CENTROS DE INVESTIGACIÓN

CENTRO ANDALUZ DE BIOLOGÍA MOLECULAR Y MEDICINA REGENERATIVA (CABIMER)

COMPOSICIÓN DEL PERSONAL DE CABIMER

Con fecha 17 de junio 2015 el número de profesionales de CABIMER compuesto por Personal Investigador, Personal Técnico, Administración y Servicios Comunes es de 198 trabajadores con el siguiente desglose:

Categoria	Institución	Total
Administracion	FPS	12
	Otros	2
Total Administracion		14
IP	CSIC	9
	FPS	4
	US	5
	UPO	2
Total IP		20
Post-doc	CSIC	7
	FPS	9
	US	20
	UPO	6
	Otros	10
Total Post-doc		52
Pre-doc	CSIC	16
	FPS	6
	US	17
	UPO	3
	Otros	34
Total Pre-doc		76
Tecnico de Laboratorio	CSIC	4
	FPS	6
	US	0
	UPO	4
	Otros	3
Total Tecnico Laboratorio		17
Técnico de Servicio	CSIC	1
	FPS	18
		0
		0
Total Técnico Servicio		19
TOTAL		198

Personal de Cabimer por entidad

Entidad	sexo	Total
CSIC	Hombre	16
	Mujer	21
	Total CSIC	37
FPS	Hombre	18
	Mujer	37
	Total FPS	55
US	Hombre	16
	Mujer	28
	Total US	44
UPO	Hombre	5
	Mujer	10
	Total UPO	15
Otros	Hombre	12
	Mujer	35
	Total Otros	47
Total	Hombre	67
	Mujer	131
	Total	198

FPS. Fundación Pública Andaluza Progreso y Salud

CSIC: Consejo Superior de Investigaciones Científicas

US: Universidad de Sevilla

UPO: Universidad Pablo de Olavide

ÁREAS DE INVESTIGACIÓN

Departamento de Biología Molecular

The main research interest of this Department is the identification and understanding of the genes and mechanisms controlling genome structure, function and genome dynamics in eukaryotes. Research is focused in mammals, including human cells and murine systems, as well as model eukaryotic organisms such as the yeast *Saccharomyces cerevisiae* and the worm *Caenorhabditis elegans.* Genomic and epigenetic disorders are the bases of hundreds of pathologies related to cell proliferation, ageing and cancer. Understanding the mechanisms and factors governing Genome Biology is, therefore, essential to study basic life processes whose disorders are responsible for congenital developmental malformation, degenerative diseases and cancer.

More than a decade of sequencing effort have finally given a verdict that complexity of genome regulation rather than the number of genes, make us human. The genome contains many different regulatory elements as well as a large number of genes with unknown function that are regulated in a complex manner. The challenge for the near future will be to interpret how genes and regulatory elements coordinate the genomic choreography. In this sense, it is worth exploring the role of small RNA´s, antisense RNA´s, and 3D structure of the nuclei. Importantly, genome dynamics, including the mechanisms of duplication, DNA damage response, and chromosome segregation, are also crucial to understand the origin of genetic diseases and cancer as well as their impact in stem cell therapy, given the need for a tight and controlled proliferation for its potential application into human beings. Understanding the genes and mechanism controlling such vital process from a genome-wide perspective is crucial in Biomedicine.

One key question in Molecular Biology and Biomedicine is how DNA replication, repair, recombination, transcription, topological changes, chromatin remodeling occur in the same DNA substrate without interfering with each other and in a coordinated manner during the cell cycle. There may be a mechanistic impossibility for the simultaneous occurrence of two different reactions on the same DNA segment or there may be sterical impediments for the action of two different machineries at the same site that are known to strongly compromise genome integrity and have an impact on chromosome segregation. The answer to these questions are important in Biology and Biomedicine, because genome instability is not only a driving force in evolution but is frequently associated with cancer and some genetic diseases.

The interconnection among different nuclear processes reveals the importance of understanding the mechanisms and factors that control gene and protein function, as well as the importance of studying genomic stability in order to learn how to control cell proliferation and differentiation. However, most cells of a multicellular organism are genetically identical, but they can be structurally and functionally very different owing to differential gene expression programs. This diversity is established by interplay between specific transcription factors and epigenetic mechanisms, which can involve both DNA and chromatin modifications, resulting in the stable inheritance of gene expression patterns without changes in the genome sequence. Inheritance of different transcriptional states, essential during cell differentiation, also involves chromatin modifications (epigenetic marks). Thus, epigenetic information (chemical modifications of base pairs and histones) confers inheritable individual characteristics to differentiated stem cells, and constitutes an additional layer of regulation.

Alterations in these epigenetic mechanisms are at the basis of major pathologies, including cancer and growth defects, congenital syndromes involving chromosomal instability and mental retardation, etc. Furthermore, understanding epigenetic mechanisms is also of paramount importance in controlling totipotency and for the use of stem cells and progress of cell-based therapies.

Therefore, genome and epigenome studies are essential to understand cancer, cell differentiation and dedifferentiation processes and ageing, which makes this research area of pivotal importance in the whole context of CABIMER's research. Only by identifying the genetics and epigenetics of/and the mechanisms of gene regulation and chromosome integrity and segregation will we be able to develop efficient and specific therapies against cancer and other genetic diseases, which constitutes the long-term goal of this Department.

Department PIs

- Andrés Aguilera.
- José C. Reyes.
- Félix Prado.
- Ralf E. Wellinger.
- Fernando Monje Casas.

Departamento de Señalización Celular

Normal cell physiology and tissue homeostasis requires the correct establishment of cell polarity as well as controlled cell growth. Indeed, loss of cell polarity, tissue disorganisation, unregulated cell death and excessive cell proliferation are hallmarks of cancer. In all advanced epithelial cancers, malignant cells have lost polarity and connections to the basement membrane and they have become proliferative, motile, and invasive. Likewise, alterations in cell polarity and increased cell death could also contribute to the progression of different degenerative pathologies. The main research interest of the Cell Signalling Department is to understand the mechanisms and factors controlling cell organization, behaviour and communication, both at individual level and in the context of organs and tissues, with the goal of advancing the knowledge of neoplasic, genetics and degenerative diseases. Our Department's global objective will be implemented by developing four different aspects of cell physiology in health and disease. Briefly, we will try to: i) characterize components essential for defining an intrinsic, autonomous, cell polarity axis, ii) examine the crosstalk between autophagy and apoptosis in normal and tumour cells, iii) characterize new small RNAs (sRNAs) involved in mitotic checkpoints and in apoptosis resulting from loss of cell-matrix interactions iv) evaluate the contribution of NGF activity to neuronal cell death and v) better understand the basis of immune cellular homeostasis in order to achieve a smart manipulation of the immune response in neurodegenerative diseases.

1) To characterize components essential for defining an intrinsic, autonomous, cell polarity axis. Cell polarity axis could be defined as the result of specific and stable interactions between two parallel and polarized systems, the endomembrane system extending from the nuclear envelope (NE) through the Golgi apparatus (GA) towards the plasma membrane (PM), and the cytoskeletal connection between the nucleus, the centrosome (CTR) and the PM. These two systems maintain the CTR-GA associated to the nucleus and to the PM. We seek a molecular characterisation of key interfaces between these two systems. The ultimate goal is to decide to what extent these connected compartments form a cell-wide polarized architecture able to channel signalling pathways. A massive two-hybrid screen, done with baits covering the full length of several pericentrosomal proteins, has identified potential partners for each of them. We focus on gene products previously shown to have a specific role in interfacing two or several compartments of the N-Ctr-GA-PM axis. We also aim at studying the continuity of this axis through cell

division or during CTR/Primary Cilium (PC) transition. This transition is a major reorganisation of cell polarity that occurs almost ubiquitously during postmitotic cell differentiation in vertebrates. The role of the primary cilium as a sensory organelle has unveiled basic cellular mechanisms underlying severe human genetic diseases known as ciliopathies.

2) To examine the crosstalk between autophagy and apoptosis in normal and tumour cells. Since the initial identification of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and TRAIL receptors there has been exceptional progress in understanding the signalling involved in the killing of tumor cells by TRAIL. Furthermore, the observation that TRAIL specifically induces cell death in tumor cells without affecting untransformed cells has inspired clinical trials with therapeutic agents designed to activate the apoptosis-inducing TRAIL receptors. On the other hand, certain cancer cells, like those of the breast are generally refractory to TRAIL-induced apoptosis. Despite these advances, many questions still remain unresolved regarding the mechanisms underlying the resistance of cells to TRAIL. The main objective of our research for the next years is to investigate the relative contribution of cellular FLICE Inhibitory Protein (FLIP), autophagy and cell cycle checkpoints to the resistance of cells to TRAIL. In this respect, we intend to examine the possible crosstalk between autophagy and apoptosis in normal and tumor cells treated with TRAIL. The regulation of FLIP expression during the cell cycle and the role of cell cycle checkpoints in the control of FLIP levels and TRAIL sensitivity will be also determined. Finally, given the important role of the epithelial-mesenchymal transition (EMT) in the progression of carcinomas and the acquisition of resistance to apoptosis inEMT, we plan to investigate the regulation of TRAIL sensitivity during EMT.

3) To characterize new small RNAs (sRNAs) involved in mitotic checkpoints and in apoptosis resulting from loss of cell-matrix interactions. Recent genome-wide studies have allowed a deep analysis of the human and mouse transcriptomes and revealed that a large portion of the eukaryotic genome is transcribed as noncoding RNAs (ncRNAs). The most studied ncRNAs are the small ncRNAs named microRNAs (miRNAs). We have recently developed a novel small RNAs expression system using lentiviral-based libraries for the identification of tumorigenesis-related genes. Using these libraries we have isolated small RNAs (sRNAs) involved in mitotic spindle checkpoint signalling and in apoptosis resulting from loss of cell-matrix interactions that we will try to characterize. In order to provide an additional platform to identify putative tumour suppressors sRNAs involved in the mitotic spindle checkpoint

signalling, anoikis and tumour cell invasion, we will also develop lentiviral libraries based on sRNAs depletion by sequestration using sRNAs sponges. We finally propose the search of natural transcripts (natural sponges) that block sRNAs activity, focusing our attention on introns and intergenic regions. Libraries based on high-throughput sequencing will be carried out to identify ncRNAs covalently crosslinked to native AGO proteins using irradiated and non-irradiated cells. The differentially expressed long ncRNAs will be analyzed as putative sponges with regulatory role in gene expression.

4) To evaluate the contribution of NGF activity to neuronal cell death. During the last few years, we have studied the signal transduction of NGF and Amyloid beta (Ab) in cultured mouse hippocampal neurons. We have demonstrated that the deleterious effects of Ab are mostly due to the impairment of the neurotrophic activity associated to NGF. Thus, we have revealed that the reinforcement of NGF signalling at various steps of its transduction pathway may counteract the neurotoxic action of Ab and save neurons from death. The final effect of the transduction pathway of NGF is the expression of Enhancer-of-split 1 (HES1) gene, which is promoted by NGF and, conversely, inhibited by Ab. Because overexpression of HES1 shows an anti-amyloid activity in vitro, we aim at validating our results in vivo. We have already constructed lentiviral vector expressing HES1. The vector will be sterereotaxically injected into the dorsal hippocampi of mice. Such mice will be double mutants of amyloid precursor protein and presenilin 1, which develop an Alzheimer-like disease early in life. After injection, the animal memory and behaviour will be studied as well as neuronal death by histochemical means after sacrifice. Results obtained, if any, will help to evaluate the extent to which the promotion of HES1 expression may help to retard the progression of Alzheimer´s disease.

5) To better understand the basis of immune cellular homeostasis in order to achieve a smart manipulation of the immune response in neurodegenerative diseases. For this purpose, we develop two approaches based on: i) Basic disease-oriented research: Characterization of the mechanisms of immune regulation, neuroprotection, and neurodegeneration of bioactive peptides in inflammatory/autoimmune disorders. Therapeutic exploitation of peptide-functionalised, nano-based drug-delivery systems in inflammatory/ autoimmune disorders. Activation of endogenous regulatory immune cells as an approach towards cell therapy. Immunologic effects and mechanisms of disease-linked protein aggregation and chaperone function and, b) Patient-oriented research: Studies in patients suffering multiple sclerosis and amyotrophic lateral sclerosis aimed to produce research results in profiling studies (such as metabolomics, immunomics) to understand disease mechanisms from a systems biology perspective as a non-invasive

approach to diagnose and grade neurodegenerative disorders with an autoimmune/inflammatory component. This could allow the assessment of new therapies during clinical trials, the identification of patients at risk to develop adverse effects during treatment, and the final implementation of new tools towards a more personalised medicine.

Department PIs

- Rosa Ríos.
- Abelardo López.
- José Antonio Pintor.
- Alfredo Rodríguez Tebar.
- David Pozo.

Departamento de Células Troncales

The main goal of the Stem Cell and Cellular Reprogramming Dept is to explore the basic mechanisms of stem cell biology, cellular reprogramming and in-vitro expansion and differentiation of stem cells to foster stem cells applications to medical needs. Research is organized in five independent groups that interact among them to provide the knowledge I translational regenerative medicine. In addition this Dept is responsible of the Cellular Medicaments Production Unit under Good Manufacture Practices standards (Core Facility), subsequently also keeps the Unit for Documentation and Management of Clinical Trials Data.

A better knowledge of the developmental signals that drive development of cells and tissues is mandatory to look forward new strategies (small molecules, in-vitro differentiation) in promoting cell and tissue regeneration. Two groups in labs 1 and 2 (Drs. Benoit Gauthier and Anabel Rojas) explore the role of PAX and GATA factors in the development of pancreas and liver. Diseases such as diabetes mellitus, liver fibrosis, pancreatitis, etc may benefit from the published and patented data.

The basicknowledge on stem cells is explored at different levels: cellular reprogramming using and innovative Pdx-1 tracer (Dr. Franz Martin), in-vitro differentiation of human embryonic stem cells and induced pluripotent stem cells (Drs. Bernat Soria and Karim Hmadcha), expansion of adult progenitors (Dr.

F. Martin), DNA damage (Dr. Felipe Cortés) and posttranslational modifications of developmental key factors (Dr. Mario García). Disease areas covered rank from cancer stem cells to diabetes and neurodegenerative diseases. Both private and public funds finance these groups: Plan Nacional de I+D, Proyectos de Excelencia de la Junta de Andalucia, RETICS (Terapia Celular), CIBER (CIBERDEM), Juvenile Diabetes Research Foundation, Corporación Tecnológica de Andalucía, Programa INNPACTO and European Union.

The Director of the Dept is also responsible for the GMP Unit which produces "cellular medicaments" (mesenchymal stem cells from adipose tissue) for 4 different clinical trials, one for multiple sclerosis and other three for peripheral arterial disease in diabetic and non-diabetic patients.

Department PIs

- Bernat Soria.
- Benoit Gauthier.
- Franz Martin.
- Mario García.
- Felipe Cortés.
- Anabel Rojas.

Departamento de Terapia Celular y Medicina Regenerativa

The department is focused on Health Biotechnology in Stem cell research. Research groups are devoted to understand basic science of cell reprogramming and translate them into useful technologies for therapy and medicine. Research is mainly conducted in Animal cell culture and mice models to answer intriguing questions related to cell death pathways which lead to Retinal degeneration, Type 2 diabetes, developmental delays, immune deficiencies and various neuropathologies. Molecular factors like genomic rearrangements and epigenetic modifications are closely studied to understand phenotypes like malignancy, ageing, cell death by apoptotic signaling in differentiated cells like neurons, photoreceptors and beta-pancreatic cells. How house keeping genes only effect a particular cell type i.e. Retina; how NO and hypoxia effect pluripotency state of stem cells and their differentiation to specific cell types, what

cellular mechanisms function surmount genomic instability in stem cells, are question which can redefine the field of regenerative medicine and pursued in the department.

The department collaborates with clinicians and hospitals to procure diseased tissue and cell samples. The two-way collaborations help in translation oriented research as well as update clinicians of novel strategies and understanding developed inside and outside our department. Concerted efforts have lead to development of novel strategies in cellular and gene therapy for ocular diseases. Cell therapy, which could provide a promising solution, is also embedded with multiple hurdles and the department has overcome some of them. Methods to reprogram patient derived and gene corrected cells into stem cells and further into desired cell type have been standardized. Protocol for differentiation of stem cells to Retinal Pigmented Epithelium, Photoreceptor, Neurons, and cells of pancreatic lineage are established and reported by the department.

Nevertheless many challenges still remain to be overcome, broadly divided into two categories quality and quantity. The need for the number of fully differentiated cells for future cell therapy trials is expected in millions for each patient.

This being the case the department is putting efforts in optimization of culture conditions for expansion of stem cells in bioreactors. Additionally, for the cells to be available for human use have to be strictly quality controlled and dealt with precision. Most important concern being malignant potential of any cell used in therapy, with focus on genomic integrity of cells produced. Keen efforts are being made for understanding genomic and epigenomic factors that could induce malignant behavior. Protocols are developed to rapidly and accurately screen any malfunction of cells produced under particular conditions. Altogether the department is focused on the establishment of a technologically adequate and scientifically sound platform for basic and translational research. The research groups and their specific areas of expertise and interests are as follows

The vision group is focused on cell therapy of patient in advanced stages of retinal degeneration. Also use reverse genetic and Genome sequencing to identify new genes and mouse models with retinal degeneration and understand their cell death mechanism. Epigenetic and genomic changes are studied during embryonic and *in vitro* differentiation toward retinal cells in a comparative manner, in generating understanding for producing authentic cells for therapy.

Stem cell signaling group is focused on understanding effects of external agents like , NO, hypoxia etc to develop better culture conditions for stem cells. They are fascinated by question related to how stem cell retain pluripotency, what are the underlying signaling mechanisms and links between apoptosis and stem cell differentiation signaling, especially towards pancreatic lineage.

The motor neuron group is focused in neuronal cell therapy and use of animal models to try new cell-based strategies that may be useful in the treatment of many neuropathologies, such as ataxia, epilepsy or West Syndrome.

The genomic instability group is interested in finding molecular mechanisms used by cells to maintaining a stable Genome, important to avoid cancer. The group has developed novel assays to detect DNA damage and identify specific pathways used for the repair and a novel and useful dimension to existing intellect of the department.

Department PIs

- Shomi Bhattacharya.
- Francisco Bedoya.
- Manuel Dolado.
- Pablo Huertas.

PROYECTOS APROBADOS

Departamento de Biología Molecular

Grupo Inestabilidad Genómica / Biogénesis de mRNPs (IP: Dr. Andrés Aguilera)

- RNA-DNA hybrids as a source of genome instability in cancer.
- TARLOOP – ERC Advanced grant.

Grupo Epigenética y Expresión Génica (IP: Dr. José Carlos Reyes)

- Cooperación entre modificadores de la cromatina para regular la actividad de enhancers durante la diferenciación celular.

Grupo Plasticidad Mitocondrial y Replicación (Dr. Ralf Wellinger)

- Metabolismo del DNA.

Departamento de Células Troncales

Grupo Desarrollo y Regeneración de Islotes Pancreáticos (IP. Dr. Benoit Gauthier)

- Pax8, deciphering new targets in the diagnostic and treatment of estational diabetes . Postdoc: Alejandro Martín Montalvo.

Grupo Terapia Celular de la Diabetes Mellitus (IP: Dr. Bernat Soria)

- Terapia Combinada con Células Mesenquimales y Células Treguladoras de Cordón Umbilical en la Diabetes Mellitus Tipo1.

Grupo Islotes Pancreáticos y Células Madre (IP. Dr. Franz Martin)

- Mecanismo de acción de la proteccion frente al sindrome metabolico y la diabetes tipo 2, de las dieta hiperlipidicas basadas en aceite de virgen extraoliva.

Grupo Daño en el ADN: Cáncer y Neurodegeneración (IP: Dr. Felipe Cortés)

- Roturas de ADN bloqueadas: mecanismos moleculares e implicaciones patológicas.
- Global dynamics of topoisomerase-induced DNA breaks. ERC Consolidator Grant.

Departamento de Señalización Celular

Grupo Terapias Avanzadas en Neuroprotección (IP: Dr. David Pozo)

- Sistemas nanoestructurados direccionados por el péptido intesinal vasoactivo (VIP) como alternativas para la detección y tratamiento de cáncer de próstata: caracterización preclínica.

Grupo: Tráfico de Membranas y Citoesqueleto en la Dinámica Celular (IP: Dr. Rosa Ríos)

- Genome- wide screen for new centrosome position regulators. Marie Curie. Postdoc: Fernando Romero.

Grupo: Ciclo Celular y Oncogénesis (IP. José Antonio Pintor)

- Regulacion transcripcional y post-transcripcional por rnas no codificantes de cadena larga (lncrnas) en la transicion epitelio-mesenquima.

Departamento de Terapia Celular y Medicina Regenerativa

Grupo Reparación de Cortes de Doble Cadena en el DNA y Patologías (IP: Dr. Pablo Huertas)

- Procesamiento de los cortes de doble cadena en el ADN y su implicación en el desarrollo tumoral.

Grupo: Degeneración de la retina: de la genética a la terapia (IP. Shomi Bhattacharya)

- EYE -Risk (Programa Marco H2020).

PRODUCCIÓN CIENTÍFICA

Publicaciones

Las publicaciones más destacadas son las siguientes:

Proc Natl Acad Sci USA

Increased Aurora B activity causes continuous disruption of kinetochore-microtubule attachments and spindle instability.

Cell Rep

BRCA1 Accelerates CtIP-Mediated DNA-End Resection.

Nature

BRCA2 prevents R-loop accumulation and associates with TREX-2 mRNA export factor PCID2.

Proc Natl Acad Sci USA

Role for RNA:DNA hybrids in origin-independent replication priming in a eukaryotic system.

PLoS Biol

Alpha-catenin-Dependent Recruitment of the Centrosomal Protein CAP350 to Adherens Junctions Allows Epithelial Cells to Acquire a Columnar Shape

EMBO J

RNA polymerase II contributes to preventing transcription-mediated replication fork stalls.

PNAS USA

Increased Aurora B activity causes continuous disruption of kinetochore-microtubule attachments and spindle instability.

El factor de impacto alcanzado por las publicaciones del Centro es de 9,19 y el 81 % de las revistas científicas están en Q1.

Magazine	FI	Q
Adv Protein Chem Struct Biol.	3,736	Q2
Curr. Biol.	9,916	Q1
Dis Model Mech.	5,537	Q1
EMBO Journal	10,748	Q1
Food Chem Toxicol	2,61	Q1
J Membr Bio	--	
J. Biol. Chem.	4,6	Q1
Med Res Rev	--	
Methods Mol Biol	--	
Mol. Cell	15,324	Q1
Nat Rev Cancer.	41,706	Q1
Neurobiol Aging.	4,853	Q1
Nucleic Acids Res	8,378	Q1
Nutrients.	3,148	Q2
Oncogene	7,719	Q1
PLoS Biol.	11,771	Q1
Plos One	3,534	Q1
Proc Natl Acad Sci U S A.	10,727	Q1
Stem Cells Int.	2,806	Q4
World J Stem Cells.	--	

PREMIOS Y RECONOCIMIENTOS

Group: Benoit Gauthier

Premiado: Alejandro Martín Calvo.

Premio Jóvenes Investigadores 2014: Fundación Real Maestranza de Caballería de Sevilla.

Grupo: Felipe Cortés

Premiado: Felipe Cortés.

Premio Joven Investigador SEBBM. Institution: Sociedad Española de Bioquímica y Biología Molecular.

Grupo: Felipe Cortés

Premido: Felipe Cortés. EMBO Young Investigators.