (Figure 1). We have also shown that PHF14 and HMG20A collaborate in regulating several pathways involved in epithelial-mesenchymal plasticity, including the Hippo and TGFβ signal transduction pathways (Gómez-Marín et al., Nuclearic Acid Research 2022). We have also shown that TGFβ upregulated lnc-Nr6a1 acts as a reservoir of miR-181 and mediates assembly of a glycogenic complex. Noncoding RNA. 8(5):62.


Current position

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

Group Members

Senior Researchers
- Rosa Luna (Assoc. Prof., US).

Postdocs
- Emilia Herrera-Moyano.
- M. Angeles Ortiz-Bazán.
- Sara Priego.
- Nibal Badra-Fajardo.

PhD Students
- M. Eugenia Soler-Oliva.
- Javier Marquetu-Gracia.
- Iván Núñez-Martín.
- Mar Bustamante-Sequeiros.
- Pablo Maraver-Cárdenas.
- Cristina Acero-Rubio.

Technicians
- Pablo Cano Jiménez.

Former Members (2021-2022)

Postdocs: Aleix Bayona-Feliu, Sonia P. Silva, José A. Mérida-Cerro.
- PhD students: Pedro Ortega, Cristina Guillén-Mendoza.
- Master students: Sandra Trujillo Sierra.
- Visiting Scientists: Prof. J. Lucas Argueso (Colorado State Univ, Fort Collins, CO, USA); Dr. Patrick Toolan-Kerr (Francis Crick Institute, London, UK); Dr. Giovana S. Leandro (Univ. Sao Paulo, Brazil); Renée Concetta-Durado (Erasmus+).
- BSc students: Marina Bejarano Franco.
- Administration: Zoé Cooper.

Research Activity

Overview
The key role of genome instability in tumorigenesis and a number of rare cancer-prone genetic diseases 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-loops. Our 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 replication fork stalling and DNA breaks;
3. to understand how a replication-born DNA break is repaired to allow replication restart and prevent chromosome aberrations and genome instability;

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

We have shown three different modes of resolving R-loops: i) by protecting the RNA by assembly; ii) by transiently closing chromatin by histone deacetylation, and iii) by removing occasional R loops co-transcriptionally. R-loops have different origins along the cell cycle with specific factors controlling their formation or resolution in nuclei and mitochondria. We have shown using Saccharomyces as a model system that whereas...
the THO complex protects cells from harmful R-loops in the G1 phase of the cell cycle, consistent with its transcriptional role, the Senataxin ortholog Sen1 only protects from R-loops during the S/G2 period, in line with a role related to the DNA damage response (San Martin-Alonso et al., Nat Commun 2021). The study has opened new perspectives on R-loops having different origins and different factors for its regulation. We have uncovered that histone acetylation by yeast Rtt109 counteracts R-loops (Cañas et al, Genetics 2022). In addition, we have shown that the human nucleoporin Tpr protects cells from RNA-mediated replication stress and R-loops in a collaborative effort that provides new clues about the link between the nuclear pore complex and genome integrity (Kossar et al, Nat Commun 2021). Finally, we have collaborated in the characterization and analysis of the involvement of new factors involved in R-loop-mediated genome integrity, such as MutSß (Sakelariou et al, Cell Rep 2022), β-catenine (Dagg et al, Nat Commun 2021), ß-catenine (Dagg et al, Nat Commun 2021), and ADAR (Jimeno et al, Nat Commun 2021) in human cells. Also, we have shown that TREX2 protects from R-loops in C. elegans (Zheleva et al, J Cell Sci 2021) and collaborated on the study of the histone deacetylase inhibitor Romidepsin as a regulator of R-loop-mediated DNA breaks (Mol Cancer Res. 2021).

2. Transcription-replication conflicts and R-loop formation.

We have shown that DNA-RNA hybrids cause transcription-replication collisions rather than being a consequence. In human cells, we have shown that hybrids can be originated before or after DNA replication. In contrast to other reports, we have demonstrated that R-loops occur in cis and independently of Rad51 and are an obstacle to DSB repair. We demonstrated a role for chromatin remodeling and modification (SWI/SNF) in resolution of transcription-replication conflicts mediated by R-loops. SWI/SNF is indeed enriched at chromatin sites where R-loops are increased genome-wide in its absence, such R-loops causing transcription-replication collisions mainly at the head-on orientation (Figure 1) (Bayona-Feliu et al, Nat Genet 2021). Related to replication stress caused by other factors we have collaborated in the analysis of WASp (Han et al, Nat Commun 2022) and a chromatin segregase (Chacin et al, Nat Commun 2021) as new players in genome integrity and replication.

3. Repair of replication-borne DNA breaks.

Replication-borne DSBs are preferentially repaired with the sister chromatid, a reaction that we can infer from the number of sister chromatid exchanges in metaphase spreads of cultured human cells (Figure 2). With newly constructed tools we have shown that DNA-RNA hybrids accumulate at DSBs by live cell microscopy in human cells (Figure 3). We have observed in yeast that these hybrids have a negative role in DNA repair in addition to provide data indicating that Rad51 is not necessary for their formation, which adds a new view on the biological meaning of unscheduled hybrids formed at DSBs (Ortega et al, eLife 2021). Finally, in human cells in a collaborative effort, we have found that DDX5 is a DNA-RNA unwinding factor involved in the resolution of DNA-RNA hybrids formed at DSBs. DDX5 works with BRCA2 as a way to remove hybrids that interfere with the repair, providing thus additional evidence that DNA-
RNA hybrids constitute an obstacle to DSB repair and we have found a BRCA2 cancer variant that impairs this interaction providing a possible cause for its role in tumorigenesis (Sessa et al, EMBO J 2021).

In addition to those highlights and others, we have edited 3 books of the Methods Mol Biol series (R-loops and DNA recombination), and contributed with specific chapters.

**Grants**
(PI is the group leader unless otherwise specified).

- 2021-2023: P18-FR-655 (PAIDI) Junta de Andalucía (co-PI: Rondón).
- 2022-2023: FIUS (Foundation Investigation Univ Seville-FIUS).
- 2022-2025: Caixa Research Foundation.
- Since 2013: VEC001/2014 FVEC-FPS. “Vencer el Cáncer” Foundation.

**Publication Highlights**
(Corresponding author(s) indicated by *)


**Grants**
(PI is the group leader unless otherwise specified).

- 2021-2023: P18-FR-655 (PAIDI) Junta de Andalucía (co-PI: Rondón).
- 2022-2023: FIUS (Foundation Investigation Univ Seville-FIUS).
- 2022-2025: Caixa Research Foundation.
- Since 2013: VEC001/2014 FVEC-FPS. “Vencer el Cáncer” Foundation.

**Publication Highlights**
(Corresponding author(s) indicated by *)


Overview
Cells have to duplicate their genomes in a faithful and timely way to ensure the correct transmission of genetic information to the daughter cells. This implies replication of DNA and assembly into chromatin, two processes that can be challenged by multiple stress conditions that cause loss of DNA integrity and alterations in the pattern of nucleosome-associated epigenetic marks, which are linked to genetic disorders and cancer. Genome duplication is not an easy task, taking into account the number of physical, chemical and genetic agents that can perturb the advance of replication forks. The fate of stressed replication forks can be stalling or breakage, which will trigger common and specific responses. Our main goal is to get a deeper insight into the mechanisms that deal with stressed replication forks and the relevance that chromatin assembly plays in these processes.

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. 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.

The recombination proteins Rad51 and Rad52 physically interacts with the MCM helicase from yeast to human cells. We have shown in Saccharomyces cerevisiae that these interactions occur in a nuclease-insoluble scaffold enriched in replication/repair factors. Rad51 accumulates in a MCM- and DNA binding-independent manner and interacts with MCM helicases located outside of replication origins and forks. MCM, Rad51 and Rad52 accumulate in this scaffold in
G1 and are released during S phase. In the presence of replication-blocking lesions, DNA replication fork progression is disrupted, and the cells enter a non-recombinogenic state. The MCM complex interacts in yeast with the HR factors Rad51 and Rad52 in a DNA damage and cell cycle-dependent manner. These interactions, which occur at a nucleosome-protected nucleoprotein scaffold enriched in DNA replication and repair factors, facilitate replication fork progression and ssDNA filling during DDT. DDK maintains these interactions during S phase under conditions of replication stress by preventing the release of these HR factors from the scaffold. DDK might perform this function by controlling either the integrity of the nucleoprotein scaffold by acting upon MCM or the binding of the HR factors to this compartment.

excess of parental nucleosomes at the invaded strand that destabilizes the sister chromatid junction formed after strand invasion through a Srs2-dependent mechanism. In addition, we have shown that a dCas9/R-loop is more recombinogenic when the dCas9/DNA-RNA hybrid interferes with the lagging than with the leading strand, and this recombination is particularly sensitive to problems in the deposition of parental histones at the strand that contains the hirandine. Therefore, parental histone distribution and location of the replication obstacle at the lagging or leading strand regulate HR.

Grants (2021-2022)

Publication Highlights
Overview
The correct metabolism of micronutrients, such as manganese (Mn) and iron (Fe), is essential for life. A main role of these transition metals consists in the activation of enzymatic activities. However, they also promote the formation of reactive oxygen species (ROS), thereby damaging lipids, proteins or nucleic acids. Moreover, Mn and Fe have a pivotal role in autophagy, stress signaling as well as in DNA dependent processes such as transcription, DNA transposition, replication and repair. Our research aims at understanding why and how micronutrients are connected to human disease. A further objective is to take advantage of micronutrients as therapeutic tools to alleviate human disease and aging.

Research Highlights
Role of biometals in metabolic regulation
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.

Model for manganese-driven TORC1 activation.
and that cytosolic excess of manganese predisposes to genomic instability and bypasses the need for S-phase cell cycle checkpoints.

Follow up research based on our previous work on the impact of manganese on genome stability, during 2020 to 2022 the lab published original and collaborative work with groups from Spain and Switzerland. Interestingly, manganese excess was previously 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 Mn serves as a metal-cofactor able to stimulate TORC1 kinase activity in vivo and in vitro.

We could show that Mn homeostasis is highly regulated and modulates key cellular processes such as autophagy, mitophagy, and mitochondrial retrograde response activation. Furthermore, by complementation assays, we also could show that NRAMP transporters are highly conserved from yeast to mice, and that Mn is a physiologically relevant TORC1 activator in yeast and human cells.

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. But even more importantly, our findings pinpoint to the molecular mechanisms underlying Mn-driven neuropathies in human.

**Cellular Mn-stress response network**

Each kind of stress requires an adequate response to optimize cell survival. How stress signalling networks manage to crosstalk with each other is not well understood, but mechanistic evidence has been provided on how oxidative stress inhibits pheromone signalling. Further characterization of stress signalling events in yeast revealed that Mn increases intracellular ROS levels. The corresponding signalling signature includes activation of stress activated MAP kinases (SAPKs) and the oxidative stress transcription factor Yap1. A yet unanswered question is how stress signalling is channelled into the MAPK Slt2 in the absence of Yap1. In addition to the hitherto unknown role of Yap1 in manganese tolerance, we find that manganese induces a rapid reduction of Yap1 protein levels. However, the molecular bases of Mn-driven Yap1 decay remains to be explored in detail. Further exploration of these findings will open new perspectives for the understanding of neurodegenerative disorders and aging-related processes.

**Grants (starting or ending 2021-2022)**

- **Enfoque fosfoproteómico hacia la comprensión y el tratamiento de una enfermedad rara; P2020_01220_PAIDI**
  I+D+i: Junta de Andalucía-European Union
- **COST action CA21115; Iron-sulphur (FeS) clusters: from chemistry to immunology (FeSImmChemNet): European Union**

**Publication Highlights**


http://canalciencia.us.es/por-que-tienen-los-humos-de-manganeso-un-efecto-tan-perjudicial-para-la-salud/


Current position
- Research Scientist CABIMER.
- Associate Professor of the University of Seville.

Positions Held
- 2004-2010: The Gurdon Institute for Cancer Research and Developmental Biology, University of Cambridge, UK.
- 2010-2015: Ramón y Cajal, University of Seville/ CABIMER.
- 2015-2016: Profesor Contratado Doctor, University of Seville/CABIMER.

Group Members
Senior Researcher
- Sonia Jimeno.
- Fernando Romero Balestra.

Postdocs
- Néstor García Rodríguez.
- Rosario Prados Carvajal.

PhD Students
- Rosa Camarillo Daza.
- Andrés Domínguez Calvo.
- Andrea Moo Bajo.
- Amador Romero Franco.
- Guillermo Rodríguez Real.
- Maria del Carmen Domínguez Pérez.

Research Activity
Overview
Double strand breaks (DSBs) repair is essential for cellular and organismal survival and fitness. While the complete inability to repair DSBs leads to embryonic lethality and cell death, mutations that hamper it causes the appearance of cancer or several genetically inherited syndromes. DSBs are repaired by two major mechanisms. The ends can be simple re-joined with little or no processing (non-homologous end-joining) or can be processed and engaged in a more complex repair pathway (homologous recombination). The balance between both pathways is exquisitely controlled and its alteration leads to the appearance of chromosomal abnormalities and contribute to the diseases aforementioned. Despite its importance, the network controlling the choice between both is poorly understood. In my laboratory, we pursue several research lines designed to investigate how such choice between is made, its relevance for survival and disease, and its potential as a therapeutic target for cancer or some genetically inherited disorders.

Research Highlights
The 2021-2022 period has represented the consolidation of the lab in the international arena, with many publications and international collaboration in high tier journals. We have cemented our position as a referent in the field at national and international level. Regarding our research, keeping the focus on the regulation of the balance between non-homologous end-joining and homologous...
recombination, we have uncovered regulatory cues that expand from the most local issues, for example the presence of non-canonical structures at the DNA such as G4s quadruplexes or R-loops, to global signals such as the cell identity. We have made unexpected links with the metabolism of the RNA, uncover new factors involved in this regulation, and established connection with the genetically inherited Aicardi-Goutieres Syndrome that we propose can be explored for the search of therapeutics interventions.

Grants (starting or ending 2020-2022)


Publication Highlights


Current position

- Group Leader at CABIMER ("Científico Titular del CSIC").

Academic Background of PI

- 2004: Degree, University of Murcia, B.Sc. in Biochemistry.
- 2008: Degree, University of Murcia, B.Sc. in Medicine.
- 2008: PhD, University of Murcia, Ph.D. Thesis in Molecular and Cellular Biology.

Positions Held

- 2004 – 2008: PhD Student, Department of Biochemistry and Molecular Biology, University of Murcia, Spain.
- 2004 – 2008: PhD Student, Department of Biochemistry and Molecular Biology, University of Murcia, Spain.
- 2004 – 2008: PhD Student, Department of Biochemistry and Molecular Biology, University of Murcia, Spain.
- 2004 – 2008: PhD Student, Department of Biochemistry and Molecular Biology, University of Murcia, Spain.
- 2004 – 2008: PhD Student, Department of Biochemistry and Molecular Biology, University of Murcia, Spain.
- 2004 – 2008: PhD Student, Department of Biochemistry and Molecular Biology, University of Murcia, Spain.

Group Members

Postdocs

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

Research assistant

- María José Morillo Chincoa (Contrato de Garantía Juvenil Junta de Andalucía).

PhD students

- Alba Guillén Benítez.
- Elena Pietrini.

Master Student

- Manuel Luque Pérez.

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 to identify 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 in the study of the biology of Common Fragile Sites, which are conserved chromosomal regions with a high propensity to break in conditions of replication stress, and which are therefore frequently altered in cancer.

Research Highlights

Our group was established at the end of 2014 at the University of Copenhagen, Denmark, and moved to CABIMER/CSIC in July 2020. In the past years, we have contributed to the understanding of the effects of replication stress on aging, embryonic stem cell fate potential, and ovarian aging (Albers E et al., Aging 2020, Atashpaz S et al., eLife 2020; Ruth et al., Nature, 2021). 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 model, identifying the DNA translocase PICH as an essential factor for embryonic development (Albers E et al., Cell Reports 2018) and a potential therapeutic target for cancer (Castejón-Griñán et al., in preparation). We are particularly interested in understanding the biology of the unstable genomic regions CFS and their contribution to cancer. We have generated the first CFS proteome, identifying among other factors the tumor suppressor ATRX to be essential to maintain CFS stability (Pladevall-Morera et al., Nucleic Acid Research 2018). We have recently developed a drug screen searching for compounds synthetic lethal with ATRX mutations (see figure below), frequently found in glioblastoma and other cancers. In this screen, we have identified RTK and specific PDGFR inhibitors (Pladevall-Morera et al., Cancers 2021) and other molecules that we are currently characterizing. We have also identified SLX4IP as a regulator of CFS stability (Ingham et al., in preparation). Finally, we have generated the first mouse model with a deletion of a whole CFS that will be used to investigate the impact of FRA3B/FHIT loss in cancer and investigate whether FHIT deficiency can be exploited as a therapeutic opportunity.
Publication Highlights


Grants
- 2016-2022: ERC-2015-STG-679068, ERC Starting Grant
- 2021-2023: PY20-00755, Junta de Andalucía
- 2021-2024: PID2020-119329RB-I00, Ministerio de Ciencia e Innovación
- 2022-2026: Horizon-MSCA-2021-101072903, MSCA ITN network

FDA-approved drug screen identifies compounds synthetically lethal with ATRX deficiency. A) Immunoblotting of HeLa clones generated by CRISPR. B) Drug screen flowchart. C) Primary drug screen. Cellular viability (WT/KO) after 48h of drug treatment. Each point represents one drug. Red dots indicate drugs with a 2-fold higher lethality effect in the ATRX KO clones compared to WT clones. Green dots indicate compounds that induce higher toxicity in ATRX WT clones compared to ATRX KO clones. D) Secondary drug screen. Cellular viability (WT/KO) after 48h of drug treatment of the 29 top hits derived from the primary screen.
Research Activity

Overview
Genomic DNA is exposed to both endogenous and exogenous DNA damaging agents. Without proper repair the resulting DNA damages would lead to 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.

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 phosphorylated in response to IR during meiosis, we performed a peptide array screening. We probed with C. elegans extracts, prepared before or after DNA damage, and radio labelled ATP on peptide arrays we identified all in vitro putative phosphorylation sites (Figure 1).

We 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. The analysis of phosphomutants revealed how the phosphorylation of the synaptonemal complex bias the repair of persistent DSBs towards inter-sister recombination (Figure 2). Importantly this work validated our peptide array screening (Garcia-Muse et al., 2019). We are characterizing the role of ATM/ATR-dependent phosphorylation of several proteins candidates from the peptide array. The analysis of some non-phosphorylable alleles has shown defects in DNA repair after IR, and we want to uncover the specific repair pathway involved. To further understand direct checkpoint regulation after DNA damage we are generating ATR/ATM versions that can be removed from the worm, especially at the germline, in a temporally controlled manner by introducing the TEV and/or AID epitopes.
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.
Current position
• Since 2021, Assistant Professor, University of Seville, Andalusian Centre for Molecular Biology and Regenerative Medicine, Seville, Spain.

Academic Background of the Emerging PI
• 2001: Degree. University of Seville Biology.
• 2007: PhD. University of Seville, Doctor in Biology.

Positions Held
• 2007-2011: Postdoctoral Fellow, Molecular Biology Department, Aarhus University, Aarhus, Denmark.
• 2011-2014: Postdoctoral Fellow (Juan de la Cierva Researcher), CSIC, Andalusian Centre for Molecular Biology and Regenerative Medicine, Seville, Spain.
• 2015-2016: Postdoctoral Fellow, University of Seville, Andalusian Centre for Molecular Biology and Regenerative Medicine, Seville, Spain.
• 2016-2021: Ramón y Cajal Researcher, University of Seville, Andalusian Centre for Molecular Biology and Regenerative Medicine, Seville, Spain.

Group Members
PhD Students
• Clara Megías-Fernández.

Postdoctorals
• Sabrina Rivero.

Technicians
• Irene Delgado-Sainz.
• Alberto León.

JAEINTRO fellow
• Alberto León.

Former members (2021-2022)
• Technicians: Valentina Buglioni.
• Master students: Ainhoa Pérez; Cristina Peral.
• Erasmus+ Master students: Angelo Meoli.

Research Activity
Overview
The maintenance of cell homeostasis requires a dynamic regulation of gene expression. Transcription output is modulated at two main levels: transcription initiation and promoter-proximal pausing that takes place shortly after starting RNA synthesis. We have recently proposed that transcription repression through promoter-proximal pausing is coordinated with topoisomerase II (TOP2) activity. Considering that TOP2 produces transient breaks in the DNA to alleviate supercoiling, and that this can lead to DNA damage; genes regulated at pause level, could have more risk of genome instability. The use of TOP2 poisons, which stimulate the induction of TOP2 breaks, as chemotherapeutic agents, can increase that threat, and eventually trigger secondary malignancies. We aim to understand the mechanisms by which gene expression changes because of the generation of TOP2 breaks and the impact of such changes in DNA repair. Our work constitutes an attempt to exploit the scientific and biomedical potential of these avenues of research.

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-seal mechanism that affects either one (type I DNA topoisomerases; mainly TOP1 in eukaryotes), or simultaneously both (type II topoisomerases; TOP2) DNA strands. Topoisomerases have therefore traditionally considered general positive facilitators of transcription. In this context, our group has discovered that TOP2 has also a negative function in transcription elongation through the removal of negative supercoiling at promoter regions. When TOP2 is inhibited, promoter-proximal pausing is disfavored and transcription of a subset of genes is upregulated (Figure 1). Early-response genes (ERG) expression are highly affected by changes in topoisomerase function because its regulation depends on the maintenance of promoter-proximal pausing.

Because of our previous work in which we established a connection between promoter-proximal pausing and TOP2 activity at promoters, we have decided to study whether factors implicated in the regulation of transcription have a function in the repair of DSB generated by TOP2. Stabilization of the cleavage complexes produced within TOP2 catalytic cycle with TOP2 poisons produce such breaks. After DNA damage, the histone variant H2AX is phosphorylated (β-H2AX) at the site of the break by ATM and ATR and this modification spreads over megabases, which can be observed with immunofluorescence experiments as foci in the nucleus. Using this approach and ChIP-seq experiments, we...
have discovered that elongation factors are specifically important for the signaling of TOP2 breaks for the recruitment of repair factors.

Overall, our results show that topoisomerase activity at promoter regions is closely related with the regulation of transcription elongation, more specifically, at promoter-proximal pausing level. Our future goal is to analyze the consequences of the generation of TOP2-breaks at promoters in gene expression at different levels, such as transcription elongation, termination, chromatin remodeling and RNA processing, and the interactions between TOP2 and regulatory factors. We will also study the relevance of changes in gene expression in response to TOP2-breaks in DNA repair. We also aim to determine whether these mechanisms are general or specific of certain subset of highly regulated genes.

**Grants (2021-2022) (starting or ending 2021-2022)**
- 2020-2023: PID2019-104484G, Ministerio de Ciencia e Innovación
- 2020-2022: AYUDA SUPLEMENTARIA VI, Universidad de Sevilla

**Publication Highlights**


**Figure 1. TOP2 function in regulation of transcription.**

TOP2A removes negative supercoiling at promoters while TOP1 removes positive supercoiling in the gene body. Under TOP2A inhibition, negative supercoiling accumulates, promoter-proximal pausing is destabilized, and transcription becomes TOP1 independent.
Current position
• Since 2020: Ramón y Cajal Researcher, University of Seville, Andalusian Center for Molecular Biology and Regenerative Medicine, Seville, Spain.
• Since 2020: Scientific responsible for the Genomic Unit at Cabimer.

Academic Background of the Emerging PI
• 2004: Degree in Biology, University of Seville.
• 2009: PhD in Biology, University of Seville.

Positions Held
• 2004-2005: Predoctoral Fellow “Formación de doctores” from Andalusian Government at Department of Genetics, University of Seville, Spain.
• 2005-2009: Predoctoral Fellow “FPU” from the Spanish Government at Andalusian Center for Molecular Biology and Regenerative Medicine associated with the Department of Genetics, University of Seville, Spain.
• 2009-2012: Postdoctoral contract at Andalusian Center for Developmental Biology, University Pablo de Olavide, Seville, Spain.
• 2012-2013: Postdoctoral contract at Andalusian Center for Developmental Biology, CSIC, Seville, Spain.
• 2013-2016: Postdoctoral Grant, Lundbeck Foundation, Biotech Research and Innovation Center, University of Copenhagen, Denmark.
• 2016-2018: Postdoctoral contract at Andalusian Center for Molecular Biology and Regenerative Medicine, CSIC.
• 2019-2019: Postdoctoral contract at Biomedicine Institute of Seville, FISEVI.

Research Activity
Overview
Chromatin replication is a necessary biological activity required to copy the genetic material that will be transferred to the daughter cells. However, it is also a very disruptive process producing a genome-wide chromatin disorganization. This includes the dilution of the epigenetic information and the reduction of DNA accessibility. Although the cell counts with specialized mechanisms to restore chromatin organization, complete restoration may take hours. This creates a window of time where transcriptional programs and gene expression may be altered. Our goal is to identify how these transient chromatin alteration may impact gene expression regulation, nuclear dynamics and human diseases.

Research Highlights
During chromatin replication, parental histones have to be evicted from the DNA to allow the passage 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 produce a genome-wide chromatin disorganization that includes reduction of chromatin accessibility and dilution of the epigenetic information.
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.

In our lab we make use of ChOR-seq technology (Chromatin Occupancy after Replication), a cutting-edge technique that we developed and that is able to purify proteins and histone PTMs associated to nascent chromatin 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 cell cycle that may play important roles on cellular function and human diseases.

Considering that the post-replicative chromatin rearrangements take hours to be restored, we are now also studying whether these changes may alter gene expression. In order to do that we are combining analysis of RNAPII activity and synthesis of nascent RNA.

Grants (2021-2022)
Current position
• Research Scientist CABIMER.
• Associate Professor of the University of Seville.

Academic Background of the Emerging PI
• PhD in Molecular Biology.

Group Members
PhD student
• María José Peña-Gómez.

Technicians
• Jesús Cea García.
• Gonzalo Pinaglia Tobaruela.

Former Members (2020-2022)
• PhD students: Paula Moreno Gordillo.
• Master student: Marina Suarez Pizarro, JAEIntro.

Research Activity
Overview
Maintenance and faithful inheritance of genetic information is essential to avoid disease. Therefore, cells evolved a wide range of protection mechanisms responsible for the preservation of the genetic material. Special group of damaging agents are those produced within our cells during cellular metabolic reactions. Our group is interested in uncovering the nature of these endogenous metabolites inflicting DNA damage, to decipher the molecular mechanisms operating during replication, that help to avoid the catastrophic consequences of genetic instability caused by endogenous processes.

Research Highlights
Accurate repair of damaged DNA is essential to ensure the faithful transmission of genetic information from a mother to its daughter cell. To avoid devastating consequences Therefore, cells have evolved several repair mechanisms that survey, detect and fix DNA lesions, in humans. Defective repair of DNA lesions underlies the Fanconi Anaemia (FA) syndrome, an ultrarare genetic instability syndrome featured by congenital abnormalities, stem cell loss and extreme cancer predisposition. The FA/BRCA repair pathway comprises 22 so far identified genes (FANCA to FANCW), essential for interstrand crosslink (ICL) repair at converging replication forks during S phase. The FA pathway received much attention since the FANCD1 gene was identified as BRCA2, the most frequently mutated gene in breast and ovarian cancer. The FA pathway play many crucial roles in genome maintenance like ICL repair, regulation of replication fork stability or avoidance of toxic DNA:RNA hybrids (R-loops) at transcription replication conflicts (TRCs) (Figure 1).

Many chemical and physical agents constantly challenge ongoing DNA replication. Our research effort focusses on the identification of metabolic agents endogenously produced that thread replication dynamics, leading to replication stress. Our research has identified 5-hydroxymethylated nucleosides (i.e. the cytosine demethylation base 5-hydroxymethyl-cytosine, 5hmC), as potential hazardous nucleoside that threatens replication and genome integrity (Peña Gomez et al. IJMS, 2022; Peña-Gomez et al. Cell Death and Disease, 2022). We have revealed that misincorporation of 5-hydroxymethylated...
DNA bases disturb replication progression leading to genome instability in the absence of the Fanconi Anaemia DNA repair pathway (Figure 2).

We also uncovered that 5hmdC is deaminated to 5-hmdU, a toxic uridine analogue (Figure 3). 5hmdU is actively removed from the genome by the concerted actions of base excision repair factors. Thus, BER deficiency, either caused by pharmacological drugs targeting PARP1, or genetic inactivation by deletion of XRCC1 exacerbates 5hmdU genotoxicity.

The mechanism by which 5hmdC and 5hmdU causes extensive genomic instability seems to be due to collisions of the replisome with ongoing BER intermediates undergoing fixation. BER intermediates, likely ssDNA gaps or AP sites are well-known potent replication stressors, therefore activating the FA pathway to promote fork stabilization.

Our main research lines are the following:

1. Molecular mechanisms of Interstrand Crosslink (ICLs) repair: Our work uncovered endogenously reactive aldehydes as a novel source of ICLs, and how the Fanconi Anaemia DNA repair pathway orchestrates ICL-repair. We are currently deciphering the molecular mechanisms employed by cells to detect, signal and repair ICLs, by focusing on the identification of new players and the characterization of the molecular mechanisms of replication-associated DNA repair.

2. Interplay of DNA repair mechanisms during replication fork impairment: During ICLs sensing and signaling by the ongoing replication fork, several distinct DNA repair pathways (Fanconi Anaemia, BER, HR, NHEJ, MMEJ…) converge to promote error-free repair. However, pathway choice determining the optimal consecution of repair event is poorly understood. We currently examine the interplay of different repair pathways in collaboration with the Fanconi Anaemia pathway to limit genome instability associated to replication fork defects during nucleoside misincorporation.

3. Molecular mechanisms of Intersstrand Crosslink (ICLs) repair: Genetic mouse models of FA offers a great opportunity to investigate novel therapeutic approaches to improve bone marrow function and prevent cancer development in these patients.

Grants (starting or ending 2021-2022)

Principal Investigator
Gonzalo Millán Zambrano
Chromatin modifications
Emerging PI

Current position

• Since 2021: La Caixa Junior Leader, University of Seville, Andalusian Centre for Molecular Biology and Regenerative Medicine, Seville, Spain.

Group Members

Postdocs
• Patrick Toolan Kerr

PhD students
• Laura López Hernandez

Master students
• Diego Polanco Alonso

Research Activity

Overview
Chromatin structure is highly repressive to processes occurring on DNA. However, we know since pioneering studies by Vincent Allfrey that histones are subjected to a wide variety of covalent post-translational modifications (PTMs) that can modulate DNA accessibility, thereby playing key roles in many biological processes. During the past three decades, we have witnessed major advances in our understanding of the functional role of histone PTMs in key cellular processes. Although most breakthrough discoveries were driven by scientific curiosity, many of them have far-reaching implications for the treatment of human disease. This is based on the notion that, unlike genetic alterations, most of the known histone PTMs are likely reversible, which offers considerable promise for therapeutic intervention. Importantly, there are increasing number of reports linking alterations of the histone PTM landscape to different cancer states. Our main interest is the characterization of the pathways leading to histone PTMs and their involvement in cancer.

Research Highlights

Recently, several novel histone PTMs have been identified by mass spectrometry studies. Although the evolutionary conservation of these modifications underscores their physiological relevance, the function of most of them still remains to be elucidated. During the 2021-2022 period we characterized the role of a novel histone PTM, mono-methylation of histone H3 at lysine 37 (H3K37me1). We demonstrated that H3K37me1 is catalyzed by Set1p and Set2p, and that it regulates DNA replication initiation (Santos-Rosa et al, Mol Cell 2021). In particular, H3K37me1 prevents MCM replicative helicase interaction with chromatin, maintaining low levels of MCM loading outside of conventional replication origins. Consistently, depletion of H3K37me1 results in aberrant DNA replication initiation at cryptic genomic sites. Thus, our results indicate that H3K37me1...
safeguards the correct execution of the DNA replication program by protecting the genome from inappropriate origin licensing.

DNA replication stress is a major cause of genome instability, which is considered a hallmark of cancer. Importantly, DNA replication stress is not a common feature of normal cells, thereby representing a promising target for cancer-specific therapies. Cancer progression involves mutations in genes regulating cell proliferation, namely oncogenes and tumor suppressors. In this regard, it is well-established that oncogene activation can cause alterations of the DNA replication program, giving rise to replication stress. This has led to the proposal of a model for cancer development in which oncogene-induced DNA replication stress, an early driver of genomic instability in pre-cancerous cells, will in turn generate the genetic diversity necessary for cancer cells to escape apoptosis. Therefore, understanding the role of H3K37me1 in the suppression of aberrant DNA replication initiation sites has potential for clinical relevance.

Publication Highlights


Grants (starting or ending 2021-2022)

The interest of the Department of Cell Dynamics and Signaling is focused on the knowledge of the mechanisms that ensure the normal functioning of the cell and that safeguard the homeostasis of the tissues. The correct development of cell division, migration, differentiation, morphogenesis and death processes is essential for the integrity of organisms. The alteration of these processes is normally associated with the development of different pathologies, among which cancer and degenerative diseases stand out. The alteration of cell division, as well as the processes of cell differentiation and death, is closely associated with the development of cancer, and together with the migratory and invasive capacity that tumor cells can acquire, are typical signs of cancer. The correct progression and coordination of these processes requires the existence of finely regulated signaling mechanisms, capable of integrating both internal and external signals to generate the appropriate responses and preserve the correct cellular physiology. The main objective of the Department is to advance in the knowledge of these signaling and response mechanisms, both in normal conditions and in altered or pathological conditions, thus contributing to define more precisely and effectively routes of therapeutic intervention against the aforementioned pathologies. Recently, two research groups initially assigned to the other departments (those of Dr. Anabel Rojas and Dr. Román González Prieto) have joined our six previously existing groups.
Current position
• Since 2009: Research Scientist CSIC / Cabimer, Seville, Spain.

Group Members
PhD students
• Vahid Jafari.

Postdocs
• Nieves Lara Ureña.

Technicians
• Rosa Mª Troya Toledo.

Former Members (2020-2021)
• Postdocs: Pablo García Gutiérrez.
• PhD students: Juan Fco. Correa Vázquez.
• Master students: Alfonso Castañeda Segura; Olga Fernández Romero.

Research Activity
Overview
The main objective of our research is to decipher the molecular mechanisms that control the transition from proliferation to differentiation, especially in relation to the development of the nervous system. In particular, we study the post-translational modification of proteins by covalent binding of the SUMO polypeptide (sumoylation), focusing mainly on transcriptional control and the analysis of chromatin. We are also interested in the relationship of the molecular mechanisms underlying these processes with cancer and cell viability. SUMO is essential in eukaryotes and is involved in the regulation of many cellular processes, in particular through the control of gene expression. On the other hand, it has been described that protein sumoylation safeguards cell viability. Knowing in detail the components of the SUMO pathway involved in these processes and the associated regulatory mechanisms is of great therapeutic interest in relation to cancer and nervous system disorders.

Research Highlights
The SUMO polypeptide is similar to the Ubiquitin and its covalent attachment to proteins has drastic consequences on protein properties and functions. A relevant role in the process of sumoylation is displayed by SUMO ligases and proteases, as they enhance and recycle SUMO from targets, respectively. To date, up to six different SUMO proteases belonging to the SENP family have been described (1-3, 5-7). Although SUMO is involved in the control of virtually all the cellular processes, very little is known about its role in initial steps of neurogenesis. To shed light on this, we have conducted a SILAC-based proteomic study to identify proteins sumoylated under proliferation and neuronal differentiation conditions, finding more than 300 proteins differentially sumoylated. This has allowed us to discover for the first time, the transcription factor UTF1, as a target of SUMO. Sumoylation modulates its chromatin affinity and mediates the recruitment of the decapping enzyme DCP1A to keep relevant development-associated bivalent genes in a transcriptional poised state for rapid activation in response to specific signaling.

We have also investigated changes in expression levels of genes coding for the different components of the sumoylation...
Figure 2. SENP7 promotes cell viability under limiting conditions of oxygen and glucose, and is a prognostic marker for colon cancer. A) Senp7 expression is downregulated under oxygen and glucose deprivation (OOG) conditions and reactivates after restoration of oxygen and glucose (ROG). B) In most cancers, the SENP7 locus is associated with greater copy number variation, whereas the SENP3 locus (previously shown to promote cell death) is associated with less copy number variation. C) A worse prognosis is observed for patients with colon cancer with a higher expression of SENP7. D) In HCT116 colon cancer cells, siRNA (si)-mediated downregulation of SENP7 (S7) sensitizes cells to death under OGD conditions in comparison with control siRNA (siC), as determined by propidium iodide (PI) and Annexin V (AV) labeling.

pathway under ischemia simulated conditions. These conditions are achieved by oxygen and glucose deprivation (OGD), which also associates with the interior of solid tumors. We have interestingly observed that under OGD conditions, the SUMO protease SENP7 is dramatically downregulated, and that restoring of normal growth conditions leads to recovering of normal SENP7 levels. We have found that overexpression of SENP7 in tumor cells leads to enhanced viability in response to deleterious OGD conditions, in contrast to SENP3 overexpression that promotes cell death, as previously described. Specially for colon cancer, SENP7 is a prognosis marker, with poorer outcomes when overexpressed.

Grants
• 2022-2025: PID2021-125791NB-I00. Ministerio de Ciencia e Innovación.

Publication Highlights
García-Gutiérrez P, García-Domínguez M. 2021. BETting on a Transcriptional Deficit as the Main Cause for Cornelia de Lange Syndrome. Front Mol Biosci. 8: 709232
Principal Investigator

Dr. Raúl V. Durán

Metabolism and cell signaling
Group Leader

Current position

• Since 2018: Senior Research Associate, Spanish National Research Council, CSIC/ CABIMER.
• Since December 2021: Deputy Director of CABIMER, Seville, Spain.

Group Members

Senior Researcher

• Dr. Socorro Murdoch (Associate Professor).

Postdoctorals

• María Jesús Fernández Ávila.
• Jonathan Martínez Fábregas.
• Dr. Macarena Morillo Huesca.
• Dr. Mercedes Tomé Montesinos.

PhD student

• Laura Zarzuela Moncada.
• Ignacio González López Cepero.

Technicians

• Ana Reina Bando.

Research Activity

Overview

The Group of Metabolism and Cell Signaling studies the crosstalk between cellular metabolic and bioenergetic flows with signaling processes, and how this interaction contributes to coordinate the growth and normal functioning of cells and tissues. In particular, we study how these interaction mechanisms are deregulated in cancer at the molecular and cellular level. During last years, the group has established the processes of interaction between the metabolism of the amino acid glutamine, the most abundant in human blood and the most important from an energetic point of view for cells, with cell signaling via the mTOR pathway, a protein complex essential in the regulation of cell growth and metabolism. Our investigations have shed light on how glutamine and mTOR interact in an altered way in tumor cells through a mechanism that we have termed “glutamoptosis”, and propose new therapeutic approaches to specifically target tumor cells in cellular and animal models.

Research Highlights

Two parallel pathways connect glutamine metabolism and mTORC1 activity to regulate glutamoptosis

Glutamoptosis is the induction of apoptotic cell death as a consequence of the aberrant activation of glutaminolysis and mTORC1 signaling during nutritional imbalance in proliferating cells. The role of the bioenergetic sensor AMPK during glutamoptosis is not defined yet. Our recent results showed that AMPK reactivation blocks both the glutamine-dependent activation of mTORC1 and glutamoptosis in vitro and in vivo. We also show that glutamine is used for asparagine synthesis and the GABA shunt to produce ATP and to inhibit AMPK, independently of glutaminolysis. Overall, our results indicate that glutamine metabolism is connected with mTORC1 activation through two parallel pathways: an acute alpha-ketoglutarate-dependent pathway, and a secondary ATP/AMPK-dependent pathway. This dual metabolic connection between glutamine and mTORC1 must be considered for the future design of therapeutic strategies to prevent cell growth in diseases such as cancer.

Glutamine, mTOR and autophagy: a multiconnection relationship

Cancer cells metabolize glutamine mostly through glutaminolysis, a metabolic pathway that activates mTORC1. The AMPK-mTORC1 signaling axis is a key regulator of cell growth and proliferation. Our recent investigation identified that the connection between glutamine and AMPK is not restricted to glutaminolysis. Rather, we demonstrated the crucial role of ASNS (asparagine synthetase) and the GABA shunt for the metabolic control of the AMPK-mTORC1 axis during glutamine sufficiency. Our results elucidated a metabolic network by which glutamine metabolism regulates the mTORC1-macroautophagy.
autophagy pathway through two independent branches involving glutaminolysis and ASNS-GABA shunt.

Glutamine Synthetase as a key factor for glutamine addiction in Notch-driven cancer

Previously, glutaminolysis inhibition has been proposed to synergise with anti-Notch therapies in T-cell acute lymphoblastic leukemia (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
- 2022 – 2025: PID2021-124251OB-I00), Ministry of Science and Innovation of Spain.
- 2021 - 2022: PY20_00757 Regional Ministry of Economy, Industry, Knowledge and Universities.
- 2021-2022: US-1381282, University of Seville and Regional Ministry of Economy, Industry, Knowledge and Universities.
- 2022: 2021AEP005, Spanish National Research Council - CSIC.

Figure 2. Glutamine is sufficient to induce bioenergetic increase in cancer cells. Seahorse analysis showed an increase in mitochondria-derived ATP production in cells treated with glutamine alone (Bodineau et al., Nat. Comms 2021).


Current position

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

Group Members

Research Associates
• Carmen Palacios Casanova.
Postdocs
• Rocío Mora Molina.
PhD Students
• Younes El Yousfi El Mourabit.
Technicians
• Francisco Javier Fernández Farrán.
• Belén Torres Agrela.

Former Members (2018-2020)

• Postdocs: Rosario Yerbes Cadenas.

Research Activity

Overview
The ability of tumor cells to adapt to various stress conditions generated in the tumor microenvironment, such as hypoxia, nutrient deprivation and oxidative stress, is decisive for the selection of aggressive tumor clones and to drive tumor progression. Despite recent advances in the field, there are still many questions to unravel concerning the mechanisms leading to an adaptive or to an apoptotic response after microenvironmental stress. The results of our group in recent years indicate that in response to microenvironmental stress, the pro-apoptotic receptor TRAIL-R2 promotes the formation in tumor cells of intracellular signalling platforms with other proteins of the extrinsic apoptosis pathway, the result of which may be cell death or a pro-tumoral response. Our project aims to decipher the molecular mechanisms regulating the activation of cell death by apoptosis upon metabolic stress and to determine the impact of the tumor microenvironment and the 3D architecture of tumor spheroids in tumor cell fate. This is essential to identify possible markers of tumor malignancy and potential therapeutic targets.

Research Highlights

Protein misfolding or unfolding and the resulting endoplasmic reticulum (ER) stress frequently occur in highly proliferative tumors. How tumor cells escape cell death by apoptosis after chronic ER stress remains poorly understood. We have investigated in both two-dimensional (2D) cultures and multicellular tumor spheroids (MCTSs) the role of caspase-8 inhibitor cFLIP as a regulator of the balance between apoptosis and survival in colon cancer cells undergoing ER stress. We have shown that downregulation of cFLIP proteins levels is an early event upon treatment of 2D cultures of colon cancer cells with ER stress inducers, preceding TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) upregulation, caspase-8 activation, and apoptosis. Maintaining high cFLIP levels during ER stress by ectopic expression of cFLIP markedly inhibits ER stress-induced caspase-8 activation and apoptosis. Conversely, cFLIP knockdown by RNA interference significantly accelerates caspase-8 activation and apoptosis upon ER stress. Despite activation of the proapoptotic PERK branch of the unfolded protein response (UPR) and upregulation of TRAIL-R2, MCTSs are markedly more resistant to ER stress than 2D cultures of tumor cells. Resistance of MCTSs to ER stress-induced apoptosis correlates with sustained cFLIP expression. Interestingly, resistance to ER stress-induced apoptosis is abolished in MCTSs generated from cFLIP knockdown tumor cells. Overall, our results suggest that controlling cFLIP levels in tumors is an adaptive strategy to prevent tumor cell’s demise in the unfavorable conditions of the tumor microenvironment.

Tumor microenvironment is significantly different from normal tissue and increasing evidences suggest that apart from chemical input, the mechanical properties of the tumor microenvironment are important determinants for tumor cell behavior. Among the multiple physical parameters, extracellular matrix rigidity can especially affect intracellular signalling events.
Figure 2. Inhibiting nuclear YAP/TAZ localization promotes intracellular TRAIL-R2 clustering and apoptosis in tumor cells.

Figure 3. Limitation of glutamine in glutamine-addicted tumor cells will lead, on the one hand, to the elevation of TRAIL-R2 levels mediated by the activation of the GCN2 pathway and, on the other hand, to the decrease of FLIPL as a result of the metabolic defect caused by the loss of αKG. Both events will result in the activation of caspase-8 at the DISC, which will activate effector caspases and apoptosis.

Influencing cancer progression and the tumor response to therapy. In this respect, our recent data revealed that matrix stiffness and nuclear localization of the transcriptional co-activators YAP/TAZ are key determinants of the apoptotic response to ER stress by controlling FLIPL levels and the activation of the extrinsic pathway of apoptosis in tumor cells.

Oncogenic transformation leads to changes in glutamine metabolism that make transformed cells highly dependent on glutamine for anabolic growth and survival. We have investigated the cell death mechanism activated in glutamine-addicted tumor cells in response to the limitation of glutamine metabolism. We have shown that glutamine starvation triggers a FADD and caspase-8-dependent and mitochondria-operated apoptotic program in tumor cells that involves the pro-apoptotic TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2), but is independent of its cognate ligand TRAIL. In glutamine-depleted tumor cells, activation of the amino acid-sensing general control non-repressible-2 kinase (GCN2) is responsible for TRAIL-R2 upregulation, caspase-8 activation, and apoptotic cell death. In addition, metabolic stress upon glutamine deprivation also results in GCN2-independent FLICE-inhibitory protein (FLIP) downregulation facilitating caspase-8 activation and apoptosis. Importantly, downregulation of the long FLIP splice form (FLIPL) and apoptosis upon glutamine deprivation are inhibited in the presence of a membrane-permeable α-ketoglutarate.

Altogether, our data support a model in which limiting glutamine utilization in glutamine-addicted tumor cells triggers a previously unknown cell death mechanism regulated by GCN2 that involves the TRAIL-R2-mediated activation of the extrinsic apoptotic pathway.

Collectively, our data suggest that cellular levels of FLIPL may play an important role in tumor cell fate decisions under the stressful conditions of the tumor microenvironment. Thus, in stressful situations, maintaining the levels of this protein that inhibits the extrinsic apoptosis pathway could enable the activation of an adaptive response in tumor cells and other tumor stromal cells, which would promote tumor growth and progression. More importantly, these results also reveal a dependence of tumor cells on maintaining FLIPL levels in the context of the tumor. Therefore, understanding the mechanisms that maintain high levels of FLIP in tumor cells should help in the design of therapeutic strategies that reduce the expression of this protein and, in this way, limit tumor growth.

Grants
- 2017-2021: CIB16/12/00421, Centro de Investigación Biomédica en Red (CIBERONC). Instituto de Salud Carlos III.
- 2021-2023: PY20_00754. Proyecto de Excelencia Junta de Andalucía.
Current position

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

Group Members

PhD Students
- Salvador Polo Generelo.

Technician
- Belén Torres Agrela.

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.

Lnc-Nr6a1 is an immediate-early regulator of EMT that is downregulated by TGF-β. Lnc-Nr6a1 is processed giving rise to two abundant polyadenylated isoforms, lnc-Nr6a1-1 and lnc-Nr6a1-2, and a longer non-polyadenylated microprocessor-driven lnc-pri-miRNA containing clustered pre-miR-181a2 and pre-miR-181b2 hairpins. Ectopic expression of polyadenylated isoforms enhance cell migration and invasive capacity of the cells, whereas the expression of these isoforms and the non-polyadenylated isoform conferred anoikis resistance. By identification of direct RNA interacting proteins (IDRIP) we defined a network of glycolytic proteins (ENO1, ALDOA, GAPDH, PKM, LDHA) interacting directly with the lnc-Nr6a1-1 isoform. This isoform acts as a scaffold molecule, supporting substrate channeling for efficient glycolysis.

We have determined and quantified the RNA molecules present in the RISC complexes of TGF-β-treated NMuMG cells. TheAGO2 protein interacts mainly with exons and 3'UTR regions. The percentage of RNAs that interact with AGO2 through exons is very similar to those that interact through the 3'UTR regions, underlining that the regulation mechanism carried out by RISC (RNA-induced silencing complex) complexes is also largely associated with exons. Remarkably the most enriched RNA in the RISC complexes after 4 hours of treatment with TGF-β was the mRNA Serpine1, it was also the mRNA that showed the greatest increase in crosslinking sites, going from 2 sites in untreated cells to 34 in TGF-β-treated cells. The Serpine1 gene is strongly and rapidly induced by TGF-β treatment. It is paradoxical that in parallel the levels of Serpine1 mRNAs...
increase strongly in the RISC complexes. This result indicates that Serpine1 mRNA, in addition to act as a protein-coding gene, it may exert a non-coding biological function. In fact, Serpine1 mRNA acts as a natural miRNA sponge to dampen the EMT inhibitor activity of miRNAs. By overexpressing ATG-mutated Serpine1 mRNA (SerpineATG4), we show that most of the effects so far associated with the SERPINE1 protein are also caused by the Serpine1 mRNA. Proteomic analysis reveals that levels of the splicing factor TRA2b increase notably after SerpineATG4 overexpression, while Tra2b mRNA levels are not affected. iCLIP and mutagenesis analysis indicate that miR-130b-5p regulates the levels of the TRA2b protein; as expected, Serpine1 mRNA contains three binding sites for miR-130b-5p, one in exon 3 and two in the 3′ UTR. An effect of the SerpineATG4 overexpression, not described until now, is the downregulation of numerous genes, most of them related to the innate immunity. This same effect is also produced by Tra2b overexpression, sharing more than 60% of the expression changes (217 genes). Likewise, 25% of alternative splicing changes produced by Tra2b overexpression are also observed with SerpineATG4.

Ph.D. Theses Defended
Salvador Polo Generelo. Identificación y análisis funcional del lnc-Nr6a1 y del mRNA Serpine1 como reguladores tempranos de la transición epitelio-mesénquima. University of Seville. 2021

Grants
- 2018-2020 MICINN. SAF 2017-86189-P: 157,300.00 €
- 2021-2023: MICINN. PID2020-119732RB-100: 108,900.00 €

Publication Highlights
Microtubule dynamics in health and disease

Group Leader

Dr. Rosa M. Ríos

Current position

- 2011-Present: Senior Research Scientist - Spanish National Research Council CSIC-CABIMER.
- From 19/02/2019-06/11/2022: On temporary leave of absence as Secretary General of University, Research and Technology - Government of Andalucía.

Group Members

Research Associates
- Laura Martínez (Assit. Prof. US).

Postdocs
- Chiara Marcozzi.

PhD Students
- Carmen García.

Technicians
- Carmen Luque.
- María Montilla.

Former Members (2021-2022)

- Postdocs: Pablo Gandolfo.
- PhD Students: Jesús Roca.
- Technicians: Loida Pérez; Laura Díaz.

Research Activity

Overview

Microtubules (MTs) are cytoskeletal filaments that serve as tracks for intracellular transport, act as scaffolds to position organelles, contribute to cell shape and motility, and control cell division. During mitosis MTs form bipolar spindles that drive chromosome segregation into the daughter cells, whereas in interphase they organise in a cell type-specific fashion to support cell physiology. The event that initiates de novo formation of MTs, known as MT nucleation, occurs in specific subcellular structures globally called Microtubule Organising Centres (MTOCs). The centrosome and the Golgi Apparatus (GA) are the two major MT-organising centres (MTOCs) in actively dividing cells, and increasing evidence underpins the idea that there is a high degree of coordination and crosstalk between their activities along the cell cycle or during cell differentiation. The main focus of my lab is to unveil the molecular mechanisms underlying MT nucleation driven by the GA and the centrosome along the cell cycle or during cell differentiation. Our aim is to widen our current knowledge on the spatiotemporal control of MTOC activities and to gain a more mechanistic comprehension of the pathways involved. We are also investigating how chemokines regulate the organisation of chemokine receptors, and what are the associated cytoskeletal proteins that orchestrate T lymphocyte migration.

Research Highlights

MT nucleation, the event that initiates de novo formation of MTs, is highly regulated process that enables cells to acquire specific architectures and to promptly respond to any cellular change. How cells assign MTOC locations and how the activities of different MTOCs are regulated and integrated in the same cell is far from being understood. During mitosis the MT nucleation activity of the centrosome greatly increases, while that of the GA is silenced. On the contrary, during cell differentiation centrosomes either disappear or become inactive, and the GA leads MT network organisation. Hence, it is of great importance to decipher the molecular mechanisms operated by these MTOCs.

The formation of new MTs is initiated by the activity of specific proteins, that act as nucleators and mediate the interaction between αβ-tubulin heterodimers. The only template-based MT nucleator identified so far is the gamma-tubulin ring complex (γTuRC), a conical structure consisting of 14 subunits of γtubulin held together by the γtubulin complex proteins (GCPs) and by additional factors. In mammalian cells, γtubulin is encoded by two genes, TUBG1 and TUBG2, that produce two isoforms differing in few amino acids at their C-terminus. In most cells, γtubulin 1 is much more abundant than γtubulin 2. Aware of the essentiality of γtubulin 1 for cell cycle progression, we generated a knockin cell
line in which ytubulin 1 was tagged with the fluorescent protein mCherry2 and the mini-Auxin Induced Degradation motif (mAID) to achieve and monitor its rapid and controlled degradation. By combining ytubulin 1 induced-degradation with ytubulin 2 silencing, we have investigated the contribution of both γ-tubulin isofoms to MT nucleation from different MTOCs.

MT nucleation analysis by live-cell imaging under these conditions have revealed that both ytubulin isoforms contribute to MT nucleation and that γTuRC-mediated MT nucleation is the only mechanism operating in non-transformed epithelial cells, contrarily to what has been reported in cancer-derived cell lines. Interestingly, we found that whereas ytubulin 1 stimulates both centrosome and GA MT nucleation, ytubulin 2 plays an inhibitory role on MT nucleation at the GA.

Further investigation on the molecular mechanisms underlying this negative control revealed that ytubulin 2 exerts its inhibitory role by competing with ytubulin 1 for the binding sites on Golgi membranes. Interestingly, our studies unveiled a new regulatory mechanisms of MT nucleation at the GA that involves the aggregation degree of the γTuRC receptors AKAP450 and CDK5RAP2 at Golgi membrane surfaces.

As mentioned before, at mitotic entry centrosome ability to nucleate MTs increases, while that of the GA is inhibited. Our previous work identified AKAP450 as responsible for GA-associated MT nucleation activity. For this reason, we focused on AKAP450 as the best candidate to mediate mitotic silencing of GA-MT nucleation. To identify cell-cycle regulated interactions potentially implicated in this mechanism, we have generated an AKAP450-mAID-m-Cherry2 knockin cell line and performed comparative proteomics of AKAP450-containing complexes purified from either G1 or G2/M synchronised cells.

As an independent although related research line, we are also interested in the dynamic and organization of chemokine receptors during leukocyte migration. Leukocyte movement is mostly driven by chemokines and their receptors that organize at the cell membrane as monomers, dimers and small oligomers (nanoclusters). We have recently found that there is a correlation between the size of chemokine receptors nanoclusters and the cell migration capacity. The chemokine receptor CXCR4 and its ligand, the CXXL12 chemokine, form a key pair in lymphocyte trafficking. Using SPT-TIRF microscopy and a T cell line expressing endogenous CXCR4-AcGFP, we studied the CXCR4 dynamic organisation during T cell migration. We identified the cytoskeletal protein filamin A as a mechanical regulator of CXXL12-mediated CXCR4 nanoclustering, which orchestrates T cell motility.

Grants

- 2020-2023: PIE 202080E095. Intramural Project. CSIC.
- 2016-2022 AO16163616GAVI. Spanish Association Against Cancer Scientific Foundation (AECC FC) (to M.P. Gavilán).
- 2021-2023 PY20_00615 Regional Government of Andalucía (to L. Martinez).
Publication Highlights


Olazábal-Morán M., Sánchez-Ortega M., Martínez-Muñoz L., Hernández C., Rodríguez M.S., Mellado M., Carrera A.C. Fluctuations in AKT and PTEN activity are linked by the E3 ubiquitin ligase c-CBL. Cells 2021; 10 (11). doi: 10.3390/cells10112803
Research Activity

Overview
Our research aims to shed light on the mechanisms that control cell division and ensure a correct distribution of the genetic material during this process. Problems with genome partitioning can give rise to aneuploidy, an alteration of the normal number of chromosomes in the cells that is a hallmark of cancer and other genetic diseases. Accordingly, cells have developed checkpoints that verify DNA integrity and the fidelity of chromosome segregation during their division. Our goal is to better understand how checkpoint function is controlled and coordinated to regulate specific cell cycle transitions. Additionally, we are interested in evaluating how cells exploit the same machinery that allows genome distribution in order to generate polarity during cell division. Errors in the establishment of asymmetry during stem cell division can lead to neurodegenerative disorders and premature aging. Hence, advances in our knowledge about asymmetric cell divisions are of pivotal social and economic importance.

Research Highlights
The mitotic spindle constitutes the molecular machinery that facilitates the segregation of the chromosomes during the division of the cells. The spindle is formed by a bipolar array of microtubules that emanate from microtubule-organizing centers (MTOCs), located at both spindle poles. In higher eukaryotes, the spindle MTOCs are known as centrosomes, while in the budding yeast Saccharomyces cerevisiae these structures are named spindle pole bodies (SPBs). 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, being therefore essential for proper spindle biogenesis, orientation and elongation. After their duplication, the pre-existent ("old") and the 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 patterns have been later described in stem cells from different organisms, including humans. Remarkably, despite this evolutionary conservation, whether the asymmetric inheritance of spindle MTOCs played any biological role had been a topic of discussion during the last years. To answer this question, we recently 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...
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 mitochondria are 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).

During the 2021-2022 period, we have been actively working to better understand the phenomenon of the differential distribution of the spindle MTOCs during asymmetric mitoses, both by more precisely describing the molecular mechanisms by which patterns of non-random MTOC distribution are established and also by further elucidating the consequences that interfering with these processes have on cellular aging. However, we have not only focused on this process, and we have additionally studied other mechanisms by which the cell can generate polarity during cell division that are dependent on the mitotic spindle but that do not rely on the intrinsic nature (“old” vs. “new”) of the MTOCs that organize this structure. In this way, we have recently demonstrated that the Bfa1/Bub2 complex, a mitotic exit inhibitor that asymmetrically localizes to the SPB that enters the daughter cell during the division of S. cerevisiae, specifically interacts with a component of the nuclear pore complex (NPC). Our studies have also revealed that this association between SPB and NPC components is important during the autophagic degradation of damaged nuclear pores during cell division. Furthermore, the asymmetric localization of the Bfa1/Bub2 complex to the SPB that enters the daughter cell during anaphase suggests that its interaction with a nucleoporin could contribute to promote the specific autophagic degradation of damaged or non-functional NPCs that, despite the existence of different mechanisms for their retention in the mother cell during mitosis, could be nonetheless inherited by the daughter cell.

Finally, we have recently initiated a novel research line in the group to extend our analyses regarding the process of non-random inheritance of spindle MTOCs to human cells. Specifically, we are evaluating the mechanisms that orchestrate the asymmetric distribution of the centrosomes after their duplication during the division of human neuroblastoma cells. The use of human cell lines will contribute not only to widen our scientific horizon, but it will also potentiate the biomedical relevance of our findings. Defects during asymmetric cell divisions have been associated with tumorigenesis, neurodegeneration and developmental problems. Therefore, unveiling the basic mechanisms that regulate these divisions is of upmost relevance to better understand the causes for these diseases.

Grants
Current position

- Assistant Professor at University Pablo de Olavide.

Group Members

PhD Students
- Noelia Arroyo Del Alba.
- Maria Bermúdez Sauco.
- Ana Alicia Montero Cabrera.

Technicians
- Irene Díaz Contreras.
- Enrique Domínguez.

Research Activity

Overview

The severity and occurrence of diseases caused by liver malfunction demand a better understanding of the molecular bases that control the activity of this organ in normal conditions and in response to damage. In our laboratory, our lines of research are focused on the molecular basis underlying the ultimate consequence of hepatic chronic disease, liver fibrosis. We pursue: i) To unravel the transcription factors and signaling pathways controlling the phenotype of hepatic stellate cells in liver fibrosis and in the resolution of the fibrosis; ii) to search for pharmacological agents to modify the hepatic stellate cell phenotype; iii) To modulate the interplay between hepatic stellate cells and hepatocarcinoma cells.

Research Highlights

Molecular and cellular basis of hepatic fibrosis

Hepatic stellate cells (HSCs) are specialized cells that are located in the liver and are involved in the storage and metabolism of vitamin A. However, in response to liver injury, HSCs can become activated and play a significant role in the development of liver fibrosis, a progressive scarring of the liver that can lead to liver dysfunction and failure. Activated HSCs 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 study of the molecular basis that control HSCs phenotype.

The GATA4 transcription factor is a protein that regulates gene expression and plays a critical role in the development and function of several organs, including the heart, gut, and liver. Our recent studies have uncovered a new role for GATA4 in the maintenance of HSC quiescence, a state of cell dormancy that helps prevent the activation of HSCs and the development of liver fibrosis. We have shown that overexpression of Gata4 in HSCs promotes the regression of liver fibrosis in mice with hepatic injury. Gene expression and ChIP sequencing analysis have revealed that GATA4 alters the expression of fibrogenic and antifibrogenic genes and directly represses the Epas1 gene (which codes for the hypoxic inducible factor 2a, Hif2a), a gene that is

Figure 2.

(A) Migration assay of Hep3B and SNU387 hepatocarcinoma cell lines coculture with Gata4-overexpressing LX2 hepatic stellate cells (LX2-GATA4) or GFP-overexpressing LX2 cells (LX2-GFP) as control.

(B) Cell proliferation assay of Hep3B and SNU387 hepatocarcinoma cell lines coculture with LX2-GATA4 or LX2-GFP.

(C) Images of tumourospheres formation of SNU387 hepatocarcinoma cells coculture with LX2-GATA4 or LX2-GFP.
known to promote the activation of HSCs and the development of liver fibrosis. Our studies could ultimately help to develop novel therapeutic alternatives to treat hepatic fibrosis regardless the etiology.

Targeting HSCs has been proposed as a potential therapeutic strategy for the treatment of liver fibrosis and liver cancer, as activated hepatic stellate cells (HSCs) are also an important component of the tumor microenvironment in hepatocarcinoma. Several approaches have been investigated to target HSCs with relative success, including the use of small molecule inhibitors, gene therapy, immunotherapy, and small molecule inhibitors of HSC activation. Currently we are investigating the potential of GATA4 to inactivate HSCs in the context of hepatocarcinoma to inhibit or ameliorate the tumorigenic features. Our preliminary studies show that HSCs (LX2 cells) inactivation mediated by GATA4 reduces tumorigenic features of hepatocellular carcinoma cell lines (Hep3B and SNU387), such as migration, proliferation and tumorospheres formation (Figure 2).

**Grants**

**Publication Highlights**


Current position
- Distinguished Researcher – EMERGIA20 program from Junta de Andalucía – Department of Cell Biology – University of Sevilla.

Academic Background of PI
- 2005 – Degree in Biology – University of Sevilla.
- 2012 – PhD. University of Sevilla – Microbial Technologies & Genetics.

Positions Held

Research Activity
Overview
The stability of our genomes depends on a plethora of proteins which are able to scaffold, replicate, repair and regulate the expression of the DNA, among other functions. Protein function is regulated by different Post Translational Modifications, including the modification of by ubiquitin and other ubiquitin-like modifiers, which is performed by an enzymatic cascade consisting of E1, E2 and E3 enzymes.

E3 enzymes confer substrate specificity for ubiquitin(-like) modifiers, and determining which E3 modifies which substrate is the next challenge in ubiquitin(-like) proteomics. I have optimized the TULIP(2) methodology, which enables to address such challenge. The human genome encodes for more than 600 different E3s. Specifically, my research focuses on the function and relevance of E3s and their substrates involved in the biology of the genome, including DNA damage repair and tolerance mechanisms and genome organization.

Group Members
- PhD Student
  - Daniel Salas-Lloret (Leiden University Medical Center).
  - Emily Esperanza Soto Hidalgo.

Research Highlights
Developing a ubiquitin(-like) mass spectrometry-based proteomics toolbox.
To identify E3-specific ubiquitination substrates I developed the TULIP methodology which was later improved by two orders of magnitude in the second iteration, TULIP2. Using this methodology, to obtain novel insight in the cross talk between ubiquitin and the ubiquitin-like modifier SUMO, we discovered that the SUMO-targeted Ubiquitin Ligase RNF4 regulates SUMO signaling by targeting the SUMOylation enzymatic machinery for proteasomal degradation, rather than individual sumoylation substrates.

Figure 1. Ubiquitination polymers.Ub moieties can modify proteins at one (mono ubiquitination) or several (multiple mono ubiquitination) Lys residues. Ub can form eight distinctive homotypic linkages, either through M1 (linear Ub chain) or internal Lys residues (K6, K11, K27, K29, K33, K48, and K63 Ub chains). Additional complexity is achieved through the formation of heterotypic Ub chains, which contain multiple Ub linkages and adopt mixed or branched topology. Cellular functions associated to these ubiquitin polymers are displayed. (From Salas-Lloret and González-Prieto (2022) Int. J. Mol. Sci. 23(16), 3281).
Identification of the non-covalent SUMO proteome.

In contrast to the covalent SUMO proteome, where more than 40k acceptor lysines for SUMO2/3 had been described, our knowledge about non-covalent SUMO interactome was more limited. We identified non-covalent binders that where specific for different SUMO isotypes and/or SUMO chains, additionally, we provided the most complete resource available of SUMO1 acceptor lysines.

Identification of the E3-specific SUMO proteome.

We adapted our TULIP2 methodology to identify substrates for SUMO E3s. In contrast to ubiquitin, the number of E3 enzymes for SUMO is more limited, thus, we performed a proteome-wide search identifying specific substrates for 8 different E3s for SUMO1 and SUMO2/3 and providing an online tool to browse the preferential E3 for a given substrate of interest.

Grants (starting or ending 2021-2022)
- Title of the project: Consequences of the Ubiquitin-like modified genome. (SUMOTIN)
- Title of the project: Construcción y validación de herramientas para el estudio de huecos de DNA de cadena sencilla derivados de estrés replicativo.
- Title of the project: UbiGap: Understanding under-replicated DNA gaps signaling and processing with a focus on ubiquitin.
- Title of the project: Identification of BRCA/BARD1 ubiquitin E3 ligase target proteins to obtain novel insight in breast- and ovarian cancer.

Figure 2. Heatmap depicting SUMO1 substrates for different SUMO E3 enzymes using TULIP2 methodology.

Figure 3. Cartoon depicting TULIP2 rationale for the BARD1 ubiquitin E3 enzyme and analysis by immunoblotting of BARD1-TULIP2 samples.

Publication Highlights


*: Equal contribution; #: corresponding author
The name of this dept was changed to better reflect the scope and lines of research conducted by the groups integrating it. Research in the department focuses on the multi-level study of the molecular mechanisms that control a wide variety of diseases. For such a holistic approach, we use multiple approaches, from cell lines and human primary cells, to experimental animal models and human samples. Groups in the department have a focus on the identification of therapies that include both the search for drugs, cell and gene therapies, as well as the identification of biomarkers as tools for the clinical diagnosis and prognosis of these diseases. All this implies that our research is necessarily translational in nature using both basic and preclinical models and patient / donor samples. We aim to identify key factors, mechanisms of action and therapeutic targets focused on the treatment of diseases related to metabolic and immune stress, neuropathies and other degenerative diseases, often associated to aging, as retinopathies.

In particular, the research activity of this department is aimed at finding drugs and therapeutic targets that promote healthy aging, cell survival, regeneration and the optimal function of organs to treat different pathologies such as atherosclerosis, diabetes, liver fibrosis, epilepsy, degenerative diseases, such as Alzheimer and amyotrophic lateral sclerosis and degenerative pathologies of the retina.

### HEAD OF DEPARTMENT

Dr. Anabel Rojas till Dec 2022.
(Current Head: Dr. Inés Pineda-Torra)

### RESEARCH GROUPS

1. Pancreatic Islets and Stem Cells  
   Dr. Franz Martin
2. Pancreatic Islet Development & Regeneration  
   Dr. Benoit Gauthier
3. Pancreas and Liver Development and Disease  
   (till Dec 2022)  
   Dr. Anabel Rojas
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. F. Díaz-Corrales
8. Stem Cells and Translational Neurology  
   Dr. V. Capilla-González
9. Metabolism, Immunology and Cardiovascular Risk  
   Dr. I. Pineda-Torra
Current position
• Since April 2022: Junta de Andalucía- Consejería de Salud y Familias Distinguish Scientist/Group Leader CABIMER, Seville, Spain.
• Since May 2022: Member of NURCAMEIN, Nuclear Receptors Spanish Excellence Network.

Current Group Members
PhD Students
• Laurel Woodbridge (UCL-London).

Technicians
• Yolanda Aguilera García.
• Nuria Mellado Damas Sanz.
• Miguel Calero.
• Alejandro González Mendoza.

Postdoctoral fellows
• Carlos Jiménez Cortejana.

Former Members (2021-2022)
• PhD student: Annalisa Maggio (UCL-London).
• Career Development Fellows (sponsored in Charity funded Career Development Fellowship): George Robinson (Versus Arthritis), Jens de Groot (British Heart Foundation).

Research Activity
Overview
Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, and the main pathology underlying ischemic CVD is atherosclerosis, which results from dysregulation and build-up of lipids alongside various immune responses in the vascular wall. My group aims to understand how lipids affect systemic and intracellular metabolic and immune pathways and how that affects disease development. During this period we aimed to a) uncover novel modes of crosstalk between lipid metabolism and immunity, b) understand the regulation of lipid metabolism at the level of gene expression, mainly mediated by the Liver X Receptor (LXR) in immune cells such as monocytes, c) elucidate the impact of sex hormones in circulating metabolites and immune responses, and d) understand the mechanisms underlying the increased cardiovascular risk in women with autoimmune disorders such as systemic lupus erythematosus (SLE). We used human and immune cells. During this period, I moved my research activities to CABIMER from the Division of Medicine at UCL.

Research Highlights
The main highlights for the period 2021-22 are:
1. LXR and membrane lipid metabolism in human immune cells

We identified a novel mode of action of LXR involving regulation of membrane lipid rafts (specifically cholesterol and glycosphingolipids-GSLs) in lymphocytes (CD4+-T) and reported a GSL biosynthesis enzyme as a novel LXR target (Waddington et al. PNAS) and Fig.1. Changes in plasma membrane lipid composition in CD4+-T-cells are associated with altered immune synapse formation, T-cell receptor-mediated signalling, reduced T-cell proliferation and modified cytokine production. To examine the effect of LXR stimulation on the kinetics of lipid reorganization during the early stages of T cell activation, we used di-4-ANEPPDHQ staining and total internal reflection fluorescence (TIRF) microscopy to assess the interaction between CD4+-T cells and antibody-coated glass coverslips (thus mimicking the ‘immune synapse’) (Fig. x2).

2. Cardiovascular risk and lipid metabolism: age & sex differences


Robinson et al. 2021, Robinson et al 2020). Furthermore, in studies with cis and transgendered adolescents, we uncovered T-cell gender specific differences (gene expression and plasma membrane/serum lipid levels) (Robinson et al 2022, Robinson et al 2021) and evidenced that sex chromosomes and sex hormones drive different kind of changes (cell frequency vs function), respectively (Robinson et al 2021).

Grants

- 2020-2022: UCL NIHR BRC Inflammation, Immunity and Immunotherapeutics (co-PI).
- 2018-2021: Diabetes UK Project Grant (co-PI).
- 2016-2021: British Heart Foundation Project Grant (co-PI).
Publication Highlights


C Parikh, J Ponnampalam, G Seligmann, L Coelewij, ... Jury E, Ciurtin C. (2021), Impact of immunogenicity on clinical efficacy and toxicity profile of biologic agents used for treatment of inflammatory arthritis in children compared to adults. *Therapeutic Advances in Musculoskeletal Disease*, 3:1759720X211002685, DOI: 10.1177/1759720x211002685

Editorials & Reviews


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.
• Since 2016: Steering Committee Member of CIBERDEM.

Group Members

Senior Researchers
• Blanca Escudero.
• Mª Ángeles Ortega.

PhD Student
• Lucía López.

Technicians
• Raquel Araujo.
• Antonio Cárdenas.
• José Moral.

Former Members (2020-2022)

• PhD student: Leticia Álvarez.
• Technicians: Amparo Luque.

Research Activity

Overview
Our main research line is to study the role of nutrients, foods and diets in the pathogenesis of diabetes, obesity, diabetes, metabolic syndrome and non-alcoholic fatty liver disease (NAFLD). Particularly we are involved in understanding the mechanisms of actions by which hypercaloric high-fat and high-carbohydrate diets promote the onset of type 2 diabetes (T2DM) mellitus and NAFLD. We try to focus this issue from system physiology approach.

Research Highlights
Our main research highlights are:

1. We found, in mouse model of high fat diet (HFD)-induced obesity, T2DM and NAFLD, that extra virgin olive oil (EVOO) intake repaired HFD-induced hepatic damage via an anti-inflammatory effect in adipose tissue and modifications in the liver lipid composition and signaling pathways. Moreover, EVOO intake regulated glucose homeostasis, improving insulin sensitivity and pancreatic β-cell function. In addition, the intake of an EVOO much richer in phenolic compounds did not increase the beneficial effects of EVOO on liver injury, insulin sensitivity and β-cell function.
2. In a female Ldlr-/- Leiden mice with HFD-induced non-alcoholic steatohepatitis (NASH), liver fibrosis, dyslipidemia and insulin resistance (IR), we found that EVOO intake improved body weight and IR but aggravated liver inflammation and fibrosis. The potential proposed mechanisms contributing to this EVOO effects 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.

Figure 2. Effect of EVOO high fat diets on pancreatic β-cell number and apoptosis at the end of the 36-week interventional study. These are confocal images showing the nuclei stained with DAPI (blue), insulin (red) and TUNEL-positive (green) cells.

3. In a female Ldlr-/- Leiden mice with HFD-induced NASH/fibrosis, dyslipidemia and IR, EVOO intake attenuated adipose tissue hypertrophy and inflammation and exerted anti-atherosclerotic effects. The EVOO vasculoprotective effects are due to a modification in gene expression related with inflammation, a repression on monocyte/macrophage infiltration and a reduction of aortic peroxynitrites production. A higher phenolic content of olive oil did not provide further benefits in the prevention of atherosclerosis.

4. When mothers are fed, during pregnancy and lactation with EVOO, there exist a protection in the offspring against the appearance of T2DM and NAFLD, after the intake of hypercaloric diets (rich in sugars and saturated fats). This protection is different depending on the gender of the animal. EVOO intake cause transgenerational epigenetic modifications in miR expression that could contribute to offspring protection against the risk of T2DM and NAFLD development, depending on the gender.

Grants


Publication Highlights


Current position

• Since 2009: Junta de Andalucía-Consejería de Salud y Familias Staff Scientist/Group Leader CABIMER, Seville, Spain.
• Since 2017: Member of CIBERDEM, Madrid, Spain.

Group Members

Lab Manager
• Nadia Cobo Vuilleumier.

Senior Researcher
• Petra Isabel Lorenzo Ovejero.

Postdoctoral fellows
• Valentine Comaills.
• Petra Isabel Lorenzo Ovejero.
• Akaitz Dorronsoro González.
• Livia López Noriega.

PhD student
• María Eugenia Martín Vázquez García.

Master student
• Sergio Manzano.

Technicians
• Cristina Cerrada Romero.
• Daniel De Lllano Teixeira.
• Pedro Antonio Soriano Gonzalez.

Former Members (2021-2022)

• Postdoctoral Fellows: Nestor Wenceslao Meza.
• Master student: Alejandro Andredas Cordero; Sebastian Bermeo (Erasmus, France).
• Technicians: Alejandra Crespo Barreda.

Research Activity

Overview

The hallmark of Diabetes Mellitus (DM) is hyperglycemia that develops as a consequence of either impaired insulin secretion from pancreatic islet beta-cells or resistance to its blood glucose lowering effect. Deficient insulin output stems from either beta-cell dysfunction (Type 2 DM; T2DM and gestational DM; GDM) or beta-cell obliteration by the immune system (Type 1 DM; T1DM). With this in mind, our research interests focus on the identification and characterization of DM associated genes implicated in beta-cell expansion, survival and function. We also seek to understand how the expression of these genes in other tissues such as brain and immune cells may influence islet function through an intricate cross talk between organs. We perform in depth genetic, molecular and cellular studies using human/mouse cell lines, mouse models and primary human tissues. The long-term goal is to develop innovative advanced and pharmacological therapies/cures for DM. Towards this goal, we have established and extensive International and National collaborative network with hospitals, research institutes and pharmaceutical partners as well as with private foundations.

Research Highlights

The main highlights for the period 2021-22 are:

1. LRH-1/NR5A2 mode of action in conveying alpha-to-beta cell transdifferentiation and anti-apoptotic capabilities to mouse islets

Figure 1: Live imaging of a pancreatic islet in which YFP expression was induced specifically in α-cells using doxycycline (DOX) in order to perform cell fate lineage tracing.

We previously shown that activation of the nuclear receptor LRH-1/NR5A2 using the small chemical agonist BL001, developed in house, reverts hyperglycaemia in several preclinical mouse models of T1DM via immunotolerization coupled to enhanced islet beta-cell survival and regeneration likely through alpha-to-beta cell trans-differentiation.

In the past 2 years, we validated through lineage tracing studies in which alpha cells are irreversibly marked by YFP expression that BL001-mediated activation of LRH-1/NR5A2 in an hyperglycaemic environment prompts the genetic reprogramming of alpha cells towards a beta cell phenotype hallmark by the expression of key markers such as INSULIN, PDX1 and GLP1R. This cellular rewiring was
enabled by BL001-mediated re-education of the immune attack, reminiscent of wound healing.

Furthermore we demonstrated that ablation of LRH-1/NR5A2 specifically in adult beta-cells abolished the BL001 anti-diabetic action in mice correlating with increased beta-cell destruction and blunted Ptg2 induction, one of the most up-regulated genes in BL001-treated islets. Islet Ptg2 inactivation led to reduced levels of its product PGE, and loss of BL001 protection against cytokines-induced apoptosis. We show that blocking the PGE, receptor Ptger1 negated BL001-mediated islet survival against cytokine induced apoptosis. Our results define the LRH-1/PTGS2/PGE2 signalling axis as a key pathway mediating BL001 survival properties.

2. LRH-1/NR5A2 agonism rewires immunome metabolism favouring an anti-inflammatory phenotype to immune cells of type 1 diabetes mellitus donors and fosters islet graft stealthiness

We also translated our murine data to human immune cells obtained from individuals with T1DM, demonstrating the capacity of BL001 to reduce the expression of pro-inflammatory markers and cytokines from macrophages as well as dendritic cells while increasing regulatory T-cells (Tregs) important for suppressing the autoimmune attack. More importantly, the expansion of cytotoxic T-cell implicated in the destruction of beta-cells was blunted by dendritic cells and Tregs exposed to BL001. At the molecular level, BL001 immuno-paralyzed pro-inflammatory macrophages through mitohormesis while increasing oxidative phosphorylation and fatty acid oxidation in dendritic cells promoting a tolerogenic phenotype. We also demonstrate that BL001 administration to diabetic immune-competent mice transplanted with human islets improved survival rate correlating with reduced hyperglycaemia and preserved beta-cell mass. Our results establish that BL001 can induce a pro-to-anti-inflammatory phenotypic switch to human immune cells, and improve human islet engraftment function, supporting the therapeutic benefits of BL001 in human.

To further understand the complex interaction between immune and islet cells and the impact of BL001 holistically, we are now modelling T1DM in vitro using IPC-derived islet organoids and immune cells obtained from diseased individuals.

3. HMG20A, a multicellular integrator to stress adaptation

We have shown that the ‘Metabesity’ factor HMG20A regulates islet beta-cell functional maturity as well as astrocyte polarization as a gluco-adaptive/neuro-protective response to physiological stress such as obesity and diabetes. We also found that HMG20A transcript levels were increased in adipose tissue of obese non-diabetic individuals as compared to obese diabetic patients indicating a key role of HMG20A in a coordinated adaptive organ response to pathophysiological conditions. Accordingly, treatment of obese mice with ORY1001, a pharmacological inhibitor of the LSD1/CoREST complex that mimic the effect of HMG20A, normalized glucose intolerance paving the way for a new therapeutic approach for Type 2 Diabetes Mellitus.

Grants

- 2022-2024: DiabetesCERO.
- 2021-2024: PID2021-123083NB-I00 Ministerio de Ciencia, Innovación y Universidades.
- 2020-2023: Vencer el Cáncer.
- 2020-2024: Amarna Therapeutics S.L.

- 2020-2023: Vencer el Cáncer.
- 2020-2024: Amarna Therapeutics S.L.
Publication Highlights


Current position


Group Members

Postdocs
- Maurizio Riga.

PhD Students
- Mª Mercedes Pérez Fernández.
- Benito Domínguez Velasco.

Technicians
- Sara Vázquez Ávila.

Former Members (2021-2022)

- Postdocs: Magdalena Martínez-Losa; Inmaculada Márquez Noriego.
- Master Students: Miriam Gonzalvo Ramón.
- Erasmus+PhD students: Adrianna Wittek.

Research Activity

Overview
We develop new cell-based therapeutic strategies for the treatment of diseases that affect the nervous system, with special interest in those related to GABAergic interneurons such as infantile epilepsy (Dravet and Stxbp1 syndromes), mental disorders (depression, schizophrenia), or neurodegenerative disease (ataxia, Alzheimer).

We perform pre-clinical assays to verify the therapeutic potential of GABAergic interneurons transplanted into the brain of infantile epilepsy models at early time points (P3-5), analysing the ability to stop their seizures and to revert cognitive and behavioural alterations.

We are also deciphering the role of the sodium voltage-gated channel Nav1.1 in the function of GABAergic interneuron of the prefrontal cortex. This is relevant to better understand the symptoms of Dravet syndrome and also the etiology of some mental disorders.

Finally, we collaborate in the design of new miniaturized neuronal recording and stimulation devices in order to improve the detection and control of brain activity through new optogenetic technologies. These systems have a possible therapeutic application in the early detection of epileptic seizures and their prevention.

Research Highlights
During these years a major effort was devoted to show the ability of GABAergic neuronal precursors to rebalance the excitatory/inhibitory equilibrium in certain pathological conditions. They increase the inhibitory tone in the transplanted area, what recover normal brain function by reducing hyperactivity. This leads to improvements in cognitive deficits and behavioral alterations. Especially relevant was our work (Neuron, 2018) showing that it is possible to rescue cognitive deficits and
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restore brain rhythms in an animal model of familial Alzheimer Disease characterized by reduced expression of the voltage-gated sodium channel Nav1.1. Similarly, the transplanted of these neuronal precursors has the potential to reduce anxiety-like behaviors, and neutralize passive coping in a model of mental disorders (Brain Struct Funct, 2021). Currently, we are exploring a possible cell-based therapeutic application for Dravet syndrome, a refractory infantile epilepsy originated by inactivating mutations in Nav1.1.

We are transplanting GABAergic precursors that overexpress Nav1.1 in a mouse model of DS and analyzing its antiepileptic effects. In addition, we are studying the role of Nav1.1 in the prefrontal cortex and its relation with the etiology of mental disorders. In parallel, we are also applying the GABAergic neuronal precursors in a model of Stxbp1 Syndrome, another infantile epileptic encephalopathy, with promising results.

Besides, we have participated in a study about the influence of the Reelin secreted by interneurons in the lamination process of the cerebral cortex during development (PNAS USA, 2022). We also collaborated with the CSIC Microelectronics Institute to generate a multiplexed neuronal recording interface that was experimentally verified in vitro with primary neuronal cultures (IEEE Trans Biomed Circuits Syst, 2021).

In resume, our results strongly suggest that naïve or genetically-modified GABAergic interneuron precursors are a promising source of cells for regenerative medicine to treat mental conditions.

Grants

- 2021-2023 Fundación Alicia Koplowitz.
- 2020-2023 Technological contract CSIC - Stxbp1 Syndrome Association.

Publication Highlights


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Current position

- Associate Professor of Biochemistry and Molecular Biology, University of Seville Medical School.

Academic Background of the PI

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

Group Members

Postdoctoral
- Zaira González Sánchez.

PhD students
- Victoria Areal Quecuty.
- Jesús A Pérez Cabello.
- Raquel García García.
- Lucía Silvera Carrasco.

Technicians
- Daniel Tejada Moreno.

Former Members (2021-2022)
- Postdoctoral Fellows: Aurea Simón-Soro.
- Master Students: Enrico Tebaldi, Dimitris Giannacopoulos, Sabine Vernon.

Research Activity

Overview

The Cellular and Molecular Neuroimmunology 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.

Academic Background of the Emerging PI

- 2005: Ph.D., The Weizmann Institute of Science, Rehovot, Israel
- 1999: Licenciatura en Biotecnología, Universidad Nacional del Litoral (UNL), Argentina

Current position

- Associate Professor of Biochemistry and Molecular Biology, University of Seville Medical School

Principal Investigator

Dr. Cintia Roodveldt

Immune Signalling in Neurodegenerative Proteinopathies

Emerging PI

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 mechanisms of immune kinases in microglial responses and neuroinflammation elicited in amyotrophic lateral sclerosis (ALS)

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 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 neuroimmunomodulators by using different models (acute brain inflammation, septic shock, EAE, ALS and Adnp haploinsufficiency 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 (Silvera-Carrasco & Pozo, under preparation). Limited bioavailability is often a bottleneck 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 & Pozo, under review). 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): In addition to the progressive loss of motor neurons, a typical characteristic of ALS is the development of neuroinflammation. We have developed new strategies, 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 & Pozo, under review). 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).
progression. The mechanisms driving microglia activation and neurotoxicity in ALS remain incompletely understood.

Another key hallmark of ALS is the intracellular accumulation of TDP-43 protein aggregates, which are thought to play a crucial role in ALS pathophysiology. Previously, we had identified a poorly characterized signaling Ser/Thr kinase, MAPK/MAK/MRK overlapping kinase (MOK), as a protein that interacts with internalized TPD-43 aggregates and alters its activation state in primary microglia and organotypic spinal cord cultures (Leal-Lasarte et al., 2017). Given that signaling kinases are known to be central mediators in immune responses, and whose functions may be dysregulated in neuroinflammation-associated neurodegenerative diseases (García-García et al., 2021), we sought to investigate the role of MOK in microglial immune responses. Apart from identifying an epigenetic reader as the first downstream-regulated molecule for MOK reported, we showed that MOK regulates both its phosphorylated levels and its functions in the cell nucleus (Pérez-Cabello & Roodveldt, under review). By applying proteomics and transcriptomics analyses, we revealed a number of key immune pathways that are activated upon immune stimulation in a MOK-dependent manner. Remarkably, we also found that MOK is altered in spinal cord tissue from ALS patients and mouse models, particularly in microglial cells (Pérez-Cabello & Roodveldt, under review). Overall, our results support a role of MOK in the pathogenic mechanisms of ALS and contribute to the search of novel and effective therapeutic targets against ALS and other neurodegenerative diseases.
Current position

- Científico titular del CSIC.

Group Members

Postdoctoral
- Isabel Espadas Villanueva.
- Raúl López-Fernández.

PhD Students
- Alejandro Sola García.
- María Ángeles Cáliz Molina.

Technicians
- Daniel González Morán.
- Naym El Kharoubi Zamudio.

Master Students
- Ryan Conesa Bakkali.
- Mercedes Ruiz Yuste.
- Ángela Vega Blanco.

Former Members (2021-2022)
- Postdoctoral: Guillermo Martínez Corrales.

Research Activity

Overview

During the last decades, life expectancy has increased considerably, but in many cases this increase in longevity is not accompanied by an optimal quality of life during old age and ~50% of people older than 80 years of age are dependent. Given the high incidence of pathologies associated with aging (e.g. sarcopenia, diabetes, neurodegenerative diseases and cancer, among others), there is an urgent need to develop therapies to prevent and treat these conditions and promote active-healthy aging. For this reason, the definition of new interventions aimed at maintaining optimal health during the old age is of great importance for our current society. Our purpose is to evaluate the potential of novel geroprotective strategies to promote healthy aging as a therapeutic weapon to prevent disorders that impedes having an optimal quality of life and independence in the elderly.

Research Highlights

The use of geroprotectors for healthy aging

Our purpose is to evaluate the potential of novel geroprotective strategies to promote healthy aging as a therapeutic weapon to prevent disorders that impedes having an optimal quality of life and independence in the elderly. At mechanistic level, we are focused to determine the relevance of two biological process which could have great potential in the modulation of aging and age-related diseases:

- The potential of the modulation of Ac-CoA metabolism in healthspan and lifespan.

We will determine the physiological effects of the pharmacological inhibition of the main enzyme responsible for Acetyl-Coenzyme A generation, the ATP-citrate lyase, in mice. We will feed wild type mice with standard or high-fat diets supplemented with inhibitors of the ATP–citrate lyase the effects on physical health, memory, metabolic homeostasis and longevity at different ages. Mechanistic studies will decipher whether alterations in the transcriptional and proteomic profile exist and the main molecular processes leading to these changes.

Figure 1. Representative images of liver sections of normal liver and liver tumors. Liver sections were stained with hematoxylin and eosin at necropsies from mice without cancer and mice with liver cancer II: inflammatory infiltrate; White head arrow: steatosis. Scale bar 100 μm. Left: normal liver. Right: primary liver epithelial neoplasm.
The potential of the modulation of cysteine post-translational modifications in healthspan and lifespan.

We will determine the possible improvements at the cellular and physiological level produced by the modulation cysteine post-translational modifications. Using cell cultures isolated from patients suffering from Alzheimer’s disease and healthy people, we will determine the possible improvements produced by the modulation cysteine post-translational modifications in processes associated with neurodegeneration. We will carry out longevity studies in rodents using wild type mice as well as experimental models of age-related diseases using this strategy.

In this phase we will evaluate physical health, neurocognitive health and metabolic homeostasis at different ages. At mechanistic level we will carry out transcriptomic and proteomic studies focused to determine total proteomic changes and specific modulations on cysteine residues. We will also define the main master regulators of metabolism that coordinate the cellular responses.

Grants
• 2022-2024 PID2021-123965OB-I00. Ministerio de Ciencia e Innovación.
• 2022-2023 202220I059. CSIC.
• 2019-2021 PI18/01590. Instituto de Salud Carlos III.

Publication Highlights

Current position
• Since 2021: Staff Scientist/Nicolás Monardes Program.
• Fundación Pública Andaluza Progreso y Salud.

Group Members

Postdocs
• Berta De La Cerda Haynes.
• Álvaro Plaza Reyes.
• Estefanía Caballanos Infante.

PhD student
• Mohamad Mehdi Moshtaghion.

Technicians
• María Lourdes Valdés Sánchez.
• María José Marin Sainz.

Former Members (2021-2022)
• Master students: Félix Puerta, Rocío Mesa Sánchez.
• Technicians: Patricia Gallego Fernández.

Overview
The Retinal Degeneration Group was created in 2009 by Dr S. Bhattacharya, who retired in 2019. Since then, Dr Díaz-Corrales began to lead the laboratory, and in 2021, he formally became the group leader. The Retinal Degeneration Group’s main goal is to perform translational medicine to treat and diagnose ophthalmological pathologies that cause blindness, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). To meet the final purpose of this group, the research program has been divided into four strategic lines of interest.
1) The study of the molecular mechanisms of retinal degenerative diseases to identify new therapeutic targets using retinal organoids and mouse models. 2) Pre-clinical evaluation of new advanced cell and gene therapies based on developing non-viral vectors for gene delivery and replacing retinal cells derived from human iPS. 3) Development and pre-clinical evaluation of small retinal-protective molecules and epigenetic drugs that modulate the SIRT1/PARP1 axis. 4)
Validation of new biomarkers present in tear fluid for early diagnosis of eye pathologies. In the frame of translational research, Dr. Diaz-Corrales is co-founder of the Spin-off Limnopharma S.L., which would boost a future clinical trial for RP. Finally, the Retinal Degeneration Group also collaborate closely with the Ophthalmology Department of the University Hospital Virgen Macarena and regional and national patient associations.

Research Highlights

Development of a new non-viral vector for the PRPF31 gene therapy approach

During the 2021-2022 period, the Retinal Degeneration Group achieved several highlighting results. One of the most relevant was publishing one patent product of a collaborative work with the Materials Science Institute of Seville (ICMS) and CABIMER. Retinitis pigmentosa (RP) is the leading cause of inherited blindness in adults. RP begins with initial manifestations of night blindness and tunnel vision. So far, mutations in more than 80 genes have been implicated in non-syndromic RP. Many of these genes encode retinal-specific proteins, but others, such as the pre-mRNA splicing factor PRPF31, have been implicated in non-syndromic RP. PRPF31 mutations. Adeno-associated viral (AAV) vectors have been used to transduce ocular tissues efficiently. However, AAVs are challenging to handle, costly to produce and scale up, and it is debatable if neutralizing antibodies in treated patients would decrease the transfection efficiency in subsequent treatments. The development of alternative, non-viral delivery platforms like nanoparticles is of great interest to extend the application of gene therapy for RP. Amino-functionalized mesoporous silica-based nanoparticles (N-MSiNPs) were synthesized at the ICMS. Then the efficacy and safety of the N-MSiNPs were evaluated in CABIMER. Transgene expression was assessed by immunofluorescence and Western blot (WB) in vitro and in vivo (Fig. 1). The safety evaluation of mice subjected to subretinal injection was evaluated by ophthalmological tests (electroretinogram, funduscopy, tomography, and optokinetic test). N-MSiNPs delivered the therapeutic transgene PRPF31 for RP, both in vitro and in vivo, showing no adverse effects. Developing new non-viral vectors such as N-MSiNPs might constitute a valuable alternative to AAVs (Valdés-Sánchez L, Borrego-González, et al. J Clin Med. 2022).

Grants

• 2021-2023, P120/00043, Instituto de Salud Carlos III.
• 2022-2023, DTS21/000086, Instituto de Salud Carlos III.
• 2021-2023, Limnopharma S.L.
• 2019-2022, EIN2019-103021, Ministerio de Ciencia e Innovación. Acciones de dinamización «Europa Investigación».
• 2022-2023, ONCE, Ayudas a la investigación en visión 2020.

Publication Highlights


Current position

- Since 2020: Miguel Servet Researcher, CABIMER, Seville, Spain.
- Since 2021: Scientific coordinator of the Cytometry Unit of CABIMER.

Group Members

Postdoctoral
- Dr. Jesús María Sierra Párraga.

PhD Student
- Laura Olmedo Moreno.
- Concepción Panadero Morón.
- Caroline Stockwell.
- Carmen Baliña Sánchez.

Technicians
- Dr. María Norma Adán Castro.
- Rubén Bueno Fernández.
- Laura López Mangas.
- Carmen Burgos Cazorla.
- Laura Ruz Servián.
- Paula Juárez Blázquez.

Former Members (2021-2022)

- Technicians: Carlos Pinto Perea, Yolanda Aguilera, Nuria Mellado-Damas.
- Master student: Carmen Baliña Sánchez, Concepción Panadero Morón, Carmen Sánchez.
- Erasmus+ Students: Adrianna Bilińska, Marta Jędrzejewska.

Research Activity

Overview
Latest advances in diagnosis and treatments have improved survival rates of people suffering brain tumors. However, adverse effects of cancer therapies are still affecting the health of many patients that survive cancer. For this reason, researchers are focusing on the development of new 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 are interested in investigating the neuroprotective effects of stem cells against radiation, but also the potential anti-cancer properties of cell-based therapies for brain tumors.

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

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.
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 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. Furthermore, we are investigating the interaction mechanisms between MSCs and glioma cells to design safer MSC-based therapies for cancer.

Grants
- 2021-2023: PI20/00341. Instituto de Salud Carlos III.
- 2021-2022: JAEINT/21/02703. CSIC.
- 2020-2024: CP19/00046. Instituto de Salud Carlos III.
- 2020-2022: IDEAS20051CAPI. Asociación Española Contra el Cáncer.
- 2020-active: Asociación Pablo Ugarte Proyecto +VIDAL.
General Core Services

SCIENTIFIC CORE SERVICES

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

MANAGEMENT UNITS
Scientific Report 2021-2022

Pilar Cebolla
Manager

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 2.7 million euros through the period 2021-2022, supported by the recently renewed partnership of the Spanish National Research Council (CSIC), the University of Seville, the University “Pablo de Olavide”, “Consejería de Universidad, Investigación e Innovación”, and also, thanks to the income from services offered by our advanced Genomic platform, 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 1.6 million euros to finance new equipment to expand the science developed at CABIMER and undertaking dissemination activities such as the Second CABIMER meeting & Cabimer in Numbers

Concerning the infrastructure, a strong investment has been carried out to improve the technical capabilities of the core services, and consequently, to enhance the research conducted by CABIMER scientists, and also for many external users of our high-standard NGS services, which already account for half of the income obtained by the core units. 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, facing a period of drastic rise of prices, especially the electricity costs, as well as the significant increase in the volume and complexity of administrative procedures.

We have continued increasing our efforts to communicate our work to society through our website, actively managing our Twitter account and, inaugurating CABIMER Youtube Channel, with videos of presentation, research groups and core services. Many guided visit has been organized in CABIMER and we welcomed more than 1.300 visitors through this period 2021-2022, mostly high-school students, patients associations and institutional representatives. We have coordinated our participation in 75 outreach events and conferences (Science Week, Science Fair, among others), and other events with companies such as BioSpain, Bio-Europe Spring, Transfiere, Medinbio, highlighting the organization of CABIMERSCompany, the first meeting to promote public-private collaboration between CABIMER research groups and pharmaceutical and biotechnological companies, where we had the honor of having the participation of Farmaindustria, ASEBIO, Roche, Janssen, “Agencia Estatal de Investigación”, and “Corporación Tecnológica de Andalucía”. We have also organized the first conference in intellectual property and tech transfer for CABIMER researchers, with the participation of personnel from the transfer offices of the CABIMER holder institutions.

By the end of 2022, 193 persons worked at CABIMER, 28 Group Leader (including 7 emerging PIs), 11 senior researchers with stable positions, and a total of 79 PhDs researchers. In addition, CABIMER has master and last-year bachelor trainee students, which usually constitute a mass of ~20 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. In 2022, we have celebrated the First CABIMER Gender Equality In Science Conference. By the end of 2022, women represented 65% of total workers but <30% of group leaders are women; although the ratio has improved in recent years to the current 27%, we still need to work harder along this line.

During this period, an average of 35 projects per year are undertaken and we have obtained resources for a total amount of 10.8 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 CAIXA, among other entities.

We still have several goals to achieve, for instance, the recognition of National Excellence Research Centre, 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.
The main aim of CABIMER Genomics Core Facility, established in 2007, is to provide internal and external investigators resources and services to support their research needs regarding High-throughput Functional Genomics. In recent years, NGS (next generation sequencing) and previously Microarray technologies have become essential in biology to perform studies of transcriptomes, epigenetics and genomes at a global scale. Nowadays, there are several technological 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 is equipped with two NGS (Next Generation Sequencing) platforms, Ion-Torrent and Illumina technologies, with three NGS instruments: Ion-Torrent PGM sequencer, Illumina NextSeq500 and Illumina NOVASeq6000 sequencers. Furthermore, a microfluidics system for partitioning and barcoding single cells (sc 10xGenomics Chromium Controller) is extending this application. 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 amounts 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 stage 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 instruments and professional people. The high standards and the use of the most modern technology has made this facility not only increasingly relevant for the research of the groups of the center, but also for the use of external laboratories from universities and research centers from all over Andalusia and a large part of Spain, with a relevant representation of studies performed for hospitals and the health system. We are certainly proud that our know-how and services have become a key part of the research of many labs in Andalusia, where we have become the public platform of reference for genome-wide sequencing.

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 2-year period, the unit has set up new equipment for imaging, Spectrum CT, and inhalational anesthetic. In addition, laboratory space and equipment is available for metabolic monitoring, behavioural test, stereotaxic surgery, electroretinography, optical coherence tomography and transgenesis, including microinjection of DNA into zygotes and rederivation of transgenic lines by embryo transfer.
advanced microscopy techniques, including:
• Three Leica DM6000B vertical fluorescence microscopes for regular microscopy experiments.
• A Nikon Ni-E automated vertical fluorescence microscope, for the acquisition of compound big image that allows to either show a whole mount/tissue section image at higher detail or to quantify cell phenotypes in large scale while maintaining high magnification/ resolution.
• A Zeiss Axio-Imager2 vertical fluorescence microscope, equipped with an ApoTome that projects light in a structured way on the sample at different focal planes, creating several images. These subsequent images are further processed in real time, removing out-of-focus information before reconstructing them into a final optical section.
• An upgraded Leica DM6000 inverted fluorescence microscope for fixed and live cell imaging optimized with a high resolution camera and a new workstation.
• A Leica Thunder Imager microscope for automatic acquisition of samples, with a high-speed stage, 8 different LEDs and a high resolution camera. Also, this system has been improved with incubation on stage for live cell imaging (see below).
• Two Leica TCS SPS confocal microscopes, one of which is also capable of visualizing live cells in real time.

The Microscopy Facility presently counts with state-of-the-art equipment for the development of advanced microscopy techniques, including:

Scientific Coordinator
Dr. Paloma Domínguez Giménez; Dr. Clara García Calderón

Technician
Dr. Pablo Huertas Sánchez

Scientific Core Services: Microscopy
Scientific Core Services: GMP

Microscopy

Scientific Core Services: Microscopy

GMP

Science Report 2021-2022

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 not being used at present, 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. It 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.
Flow Cytometry is a powerful tool that measures functional and structural characteristics of heterogeneous mixtures of cells. Measurements are performed in liquid samples of single cells, which flow one 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, cell death 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 Flow Cytometry Core Facility of CABIMER is equipped with two BD FACSCalibur Analyzers to perform routine flow cytometry measurements and one BD LSRFortessa X-20 instrument with four laser beams to cover advanced multi-color flow cytometry experiments. This last equipment allows the simultaneous measurement of up to 16 fluorescence parameters, in addition to the analysis of cell size and complexity. It also includes a loader to automate sample acquisition in 96- and 384-well plates. In addition, the Facility has also a BD FACSariaIIu Cell Sorter that provides researchers the capability to analyze and sort cells by differences in physiology, metabolism, morphology and other characteristics. This sorter can separate up to 4 defined populations simultaneously, as well as perform single cell cloning and index sorting. Importantly, the Facility provides software to help researchers perform analysis and representation of their data quickly and effectively. Recently, three FlowJo and one FCS Express software licenses have been acquired, thus improving final interpretation of the results generated in the unit.

The specialized professionals of the Flow Cytometry Core Facility of CABIMER are responsible for the training and advice of internal and external researchers to develop efficient and reliable flow cytometry assays. The main goal of the Facility is to offer the highest quality services to advance fundamental and applied science.

Cell Culture

The Cell Culture Core Facility in CABIMER contains different restricted areas where primary and cell line cultures are carried out. Seven rooms are destined to established cell lines, one room to non-human primary cultures, a biosafety level II room for infecting cells with viruses, and a new room to carry out human primary cultures. The Facility attends to the requirements from the researchers in order to facilitate the use of equipment, providing main reagents used in cell cultures such as serum, trypsin, antibiotics, glutamine and PBS. In addition, different fetal bovine serum (FBS) batches are tested 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 contains a cell analyzer xCELLigence® RTCA DP to quantify cell proliferation and morphology changes in a real-time manner, an ultracentrifuge for isolation of viral vectors and three 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).

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 and isothermal storage for samples without liquid nitrogen contact; a new transfection system Invitrogen™ Neon™, which offers an innovative electroporation method that generates a more uniform electric field for a significant increase in transfection efficiency and cell viability; an ultra-low temperature (ULT) freezer Eppendorf CryoCube F101h (for storing viral samples) and two new TELSTAR Biological Safety Cabinets Class II.

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

Scientific Coordinator
• Dr. Anabel Rojas González

Technician
• Dr. Daniel Rodríguez Martínez

Histology

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

In order to meet the demands of researchers, CABIMER has built a highly specialized histology service, which includes tumor tissue characterisation, embryo histology, and animal pathology. The samples gathered for analysis are handled with the highest quality standards and cutting-edge technology, allowing us to provide a full range of histology services to our research community as well as the neighboring 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 facility provides guidance, 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 Histology unit offers methods for the histological analysis of human and animal biological samples. Some of the procedures accessible in this service include the preparation of paraffin-embedded samples in the automatic processor of tissue, which streamlines the work of the researches in terms of samples manipulation and protocol time. Histological slices of paraffin blocks and frozen tissues can be generated using an automated microtome and a cryostat, respectively. A vibratome is used for floating samples. Histology Core Facility also provides Tissues Microarrays (TMA), allowing researchers to investigate a large number of tissue samples integrated on a single histologic slide. The Histology Core also offers staining techniques for various cellular structures. A Cytospin is also available for the processing of biological fluids and cell cultures at the facility.
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 Biohazard 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.

Scientific Coordinator
• Dr. Ralf Wellinger

Scientific Coordinator
• Dr. Ralf Wellinger

Technician
• Mª Jose Figueroa
• Mª Dolores Carrión

The Biosafety service 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. At the disposal of authorized users there is also a biological irradiator BioBeam 8000 that allows the study, among other applications, of the repair of genetic damage in different experimental models. The Service manages, together with the Cell Culture Unit, a Biosafety level 2 laboratory (BSL2) 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 28 Tm in 2020-2022.

Scientific Coordinator
• Dr. José Carlos Reyes

Technician
• Juan Carlos Ostos
Management Units

Manager
- Pilar Cebolla

Executive Assistant
- Berta Ferrer

Human Resources
- Irene González

Labor Risk Prevention
- Juan Carlos Ostos

Project and economic management
- Carmen Ramos
- Inmaculada Uclés
- Paula Mauri

Purchasing and supplies
- Francisco J. Dorantes
- María Isabel Tovaruela
- Jennifer Chiguano
- Esperanza Muñoz
- Lucía Díaz

IT Service
- Arturo Fernández
- Modesto Jurado

Maintenance
- Rafael León
Scientific Publications

2021


García-Gutiérrez P, García-Dominguez M. BETing on a Transcriptional Deficit as the Main Cause for Cornelia de Lange Syndrome. Front Mol Biosci. 7:809232


Gauthier BR, Comalli S. Nuclear Envelope Rupture during Metastasis: The Key for Success. Cancers. 14, no. 1: 83


Gómez-González B, Sessa G, Carreáa A. Aguilera A. A new interaction between BRC2A and DDX5 promotes the repair of DNA breaks at transcribed chromatin. Mol Cell Oncol. 8(3):1910474


Katherine S Ruth et al. Genetic insights into biological mechanisms governing human ovarian ageing. NATURE. 596(7872):393-397


Vakilin M, Gheddi K. A new hypothetical model for pancreatic development based on change in the cell division orientation. Gene. 785:145607


2022


Mora-Molina R, Stöhr D, Rehm M, López-Rivas A. cFLIP downregulation is an early event upon Endoplasmic Reticulum Stress as a genome function.


2021

Inés García de Oya
"Mecanismos que regulan la salida de mitosis para el control de la correcta ploidía celular”
Thesis Supervisor: Dr. Fernando Monje. Universidad de Sevilla.

José Antonio Guerrero Martínez
"Identificación y caracterización de elementos regulatorios distales controlados por TGFβ.”
Thesis Supervisor: Dr. Jose Carlos Reyes Rosa. Universidad de Sevilla.

Ana Belén García Delgado
"Terapias avanzadas en enfermedades degenerativas de la retina”. Thesis Supervisors: Dr. Francisco Javier Díaz Corrales and Dr. Shom Shanker Bhattacharya. Universidad de Sevilla.

Pedro Ortega Moreno
"Influencia de factores de cromatina y DNA-RNA híbridos en el reparo de lesiones de cromatina.”
Thesis Supervisors: Prof. Andrés Aguilera López and Dr. Belén Gómez González. Universidad de Sevilla.

2022

Hayat Heluani Gahete
"Identification and characterization of factors involved in sodium selenite toxicity.”
Thesis Supervisor: Dr. Ralf-Erik Welling. Universidad de Sevilla

Juan Francisco Correa Vázquez
"Función de SUMO en el control de la neurogenesis”. Thesis Supervisor: Dr. Mario García Domínguez. Universidad de Sevilla.

Esther Marchena Cruz

Rocío Mora Molina

José Terrón Bautista
"Global Dynamics of Topoisomerase II Activity”. Thesis Supervisors: Dr. Felipe Cortés Ledesma and Prof. Andrés Aguilera López. Universidad de Sevilla.

Salvador Polo Generelo
"Identificación y análisis funcional del Inc-Nr6a1 SERPINE1 como reguladores tempranos de la transición epitelio-mesénquima”. Thesis supervisor: Dr. José Antonio Pintor Toro. Universidad de Sevilla.

Jesús Roca García

José Antonio Bautista
"Identificación y caracterización de la interacción física entre los complejos MCM y RNR en respuesta a daños en el DNA”. Thesis Supervisor: Dr. Félix Prado Velasco. Universidad de Sevilla.

Ana Belén García Delgado
"Terapias avanzadas en enfermedades degenerativas de la retina”. Thesis Supervisors: Dr. Francisco Javier Díaz Corrales and Dr. Shom Shanker Bhattacharya. Universidad de Sevilla.

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Jesús Roca García
January 2021

“Alternative Lengthening of Telomeres in cancer: triggers and alleviators” January 15th. Clau Azzalin. Instituto de Medicina Molecular, Lisboa, Portugal

“Genome-wide analysis of DNA repair at single-nucleotide resolution” January 22nd. Andrés Clemente. Instituto de Biología Funcional y Genómica (IBFG), Salamanca, Spain

“Mitochondrial dynamics and metabolic disorders” January 29th. Antonio Zorzano. Institute for Research in Biomedicine (IRB), Barcelona, Spain

February 2021

“Can melatonin reduce the severity of COVID-19 pandemic?” February 5th. Germaine Escames. Centro de investigación Biomédica de la Universidad de Granada, Granada, Spain

“Understanding beta cell heterogeneity from the single protein to the intact islet” February 19th. David Hodson. Institute of Metabolism and Systems Research (IMSR), and Centre of Membrane Proteins and Receptors (COMPARE), University of Birmingham (UK)

March 2021

“Redox control of protein aggregation through the autophagy master regulator TFEB/HLH-30” March 5th. Antonio Miranda. Instituto de Biomedicina de Sevilla (IBIS), Sevilla, Spain

April 2021

“Pathogenic mechanisms of CoQ deficiency” April 8th. Plácido Navas. Centro Andaluz de Biología del Desarrollo (CABD), Sevilla, Spain

May 2021

“Targeting the DNA-damage response in cancer treatment” May 7th. Josep Vicent Forment. DNA, Damage Response biology Oncology R&D AstraZeneca, Cambridge, UK

“Unraveling the Dynamic nano- and meso-scale architecture of the living cell membrane” May 14th. María García Parajo. The institute of Photonic Sciences (ICFO), Barcelona, Spain

“Cytoskeleton meets Chromatin: the role of Myosin VI in DSB repair” May 21st. Hans-Peter Wollheiland. Institute of Molecular Biology (IMB), Mainz, Germany

“Pathogenic mechanisms of CoQ deficiency” May 28th. Plácido Navas. Centro Andaluz de Biología del Desarrollo (CABD), Sevilla, Spain

June 2021

“A CRIPR view of transcriptional termination” June 4th. Steven West. University of Exeter, Exeter, UK

“Modulation of microglía and macrophage phenotype to mediate repair after central nervous system injury” February 11th. Rubén López-Vales. Instituto de Neurociencias, Universidad Autónoma de Barcelona, Barcelona, Spain

July 2021

“Unraveling the Dynamic nano- and meso-scale architecture of the living cell membrane” May 14th. María García Parajo. The institute of Photonic Sciences (ICFO), Barcelona, Spain

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“Pathogenic mechanisms of CoQ deficiency” May 28th. Plácido Navas. Centro Andaluz de Biología del Desarrollo (CABD), Sevilla, Spain

August 2021

“SEACing to understand TORC1 regulation” January 21st. Robbie Loewith. University of Geneva, Geneva, Switzerland

“Use of functional genomics for the study of the role of SWI/SNF in lung cancer” January 28th. Ignacio Varela. Instituto de Biomedicina y Biotecnología de Cantabria, Universidad de Cantabria, Cantabria, Spain

September 2021

“Principles and consequences of spatial organization of the genome” July 9th. Peter Askjaer. Centro Andaluz de Biología del Desarrollo (CABD), Sevilla, Spain

November 2021

“Mechanisms of DNA crosslink repair” February 18th. Julien Duxin. Novo Nordisk Foundation center for protein Research (CPR), University of Copenhagen, Copenhagen, Denmark

December 2021

“A new function of the TRESLIN-MTBP complex in human cells: regulation of the S/G2 transition” December 3rd. Luis Toledo. Center of Chromosome Stability, University of Copenhagen, Copenhagen, Denmark

2022

January 2022

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February 2022

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“Pathogenic mechanisms of CoQ deficiency” May 28th. Plácido Navas. Centro Andaluz de Biología del Desarrollo (CABD), Sevilla, Spain

November 2021

“Protein kinases and phosphatases regulating autophagy” November 26th. Jörn Dengjel. Department of Biology, University of Fribourg, Fribourg, Switzerland

December 2021

“A new function of the TRESLIN-MTBP complex in human cells: regulation of the S/G2 transition” December 3rd. Luis Toledo. Center of Chromosome Stability, University of Copenhagen, Copenhagen, Denmark

2022

January 2022

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February 2022

“Modulation of microglía and macrophage phenotype to mediate repair after central nervous system injury” February 11th. Rubén López-Vales. Instituto de Neurociencias, Universidad Autónoma de Barcelona, Barcelona, Spain

“Mechanisms of DNA crosslink repair” February 18th. Julien Duxin. Novo Nordisk Foundation center for protein Research (CPR), University of Copenhagen, Copenhagen, Denmark
March 2022

“Chromatin replication and epigenome Stability” March 4th. Anja Groth. Novo Nordisk Foundation center for protein Research (CPR), University of Copenhagen, Copenhagen, Denmark

“Insights into KRAS biology to identify novel therapeutic strategies for cancer” March 11th. Chiara Ambrogio. University of Torino, Torino, Italy

“Novel players in chromatin” March 18th. Rob Schneider. Institute of Functional Epigenetics, Helmholtz Center, Munich, Germany

“LHR-1 regulated extra-adrenal glucocorticoid synthesis as an immune escape mechanism of colorectal tumors” March 22nd. Thomi Brunner. University of Konstanz, Konstanz, Germany

April 2022

“Establishment and function of Chromatin Structure around Eukaryotic Chromosome Replication Origins” April 21st. Christoph Kurat. Biomedical Center Munich (BMC), Ludwig-Maximilians University (LMU), Munich, Germany

“Centriole architecture: from molecular assembly to diseases” April 29th. Virginie Hamel. University of Geneva, Department of Cell Biology, Faculty of Science, Geneva, Switzerland

May 2022

“Multi-omics integration and long read sequencing at the forefront of transcriptome research” May 13th. Ana Conesa. Institute for Integrative Systems Biology (I2SysBio), CSIC, Valencia, Spain

“Chromosome tracing” May 20th. Marc Martí-Renom. The National center for Genomic Analysis-Center for Genomic Regulation (CNAG-CRG), Barcelona, Spain

“Establishment and function of Chromatin Structure around Eukaryotic Chromosome Replication Origins” May 22nd. Christoph Kurat. Biomedical Center Munich (BMC), Ludwig-Maximilians University (LMU), Munich, Germany


“Non-coding RNA roles in coordinating DNA replication and its associated stress response” October 28th. Malte Huarte. CIMA Universidad de Navarra, Navarra, Spain

November 2022

“Metabolism in the single cell era: approaches to sharpen the cutting edge of the metabolism field” November 4th. Rafael Arguello. Centre d’Immunologie de Marseille-Luminy, Marseille, France

Characterization of bursts of structural genomic variation in budding yeast” November 11th. Juan Lucas Argueso. Colorado State University, Colorado, USA
International Workshops

Trends in Cancer Biology & Advanced Therapies
February 23rd, 25th, 2022, CABIMER, Sevilla, Spain

Speakers:
Rafael Durán (ES)
Abelardo López-Rivas (ES)
Ana Begoña (ES)
Rosa Bautista (ES)
David Cervera (ES)
Alfredo Cerrada (ES)
Sergio Gómez (FR)
Christian Fregue (ES)
Ricardo García (ES)
Rafael González (ES)
Maximiliano Mazzona (NL)
Pablo Miranda Ferrer (UK)
Ángel Menéndez (ES)
Federico Bruno (ES)
Kevin Ryan (UK)
Vera Bélem (DK)
María Soledad (ES)

Workshops, Retreats & Seminars

Scientific Report 2021-2022

Scientific Report 2021-2022

Workshops, Retreats & Seminars

Predoc and Postdoc Retreats

IV Predoc & Junior Postdoc Retreat
30.12.2021 Cortijo del Alamillo

9:00 – 9:15 Arrival and Presentation
9:30 Rocío Mora Molina: Role of cFLIP in endoplasmic reticulum stress-induced apoptosis in tumor cells
9:50 Lucía López Bermúdez: Maternal high-fat diets based on olive oil protect offspring against NAFLD features through epigenetic changes
10:10 Alejandra Álvarez Llamas: Zebrafish model for studying the role of neural stem cells in the adult brain
10:30 Paula Aguilera Aguilera: CRISPR activation screen to define strategies for cancer prevention
10:50 Federica Bruno: ChOR-seq: a new technology to study chromatin replication in mammalian cells
11:10-11:45 Coffee break
11:45 Alejandra Crespo Barreda: Human placental MSCs and their exosomes as vehicles for the Na+/I− symporter (hNIS): a new theragnostic agent
12:05 Amador Romero Franco: Regulation of DNA repair by the circadian clock
12:25 Alejandro Sola García: The ACLY inhibitor SB204990 does not alter lysine histone acetylation in mouse liver
12:45 Cristina Guilell Nedela: Exploring epigenetic compounds that induce genetic instability
13:05 Nuria Fernández Fernández: Generating phosphate-mutants in C. elegans by CRISPR-Cas9
13:25 Álvaro Plaza Reyes: Modeling Retinitis Pigmentosa using iPSC-derived Retinal Organoids
13:45 Lunch
15:30 Team-building games
17:00 End of the Retreat

Organizers:
Noelia Arroyo de Alba
Laura Olmedo Moreno
Concepción Panadero Morón
1. CABIMER WORKSHOP

December 2022

Thursday 22nd
9:15 Welcome
9:30 Franz Martín Bermudo
Boosting mitochondrial activity in metabolic liver diseases is organ-dependent
10:00 Amador Romero Franco
Human Cryptochrome1 dampens homologous recombination at nightfall
10:30 Laura Olmedo Moreno
Cross-talk between mesenchymal stem cells and glioblastoma
11:00 Coffee Break
11:30 Zaira González Sánchez
The versatile role of glutamate carboxypeptidase II (GCPII/PS-MA) and its potential as a smart delivery platform for neurodegeneration
12:00 Belén Gómez González
A new activity for the resolution of harmful R-loops
12:30 Manuel Álvarez Dolado
A shared Cell-therapy for Alzheimer and Dravet Syndrome
13:00 Concluding remarks

Workshop Program Coordinator: Ana G. Rondón

2. Internal Workshops

CABIMER WORKSHOP

December 2022

Hélène Gaillard: “Manganese is a physiologically relevant TORC1 activator in yeast and mammals”
09:30-10:00

María Castejón Griñán: “PICH as a potential therapeutic target in lymphoma”
10:00-10:30

Coffee break

Román González Prieto: “Genome (Ubiquitin-like) Proteomics”
11:00-11:30

Fernando Monje-Casas
Concluding remarks
12:30-12:45


Retreat Cabimer

4. Workshops, Retreats & Seminars
Conference Series

November

- Non-coding RNA roles in coordinating DNA replication and its associated stress response
  - Maite Huarte
  - CIMA Universidad de Navarra, Navarra, Spain

- Cohesin and Chromosome Segregation in Oocytes: a Goldilocks scenario
  - Neil Hunter
  - University of California, Davis, USA

- HnRNPA1 and G-quadruplexes regulatory role in KRAS expression
  - Gilmar Salgado
  - Université de Bourdeaux, Bordeaux, France

- Harnessing the healing power of macrophages: a journey aided by epigenomic and high-dimensional biology approaches
  - Laszlo Nagy
  - Johns Hopkins All Children’s Hospital, Florida, USA

March

- SLX4: playing with nucleases, helicases and beyond
  - Pierre Henri Gaillard
  - CRCM - Marseille, Marseille, France

- SNAREopathies and STXBP1 syndrome disease mechanisms
  - Matthijs Verhage
  - CNCR - Vrije Universiteit Amsterdam, Amsterdam, Netherlands

- Targeted protein degradation: a novel paradigm in drug development
  - Cristina Mayor-Ruiz
  - IRB Barcelona, Barcelona, Spain

February

- Dual functional role of Gasdermin B in breast cancer
  - Gema Moreno Bueno
  - IIIB, Madrid, Spain

- Modeling liver fibrosis with induced pluripotent stem cells (iPSC)
  - Pau Sancho Bru
  - IDIBAPS, Barcelona, Spain

January

- How does nucleolar stress lead to ageing in mammals? Understanding neurogeneration from a ribosome perspective
  - Oskar Fernández Capetillo
  - CNIO, Madrid, Spain

- Characterization of bursts of structural genomic variation in budding yeast
  - Juan Lucas Argueso
  - Colorado State University, Colorado, USA

- Metabolism in the single cell era: approaches to sharpen the cutting edge of the metabolism field
  - Rafael Arguello
  - Centre d’Immunologie de Marseille-Luminy, Marseille, France

April

- Unravelling the genetic pathways underlying ageing in mice
  - Colin Selman
  - University of Glasgow, Glasgow, United Kingdom

- Controlling nucleases and helicases that determine our genetic make-up
  - Joao Matos
  - Max Perutz Labs, Vienna, Austria

- Replication fork remodelling in cancer and stem cells
  - Massimo Lopes
  - ETH Institute of Biochemistry, Zurich, Switzerland

May

- Role of neuroinflammation in ALS and FTD pathogenesis
  - Robert Baloh
  - Novartis Institutes for Biomedical Research (NIBR), Basel, Switzerland

- Advancing knowledge in the biology of the oval cell and its role in liver pathology
  - Ángela Martínez Valverde
  - Instituto de Investigaciones Biomédicas Alberto Sols (IIBM), Madrid, Spain

June

- The importance of Post-translational control in liver disease
  - Malu Martínez-Chantar
  - CICbioGUNE, Bilbao, Spain

- Molecular mechanisms in transcription-coupled DNA repair
  - Martijn Luijsterburg
  - Leiden University Medical Center, Leiden, Netherlands

- New mechanisms and models in ALS
  - Abraham Acevedo
  - Hospital Universitario de Canarias, Tenerife, Spain

Conference on Equality in Science

1ª Jornada sobre Igualdad en Ciencia de CABIMER
Lunes 27 de octubre 2022, CABIMER, Sevilla
Organizadores: Unidad de Igualdad* CABIMER

Programa

9:30  Inicio
9:40  “Matemáticas con M de mujer”
  - Clara Grima (Profesora Titular de Matemática Aplicada, Universidad de Sevilla y divulgadora)
10:20  “La física, ¿un mundo masculino?”
  - Mª Isabel Gallardo (Catedrática jubilada de Física Atómica, Molecular y Nuclear. Dpto. de Física Atómica, Molecular y Nuclear, Universidad de Sevilla)
11:00  Coffee break
11:30  “Percepciones y experiencias personales como mujer en ciencia”
  - Maite Huarte (Investigadora principal. CIMA, Universidad de Navarra)
12:10  Mesa redonda
13:20  Conclusiones

*Carmen Ramos, Cristina González, Fernando Romero, Macarena Morillo, Sonia Jimeno y Tatiana García

Registro hasta completar aforo.
Actividad válida para los cursos de doctorado.
XXXIV Night Race of Guadalquivir

Cabimer & Company

05/11/2021

Scientific Report 2021-2022

Workshops, Retreats & Seminars
Science Week in Andalusia

European Night of Researchers

Instituto de Investigaciones Biomédicas "Augusto Piérola"
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Where we are

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