

# INSTITUTO UNIVERSITARIO DE BIOLOGÍA MOLECULAR (IUBM)

**UAM**

**INSTITUTE FOR MOLECULAR BIOLOGY-UAM**

## **ANNUAL REPORT 2023**



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## Foreword by the Director

The Institute for Molecular Biology (IUBM) of the Autonomous University of Madrid (UAM) was created in 1971, being the first university research institute established in our country. The Institute, initially located in the Faculty of Sciences of the UAM, had from its origin a very close relationship with the Department of Molecular Biology of the UAM formed under the leadership of Prof. Federico Mayor Zaragoza. In September 1975, the IUBM-UAM joined the new Center for Molecular Biology, founded under the auspices of Prof. Severo Ochoa as a joint institution of the Spanish National Research Council (CSIC) and the UAM. Since then, the IUBM-UAM assembles all the UAM personnel who develops their research at the laboratories of the Center for Molecular Biology Severo Ochoa (CBM) in fields related to molecular biology and biomedicine.

In 2023, the scientific staff of the IUBM-UAM comprised **69 permanent members**, including full professors (“catedráticos/as”), associated professors (“profesores/as titulares”), assistant professors (“profesores/as contratados doctor and ayudantes doctor”) and “Ramón y Cajal” and Talento junior researchers, who carry out their teaching in different UAM Departments (Molecular Biology, Biology, Neuroscience, Applied Physical Chemistry and Physics of Condensed Matter). The IUBM-UAM members are distributed according to their research interests among the main Scientific Programs in which the CBM is structured: Genome Dynamics and Function (including Genome decoding and Genome maintenance and instability Research Units), Tissue and Organ Homeostasis (including Cell architecture and organogenesis and Cell-cell communication and inflammation Units), Physiological and Pathological Processes (including Molecular Neuropathology and Metabolic and signaling networks in disease Units) and Interactions with the environment (including Immune system development and function and Microbes in health and welfare Units). **47 staff members** of the IUBM-UAM are **principal or co-principal investigators** in research projects ongoing at the CBM. In addition, **11 postdoctoral fellows and circa 30 PhD students** were ascribed to the IUBM-UAM during 2023 as non-permanent members.

During 2023, the scientific personnel of the IUBM-UAM has published **77 research articles** and directed **61 ongoing research projects**, funded by different national, European and international institutions. The research interests, publications, and funded projects of IUBM PIs are detailed in this Annual Report. It is also worth noting that, in addition to their active involvement in research, the IUBM-UAM members intensively participate in undergraduate and graduate teaching, and also in PhD programs related to their investigation fields. In 2023, **15 doctoral theses** directed by members of the IUBM-UAM were presented and many more are ongoing.

In 2023 we held the second meeting of our External Scientific Advisory Board, who made very helpful suggestions and reassuring comments regarding the activities of the IUBM. To encourage young investigators, the IUBM continued supporting in 2023 an Award to the best doctoral thesis presented at the CBM during this period, as well as awards for the best Oral Communication and the best Poster presented at the X Workshop of Students & Posdocs organized by these students at the CBM.

It is worth mentioning that in 2023 took place the entry into force of the new Agreement and Internal Regime Regulations of the CBM, that hopefully will continue to guarantee a close collaboration between UAM and CSIC in our center. During this year the CBM has started to implement different initiatives in the context of **the accreditation as a Severo Ochoa Centre of Excellence for the period 2023-2027**. This is both a great opportunity and a challenge for the CBM and the IUBM-UAM to foster and consolidate first-level synergic research lines and scientific infrastructures and to recruit talented young investigators to secure faculty renovation in the next years.

Federico Mayor  
Professor of Biochemistry and Molecular Biology  
Director IUBM-UAM

## Activities IUBM-UAM 2023



Delivery of the **PINP AWARD TO THE BEST DOCTORAL THESIS** presented at the CBMSO during the year 2023. **Dr. Carl Lehmann** and Prof. Paola Bovolenta, Director of the CBMSO. December, 2023.



Delivery of the Best Poster Award (**Jorge Galán Cruz**), and the Best Oral Communication Award (**Andrés Soto Zaragoza**), X WORKSHOP STUDENTS & POSDOCS CBM. Photo also includes Prof. Federico Mayor, IUBM-UAM Director, Prof. Paola Bovolenta, Director CBM and members of the Organizing Committee. November 2023.

## ACTO HOMENAJE AL PROFESOR

# José M. Cuezva



**Jueves 6 de julio de 2023**

Sala Ramón Areces,  
 Centro de Biología Molecular Severo Ochoa  
 (CBMSO, UAM-CSIC)  
 Universidad Autónoma de Madrid  
 c/ Nicolás Cabrera 1, 28049, Madrid

## PROGRAMA

*Maestras de ceremonia Sara Cogliati y Laura Formentini*

- 11:00h Apertura del Acto: **Prof. Laura Formentini**. CBMSO
- *Intervención invitado de honor*
- *Intervenciones de maestros, colegas, discípulos y amigos*
- Prof. José M<sup>a</sup> Medina. Universidad de Salamanca.
- Prof. Fernando Valdivieso. UAM
- Prof. Magdalena Ugarte. UAM-CEDEM
- Prof. Rafael Garesse. UAM
- Prof. Federico Mayor Zaragoza. UAM-Fundación Cultura de Paz
- Prof. Jorgina Satrústegui. CBMSO
- Prof. Sebastian Vieira. UAM
- Prof. Luis Viña Liste. UAM
- Prof. Isabel Fabregat. IDIBELL Barcelona
- Cristina Nuñez de Arenas. CBMSO
- *Videos y mensajes*
- *Recorrido científico/histórico del trabajo del Prof. J.M Cuezva*
- Prof. José Antonio Enríquez. Centro Nacional de Investigaciones Cardiovasculares
- *Intervenciones Institucionales*
- Prof. Federico Mayor Menéndez. Director Instituto IUBM– UAM
- Prof. María Fernández Lobato. Directora Departamento Biología Molecular– UAM
- Prof. Paola Bovolenta. Directora CBMSO-UAM/CSIC.
- *Intervención del Prof. José Manuel Cuezva*
- *Cierre del Acto*
- Prof. Manuel Chicharro. Decano de la Facultad de Ciencias-UAM
- 14:30h *Vino español.*



## Director

 Prof. Federico Mayor Menéndez. *Universidad Autónoma de Madrid.*

## Scientific Secretary

 Prof. María Yáñez Mo. *Universidad Autónoma de Madrid.*

## External Scientific Advisory Board

 Prof. Antonio Zorzano Olarte. *Universidad de Barcelona*

 Prof. Isabel Fariñas Gómez. *Universidad de Valencia*

 Prof. M<sup>a</sup> Ángela Nieto Toledano. *Instituto de Neurociencias, Universidad Miguel Hernández (UMH) Elche-CSIC*

 Prof. José M<sup>a</sup> Valpuesta Moralejo. *Centro Nacional de Biotecnología CSIC.*

 Prof. María Molina Martín. *Universidad Complutense de Madrid.*

## SCIENTIFIC STAFF IUBM-UAM 2022

### ➤ Permanent members

ALMENDRAL DEL RIO, JOSE MARIA  
 AMILS PIBERNAT, RICARDO.  
 ARCO MARTÍNEZ, ARACELI  
 BALSA MARTÍNEZ, EDUARDO  
 BENITEZ MORENO, MARIA JOSÉ  
 BERENGUER CARLOS, JOSE\*  
 BERLANGA CHIQUERO, JUAN JOSE  
 BONAY MIARONS, PEDRO.  
 BULLIDO DE LAS HERAS, MARIA JESUS  
 CABRERA SOLA, MARGARITA  
 CARRASCO CERRO, ELISA  
 CARRASCOSA BAEZA, JOSE MARIA  
 COGLIATI, SARA  
 CONTRERAS BALSA, LAURA  
 CORREAS HORNERO, ISABEL

CUBELOS ALVAREZ, BEATRIZ  
CUEZVA MARCOS, JOSE MANUEL \*  
DIAZ NIDO, JAVIER  
DIEZ GUERRA, FRANCISCO JAVIER  
FORMENTINI, LAURA  
FRESNO ESCUDERO, MANUEL.  
GÁMEZ ABASCAL, ALEJANDRA  
GARCIA-ESCUADERO BARRERAS, VEGA  
GARCIA MATEU, MAURICIO  
GARCÍA-HIGUERA, IRENE  
GIRONES PUJOL, NURIA  
HERNANDEZ PÉREZ, FÉLIX  
HERRERO SOLANS, MARIA PILAR\*  
HIDALGO HUERTAS, AURELIO  
IÑIGUEZ PEÑA, MIGUEL ANGEL  
JIMÉNEZ MARTÍNEZ, JUAN SALVADOR  
LOPEZ BUENO, ALBERTO  
LOPEZ CORCUERA, BEATRIZ  
LOPEZ GUERRERO, JOSE ANTONIO  
MAYOR MENENDEZ, FEDERICO  
MENCÍA CABALLERO, MARIO  
MÍGUEZ GÓMEZ, DAVID  
MURGA MONTESINOS, CRISTINA  
NAVARRO LÉRIDA, INMACULADA  
PAZOS DON PEDRO, MANUEL  
PARDO MERINO, BEATRIZ  
PENELA MARQUEZ, PETRONILA  
PÉREZ ALVAREZ, MARIA JOSÉ  
PÉREZ ARNÁIZ, PATRICIA  
PEREZ GONZALEZ, BELEN  
PÉREZ PEREIRA, MARTA  
PORLAN ALONSO, EVA  
PUCCIARELLI, M<sup>a</sup> GRACIELA  
RASTROJO LASTRAS, ALBERTO  
REGLERO REAL, NATALIA  
REMACHA MORENO, MIGUEL  
REQUENA ROLANIA, JOSE MARIA  
RIBAS NUÑEZ, CATALINA  
RICHARD RODRIGUEZ, EVA  
RODRIGUEZ GABRIEL, MIGUEL ANGEL  
RODRIGUEZ POMBO, PILAR  
RUANO GALLEGO, DAVID  
RUIZ DESVIAT, LOURDES  
RUIZ GOMEZ, ANA  
SANTOS HERNÁNDEZ, JAVIER  
SATRUSTEGUI GIL-DELGADO, JORGINA.  
SOTO ALVAREZ, MANUEL  
STAMATAKIS ADRIANI, KONSTANTINOS



TRABA DOMÍNGUEZ, JAVIER  
 VALBUENA JIMÉNEZ, ALEJANDRO  
 VAQUERO LORENZO, CONCEPCIÓN  
 VILLA MORALES, MARIA  
 VENTOSO BANDE, IVAN  
 YÁÑEZ MO, MARIA  
 ZAFRA GOMEZ, FRANCISCO

**\* Members retired during the year 2023**

➤ **Non-permanent postdoctoral members**

ALDUDO, JESUS  
 BOSCH REÑE, SANDRA  
 CECCHINI, DAVIDE AGOSTINO  
 COBOS FERNÁNDEZ, M<sup>a</sup> ANGELES  
 FRANCO QUIJORNA, ISAAC  
 GIMENO PÉREZ, MARIA  
 JARAÍZ RODRIGUEZ, MARIA DEL PILAR  
 LAINE MENÉNDEZ, SARA  
 LÓPEZ NIEVA, PILAR  
 PORTILLA, YADILENY  
 VIDA RUEDA, CARMEN

➤ **PhD Students**

1. ALBITRE SANZ, ANGELA\*
2. ANDRÉS HERNÁIZ, RAQUEL DE
3. ASENSIO LÓPEZ, ALEJANDRO
4. BARRIOS MUÑOZ, ANA LAURA
5. DE ANDRÉS HERNÁIZ, MIGUEL \*
6. DE LA FLOR GARCÍA, MIGUEL
7. FULGENCIO COBIAN, ALEJANDRO
8. GALLEGO GARCÍA, DIANA
9. GARCÍA GONZÁLEZ, DIEGO MARIN
10. GARCÍA PRIETO, TERESA\*
11. HERREROS CABELLO, ALFONSO
12. LÓPEZ FONSECA, CARLA
13. MAROLDA, VIVIANA
14. MARTINEZ BLANCO, ELENA
15. MARTÍNEZ BONILLA, ADRIÁN
16. MERINO VALVERDE, JAVIER
17. MORENO JIMÉNEZ, ELENA
18. MUÑOZ LÓPEZ, SARA
19. ORTIZ DEL CASTILLO, BELÉN\*
20. PIEDRABUENA ESTRADA, DAVID\*
21. RAMÍREZ CHUECA, ESTEBAN
22. RODRÍGUEZ RUBIO, MARINA
23. ROMERO CARRAMIÑANA, INÉS\*

24. RUIZ GARCÍA, SARA
25. SOTO HEREDERO, GONZALO
26. STANCIC, BRINA
27. TERREROS RONCAL, JULIA
28. TORIBIO SERRANO, VICTOR\*
29. TORRES GERICA, PATRICIA\*
30. VERDÚ CANO, CARLOS\*
31. VELA MARTIN, LAURA
32. VILAS LAGOA, ALICIA\*

## FINANCING AND BUDGET IUBM-UAM YEAR 2022

In the year 2023 the members of the IUBM-UAM raised through research projects circa **4.1 million euros**. According to the current agreement joint agreement CSIC-UAM, the overheads corresponding to these projects are assigned and managed directly by the CBM Severo Ochoa.

The UAM endowed the IUBM-UAM with a specific budget of 3,600 euros for the year 2023.

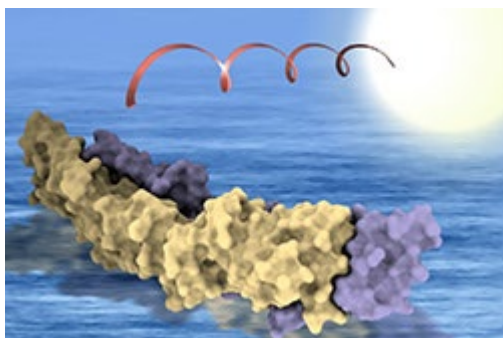
This budget was used for the following purposes:

**Sponsorship** of the PINP 2023 Award for the Best Doctoral Thesis 2023 in the CBMSO, Awards for the Best Oral Communication and the Best Poster in the X WORKSHOP STUDENTS & POSDOCS CBMSO 2023, and Tribute to Prof. José M. Cuezva, July 2023.

**Equipment:** acquisition of informatic and laboratory supplies to assist in the scientific tasks and administrative management of the IUBM-UAM and the CBM.

## SCIENTIFIC PROGRAMMES AND UNITS

### 🚦 Genome dynamics and function Programme



#### ➤ Genome decoding UNIT

Regulation of mRNA translation in eukaryotes and its implications for organismal life

<https://www.cbm.uam.es/iventoso>

- Prof. Iván Ventoso Bande. Profesor Titular. Departamento de Biología Molecular. UAM.
- Prof. Miguel Ángel Rodríguez Gabriel. Profesor Titular. Departamento de Biología Molecular. UAM.
- Prof. Juan José Berlanga. Profesor Titular. Departamento de Biología Molecular. UAM.
- Prof. Margarita Cabrera Solans. Profesora Ayudante Doctora. Departamento de Biología Molecular. UAM.

#### Research summary

We continue to investigate how eukaryotic systems (mammals, yeast and RNA viruses) regulate translation initiation at both global and message-specific manner, trying to identify new elements in ribosomes and mRNAs, and new initiation factor (eIFs) activities involved in the differential translation of mRNAs during cell proliferation and stress response. In the last two years, we further characterized the role of ES6S region of 40S ribosomal subunit in mRNA entry and ribosome scanning in different eukaryotic species (mammals, plants, insects and yeast). Our data suggest the ES6S region could be serving as a platform for the recruitment of RNA helicases (eIF4A and DDX3, among others) involved in RNA secondary structure unwinding. By using the nsp1 protein of SARS-CoV2 as a tool, we are also studying how the base composition of 5' UTR and CDS regions shape translation and mRNA stability in human cells.

We continue to study how cells reprogramme translation during the stress response in yeast and mammals by modulating the activity of eIF2 and eIF2A factors, and the physiological impact of this response on cell and organismal adaptation, survival and aging. Thus, we recently found that preventing eIF2 $\alpha$  phosphorylation not only impaired stress response, but also accelerated aging in yeast by a mechanism that involves proteostasis disruption. In this context, our research will focus on the study of key processes regulating proteostasis such as protein aggregation and autophagy and how they affect cell longevity.

## Projects

- Reprogramación traduccional inducida por estrés en eucariotas y su influencia sobre la proteostasis celular. PID2021-125844OB-I00 (FEDER-UE). IP. Iván Ventoso. MINECO. 1.9.2022-31.8.2025.

## Genetics and cell biology of cancer: T-cell lymphoblastic neoplasms

<http://www.cbm.uam.es/jfpiqueras>

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- **Prof. Javier Santos. Catedrático. Departamento de Biología. UAM.**
  - **Prof. María Villa. Profesora Titular. Departamento de Biología. UAM.**
  - **Prof. Alfonso Blázquez Castro. Profesor Ayudante Doctor. Departamento de Biología UAM.**
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## Research summary

T-cell lymphoblastic leukaemia/lymphoma (T-LBL and T-ALL) are haematological diseases with an urgent need for reliable prognostic biomarkers that allow therapeutic stratification and dose adjustment. Therefore, the major aim of our work is to decipher new molecular biomarkers and to propose more effective and less toxic treatments. To this end, we integrate data from genomics, transcriptomics and proteomic approaches as a start point to identify new driver-molecular mechanisms. During the 2021-2022 period In the last year we have continued with the identification of new mutations and changes in gene expression that have allowed us to propose new therapy strategies. In this sense, we have evidenced that the efficacy of  $\gamma$ -secretase inhibitors depends on the gene dosage of the *MYC* gene. We have also performed a proteomic analysis that reveals new non-apoptotic functions of FADD protein in these neoplasms. In order to improve our understanding on the efficacy of radiation , we have demonstrated the advantages of combined radiation regimens in controlling tumorigenesis that allow better control of healthy tissue homeostasis and facilitate tumour cell death. In addition, we are currently interested in evaluating the dysregulation of circular RNAs and long and short ncRNAs, to achieve a comprehensive view of the complex regulatory lncRNA/circRNA-miRNA-mRNA axes dysregulated in T-cell lymphoblastic neoplasms in the context of a personalized precision medicine. To this end, we have investigated the differential expression patterns of circRNAs in different development stages of human thymocytes to perform predictions in silico regarding the ability of specific circRNAs when controlling t in he expression of genes involved in thymocyte differentiation. Our study provides, for the first time, significant insights into the usefulness of circRNAs in discriminating between different stages of thymocyte differentiation and provides new potential circRNA-miRNA-mRNA networks capable of controlling the expression of genes involved in T-cell differentiation in the thymus. Regarding the analysis of lncRNAs, we have reported a new easy-to-use method, by coupling the specificity of a peptide nucleic acid (PNA)-labelled probe with flow cytometry (RNA-Flow FISH method that allows a reliable quantification of long lncRNAs, in particular those related to telomeres (TERRA and TERC) in cell lines and blood, with broad applications in basic research and clinical diagnostics.

## Publications

- Alanazi A, Jay-Gerin JP, Blázquez-Castro A. Is singlet oxygen involved in FLASH-RT?. *J Appl Clin Med Phys.* 2023 Jul;24(7):e13974. doi: 10.1002/acm2.13974. Epub 2023 Mar 25. PMID: 36964949
- Lahera A, López-Nieva P, Alarcón H, Marín-Rubio JL, Cobos-Fernández MÁ, Fernández-Navarro P, Fernández AF, Vela-Martín L, Sastre I, Ruiz-García S, Llamas P, López-Lorenzo JL, Cornago J, Santos J, Fernández-Piqueras J, Villa- Morales M. SOCS3 deregulation contributes to aberrant activation of the JAK/STAT pathway in precursor T-cell neoplasms. *Br J Haematol.* 2023 May;201(4):718-724. doi:

10.1111/bjh.18694. Epub 2023 Feb 14. PMID: 36786170.

- Lahera A, Vela-Martín L, Fernández-Navarro P, Llamas P, López-Lorenzo JL, Cornago J, Santos J, Fernández-Piqueras J, Villa-Morales M. The JAK3<sup>Q988P</sup> mutation reveals oncogenic potential and resistance to ruxolitinib. *Mol Carcinog.* 2024 Jan;63(1):5-10. doi: 10.1002/mc.23632. Epub 2023 Sep 15. PMID: 37712558.
- Lahera A, Vela-Martín L, López-Nieva P, Salgado RN, Rodríguez-Perales S, Torres-Ruiz R, López-Lorenzo JL, Cornago J, Llamas P, Fernández-Navarro P, Sánchez-Domínguez R, Segovia JC, Sastre I, Cobos-Fernández MÁ, Menéndez P, Santos J, Fernández-Piqueras J, Villa-Morales M. Comprehensive characterization of a novel, oncogenic and targetable SEPTIN6::ABL2 fusion in T-ALL. *Br J Haematol.* 2023 Aug;202(3):693-698. doi: 10.1111/bjh.18901. Epub 2023 Jun 2. PMID: 37264982.
- Tundidor I, Seijo-Vila M, Blasco-Benito S, Rubert-Hernández M, Adámez S, Andradas C, Manzano S, Álvarez-López I, Sarasqueta C, Villa-Morales M, González-Lois C, Ramírez-Medina E, Almoguera B, Sánchez-López AJ, Bindila L, Hamann S, Arnold N, Röcken C, Heras-Murillo I, Sancho D, Moreno-Bueno G, Caffarel MM, Guzmán M, Sánchez C, Pérez-Gómez E. Identification of fatty acid amide hydrolase as a metastasis suppressor in breast cancer. *Nat Commun.* 2023 May 30;14(1):3130. doi: 10.1038/s41467-023-38750-9. PMID: 37253733; PMCID: PMC10229544.
- Villa-Morales M, Pérez-Gómez L, Pérez-Gómez E, López-Nieva P, Fernández-Navarro P, Santos J. Identification of NRF2 Activation as a Prognostic Biomarker in T-Cell Acute Lymphoblastic Leukaemia. *Int J Mol Sci.* 2023 Jun 19;24(12):10350. doi: 10.3390/ijms241210350. PMID: 37373496; PMCID: PMC10299336.

### Regulation of gene expression in *Leishmania*

<http://www.cbm.uam.es/jmrequena>

- 
- **Prof. José M<sup>a</sup> Requena Rolanía. Profesor Titular. Departamento de Biología Molecular. UAM.**
  - **Prof. Manuel Soto Alvarez. Profesor Titular. Departamento de Biología Molecular. UAM.**
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### Research summary

The early-diverging protozoan parasite *Leishmania* causes leishmaniasis in many regions of the world. This disease is ranked second (after malaria) among parasitic diseases. No acceptable vaccine for preventing leishmaniasis exists and treatment options are limited. Moreover, *Leishmania* is an atypical eukaryote regarding genome organization and gene expression regulation: genes are expressed as long transcription units requiring extensive post-transcriptional processing. Thus, *Leishmania* is an adequate model for studying post-transcriptional regulation without the interference of transcriptional regulation. The main research activity of our group is focused on genome organization and gene expression studies. Still, we maintain some activity in developing vaccines to prevent leishmaniasis and improving diagnosis/typing methods.

In the last couple of years, our group has continued improving the genomic assemblies of prototypical *Leishmania* species, by a combination of second and third-generation NGS methodologies. In this regard, the collaboration with the Genomics & Massive Sequencing service at CBMSO (headed by Dr Begoña Aguado) is paramount. In particular, we have generated a de novo assembly for *Leishmania major* (Friedlin) genome, which was the first *Leishmania* genome sequenced (in 2005) and from then it became a reference and source for many molecular

studies. In consequence, the new assembly generated by our group has gained general acceptance (TriTrypDB). Also, our group has determined the poly-A+ transcriptome for this species and generated complete gene models, paving the way for addressing differential gene expression. Genomic annotations require a continuous process of curation, derived from new studies that uncover functional roles of genes/proteins previously unknown or by the characterization of new transcripts/peptides that obligate to reconsider some gene models. Thus, the alliance of proteomics, genomics, and transcriptomics has resulted in a powerful combination for improving the annotation of the *Leishmania* genomes. For hosting the genomics/transcriptomics data generated (and curated) by our group for four *Leishmania* species (*L. major*, *L. infantum*, *L. donovani* y *L. braziliensis*), a web page was created: <http://leish-esp.cbm.uam.es>.

Finally, as members of the Tropical Diseases network (ISCIII; <http://www.ricet.es/es/>), which moved to a CIBER in infectious diseases (CIBERinfec; <https://www.ciberinfec.es>) in 2022, our group was engaged in collaborative research dealing with the molecular diagnosis and typing of *Leishmania* strains isolated from patients. In particular, we have characterized the *Leishmania* mitochondrial genome (aka, kinetoplast DNA or kDNA) which usually is ignored in genomic studies due to its structural complexity. After a characterization of the kDNA for several *Leishmania* species (and other trypanosomatids), we demonstrated that the kDNA maxicircle is a superior molecular marker for taxonomic and typing purposes in trypanosomatids.

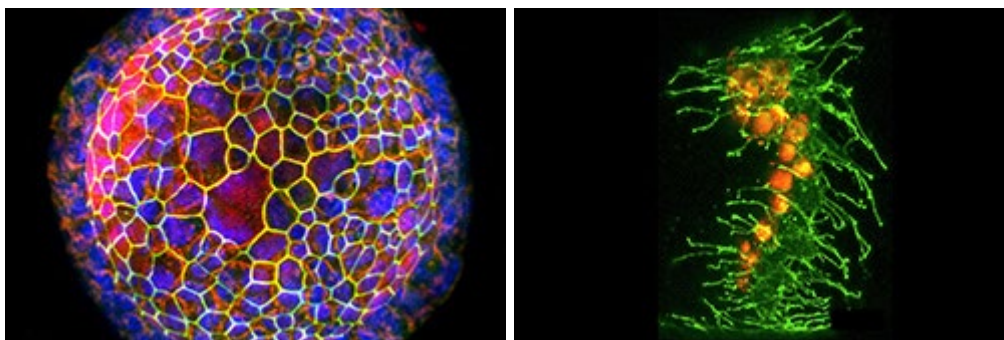
## Publications

- Callejas-Hernández F, Robello C, Requena JM. Editorial: Protozoan parasites in the multi-omics era: present and future. *Front Cell Infect Microbiol.* 2023 Sep 14;13:1281638. doi: 10.3389/fcimb.2023.1281638. PMID: 37780851; PMCID: PMC10539553.
- Camacho E, González-de la Fuente S, Solana JC, Tabera L, Carrasco-Ramiro F, Aguado B, Requena JM. *Leishmania infantum* (JPCM5) Transcriptome, Gene Models and Resources for an Active Curation of Gene Annotations. *Genes (Basel).* 2023 Apr 4;14(4):866. doi: 10.3390/genes14040866. PMID: 37107624; PMCID: PMC10137940.
- González-de la Fuente S, Requena JM, Aguado B. Datasets of Iso-Seq transcripts for decoding transcriptome complexity in four *Leishmania* species. *Data Brief.* 2023 Nov 20;52:109838. doi: 10.1016/j.dib.2023.109838. PMID: 38076479; PMCID: PMC10698239.
- Sánchez-Salvador A, González-de la Fuente S, Aguado B, Yates PA, Requena JM. Refinement of *Leishmania donovani* Genome Annotations in the Light of Ribosome-Protected mRNAs Fragments (Ribo-Seq Data). *Genes (Basel).* 2023 Aug Luque D, Ortega-Esteban A, Valbuena A, Luis Vilas J, Rodríguez-Huete A, Mateu MG, Castón JR. Equilibrium Dynamics of a Biomolecular Complex Analyzed at Single-amino Acid Resolution by Cryo-electron Microscopy. *J Mol Biol.* 2023 Apr 15;435(8):168024. doi: 10.1016/j.jmb.2023.168024. Epub 2023 Feb 23. PMID:36828271.

## Projects

- Integrating OMICS data to decipher *Leishmania* gene organization and expression: clues for tackling leishmaniasis (Leish-OMICS). Agencia Estatal de Investigación. Ref. PID2020-117916RB-I00. PIs: Jose M. Requena & Begoña Aguado. Sep, 2021-2024
- CIBER en Área Enfermedades Infecciosas (CIBERINFEC). Instituto de Salud Carlos III. Ref. CB21/13/00018. PI: Javier Moreno. From 2022.

## Tissue and organ homeostasis PROGRAMME



## ➤ Cell architecture & organogenesis UNIT

### Cytoskeleton-plasma membrane interaction

<http://www.cbm.uam.es/maalonso>

- Prof. Isabel Correas Hornero. Catedrática. Departamento de Biología Molecular.UAM. (Co-PI with Dr. Miguel Alonso, CSIC-CBMSO).

### Research summary

Our aims during this period have been: 1) to study the mechanism of biogenesis of the primary cilium in polarized epithelial cells, 2) to investigate the regulation of the formin INF2, and 3) to characterize a novel member of the MAL family of proteins.

Previous work in our laboratory established a critical role for the midbody remnant in primary cilium formation in polarized epithelial cells. We have now observed that the majority of midbody remnants are physically connected to the plasma membrane through a membranous stalk derived from an intact arm of the cytokinetic bridge. Thanks to this physical continuity, the midbody remnant delivers a specialized membrane patch that the centrosome uses to build the ciliary membrane. Our study shows how the ciliary membrane and the primary cilium originate in polarized epithelial cells.

Formins are a family of proteins involved in the assembly of actin filaments. Most formins, such as mDia1, contain a diaphanous inhibitory domain (DID) at the N-terminal region that interacts with the C-terminal region to maintain the molecule in an inactive state. mDia1 and other formins are regulated by the binding of Rho GTPases to the DID. INF2 is a formin linked to inherited renal and neurological disease in humans. INF2 possesses an N-terminal extension of unknown structure and function that precedes the DID. Our work has demonstrated that this extension is organized into two  $\alpha$ -helices, the first of which interacts directly with  $\text{Ca}^{2+}$ /calmodulin through a peptide motif that is conserved in vertebrates. Consistent with this interaction, INF2 produces massive actin polymerization in response to increased  $\text{Ca}^{2+}$  levels. Our study reveals that, unlike other formins, INF2 is regulated by interaction of  $\text{Ca}^{2+}$ /calmodulin with the INF2 N-terminal extension.

The MAL family of proteins has been the focus of our laboratory's research for a long time. Our third project has dealt with the characterization of MALL, a membrane tetraspanning member of this family. We have found endogenous MALL in membranes and, unexpectedly, in nuclear-membraneless structures, the PML bodies. Our study suggests that MALL can adopt a membrane-embedded or a water-soluble conformation depending on its physical environment—lipidic or aqueous—in the cell. During mitosis, overexpressed MALL aggregates at the cytokinetic bridge into large solid structures that produce cytokinesis failure and lead to cells with aberrant chromosome content. Since MALL is overexpressed in some types of cancer, an excess of MALL could contribute to malignancy by inducing chromosome instability.



## Publications

- Labat-de-Hoz L, Rubio-Ramos A, Correas I, Alonso MA. The MAL Family of Proteins: Normal Function, Expression in Cancer, and Potential Use as Cancer Biomarkers. *Cancers (Basel)*. 2023 May 17;15(10):2801. doi: 10.3390/cancers15102801. PMID: 37345137; PMCID: PMC10216460.

## Genetic analyses of signaling pathways during epithelial development in *Drosophila melanogaster*

<https://www.cbm.uam.es/jfdecelis>

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- **Prof. Ana Ruiz Gómez. Profesora Titular. Departamento de Biología Molecular.UAM. (Staff scientist with PI Dr. José F de Celis, CSIC-CBMSO)**
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### Research summary:

We aim to understand how genetic information is translated into spatial patterns of cell differentiation in epithelial tissues. We use the *Drosophila melanogaster* wing as our main experimental model and we carry out three research projects. The first project involves the analysis of the functional requirements of *Drosophila* genes in the wing. We grouped the 14.000 *Drosophila* genes into 16 functional groups (Fig. 1) and screened UAS-RNAi lines targeting 10918 of these genes. We classified the resulting phenotypes into morphological classes affecting the size, pattern or differentiation of the wing (Fig. 1), and correlated each mutant phenotype with the expression of the corresponding gene. Wing phenotypes reveal functional requirements, either in basic cellular functions impinging on cell viability or in wing-specific functions related to its growth and patterning, and together with gene expression patterns constitute an optimal entry point to undertake detailed functional analysis. The second project is the analysis of the transcriptional effects of one *Drosophila* transcription factor (Spalt) that has a prominent role in the development of the wing disc. Spalt is a nuclear protein containing three pairs of Zn fingers and its human orthologs are involved in Towles-Brokes disease and Okhiro syndrome. We have identified a minimal DNA response element for Spalt through the analysis of the regulatory region of one of its downstream genes and now we are defining the effects of Spalt on chromatin conformation as well as searching for Spalt co-repressors with the objective of understanding the Spalt mechanism of action. The third project concerns the Ras gene. Mutations in human Ras are common in multitude of cancers, and the *Drosophila* Ras gene has been used to model cancer progression in flies. Using Crisper/Cas9 and homologous recombination we have generated *Drosophila* transgenic lines carrying altered versions of the fly and human Ras genes. We are characterizing the consequences of activating Ras mutations when the gene is expressed at normal levels in the wing, the ovary and the lymph gland. We expect to generate genetic combinations in a background of endogenous activated Ras allowing us to model the formation and progression of tumors.

### Systems Biology Lab

<https://www.cbm.uam.es/dmiguez>

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- **Prof. David Míguez Gómez. Profesor Titular. Departamento de Física de la Materia Condensada. UAM.**
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### Research summary:

The cellular machinery is governed by interacting proteins, genes and metabolites that form complex and highly interconnected networks of interactions. This way, extracellular stimuli triggers pathways of biological events that regulate gene expression, protein activity, and ultimately, cell response. The architecture of these signaling cascades is highly nonlinear, integrating multiple layers and loops of feedback and feedforward regulation. These nonlinearities strongly affect the dynamics of activation and de-activation of the signaling cascades, inducing emerging properties such as bistability, oscillations or ultra-sensitivity. To understand cellular decisions, it is not sufficient to understand the function of each of the proteins in a pathway, and a deep understanding of the consequences of the nonlinear wiring of the pathway is required. We use *in vivo* experiments and theoretical approaches to understand how the wiring of the pathways affects the role of the proteins that regulate these decision, in the context of balance between proliferation and differentiation of stems cells during neurogenesis.

### Projects

- OSCAR, an Object Segmentation, Counter, Analysis Resource. PDC2022-133147-I00 (PRTR). PI David Míguez Gómez. 1.12.2022-31.11.2024. MINECO.
- Interacción entre mecanismos físicos y moleculares en la regulación de la formación de la retina de vertebrados. PID2022-140421NB-I00 (FEDER, UE). 1.9.2023-31.8.2026. MINECO

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## ➤ Cell-cell communication and inflammation UNIT

**Tetraspanin-enriched membrane microdomains in extracellular vesicles and cell adhesion and migration.**

<http://www.cbm.uam.es/myanez>

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- **Prof. María Yáñez-Mo. Profesora Contratada Doctora. Departamento de BiologíaMolecular. UAM.**
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### Research summary:

Our group is focused on the role of tetraspanin-enriched membrane nanodomains in extracellular vesicles (EVs). We pursue both biotechnological applications for EV detection, isolation or characterization as well as fundamental knowledge on tetraspanin involvement in the molecular mechanisms of EV biogenesis, cargo selection and uptake.

Our latest data suggest that tetraspanins finely regulate the dynamics of endosomal compartments and their interrelation with autophagy and mitophagy pathways. Thus, tetraspanins emerge as potent regulators of the metabolic fitness of the cell, with novel therapeutic implications in the fight against cancer.

### Publications

- Benayas B, Morales J, Gori A, Strada A, Gagni P, Frigerio R, Egea C, Armisén P, Cretich M, Yáñez-Mó M. Proof of concept of using a membrane-sensing peptide for sEVs affinity based isolation. Front

Bioeng Biotechnol. 2023 Aug 11;11:1238898. doi: 10.3389/fbioe.2023.1238898. PMID: 37636002; PMCID: PMC10457001.

- Toribio V, Yáñez-Mó M. Two Complementary Strategies to Quantitate Extracellular Vesicle Uptake Using Bioluminescence and Non-Lipidic Dyes. *Methods Mol Biol.* 2023;2668:133-144. doi: 10.1007/978-1-0716-3203-1\_11. PMID: 37140795.
- Yáñez-Mó M, Siljander PR. Editorial- Insights of extracellular vesicles in cell biology. *Eur J Cell Biol.* 2023 Sep;102(3):151327. doi: 10.1016/j.ejcb.2023.151327. Epub 2023 Jun 7. PMID: 37330395

## Projects

- Microdominios de membrana, exosomas, virus y vacunas. PID2020-119627GB-I00, Proyectos I+D Generación de Conocimiento. Principal Investigator: María Yáñez-Mó. 01/09/2021-31/08/2024.
- VALIDACION CLINICA DE UN SISTEMA PARA DETECTAR TRANSLOCACIONES DE ALK EN VESICULAS EXTRACELULARES EN PLASMA. DTS21/00134, Instituto de Salud Carlos III. Principal Investigator: María Yáñez-Mó. 01/01/2022-31/12/2023.
- Vacunas basadas en exosomas miméticos. PDC2021-121052-I00. Ministerio de Ciencia e Innovación. Principal Investigator: María Yáñez-Mó. 01/12/2021-30/11/2023.
- Doctorados industriales CM 2029. IND2019/BMD-17100. 03/08/2020-02/08/2023 - Comunidad de Madrid

## Thesis

Víctor Toribio Serrano. El papel de las tetraspaninas en la relación del aparato endosomal con el metabolismo celular y la identificación de nuevos mecanismos moleculares implicados en la captación de vesículas extracelulares. Programa de Doctorado en Biociencias Molecular. 2023

## Immunometabolism and Inflammation Lab

<http://www.cbm.uam.es/mittelbrunn>

- 
- Prof. Elisa Carrasco. Profesora Ayudante Doctora. Departamento de Biología. UAM.
  - Dr. Enrique Gabandé. Investigador Juan de la Cierva. Departamento de Biología Molecular. UAM.
  - Dr. Jorge Oller. Investigador Juan de la Cierva. Departamento de Biología Molecular. UAM.
  - Dr. Isaac Francos. Investigador Juan de la Cierva. Departamento de Biología Molecular. UAM.

(Staff scientists with PI Dr. María Mittelbrunn, CSIC-CBMSO)

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## Research summary

Our research goal is to identify new **strategies to targeting immune cells for boosting systemic resilience to inflammaging, cellular senescence and age-related multimorbidity**. Our most important discoveries in the last years are:

1. To demonstrate that mimicking age-associated mitochondrial dysfunction in T cells does not only recapitulate immunosenescence, but causes a general, body-wide deterioration of health with multiple

aging-related features, including metabolic, musculoskeletal, cardiovascular and cognitive alterations, altogether resulting in premature death (**Science**, 2020). These results place the metabolism of T cells at the crossroad between inflammation, senescence and aging, highlighting that immunometabolism can be a therapeutic target to delay aging.

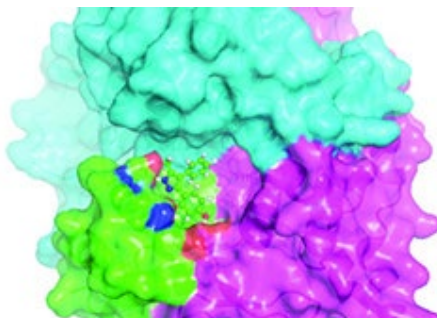
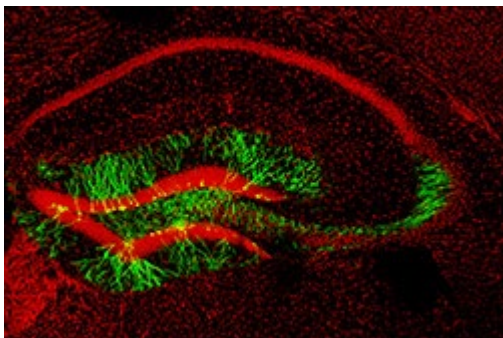
2. To decode the molecular mechanisms by which aged T cells contribute to inflammaging and age-related diseases. (a) Th1-Cytokines induce cellular senescence (b) Loss of Self-tolerance mechanisms. (c) Defective immuno-surveillance of senescent cells. (d) Altered gut microbiota. (**Cell Metabolism** 2021; **Nature Rev Immunol**, 2022; **Annual Rev Immunol**, in press).
3. To propose new therapeutic to reverse aortic aneurysms and prevent sudden death due to aortic dissections by boosting mitochondrial metabolism using NAD Precursors (**Circulation**, 2021; **Atherosclerosis, Thrombosis Vascular Biology**, 2022; **Br J Pharmacol**. 2022)

## Publications

- Francos-Quijorna I, Carrasco E, Gabandé-Rodríguez E. Editorial: Molecular and epigenetic mechanisms: neuroinflammation and neurodegeneration. *Front Aging*. 2023 Aug 14;4:1271714. doi: 10.3389/fragi.2023.1271714. PMID: 37645543; PMCID: PMC10461551.
- Gabandé-Rodríguez E, Pfeiffer M, Mittelbrunn M. Immuno(T)herapy for age- related diseases. *EMBO J Med*. 2023 Jan 11;15(1):e16301. doi: 10.15252/emmm.202216301. Epub 2022 Nov 14. PMID: 363733; PMCID: PMC9832825.

## Projects

- Estrategias nutricionales de precisión para reactivar el sistema inmune deteriorado como consecuencia de la edad, la obesidad o la quimioterapia. CAM-Y2020/BIO-6350. PIs: Ana Ramírez y Elisa Carrasco. Agencia financiadora: Comunidad de Madrid. 2022-2024



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## ➤ Molecular Neuropathology UNIT

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### Pathogenic mechanisms of Alzheimer's disease

<http://www.cbm.uam.es/mjbullido>

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- **Prof. M<sup>a</sup> Jesús Bullido Gómez-Heras. Profesora Titular. Departamento de Biología Molecular. UAM.**
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### Research summary

We continue the study of mechanisms mediating the neurodegenerative cascade leading to Alzheimer's disease (AD) in neuronal cell models. Based on previous results of degeneration induced by herpes simplex 1 virus (HSV-1), we are focused on the endo-lysosomal pathway and cholesterol metabolism as major functions mediating HSV-1 induced, AD-like neurodegeneration.

To expand the screening of these pathways, we have recently started to develop 2D and 3D neural models derived from the human progenitors LUHMES and ReN cell lines. We have been able to obtain different neural types (oligodendrocytes, astrocytes and neurons), and proved the ability of both progenitors and differentiated cells to resemble an AD-like phenotype that includes intracellular accumulation of A $\beta$  and hyperphosphorylated tau, inhibition of A $\beta$  secretion, alterations in autophagy-lysosomal pathway and changes in cholesterol levels, following HSV-1 infection. These preliminary results pave the way for the development of interesting research platforms, in which we plan to validate candidate genes like LAMP2 and MMP14 and to deepen our knowledge about the link between cholesterol and lysosome alterations and the AD like neurodegeneration induced by HSV-1.

To evaluate the translational potential of findings obtained in the models, we are analyzing genes and biomarkers in samples of controls and AD patients at dementia and pre-dementia stages. Putting together the urgent need of peripheral biomarkers and the widely supported involvement of the immune system in AD, we have selected peripheral blood mononuclear cells (PBMCs) as the material to be screened. Measurement of PBMC free cholesterol levels in two independent case-control samples totaling 480 participants revealed decreased cholesterol content in patients from early, pre-dementia disease stages, as well as in control subjects bearing the APOE4 allele. We also detected increased CD16+ and decreased CD8+ cell percentages in patients with moderate or severe dementia. These results support the presence of changes in peripheral blood cells of AD patients and suggest that alterations of cholesterol metabolism in these cells could be prodromal events. In addition, they suggest a relationship between APOE genotype and cholesterol levels in PBMC, which could manifest even in healthy individuals and perhaps partly explain the involvement of APOE4 in AD.

Therefore, our studies in cell models and patients continues supporting that failures of lysosomal function and cholesterol homeostasis are relevant in neurodegeneration, with the candidates under study having the potential to be early biomarkers or pharmacological targets for AD.

## Publications

- European Alzheimer's & Dementia Biobank Mendelian Randomization (EADB-MR) Collaboration; Luo J, Thomassen JQ, Bellenguez C, Grenier-Boley B, de Rojas I, Castillo A, Parveen K, Küçükali F, Nicolas A, Peters O, Schneider A, Dichgans M, Rujescu D, Scherbaum N, Jürgen D, Riedel-Heller S, Hausner L, Porcel LM, Düzel E, Grimmer T, Wiltfang J, Heilmann-Heimbach S, Moebus S, Teges T, Scarmeas N, Clarimon J, Moreno F, Pérez-Tur J, Bullido MJ, Pastor P, Sánchez-Valle R, Álvarez V, Boada M, García-González P, Puerta R, Mir P, Real LM, Piñol-Ripoll G, García-Alberca JM, Royo JL, Rodríguez-Rodríguez E, Soininen H, Kuulasmaa T, de Mendonça A, Mehrabian S, Hort J, Vyhnaek M, van der Lee S, Graff C, Papenberg G, Giedraitis V, Boland A, Bacq-Daian D, Deleuze JF, Nicolas G, Dufouil C, Pasquier F, Hanon O, Debette S, Grünblatt E, Popp J, Benussi L, Galimberti D, Arosio B, Mecocci P, Solfrizzi V, Parnetti L, Squassina A, Tremolizzo L, Borroni B, Nacmias B, Sorbi S, Caffarra P, Seripa D, Rainero I, Daniele A, Masullo C, Spalletta G, Williams J, Amouyel P, Jessen F, Kehoe P, Tsolaki M, Rossi G, Sánchez-Juan P, Sleegers K, Ingelsson M, Andreassen OA, Hiltunen M, Van Duijn C, Sims R, van der Flier W, Ruiz A, Ramirez A, Lambert JC, Frikke-Schmidt R. Genetic Associations Between Modifiable Risk Factors and Alzheimer Disease. *JAMA Netw Open*. 2023 May 1;6(5):e2313734. doi: 10.1001/jamanetworkopen.2023.13734. Erratum in: *JAMA Netw Open*. 2023 Jun 1;6(6):e2321189. PMID: 37195665; PMCID PMC10193187.
- García-González P, de Rojas I, Moreno-Grau S, Montreal L, Puerta R, Alarcón-Martín E, Quintela I, Orellana A, Andrade V, Adami PVM, Heilmann-Heimbach S, Gomez-Garre P, Periñán MT, Alvarez I, Diez-Fairen M, Nuñez Llavés R, Olivé Roig C, Garcia-Ribas G, Menéndez-González M, Martínez C, Aguilar M, Buongiorno M, Franco-Macías E, Saez ME, Cano A, Bullido MJ, Real LM, Rodríguez-Rodríguez E, Royo JL, Álvarez V, Pastor P, Piñol-Ripoll G, Mir P, Lara MC, Padilla MM, Sánchez-Juan P, Carracedo A, Valero S, Hernandez I, Tàrraga L, Ramirez A, Boada M, Ruiz A. Mendelian Randomisation Confirms the Role of Y-Chromosome Loss in Alzheimer's Disease Aetiopathogenesis in Men. *Int J Mol Sci*. 2023 Jan 4;24(2):898. doi: 10.3390/ijms24020898. PMID: 36674414; PMCID: PM
- Guardiola M, Muntané G, Martínez I, Martorell L, Girona J, Ibarretxe D, Plana N, Bullido MJ, Vilella E, Ribalta J. Metabolic Overlap between Alzheimer's Disease and Metabolic Syndrome Identifies the *PVRL2* Gene as a New Modulator of Diabetic Dyslipidemia. *Int J Mol Sci*. 2023 Apr 18;24(8):7415. doi: 10.3390/ijms24087415. PMID: 37108578; PMCID: PMC10139078.
- Le Guen Y, Luo G, Ambati A, Damotte V, Jansen I, Yu E, Nicolas A, de Rojas I, Peixoto Leal T, Miyashita A, Bellenguez C, Lian MM, Parveen K, Morizono T, Park H, Grenier-Boley B, Naito T, Küçükali F, Talyansky SD, Yogeshwar SM, Sempere V, Satake W, Alvarez V, Arosio B, Belloy ME, Benussi L, Boland

A, Borroni B, Bullido MJ, Caffarra P, Clarimon J, Daniele A, Darling D, Debette S, Deleuze JF, Dichgans M, Dufouil C, During E, Düzel E, Galimberti D, Garcia-Ribas G, García-Alberca JM, García-González P, Giedraitis V, Goldhardt O, Graff C, Grünblatt E, Hanon O, Hausner L, Heilmann-Heimbach S, Holstege H, Hort J, Jung YJ, Jürgen D, Kern S, Kuulasmaa T, Lee KH, Lin L, Masullo C, Mecocci P, Mehrabian S, de Mendonça A, Boada M, Mir P, Moebus S, Moreno F, Nacmias B, Nicolas G, Niida S, Nordestgaard BG, Papenberg G, Papma J, Parnetti L, Pasquier F, Pastor P, Peters O, Pijnenburg YAL, Piñol-Ripoll G, Popp J, Porcel LM, Puerta R, Pérez-Tur J, Rainero I, Ramakers I, Real LM, Riedel-Heller S, Rodriguez- Rodriguez E, Ross OA, Royo LJ, Rujescu D, Scarmeas N, Scheltens P, Scherbaum N, Schneider A, Seripa D, Skoog I, Solfrizzi V, Spalletta G, Squassina A, van Swieten J, Sánchez-Valle R, Tan EK, Tegos T, Teunissen C, Thomassen JQ, Tremolizzo L, Vyhalek M, Verhey F, Waern M, Wiltfang J, Zhang J; EADB; GR@ACE study group; DEGESCO consortium; DemGene; EADI; GERAD; Asian Parkinson's Disease Genetics consortium; Zetterberg H, Blennow K, He Z, Williams J, Amouyel P, Jessen F, Kehoe PG, Andreassen OA, Van Duin C, Tsolaki M, Sánchez-Juan P, Frikke Schmidt R, Slegers K, Toda T, Zettergren A, Ingelsson M, Okada Y, Rossi G, Hiltunen M, Gim J, Ozaki K, Sims R, Foo JN, van der Flier W, Ikeuchi T, Ramirez A, Mata I, Ruiz A, Gan-Or Z, Lambert JC, Greicius MD, Mignot E. Multiancestry analysis of the HLA locus in Alzheimer's and Parkinson's diseases uncovers a shared adaptive immune response mediated by <i>HLA-DRB1\*04</i> subtypes. Proc Natl Acad Sci U S A. 2023 Sep 5;120(36):e2302720120. doi: 10.1073/pnas.2302720120. Epub 2023 Aug 29. PMID: 37643212; PMCID: PMC10483635.

- Salgado B, Sastre I, Bullido MJ, Aldudo J. Herpes Simplex Virus Type 1 Induces AD-like Neurodegeneration Markers in Human Progenitor and Differentiated ReNcell VM Cells. Microorganisms. 2023 May 4;11(5):1205. doi: 10.3390/microorganisms11051205. PMID: 37317179; PMCID: PMC10221020.

## Projects

- Cholesterol homeostasis and lysosome pathway in HSV-1 induced neurodegeneration and in Alzheimer's disease: Pathogenic mechanisms and biomarkers. PID2020-113921RB-I00. PI Bullido MJ & Frank-Garcia A. 01/09/2021-31/08/2024.
- Networked Center of Biomedical Research. Neurodegenerative diseases -CIBERNED- (<https://www.ciberned.es/grupos/grupo-de-investigacion?id=28805> )
- Hospital la Paz Institute for Health Research - IdiPaz. (<http://www.idipaz.es>) Group "Neurology and cerebrovascular diseases", PI E Díez-Tejedor
- Dementia Genetics Spanish Consortium (DEGESCO). Participant group. (<https://www.ciberned.es/plataformas/degesco>)
- European Alzheimer's Disease BioBank & International Genomics Alzheimer's Project (IGAP). Associated group. (<https://consortiapedia.fastercures.org/consortia/igap/>)

## Physiopathology of Glycine Transporters in Glycinergic neurotransmission: Hyperekplexia and Pain.

<http://www.cbm.uam.es/blopez>

- **Prof. Beatriz López-Corcuera. Catedrática. Departamento de Biología Molecular.UAM.**

## Research summary

At present, the group studies the physiology and pathologies of glycinergic neurotransmission including hyperekplexia and pain. Hyperekplexia is a rare sensorimotor disorder provoked by defective glycinergic inhibition that may have severe consequences in neonates. The neuronal glycine transporter GlyT2, which is crucial for the recycling of synaptic neurotransmitter and supplies glycine for synaptic vesicle refilling, is nonfunctional in the presynaptic form of the disease. One of our aims is to identify and characterize new mutations in the human GlyT2 gene (*SLC6A5*) found in hyperekplexia patients. After the identification and assessment of the pathogenic mechanisms of several hyperekplexia-associated GlyT2 variants, we have now shown some of them are amenable to rescue from its trafficking defect by chemical chaperones. This may help developing more specific pharmacochaperones as candidate therapeutic tools for hyperekplexia with the help of 3D computational models we have developed. Some other hyperekplexia mutations have revealed interesting unknown aspects on transporter oligomerization we study with refined oligomer modeling. Moreover, we have found new components of GlyT2 interactoma, some of which are candidate hyperekplexia genes that remain to be identified, besides revealing a role in ion homeostasis for GlyT2 and its partners. An additional aspect of our research led us advance in the knowledge of the mechanisms of GlyT2 regulation. First, we have shown GlyT2 is regulated by the Hedgehog pathway in vitro and in vivo. GlyT2 control by this signaling cascade, clearly involved in development, moved us to investigate a possible role for GlyT2 in the development of glycinergic neurotransmission. We have also studied the role of transporters in the processing of nociceptive information by exploring mechanisms of GlyT2 regulation by M2 muscarinic acetylcholine receptors, the most clearly involved in pain processing in the spinal cord. Finally, we explored modulators of GlyT2 activity to obtain information applicable to analgesia. We analyzed the comparative docking of the two selective GlyT2 inhibitors with nanomolar affinity and defined their differential interactions with the transporter protein. Structural information about the interactions with GlyT2 may provide useful tools for new drug discovery applicable to analgesia.

## Projects

- PID2020-119399RB-I00. The neuronal glycine transporter GlyT2 in pain and in hyperekplexia: pathological implications in development. Ministry of Science and Innovation. PI: B. López Corcuera. 2021-2024.
- CIVP20A6612, Fundación Ramón Areces. El transportador neuronal de glicina GlyT2 en hiperplexia: una patología glicinérgica del desarrollo. PI: B. López Corcuera. 01/05/2021 to 01/05/2024

## Thesis

Raquel Felipe Mendía. Regulación y modificación del transportador de glicina GlyT2 Programa de Doctorado en Biociencias Moleculares. Directora: Beatriz López Corcuera. 2023.

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## Human stem cell biology in translational neuroscience

<https://www.cbm.uam.es/m.pereira>

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- **Prof. Marta Pérez Pereira. Profesora Ayudante Doctora. Departamento de Biología Molecular. UAM**
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## Research summary:

The concept of treating diseases with replacement cells is not new; blood transfusions, skin grafts and organ transplantation are all forms of cell replacement therapy. Many neurological diseases, like PD, are the result of cell death or degeneration. The exponentially growing impairment/death rate of dopaminergic neurons (DAn) in the midbrain's substantia nigra (the A9 subgroup) in PD limits the therapeutic window of the treatments available that are known to increase the quality of life of patients although none can prevent the progression of PD.

Consequently, repairing damaged tissue becomes the goal; when cell loss cannot be prevented, cell replacement holds the key to recovery. Cell replacement therapy for PD is based on the concept that DAn implanted ectopically may functionally restore and maintain the DA levels lost in the disease. Clinical research using human fresh fetal ventral mesencephalic (VM) tissue (hfVM, containing some DAn precursors and many other cell types) provided proof of principle of the therapeutic efficacy of dopaminergic transplants on a long-term basis. However, limitations in hfVM supply, along with the variability of results of different clinical trials and the appearance of graft-induced dyskinesias in some patients, have precluded the implantation of tissue transplantation as a clinical therapy. In this context, research on the basic biology of human stem cells acquires special relevance. Our research group is interested in the basic biology of stem cells and the developmental events leading to maturation of neuronal derivatives of use in the study of the human brain and the development of novel cell-based therapies for neurodegenerative diseases (e.g. Parkinson's and Alzheimer's disease).

We have studied the trophic actions of human neural and mesenchymal stem cells in experimental in vivo models of PD focusing on the parallelism between pathological changes occurring in the brain vs. neurological and motor alterations. With a multidisciplinary approach, we have worked in the development of the technology for externally controllable bioimplants of therapeutic cells on-demand. These bioimplants consisting in multifunctional leaky optoelectrical fiber for potential neuromodulation and as a cell substrate for application in combined optogenetic stem cell therapy.

With the aim of minimizing the number of laboratory animals used for basic research while increasing the body of knowledge on the biology human neural tissue we have developed a research line devoted to the generation of human cerebral organoids with improved features facilitating patterning studies and useful for improving current preclinical research testing.

## Publications

- Pereira MP, García-Bueno B, Caso JR. Editorial: Neuroinflammatory and oxidative/nitrosative pathways in neuropsychiatric and neurological diseases and their possible neuropharmacological regulation, Volume II. *Front Pharmacol.* 2023 Mar 31;14:1191907. doi: 10.3389/fphar.2023.1191907. PMID: 37063292; PMCID: PMC10102634.

## Projects

- OpenMIND (Opto-Electronic Neural Connectoid Model Implemented for Neurodegenerative Disease). GA-101047177. From 2022 to 2025
- ASCTN-Training (Training for Advanced Stem Cell Technologies in Neurology). GA-813851. From 2018 to 2023

## Pathophysiology and Therapy of Neurodegenerative Diseases: Friedreich's Ataxia.

- **Prof. Javier Díaz Nido. Catedrático. Departamento de Biología Molecular. UAM.**

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### Research summary:

Our research group is interested in the study of neurodegenerative diseases. Among them are ataxias, which are characterized by the loss of neurons in the cerebellum and spinal cord. In particular, we have focused on Friedreich's ataxia, which is one of the most common hereditary ataxias. We try to clarify the molecular bases of this pathology and develop therapies (pharmacological, gene and cellular) that may be effective for its treatment. Friedreich's ataxia is an autosomal recessive neurogenetic disease caused by a deficiency of frataxin, a protein located mainly in mitochondria. In addition to the neurodegenerative component, many patients also suffer from musculoskeletal disorders, hypertrophic cardiomyopathy, and diabetes. Friedreich's ataxia is a degenerative disease with a very early onset, and it can serve as a very useful model for other degenerative diseases in which mitochondrial dysfunction also plays a very important role. More generally, we are also interested in the crucial role of mitochondrial metabolism in neuronal homeostasis and its alterations in pathological situations.

### Projects

- REGULACIÓN DEL METABOLISMO ENERGÉTICO EN EL CEREBRO: IMPLICACIONES PARA LA NEURODEGENERACIÓN EN LA ATAXIA DE FRIEDREICH. PID2019-111338RB-I00. 1.6.2020-31.05.2023.
- Neurodegeneración en el cerebelo de modelos de ataxia de Friedreich: Bases moleculares y aproximaciones terapéuticas. PID2022-143030OB-I00 (FEDER, UE). 1.9.2023-31.8.2026.

### Thesis

Andrés Vicente Acosta. Efectos de la deficiencia de frataxina en astrocitos y su modulación por el agonista de Sonic hedgehog SAG. Programa de Doctorado en Biociencias Moleculares. Director: Javier Díaz Nido. 2023.

### Molecular Bases of Neuronal Plasticity

<http://www.cbm.uam.es/fjdiez>

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- **Prof. Francisco Javier Díez-Guerra. Catedrático. Departamento de Biología Molecular. UAM.**
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### Research summary:

Higher cognitive functions differentiate humans from other animal species. These functions depend on the activity of complex neural networks in our forebrain. As we age or due to neurological or psychiatric disorders, these networks lose functionality caused by the dysfunction and loss of synapses and eventually neurodegenerative events. In the development of the mammalian central nervous system there are periods of active synaptogenesis and synaptic remodeling, driven by sensory experience and essential for the proper configuration of adult neural networks. Until we understand in depth how these high synaptic plasticity events work and how to induce them, it will be difficult to imagine actions to prevent, alleviate or recover the loss of cognitive functionality associated with age or pathologies. In our laboratory, we have been able to reproduce several features of these periods of high plasticity using in vitro models based on primary cultures of dissociated embryonic neurons. We have found that neuronal electrical activity is critical and want to understand the underlying molecular and cellular mechanisms. To this end, we are focused on determining how synaptic activity, and more specifically, local intracellular calcium ( $\text{Ca}^{+2}$ ) oscillations modulate signaling pathways leading to synapse production and reinvigoration. Calmodulin (CaM), a calcium-binding protein, transduces  $\text{Ca}^{+2}$

oscillations into intracellular signaling events that lead to short-term and long-term effects, including the modulation of gene expression patterns. CaM activity is locally regulated by proteins such as Neurogranin (Ng), an abundant CaM-sequestering protein in the post-synaptic compartment of forebrain neurons. Ng brain levels and cognitive performance are closely and directly correlated in the human brain. Therefore, we have set as our research goals the study of the regulation of Ng expression and its functional role in the postsynaptic environment. We use techniques in the areas of biochemistry, cellular and molecular biology, gene expression manipulation, transcriptomics, proteomics and advanced light microscopy and image analysis, and build genetically-encoded biosensors, to identify the actors and the interactions that are relevant for synaptic generation and remodeling. We propose Ng as a target for strategies to prevent, alleviate or cure impaired cognitive function. Since Ng expression is restricted to some forebrain areas and late developmental stages, interventions to promote Ng expression will be likely devoid of undesired side-effects. In summary, a deeper understanding of the role of CaM-sequestering proteins in synaptic plasticity will make it possible to develop new therapies to improve cognitive functions and quality of life of aging individuals and patients of neurological diseases.

### Thesis

Raquel de Andrés Hernáiz. Estudio de la regulación de la expresión de Neurogranina por actividad sináptica. Programa de Doctorado en Biociencias Moleculares Director. Javier Díez-Guerra. 2023.

### Molecular mechanisms of Oligodendrocyte-Neuron interaction and myelin pathologies

<https://www.cbm.uam.es/bcubelos>

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- **Prof. Beatriz Cubelos Alvarez. Profesora Contratada Doctora. Departamento de Biología Molecular. UAM.**
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### Research summary:

In our laboratory we study the neurological component of demyelinating pathologies and investigate the molecular mechanisms responsible for the processes of myelination in the Central Nervous System (CNS). Adequate myelination is essential for the correct transmission of the nerve impulse. In the CNS, oligodendrocytes (OLs) are the responsible cells for myelination of neuronal axons, through a complex process that requires multiple cellular interactions. In the absence of a correct myelination, diseases such as Multiple Sclerosis or leukodystrophies appear, currently orphans of an effective treatment. The possibility of generating therapies based on the neurological component of these diseases could stimulate the regeneration of new oligodendrocytes or increase the capacity of the remaining set of oligodendrocytes to produce more myelin and reestablish correct myelination. Our group has demonstrated the importance of the GTPases R-Ras1 and R-Ras2, essential proteins in the differentiation and survival of OLs. Moreover, we have described the relevance of their presence for the maintenance of energetic homeostasis and for the correct functioning of the nerve impulse transmission. Models lacking R-Ras1 and/or R-Ras2 faithfully reproduce the symptomatological characteristics of myelin diseases and could be used as models for the development of new treatments based on the neurological component.

### Projects

- Role of R-Ras1 and R-Ras2 in oligodendrocyte differentiation and specification. PID2021-123269OB-I00. Spanish Ministry of Economy and Competitiveness. PI Beatriz Cubelos. 2022-2024.

## Tau function and dysfunctions in Alzheimer disease

<http://www.cbm.uam.es/javila>

- **Prof. Félix Hernández Pérez. Profesor Titular. Departamento de Biología Molecular. UAM. (Co-PI with Dr. Jesús Avila, CSIC-CBMSO)**
- **Prof. Vega García-Escudero. Profesora Contratada Doctora Interina. Departamento de Anatomía, Histología y Neurociencias. UAM.**

### Research summary:

Tau is mainly a neuronal protein that could be involved in several cellular functions in addition of being a microtubule associated protein. At the present, we are analyzing those functions and we continue with the study of the possible role of tau in Alzheimer disease (AD) and other tauopathies. During 2021-2022, we have tested: a) the presence of tau in non-neuronal cells, b) the presence of new tau isoform and c) we have started to look for a possible specific role of tau in neuronal aging, since aging is the main risk factor for Alzheimer disease.

About the presence of tau in non-neuronal cells, we have found that tau could be present in microglia cells, being that presence the consequence of the endocytosis of extracellular (neuronal) tau into microglia cells. Also, we have found that the effect of tau in microglia cells results in the activation of p38 kinase that could be toxic for the cell. In that way, inhibition of p38 kinase decreases tau toxicity in microglia cells and improves microglia phagocytic function. Additionally, tau expression was found in kidney cells playing, this kidney tau, a role in podocyte architecture.

A new tau isoform raised by intron 12 retention has been described. This new tau isoform contains an extra 16aa peptide, only present in humans, with two tryptophan residues and we named it as W-Tau isoform. Looking at W-Tau isoform, we have found that it has a low capacity for self-aggregation, unlike of the previously known human tau isoforms. Also, W-Tau isoform could prevent the aggregation of the other tau isoforms. *In vitro* experiments, using the 16aa peptide, specific for W-Tau, have indicated that such peptide could prevent not only tau self-assembly but also beta amyloid peptide aggregation.

During this period, we have studied aging at the dentate gyrus (DG) and hippocampal region of old mice, since DG is one of the regions that are earlier affected in AD. Previously, we described, *in vivo*, that aging features in DG from old mice could be ameliorated expressing the so-called Yamanaka Factors (YF). Now, we are looking for more simple factors that could replace the action of YF and starting to look for a specific tau function in neuronal aging.

Finally, our group has done several collaborations, located inside and outside of the CBMSO, in aspects related to Alzheimer disease and other neurodegenerative disorders like aging.

### Publications

- Vallés-Saiz L, Ávila J, Hernández F. Lamivudine (3TC), a Nucleoside Reverse Transcriptase Inhibitor, Prevents the Neuropathological Alterations Present in Mutant Tau Transgenic Mice. *Int J Mol Sci.* 2023 Jul 6;24(13):11144. doi: 10.3390/ijms241311144. PMID: 37446327; PMCID: PMC10342792.
- Antón-Fernández A, Vallés-Saiz L, Avila J, Hernández F. Neuronal nuclear tau and neurodegeneration. *Neuroscience.* 2023 May 10;518:178-184. doi: 10.1016/j.neuroscience.2022.07.015. Epub 2022 Jul 22. PMID: 35872252.

- Hernández F, Ferrer I, Pérez M, Zabala JC, Del Rio JA, Avila J. Tau Aggregation. *Neuroscience*. 2023 May 10;518:64-69. doi: 10.1016/j.neuroscience.2022.04.024. Epub 2022 May 4. PMID: 35525497.
- Molinero N, Antón-Fernández A, Hernández F, Ávila J, Bartolomé B, Moreno- Arribas MV. Gut Microbiota, an Additional Hallmark of Human Aging and Neurodegeneration. *Neuroscience*. 2023 May 10;518:141-161.

## Projects

- Neurorregeneración en la enfermedad de Alzheimer a través de la expresión de factores de pluripotencia in vivo. PID2020-113204GB-I00. PI Félix Hernández Pérez. MINECO. 1.9.2021-31.8.2024.
- Part of the Networking Research Center on Neurodegenerative Diseases (CIBERNED).

## Molecular mechanisms of neurodegeneration

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- **Prof. Juan Salvador Jiménez. Profesor Emérito. Departamento de Química Física Aplicada. UAM.**
  - **Prof. María José Benítez Moreno. Profesora Titular. Departamento de Química Física Aplicada. UAM.**
  - **Prof. M<sup>a</sup> José Pérez Alvarez. Profesora Titular. Departamento de Biología. UAM.**
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## Neural Stem Cells in the Adult Brain: intrinsic and extrinsic factors that regulate their self-renewal and differentiation.

<https://www.cbm.uam.es/eporlan>

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- **Prof. Eva Porlan. Profesora Contratada Doctora. Departamento de Biología Molecular. UAM.**
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## Research summary:

In adult vertebrates, somatic stem cells (SC) are self-renewing and multipotent undifferentiated cells, that maintain the integrity of the host tissue and offer a potential source of cells for regeneration after injury at young ages. Impairing the balance between SC self-renewal and differentiation paves the way to either tissue functional and structural impairment and may lead to tumorigenesis. SC have been found in the mammalian central nervous system, where they contribute to the homeostatic balance by addition of new neurons and glial cells to the brain once development has concluded. Within specialized niches, the microenvironments where they dwell, neural stem cells (NSC), derived progenitors and differentiated progeny are stratified within a highly regulated hierarchy and coordinated to maintain the necessary cellular production to uphold adult tissue renewal. Notwithstanding NSC contribution to homeostasis, their regenerative capacity is limited and unable to replace lost neural populations to induce a real functional recovery in situations of brain damage. However, since they can activate in reaction to some types of lesions, the population of NSC is regarded as a potential cellular target for regenerative medicine.

In our group, we focus on the molecular characterization of the pathways involved in mammalian NSC self-

renewal and differentiation to neuronal and glial populations. To this end, we use tissue specific conditional and inducible loss- and gain-of-function mouse models. We are mostly interested in pinpointing molecular targets to effectively manipulate these processes on demand. This strategy holds the potential for exploiting NSC and their progeny for replacement/regenerative therapeutic interventions, in physiological ageing or pathological situations stemmed from neurodegeneration or demyelination.

Polo like kinase 1 (*PLK1*) is an essential gene coding a druggable serine/threonine kinase with crucial roles. Although the canonical functions of PLK1 are related to cell proliferation, as to drive mitotic cell cycle and serving to establish a functional bipolar spindle during mitosis, unexpected mitosis-independent roles are emerging. In this regard, we have contributed to describing the role of Plk1 in the control of cell fate during embryonic neural progenitor division (Gonzalez-Martinez, et al., 2022), and we have established that Plk1 is a key player in adult NSC self-renewal and neuronal differentiation (Barrios-Muñoz, PhD Thesis, 2021).

### Publications

- Del Puerto A, Lopez-Fonseca C, Simón-García A, Martí-Prado B, Barrios-Muñoz AL, Pose-Utrilla J, López-Menéndez C, Alcover-Sanchez B, Cesca F, Schiavo G, Campanero MR, Fariñas I, Iglesias T, Porlan E. Kidins220 sets the threshold for survival of neural stem cells and progenitors to sustain adult neurogenesis. *Cell Death Dis.* 2023 Aug 4;14(8):500. doi: 10.1038/s41419-023-05995-7. PMID: 37542079; PMCID: PMC10403621.
- Sierrol-Piquer MS, Morante-Redolat JM, Porlan E. Editorial: "Unravelling neural stem cell biology: players and strategies". *Front Cell Dev Biol.* 2023 May 2;11:1206339. doi: 10.3389/fcell.2023.1206339. PMID: 37200629; PMCID: PMC10185880.

### Projects

- PID2019-104763RB-I00. Novel druggable regulators of adult neurogenesis and direct lineage reprogramming: implications for regeneration. Acronym: NeuroRepReg. AEI and FEDER. PI Eva Porlan. 06/2020 - 05/2023.
- Instituto de Investigación Hospital Universitario La Paz "Hospital La Paz Institute for Health Research" (IdiPAZ).

### Molecular basis of neurotransmission and its implication in neuropathology

<https://www.cbm.uam.es/fzafra>

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- **Prof. Francisco Zafra Gómez. Catedrático. Departamento de Biología Molecular.UAM.**
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### Research summary:

Our laboratory is interested in the molecular mechanisms of neurotransmission and its relationship with various pathologies of the nervous system. Communication between neurons implies an interplay between excitatory pathways mediated by glutamate and inhibitory neurotransmission mediated by GABA and glycine. The modulating action of less abundant neurotransmitters, such as dopamine, is added on top of these major pathways. This neurotransmitter crosstalk is controlled by a series of membrane proteins including ion channels, receptors and transporters. Alterations in these proteins are associated with diseases such as stroke,

epilepsy or schizophrenia. Our objectives include the study of the interactions between some of these proteins and their environment, represented by the interactome and the lipidome. By using proximity labeling proteomic techniques we have been able to find new proteins and lipids that control the activity of the dopamine transporter. On the other hand, we have been able to find new interactions with the AKT1 signaling pathway with the sodium ion channel (Na<sub>v</sub>1.1), which controls the activity of GABAergic neurons and whose alteration is associated with a form of severe epilepsy called Dravet syndrome. We have also investigated regulatory mechanisms of glycine transporters, which participate in the transmission of pain in the spinal cord and of sensory information in the retina. In a model of neuropathic pain, we have obtained evidence indicating a readjustment of the levels of the glycinergic marker GlyT2 in response to microglia activation. In the retina, we have described a new regulatory mechanism by microRNAs that adjusts the levels of the GlyT1 to the intensity of light.

During this time, we have maintained collaborations with the groups of Dr. F.J. Díez-Guerra, Drs. B. López-Corcuera (CBMSO) and C. Avendaño (UAM) on the role of glycinergic pathways; Drs. A. Rodríguez Artalejo (UCM) and D. Bartolomé-Martín (la Laguna) in the study of the activity of the sodium and potassium channels. We have also collaborated with clinicians of the Sant Joan de Déu Hospital in Barcelona (Dr. J. Armstrong), the San Sebastián University Hospital (Dr. I. Martí-Carrera) and the University Hospital of Mostoles (Dr. A. Díaz de Bustamante) with whom we have participated in the investigation of the pathogenic mechanisms underlying a form of epilepsy due to mutations in the GABA transporter.

In summary, our work deepens our understanding of the mechanisms of communication in the brain under physiological and pathological conditions.

#### Publications

- Piniella D, Canseco A, Vidal S, Xiol C, Díaz de Bustamante A, Martí-Carrera I, Armstrong J, Bastolla U, Zafra F. Experimental and Bioinformatic Insights into the Effects of Epileptogenic Variants on the Function and Trafficking of the GABA Transporter GAT-1. *Int J Mol Sci.* 2023 Jan 4;24(2):955. doi: 10.3390/ijms24020955. PMID: 36674476; PMCID: PMC9862756.
- Piniella D, Zafra F. Functional crosstalk of the glycine transporter GlyT1 and NMDA receptors. *Neuropharmacology.* 2023 Jul 1;232:109514. doi: 10.1016/j.neuropharm.2023.109514. Epub 2023 Mar 31. PMID: 37003571.

#### ➤ **Metabolic and Signaling Networks in Disease UNIT**

##### **Mitochondrial dysfunction in metabolic diseases**

<https://www.cbm.uam.es/balsalab>



- **Prof. Eduardo Balsa. Investigador Ramón y Cajal. Departamento de Biología Molecular. UAM.**

#### **Research summary:**

Mitochondria are unique and complex organelles that carry out critical metabolic functions within the cells. Once considered to be mere sites of ATP generation, it is now evident that these organelles participate in a wide range of cellular processes including calcium homeostasis, apoptosis, redox balance or cell fate. Because

of this multifaceted contribution of mitochondria to key biologic and metabolic pathways it is not surprising that mitochondrial dysfunction has been linked to many human disorders including neurodegeneration, diabetes, cancer or aging.

Specifically, our lab focuses on defects in the oxidative phosphorylation system (OXPHOS) occurring from mitochondrial disease mutations that compromise cellular fitness and survival. This biochemical failure is thought to underlie pathologies associated with mitochondrial dysfunction. However, the precise metabolic processes, signaling pathways and compensatory responses resulting from a defective mitochondrial Electron Transport Chain (ETC) that drive these fatal disorders are not entirely understood. Although diminished ATP production has been considered a hallmark of mitochondrial dysfunction, our recent discoveries highlighted that other metabolic failures such as disturbed redox hemostasis due to accumulated levels of NADH can be equally detrimental. Moreover, which cell types contribute the most to the disease and whether disease-carrying cells negatively impact the function of its surrounding wild-type neighbors or distant organs remain poorly characterized.

The long-term goal of our lab is to understand the molecular components that regulate mitochondrial metabolism, in the context of physiology and diseases, and use this knowledge to develop successful therapies.

We are currently exploring two central areas. First, we aim to elucidate the molecular mechanisms whereby mitochondrial dysfunction compromise cellular fitness and leads to organ failure in the context of human diseases. Second, we focus on understanding the metabolic vulnerabilities of metastasizing cancer cells and to define novel therapeutic approaches to prevent cancer progression.

To accomplish these goals, we are employing cutting-edge technologies such CRISPR/Cas9-based genetic screenings, multi-omics platform, single cell clonal tracking and preclinical mouse models.

## Publications

- Sanmarco LM, Rone JM, Polonio CM, Fernandez Lahore G, Giovannoni F, Ferrara K, Gutierrez-Vazquez C, Li N, Sokolovska A, Plasencia A, Faust Akl C, Nanda P, Heck ES, Li Z, Lee HG, Chao CC, Rejano-Gordillo CM, Fonseca-Castro PH, Illouz T, Linnerbauer M, Kenison JE, Barilla RM, Farrenkopf D, Stevens NA, Piester G, Chung EN, Dailey L, Kuchroo VK, Hava D, Wheeler MA, Clish C, Nowarski R, Balsa E, Lora JM, Quintana FJ. Lactate limits CNS autoimmunity by stabilizing HIF-1 $\alpha$  in dendritic cells. *Nature*. 2023 Aug;620(7975):881-889. doi: 10.1038/s41586-023-06409-6. Epub 2023 Aug 9. PMID: 37558878; PMCID: PMC10725186.
- Jaraíz-Rodríguez M, Del Prado L, Balsa E. Metabolic remodeling in astrocytes: Paving the path to brain tumor development. *Neurobiol Dis*. 2023 Nov;188:106327. doi: 10.1016/j.nbd.2023.106327. Epub 2023 Oct 13. PMID: 37839712.

## Projects

- ERC Starting Grant (2020 ERC-Stg) 948478 -MitoCure-. Funded by the EC-European Research Council. 01/01/2021 - 31/12/2025. Coordinator/PI: Eduardo Balsa Martinez.
- METABOLIC HETEROGENEITY AS A CRITICAL DETERMINANT OF MELANOMA METASTASIS PROJECT. PR\_EX\_2022\_01. FUND. CRIS. 1.3.2023-31.03.2028
- Descifrando el metabolismo mitocondrial como diana para la progresión tumoral y la metastasis. PID2022-137404OB-I00 (FEDER, UE). 1.9.2023-31.8.2026.



## Physiopathology studies and therapeutic approaches in animal and cellular models of neurometabolic diseases

<https://www.cbm.uam.es/lab220>

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- **Prof. Lourdes Ruiz-Desviat. Catedrática. Departamento de Biología Molecular. UAM.**
  - **Prof. Eva M<sup>a</sup> Richard Rodríguez. Profesora Titular. Departamento de Biología Molecular. UAM.**
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### Research summary

Our research is focused in neurometabolic diseases, propionic acidemia (PA) and hyperphenylalaninemias (HPAs) among others, enzymatic deficiencies of autosomal recessive inheritance, characterized by the toxic accumulation of precursors and lack of downstream metabolites.

Previous results from our group include the generation of patient-derived iPSCs from PA patients' fibroblasts and a CRISPR/Cas edited isogenic control. In this period, we have differentiated them to cardiomyocytes which have been characterized in relation to the biochemical phenotype, expression of miRNAs and genes in different signaling pathways related to mitochondrial function and cardiac alterations, which are one of the major life-threatening complications in patients with the disease. We have also successfully differentiated iPSC to neuronal precursors and astrocytes, which in PA samples show a maturation defect, mitochondrial dysfunction, increased ROS levels and altered miRNAs expression signatures.

In a collaborative study and using a hypomorph PA mouse model, we have demonstrated that pharmacological inhibition of O-GlcNAcase, the enzyme removing O-GlcNAc from proteins, and specifically from CPS1, catalysing the first step in the urea cycle, resulted in clinically relevant reductions of systemic ammonia, hallmark of PA disease, a strategy that can also be applied to other genetic and acquired liver diseases.

Ongoing projects related to splice modulation include providing the proof of concept of the therapeutic use of antisense oligonucleotides (ASO) for a number of neurometabolic gene defects. For this aim, we have generated by CRISPR/Cas novel cellular and animal models with specific splicing variants in the *PAH* gene, responsible for phenylketonuria. The aim is to study the molecular pathogenesis of patient specific mutations and to identify therapeutic ASO to correct the splice defect. In other gene defects, we have focused on the correction of the aberrant insertion in the mRNA of pseudoexons activated by deep-intronic mutations. Such events are heavily underreported, a situation that may change with the incorporation of transcriptome sequencing as part of the diagnostic pipeline. Thus, we have identified several pseudoexons prone to activation by different point mutations in the *PTS* gene, responsible for a tetrahydrobiopterin (BH<sub>4</sub>) synthesis defect resulting in hyperphenylalaninemia and monoamine neurotransmitter deficiency. We have identified several ASO that can correct the aberrant insertion of four overlapping pseudoexons activated by different mutations, resulting in protein recovery.

In addition to our work with splicing defects in neurometabolic diseases, we have recently identified a series of ASO that modulate missplicing of a neuronal microexon involved in autism spectrum disorders and schizophrenia (collaboration with Dr. Jose J Lucas, CBMSO and Dr. Brage S. Andresen, University of Southern Denmark; patent PCT/EP2022/077882).

### Publications

- Álvarez M, Ruiz-Sala P, Pérez B, Desviat LR, Richard E. Dysregulated Cell Homeostasis and miRNAs in Human iPSC-Derived Cardiomyocytes from a Propionic Acidemia Patient with Cardiomyopathy. *Int J Mol Sci.* 2023 Jan 22;24(3):2182. doi: 10.3390/ijms24032182. PMID: 36768524; PMCID: PMC9916417.
- Martínez-Pizarro A, Calmels N, Schalk A, Wicker C, Richard E, Desviat LR. Functional analysis of novel variants identified in cis in the PCCB gene in a patient with propionic acidemia. *Gene.* 2024 Jan 30;893:147902. doi: 10.1016/j.gene.2023.147902. Epub 2023 Oct 13. PMID: 37839763.
- Spangsberg Petersen US, Dembic M, Martínez-Pizarro A, Richard E, Holm LL, Havelund JF, Doktor TK, Larsen MR, Færgeman NJ, Desviat LR, Andresen BS. Regulating *PCCA* gene expression by modulation of pseudoexon splicing patterns to rescue enzyme activity in propionic acidemia. *Mol Ther Nucleic Acids.* 2023 Dec 13;35(1):102101. doi: 10.1016/j.omtn.2023.102101. PMID: 38204914; PMCID: PMC10776996

## Projects

- “Elucidation of cardiac electrophysiological alterations in propionic acidemia: Towards the identification of targets for therapeutics”. Propionic Acidemia Foundation (PAF-113). (2022-2023). PI: Eva María Richard Rodríguez.
- MECANISMOS RESPONSABLES DEL FENOTIPO PATOLÓGICO EN ENFERMEDADES NEUROMETABÓLICAS RARAS Y APROXIMACIONES TERAPÉUTICAS. PID2019-105344RB-I00. IP Lourdes Ruiz Desviat. 1.6.2023-31.5.2023.
- Enfermedades neurometabólicas raras: de la investigación en nuevos modelos de enfermedad a terapias dirigidas. PID2022-137238OB-I00 (FEDER, UE). IP Lourdes Ruiz-Desviat. 1.9.2023-31.8.2026.
- “Acidemia propiónica: impacto en el epigenoma y el proteoma en relación con el fenotipo cardíaco y neurológico”. Fundación Ramón Areces, XX concurso nacional para la adjudicación de ayudas a la investigación en ciencias de la vida y de la materia 2020 (May 2021-May 2024). PI: Eva María Richard Rodríguez.
- European cooperation in Science and Technology (COST) Action CA17103. Delivery of RNA therapy (2018-2023). Lourdes R Desviat, Management Committee member Spain.
- CIBER DE ENFERMEDADES RARAS (CIBERER). ISCIII CB06/07/0017.
- Instituto de Investigación Sanitaria Hospital La Paz (IdiPaz).

## Functional Glycogenomics

<https://www.cbm.uam.es/es/investigacion/programas/procesos-fisiologicos-y-patologicos/redes-metabolicas-y-senalizadoras-en-la-enfermedad/glicogenomica-funcional>

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- **Prof. Pedro Bonay Miarons. Profesor Titular. Departamento de Biología Molecular.UAM.**
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## Research summary

The Glycosylation is the most abundant, diverse and dynamic post-translational modification in nature, generating one of the most complex biological molecules found in nature, the glycans. Those are covalent conjugates of an oligosaccharide to certain amino acid residues on the protein backbone, resulting in a plethora of glycoforms potentially exhibiting a wide spectrum of functional and biological proteins for a single gene product. Almost all secreted and membrane proteins are glycosylated and hence almost all plasma and serum proteins are glycoproteins. This co-translational modification widens the functional spectra of proteins at least

one magnitude order. Glycan biosynthesis is more significantly affected by disease states than by protein production. Glycomics, therefore holds considerable promise specifically as disease markers. The nonlinear and non-template based biosynthesis of glycans make head to head compare glycomics to proteomics is not technically possible, and complex structural analysis of glycome is necessary in order to get a glycomic profile.

The group has devoted the last five years to assemble, implement and validate a novel technological platform that allows us to analyze the N-glycome from minute amounts of biological samples: sera, plasma or tissues, unique at the UAM campus and second in Spain, and fourth in Europe behind Croatia and Ireland. The group has curated one of the largest collections of clinically well characterized biological samples of American tripanosomiasis biological samples (around 5000), leishmaniasis visceral and Neurocysticercosis from all stages of the diseases, before and after chemotherapeutic treatment.

The glycomic evaluation of individuals (not populations) allows to establish associations to disease progression, therapeutic efficacy or failure and reinfections. The system has been used to analyze samples from three defined infectious disease from which we have clinically defined cohorts (Chagas disease, Leishmaniasis and Neurocysticercosis). From our previous studies on tyiortal sera N-glycome we have moved to study the effector profile of human Immunoglobulin G derived from its glycosylation profile. By using this novel approach, we have been allowed to identify some molecular markers for efficacy during the treatment with Benznidazole for acute Chagas disease patients, and able to discriminate the latent form active form of neurocysticercosis, previously only possible by using classical image systems like NMR or PET-TAC.

### **Molecular mechanisms of sex-differences in metabolism physiology and disease.**

[www.cbm.uam.es/scogliati](http://www.cbm.uam.es/scogliati)

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- **Prof. Sara Cogliati. Investigadora Ramón y Cajal. Departamento de Biología Molecular. UAM.**
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#### **Research summary**

Our laboratory aims to understand the molecular mechanisms of metabolic sex differences in health and disease, explicitly exploring mitochondria's role. Indeed, mitochondria are the central hub of metabolism and targets of sexual hormones, with a suggested role in modulating sex-specific differences in many physio-pathological conditions.

We are currently running two projects: one considering metabolism and one for cardiovascular disease. Since metabolism shows considerable differences between the two sexes, we are exploring the hypothesis that mitochondrial functions can be differently modulated in males and females and therefore determine important physiological differences.

To prove this, we are performing a wide analysis of mitochondrial functions and morphology, together with gene expression analysis and metabolomics approach (in collaboration with Christian Frezza's laboratory, CECAD, Cologne). Our target tissues are the liver, muscle, and white adipose tissue of males and females mice, further clustered according to the estrous phase.

In parallel, to be able to study the role of sex steroids and different growth conditions on mitochondrial functions in vitro, we are generating two fibroblast cell lines from female and male mice that constitutively over-express the estrogen and androgen receptors.

Cardiovascular disease is the first death cause in women worldwide. Nowadays, we know that biological sex has a strong impact on cardiovascular performance however the molecular mechanisms are still unknown. In

our lab, we aim to understand the mitochondrial role in the development of heart failure, a pathological condition that presents important clinical sex differences. Applying a biochemistry approach, electronic microscopy, and gene expression analysis, we are mapping the mitochondrial differences between male and female mice during the progression of heart failure. The ultimate goal is to identify some mitochondrial pathways that could be potential therapeutic targets for heart failure. Our preliminary data suggest that after transaortic constriction, fertile female mice are protected from cardiac hypertrophy and this correlates with less fibrosis and the maintenance of the mitochondrial network analyzed by electron microscopy.

## Projects

- Dimorfismo sexual en el metabolismo de la glucosa: caracterización del papel mitocondrial. PID2020-114054RA-I00. IP Sara Cogliati. MINECO. 1.9.2021-31.8.2024.

## The Role of Mitochondria in Human Pathology

<http://www.cbmsso.es/jmcuezva>

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- **Prof. José M. Cuezva Marcos. Catedrático. Departamento de Biología Molecular. UAM. Retired 31.8.2023.**
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## Research summary

Mitochondria play key roles in cellular metabolism, bioenergetics, the execution of cell death and intracellular signaling. Consistent with its prime physiological roles mitochondrial dysfunction is involved in the genesis and progression of ageing and of a plethora of human pathologies including cancer, metabolic syndrome, neurodegeneration and rare disorders. The mitochondrial ATP synthase is a key transducer in energy conservation by oxidative phosphorylation (OXPHOS), in the execution of cell death and in intracellular signaling by calcium and reactive oxygen species (ROS). Previously, we documented the mechanisms and role-played by the ATP synthase in metabolic reprogramming during liver development and in human carcinomas. More recently, we demonstrated that the inhibitor of the ATP synthase, named ATPase Inhibitory Factor 1 (IF1), is highly overexpressed in carcinomas playing a pivotal role in metabolic reprogramming of cancer and stem cells. We showed that binding of IF1 to the ATP synthase inhibits the enzyme under normal physiological conditions and this binding is prevented by phosphorylation of IF1-S39 through the activity of a cAMP-dependent protein kinase A like activity. Inhibition of the ATP synthase is required for adaptation to hypoxia, cell cycle progression and in cancer. Contrariwise, dephosphorylation of IF1 is required to increase the mitochondrial output of ATP in response to an increase in energy demand. Moreover, the IF1-mediated inhibition of the ATP synthase triggers a ROS signal that promotes the activation of nuclear programs of proliferation and resistance to cell death. Hence, IF1 is a most relevant mitochondrial protein that participates in defining the cellular phenotype.

A main objective of our group is to deepen into the cellular biology and role of the ATP synthase/IF1 axis in cancer and other metabolic disorders, neuronal and immune functions and in ageing. To cover these aims, we have developed transgenic mice (Tg-IF1) that conditionally overexpress human IF1 in neurons, liver, colon, heart and skeletal muscle, and generated the *ATP5IF1* lox/lox mouse which has been successfully used to knock-out IF1 (IF1-KO) in neurons, enterocytes and immune cells. With these models, we have demonstrated *in vivo* the role of the ATP synthase/IF1 in metabolic reprogramming and in signaling adaptive cellular and tissue responses in normal and pathophysiological situations (Fig. 1). Moreover, we have developed (i) the PROTEOmAb Platform for the identification of metabolic proteins as biomarkers of disease and (ii) identified FDA-approved small molecules that regulate OXPHOS for targeting mitochondria and effective bedside translation of the drugs to patients affected by mitochondrial dysfunction.

## Publications

- Domínguez-Zorita S, Cuezva JM. The Mitochondrial ATP Synthase/IF1 Axis in Cancer Progression: Targets for Therapeutic Intervention. *Cancers (Basel)*. 2023 Jul 25;15(15):3775. doi: 10.3390/cancers15153775. PMID: 37568591; PMCID: PMC10417293.
- Domínguez-Zorita S, Romero-Carramiñana I, Santacatterina F, Esparza-Moltó PB, Simó C, Del-Arco A, Núñez de Arenas C, Saiz J, Barbas C, Cuezva JM. IF1 ablation prevents ATP synthase oligomerization, enhances mitochondrial ATP turnover and promotes an adenosine-mediated pro-inflammatory phenotype. *Cell Death Dis*. 2023 Jul 12;14(7):413. doi: 10.1038/s41419-023-05957-z. PMID: 37433784; PMCID: PMC10336053.
- García-Arroyo R, Domènech EB, Herrera-Úbeda C, Asensi MA, Núñez de Arenas C, Cuezva JM, Garcia-Fernández J, Pallardó FV, Mirra S, Marfany G. Exacerbated response to oxidative stress in the Retinitis Pigmentosa Cerkl<sup>KD/KO</sup> mouse model triggers retinal degeneration pathways upon acute light stress. *Redox Biol*. 2023 Oct;66:102862. doi: 10.1016/j.redox.2023.102862. Epub 2023 Aug 28. PMID: 37660443; PMCID: PMC10491808.
- Romero-Carramiñana I, Esparza-Moltó PB, Domínguez-Zorita S, Nuevo-Tapióles C, Cuezva JM. IF1 promotes oligomeric assemblies of sluggish ATP synthase and outlines the heterogeneity of the mitochondrial membrane potential. *Commun Biol*. 2023 Aug 12;6(1):836. doi: 10.1038/s42003-023-05214-1. PMID: 37573449; PMCID: PMC10423274.

## Projects

- “Mitochondria and its dysfunction in pathology: The role of IF1”. PID2019-108674RB-100. Ministerio de Ciencia, Innovación y Universidades. PI: José M. Cuezva. 01/06/20 -31/07/23.
- José M. Cuezva is leader of unit “U713” of the CIBER of Enfermedades Raras (CIBERER) and of the Research Group “Metabolismo Energético Traslacional” of the Instituto Universitario Hospital 12 de Octubre (i+12), both are initiatives of the “Instituto de Salud Carlos III”. In addition, forms part of the Network of Excellence RED2018-102379-T METABOCANCER.

## Role of mitochondrial metabolism on the pathophysiology of skeletal muscle

<https://www.cbm.uam.es/lformentini>

- **Prof. Laura Formentini. Profesora Contratada Doctor. Departamento de Biología Molecular. UAM.**

## Research summary

Our investigation aims at understanding how mitochondrial bioenergetics participate in the integration of different cellular functions. Complex regulatory mechanisms enable mitochondrial metabolism to match cell demands, which extend beyond the production of ATP: during the last decade we demonstrated that mitochondrial oxidative phosphorylation (OXPHOS) plays further roles in controlling cell death (*EMBO J*, 2014, 33(7):762-78); immunity (*Cell Reports*, 2017, 19(6):1202-1213) and oncogenesis (*Mol Cell*, 2012, 45(6):731-42; *Nat Comm*, 2020, 11:3606). Impaired mitochondrial function also deeply alters lipid species and metabolism (*Diabetologia*, 2017, 60(10):2052-2065; *EMBO J*. 2020, e103812) and is emerging as a pivotal hallmark of metabolic disorders. Understanding which products of metabolism are limiting for correct cell function, and how cells obtain or transform them in physiological tissue environments, is crucial to exploit mitochondrial metabolism for therapy.

The main achievement of our research over the last two years was to deepen our knowledge of mitochondrial

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metabolism in the pathophysiology of skeletal muscle, the highest oxidative tissue in mammals. We defined how chronic mitochondrial dysfunctions drive the formation of muscular tubular aggregates (TA), honeycomb-like arrays of sarcoplasmic reticulum (SR) tubules that induce severe sarcomere disorganization and muscular pain. TA develops in the skeletal muscle of patients with Tubular Aggregate Myopathy (TAM, ORPHA:2593; OMIM:160565, 615883) as well as in other disorders, including endocrine syndromes, diabetes, and aging, although their primary cause is unknown. We investigated the molecular mechanisms of TA onset and a potential therapy in a preclinical mouse model of the disease. We showed that upon chronic *in vivo* inhibition of the mitochondrial ATP synthase, oxidative soleus muscle experiments a metabolic and structural switch towards glycolytic fibers, increases mitochondrial fission, and activates mitophagy to recycle damaged mitochondria. TA results from the over-response of the fission controller DRP1, which upregulates the Store-Operate-Calcium-Entry and increases the mitochondria-SR interaction in a futile attempt to buffer calcium overloads upon prolonged OXPHOS inhibition. Accordingly, hypoxic muscles cultured *ex vivo* show an increase in mitochondria/SR contact sites and autophagic/mitophagic zones, where TA clusters grow around defective mitochondria. Moreover, hypoxia triggered a stronger TA formation upon ATP synthase inhibition, and this effect was reduced by the DRP1 inhibitor mDIVI. *In vivo* edaravone treatment in mice with restrained OXPHOS restored a healthy phenotype by prompting mitogenesis and mitochondrial fusion. Altogether, our data provide a functional link between the ATP synthase/DRP1 axis and the setting of TA, and repurpose edaravone as a possible treatment for TA-associated disorders (Cell Death Dis. 2022 Jun 22;13(6):561).

Ultimately, our investigation aims to provide knowledge based on new mitochondrial aspects for better prevention, diagnosis, and therapy of metabolic and rare diseases that target skeletal muscle.

## Projects

- Role of mitochondrial metabolism on the pathophysiology of skeletal muscle: effect of the FAD-dependent dehydrogenases associated to oxidative phosphorylation“.PID2019-104241RB-I00 Ministerio de Ciencia e Innovación, Spain. 2020-2023. PI: Laura Formentini
- Disfunción de la actividad mitocondrial en patología: la beta-oxidación de ácidos grasos en el mantenimiento de la homeostasia del organismo. PID2022-137238OB-I00 (FEDER, UE). PI: Laura Formentini. 1.9.2023-31.8.2026.

## Patho-physiological implications of G protein-coupled receptors signaling networks.

<http://www.cbm.uam.es/fmayor>

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- **Prof. Federico Mayor Menéndez. Catedrático. Departamento de Biología Molecular.UAM.**
  - **Prof. Cristina Murga Montesinos. Catedrática. Departamento de Biología Molecular.UAM (co-PI)**
  - **Prof. Irene García-Higuera. Profesora Contratada Doctora. Departamento de Biología Molecular. UAM**
  - **Dra. Carmen Vida. Investigadora “Juan de la Cierva”. Departamento de Biología Molecular. UAM.**
  - **Prof. Natalia Reglero Real. Investigadora “María Zambrano”. Departamento de Biología Molecular. UAM.**
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## Research summary:

Our laboratory is interested in understanding the role of key regulatory hubs in the maladaptive rewiring of cell signaling networks that takes place during the onset or progression of metabolic, cardiovascular and inflammatory diseases and in cancer. G protein-coupled receptor kinase 2 (GRK2) acts as a relevant node by

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modulating signaling mediated by many GPCRs and via phosphorylation or scaffolding interactions with a growing array of cellular partners. Our laboratory has pioneered the research on such complex “interactome” and on the mechanisms regulating GRK2 levels and functionality. In obesity and insulin resistance-related contexts, we have described that age and sex-related factors modulate maladaptive changes in cardiac GRK2 levels and described tissue-specific roles of GRK2 in the modulation of metabolic homeostasis. In collaboration with P. Penela and C. Ribas, we have shown that GRK2 acts as an oncomodulator in breast cancer and in stratified epithelial tumors, by interacting with networks related to the hallmarks of cancer in a cell type-dependent manner, and that the GRK2 interactor  $G\alpha_q$  regulates the autophagic machinery upon nutrient fluctuations.

Since complex intercommunication among cell types from different tissues and with the cells of the immune system is essential for cellular and organismal homeostasis, our current aim is to elucidate how cell-type specific GRK2 interactomes are involved in cell-cell communication in defined physiological and pathological conditions. In close collaboration with other PIs of our Programme, we will use cellular and animal models with altered GRK2 levels or functionality in specific cell types to study:

-Maladaptive reshaping of metabolic and inflammatory networks in different tissues in physio-pathological situations related to aging, obesity, insulin resistance and cardiovascular alterations, with particular emphasis on the role of GRK2 in myeloid (neutrophils and macrophages) and other immune cells in inter-organ crosstalk in such disease contexts (objectives led by C. Murga, I. García-Higuera and N. Reglero-Real).

-Autophagy, endothelial dysfunction and inflammation. N. Reglero-Real and C. Ribas will collaborate in elucidating the modulation of these processes by  $G_q$  and other signalling networks.

-Crosstalk of signaling cascades within the tumor microenvironment. Connections among tumor microenvironment stresses, chemokine and growth factor-receptors and GRK2 interactors (HDAC6, HuR, Mdm2, Lyn) in the rewiring of breast cancer cell phospho-proteome, acetylome and ubiquitome leading to metastatic features (in collaboration with P. Penela and the Oncornet 2.0 consortium).

-Epidermal homeostasis and keratinocyte-immune cells crosstalk. Impact of GRK2 deletion in keratinocytes in the skin immune cell landscape, barrier function, skin-microbiome interaction and hair follicle homeostasis, and in the susceptibility to inflammatory diseases and squamous cell carcinomas (in collaboration with C. Ribas).

## Projects

- European Union:H2020-MSCA Programme, Grant agreement 860229-ONCORN2.0 (ONCOgenic Receptor Network of Excellence and Training) -Coordinator: Martine Smit, Amsterdam, F. Mayor Network group PI, 2020-2024.
- CIBER CARDIOVASCULAR, Instituto de Salud Carlos III, Group CB16/11/00278 (PI, F Mayor) 2017-2023.
- INTEGRAMUNE-CM. S-2022/BMD-7902. Coordinador. Comunidad de Madrid. 1.1.2023-31.12.2026.
- Desenmascarando nuevos papeles de los procesos de autofagia endotelial en la inflamación. PID2022-137552OA-I00 (FEDER, UE) (PI: N. Reglero). 1.9.2023-31.8.2026.
- Instituto de Investigación Sanitaria Hospital La Princesa. Group 11 (PI: F. Mayor)
- Instituto de Investigación Sanitaria Hospital La Princesa. Group 17 (PI: C. Murga)
- PID2020-117218RB-I00. Integrated GRK2 signaling networks and molecular mechanisms of disease. PI: Federico Mayor Jr. and Cristina Murga (co-PI). 2021-2024.

## Thesis

Angela Albitre Sanz. Redes señaladoras de GRK2 en el desarrollo de la glándula mamaria y el cáncer de mama. Programa de Doctorado de Biociencias Moleculares. Directores: Federico Mayor Menéndez and

Petronila Penela Márquez. 2023.

### Calcium signaling in mitochondria: metabolic control and mitochondrial physiopathology

<http://www.cbm.uam.es/jsatrustegui>

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- **Prof. Jorgina Satrústegui. Profesora Emérita. Departamento de Biología Molecular.UAM.**
  - **Prof. Beatriz Pardo. Profesora Titular Departamento de Biología Molecular. UAM (co-PI)**
  - **Prof. Araceli del Arco. Profesora Titular Universidad de Castilla-La Mancha (co-PI)**
  - **Prof. Laura Contreras Balsa. Profesora Ayudante Doctora. Departamento de Biología Molecular. UAM.**
  - **Prof. José M<sup>a</sup> Carrascosa Baeza. Catedrático. Departamento de Biología Molecular.UAM.**
  - **Prof. Elena Bogónez Peláez. Profesora Titular. Retired August 2022. Departamento de Biología Molecular.UAM.**
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#### Research summary:

Our interests are understanding calcium regulation of mitochondrial function by way of the calcium-dependent mitochondrial carriers of aspartate-glutamate/AGCs (Aralar/AGC1 and citrin/AGC2), components of the malate aspartate shuttle (MAS), or ATP-Mg<sup>2+</sup>/Pi carriers (SCaMCs). These carriers have Ca<sup>2+</sup>-binding motifs facing the intermembrane space and are not activated by matrix calcium. We also aim at learning the role of these carriers in health and disease.

In neurons, calcium is thought to regulate neuronal activation, by adjusting ATP production to ATP consumption. This occurs thanks to stimulation of glycolysis and OXPHOS. The mitochondrial calcium uniporter (MCU) was thought to play a major role by increasing mitochondrial calcium and OXPHOS in response to activation. We have tested this possibility in neurons using glucose and have found that MCU is dispensable for the increase in respiration in response to neuronal stimulation. Instead, using intracellular sensors of glucose, pyruvate and lactate, we find that Aralar-MAS is required to stimulate glycolysis, pyruvate production and respiration, revealing a calcium dependent mechanism essential to boost glycolysis and respiration in neurons using glucose.

In humans, Aralar/AGC1 deficiency is a rare disease presenting neurological and muscular affectation. Postnatal hypomyelination, epilepsy, hypotonia and delayed neurodevelopment are the main traits in patients. Global Aralar-KO mice have a short lifespan and well recapitulates the human phenotype. Our main interest is focused on deciphering the physiopathological role of Aralar/AGC1 in specific brain cell types and in muscle. To face these issues, we have generated oligodendroglial- and neuron-specific Aralar-KO mice. To answer relevant questions as: (a) the role of neuronal Aralar in the severe phenotype of the global Aralar-KO mice (b) the involvement of muscular- and neuronal-Aralar in motor coordination deficits and hypotonia, or (c) the contribution of oligodendroglial and neuronal Aralar to postnatal myelination, and demyelination-remyelination processes.

Citrin deficiency is an urea cycle disorder with different manifestations. Citrin/AGC2 is mainly expressed in liver and main clinical symptoms are hypoglycemia, hyperammonemia and dyslipidemia. In the frame of the Citrin Foundation, we are exploring i) the exogenous expression of Aralar, which has low expression in human liver, as possible therapy for Citrin deficiency and ii) the role of citrin/AGC2 in liver in the mitochondrial response



to Ca<sup>2+</sup> mobilizing agonists and its impact in liver metabolism. For that purpose, we will generate cellular and transgenic mouse models to better recapitulate the human disease.

As part of a COVID-19 project (CvK), a therapy targeting senescent cells, was shown to reduce mortality and morbidity induced by SARS CoV 2 in the transgenic animal models used.

## Publications

- Del Arco A, González-Moreno L, Pérez-Liébana I, Juaristi I, González- Sánchez P, Contreras L, Pardo B, Satrústegui J. Regulation of neuronal energy metabolism by calcium: Role of MCU and Aralar/malate-aspartate shuttle. *Biochim Biophys Acta Mol Cell Res.* 2023 Jun;1870(5):119468. doi: 10.1016/j.bbamcr.2023.119468. Epub 2023 Mar 28. PMID: 36997074.
- González-Moreno L, Santamaría-Cano A, Paradela A, Martínez-Chantar ML, Martín MÁ, Pérez-Carreras M, García-Picazo A, Vázquez J, Calvo E, González- Aseguinolaza G, Saheki T, Del Arco A, Satrústegui J, Contreras L. Exogenous aralar/slc25a12 can replace citrin/slc25a13 as malate aspartate shuttle component in liver. *Mol Genet Metab Rep.* 2023 Mar 16;35:100967. doi: 10.1016/j.ymgmr.2023.100967. PMID: 36967723; PMCID: PMC10031141.

## Projects

- Generation of a new human-like citrin-deficiency mouse model to study Citrin deficiency. CITRIN Foundation Research Grants. PIs: Laura Contreras & Araceli del Arco. 06/2022-10/2024
- Transportadores mitocondriales regulados por calcio: Papel de SCaMC3 y citrin en la señalización por calcio en el hígado y de Aralar en la comunicación intercelular en el SNC (PI: B. Pardo). PID2020-114499RB-I00. 1.9.2021-31.8.2024.
- This group is Member of the Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS FJD) as “Señalización mitocondrial del calcio” unit.

## Cellular Signaling Networks in Cancer (ONCO-RESECEL)

<https://www.cbm.uam.es/ppenela>

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- **Prof. Petronila Penela Márquez. Profesora Titular. Departamento de Biología Molecular. UAM.**
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## Research summary:

Intratumor cell heterogeneity and the intrinsic adaptability of tumour cells are fundamental features of cancer that have major consequences for the tumour evolution and the emergence of resistances. Cellular heterogeneity may result from either clonal evolution driven by genetic instability and/or from differentiation of stem-like cells, whereas the dynamic rewiring of signaling networks contributes to cell adaptability. Moreover, lifestyle factors also affect the incidence of cancer and the efficacy of treatments. Therefore, it is urgent to find out the mechanisms involved and the molecular dependencies of tumours for better tackling with cancer treatments. Even though oncogenes and tumour suppressors are main players in transformation

and malignant progression, they only account for a limited proportion of the differential gene expression observed in tumoral tissues, pointing out the involvement of additional factors in supporting and scaling up tumours. In this regard, dysregulation of proteins acting as signaling nodes and eliciting post-translational modifications might play a relevant role in different aspects of tumour cell behaviour (motility, cell cycle control, stress responses). Our group is interested in the role of kinases and other posttranslational modifiers in the dynamic rewiring of cell signaling networks, which could be susceptible to being therapeutically targeted.

Results of our laboratory showed that G protein-coupled receptor kinase2 (GRK2) is a versatile molecular hub that modulates signalling mediated by many GPCRs and a growing array of cellular partners. GRK2 is emerging as a relevant onco-modulator in breast cancer through complex regulatory loops affecting stress-related RNA binding proteins (HuR) in the angiogenic response to hypoxic and adrenergic stresses, E3 ubiquitin ligases (MDM2) on centrosome dynamics or cytosolic protein deacetylases (HDAC6) to foster EGF signalling and motility, and the concurrent up-regulation of GRK2 and these activities emerges as a functional signature in breast cancer types beyond the hormone-dependent status.

Our research aims are to identify a) GRK2-governed signalling circuits involved in breast cancer progression and resistance, deciphering the relevant targets modified by phosphorylation, acetylation, ubiquitination; b) consequences of GRK2-based signalosomes on cell cycle dynamics under stress conditions, and their role in cell cycle decision-making processes to differentiation, proliferation or senescence; c) influence of hormonal (adrenergic, estrogenic), metabolic stresses and micro-environmental conditions on GRK2 intertwinement with relevant partners for genomic stability an stroma remodelling, analysing changes in mammary gland morphology and epithelial organization, altered angiogenic processes and tissular fibrosis that facilitate tumour growth and dissemination.

## Projects

- CIBER CARDIOVASCULAR, Instituto de Salud Carlos III, Group CB16/11/00278 (PI, F Mayor) 2017-2023. Group member
- “Exploring post-translational regulation of angiogenic and inflammatory-related processes during colorectal cancer progression and differential recurrence”. CIVP20A6618. Fundacion Ramón Areces, 2021-2024. Principal Investigator: P. Penela
- “Exploring the role of GRK2 in BRCA1 dysfunction and mechanisms of PARP-inhibitor resistance in breast tumor models beyond BRCA status”. PI21/01834 Carlos III Institute of Health (FIS). 2022-2024. Principal Investigator: P. Penela
- INTEGRAMUNE-CM. S-2022/BMD-7902. Coordinador F. Mayor. Comunidad de Madrid. 1.1.2023-31.12.2026.

## Thesis

Belén Ortíz del Castillo. Papel de GRK2 en la orientación de las divisiones celulares y la toma de decisiones durante el ciclo hacia la proliferación. Programa de Doctorado en Biociencias Moleculares. Director. Petronila Penela Márquez. 2023.

Angela Albitre Sanz. Redes señalizadoras de GRK2 en el desarrollo de la glándula mamaria y el cáncer de mama. Programa de Doctorado de Biociencias Moleculares. Directores: Federico Mayor Menéndez and Petronila Penela Márquez. 2023.

## Translational medicine in inborn errors of metabolism and other rare genetic diseases

<https://www.cbm.uam.es/bperez>

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- Prof. Belén Pérez González. Catedrática. Departamento de Biología Molecular. UAM.
  - Prof. Pilar Rodríguez Pombo. Profesora Titular. Departamento de Biología Molecular. UAM
  - Prof. Alejandra Gámez Abascal. Profesora Titular. Departamento de Biología Molecular. UAM.
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### Research summary:

**Inborn errors of metabolism (IEM)** are one of the major groups of rare diseases (1 every 800 newborns have one). Genomic high-throughput sequencing has dramatically accelerated gene discovery and transformed **metabolic precision medicine**. However, more than half of patients remain without a genetic cause identified. From the more than 1400 pathologies categorized as IEM, there are only therapies for hundreds of IEMs. Using a multi-omic layer approach in combination with functional genomics, we have contributed to identify new defects associated with pathology. We are highlighting identification of pathogenic variants: i) in a gene involved in the synthesis of coenzyme A associated with a severe dilated cardiomyopathy (PPCDC), ii) in the moonlighting H-protein encoded by GCSH that has a dual role in protein lipoylation required for bioenergetic enzymes iii) in genes other than *SLC2A1* that usually has been associated with GLUT1 transporter deficiency and iv) in *YIF1B* associated with a severe neurodevelopment delay describing a new defect that combines a ciliopathies with a Golgiopathy.

Regarding therapies, we have been involved in the development of small chemical drugs targeted to rescue the activity of destabilizing mutant proteins as a common mechanism for loss and gain of function mutations in IEM. We have published evidence regarding the possible use of small chemical molecules such as celastrol in combination with pharmacological chaperones (PC) in the treatment of the severe rare diseases PMM2-CDG and methylmalonic aciduria, this last in combination with vitamin B12. Advancing the development of pharmaco-chaperoning, we have obtained five complete crystal structures of hPMM2 (free and bound to the essential activator glucose-1,6-bisphosphate, three for the wild type and two for the destabilizing p.Thr237Met variant). Using the structure, we have proposed that ~80% and ~50% of the missense variants of the core and cap domains respectively are potential candidates for treatment with PC. Furthermore, we have developed a drug discovery and screening platform using recombinant proteins and cellular models generated by CRISPRcas9 gene editing.

For preclinical evaluation, we have generated cellular models from patients and healthy hiPSC. We highlight the development of a protocol for the differentiation of iPSCs to hepatocyte-like cells (HLC) and their use as a preclinical model for the evaluation of PCs. In MMA, the HLC exhibited MMA disease hallmarks, and the pharmaco-chaperon treatment in combination with B12 significantly reduced the methylmalonic acid levels and rescue the liver damage associated with the disease.

### Publications

- Arribas-Carreira L, Dallabona C, Swanson MA, Farris J, Østergaard E, Tsiakas K, Hempel M, Aquaviva-Bourdain C, Koutsoukos S, Stence NV, Magistrati M, Spector EB, Kronquist K, Christensen M, Karstensen HG, Feichtinger RG, Achleitner MT, Lawrence Merritt II J, Pérez B, Ugarte M, Grünwald S, Riela AR, Julve N, Arnoux JB, Haldar K, Donnini C, Santer R, Lund AM, Mayr JA, Rodríguez-Pombo P, Van Hove JLK. Pathogenic variants in GCSH encoding the moonlighting H-protein cause combined nonketotic hyperglycinemia and lipoate deficiency. *Hum Mol Genet.* 2023 Mar 6;32(6):917-933. doi: 10.1093/hmg/ddac246. PMID: 36190515; PMCID: PMC9990993.
- Musokhranova U, Grau C, Vergara C, Rodríguez-Pascau L, Xiol C, Castells AA, Alcántara S, Rodríguez-Pombo P, Pizcueta P, Martinell M, García-Cazorla A, Oyarzábal A. Mitochondrial modulation with

- leriglitazone as a potential treatment for Rett syndrome. *J Transl Med.* 2023 Oct 26;21(1):756. doi: 10.1186/s12967-023-04622-5. PMID: 37884937; PMCID: PMC10601217.
- Tangaas T, Constante JR, Backe PH, Oyarzábal A, Neugebauer J, Weinhold N, Boemer F, Debray FG, Ozturk-Hism B, Evren G, Tuba EF, Ummuhan O, Footitt E, Davison J, Martinez C, Bueno C, Machado I, Rodríguez-Pombo P, Al-Sannaa N, De Los Santos M, López JM, Ozturkmen-Akay H, Karaca M, Tekin M, Pajares S, Ormazabal A, Stoway SD, Artuch R, Dixon M, Mørkrid L, García-Cazorla A. BCKDK deficiency: a treatable neurodevelopmental disease amenable to newborn screening. *Brain.* 2023 Jul 3;146(7):3003-3013. doi: 10.1093/brain/awad010. PMID: 36729635.
  - Pena-Burgos EM, Regojo RM, Sáenz de Pipaón M, Santos-Simarro F, Ruiz-Sala P, Pérez B, Esteban-Rodríguez MI. Neuropathological Findings in Short-Chain enoyl-CoA Hydratase 1 Deficiency (ECHS1D): Case Report and Differential Diagnosis. *Pediatr Dev Pathol.* 2023 Mar-Apr;26(2):138-143. doi: 10.1177/10935266221134650. Epub 2022 Dec 14. PMID: 36515364.

## Projects

- Genomic Medicine – IMPACT Genómica” (IMP/00009). 2021-2023. Inst. Salud Carlos III. Participant group. PI: Angel Carracedo
- Belen Pérez is Head of a CIBERER group (CB06/07/0004) and a IdiPAZ group
- Cross-omic approach for the discovery of the genetic basis of inborn errors of metabolism and for a personalized therapeutic intervention. (PI19/01155). 2020- 2023. PI Belén Pérez. Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III

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## Thesis

Laura Arribas Carreira. Implicaciones del metabolismo de la glicina en la salud y la enfermedad humana: Hiperglicinemia no Cetósica, una enfermedad con fenotipo clínico neurológico. Programa de Doctorado en Biociencias Moleculares. Directora: Pilar Rodríguez-Pombo. 2023.

Cristina Segovia Falquina. Generación de una plataforma de análisis funcional de variantes en PMM2 con fines diagnósticos y terapéuticos. Programa de Doctorado en Biociencias Moleculares. Directora: Belén Pérez González.

Alicia Villas Lagoa. Desarrollo de modelos con fines diagnósticos y terapéuticos para la deficiencia de fosfomanomutasa 2. Programa de Doctorado en Biociencias Moleculares. Directora: Belén Pérez González.

## Regulatory functions and mechanisms of cell signaling pathways through G proteins: a new interactome

<https://www.cbm.uam.es/cribas>

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- **Prof. Catalina Ribas Núñez. Profesora Titular. Departamento de Biología Molecular.UAM.**
  - **Prof. Inmaculada Navarro. Profesora Ayudante Doctora. Departamento de BiologíaMolecular. UAM.**
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## Research summary

Our laboratory is investigating key nodes in signaling networks involved in both physiological and pathological conditions and the molecular mechanisms involved. G-protein-coupled receptors (GPCRs) are a family of membrane proteins with great physiological and pharmacological importance. In particular, Gq protein-coupled receptors (Gq-GPCR) are increasingly involved in pathologies such as cardiovascular/metabolic diseases and cancer. In recent years, the Gq interactome has expanded considerably with the description of new effectors,

helping to improve our understanding of the cellular and physiological events controlled by this G $\alpha$  subunit. Recently, our group has contributed in the last year to unveil a new adapter role for Gq, through a new interaction region in G $\alpha_q$ , different from the classical effector-binding region. Our recent results reveal an unforeseen connection between non-canonical Gq signaling and cell homeostasis. Furthermore, G $\alpha_q$  is known to interact with various components of the cytoskeleton, as well as with important membrane microdomain organizers, suggesting the existence of signaling complexes that could be limited to specific subcellular environments.

The main objective of our group is to understand how changes in Gq-GPCR signaling (involving different types of cells and tissues) are integrated at the cellular and organism level, and how they can promote the progression of pathologies, using cell and animal models with altered expression/activity of this protein, as well as samples from patients or animal models of disease. We will focus particularly on the functional impact of this new interactome of G $\alpha_q$  and its modulation by accessory proteins (such as GRKs, Caveolins, AGS, RGS, EBP50, Ric8), with emphasis on how chemical and/or mechanical inputs on Gq signaling play a role in autophagy/exosome trafficking, endothelial dysfunction/inflammation and tumor microenvironment/cancer progression. The identification of new signaling pathways that relate G $\alpha_q$  to the crosstalk between different cell homeostasis and communication machineries will provide a better understanding of the impact of maladaptive Gq-coupled GPCR activation in pathological conditions.

In addition, and in close collaboration with other members of our CBMSO Programme, we use cellular and animal models with altered GRK2 levels or functionality to study:

- Epidermal homeostasis and keratinocyte-immune cells crosstalk. Impact of GRK2 deletion in keratinocytes in the skin immune cell landscape, barrier function, skin-microbiome interaction and hair follicle homeostasis, and in the susceptibility to inflammatory diseases and squamous cell carcinomas (in collaboration with F.Mayor).

## Projects

- CIBER CARDIOVASCULAR, Instituto de Salud Carlos III, Group CB16/11/00278 (PI, F Mayor) 2017-2023.
- Participation in ERNEST (European Research Network on Signal Transduction) COST ACTION (European cooperation in Science and Technology)
- Redes de señalización de G $\alpha_q$  en la homeostasis y comunicación celular: repercusión en disfunción endotelial e inflamación. PI22/00966. Instituto de Salud Carlos III. Principal investigador: Catalina Ribas (FUNDACION PARA LA INVESTIGACION BIOMEDICA DEL HOSPITALUNIVERSITARIO "LA PRINCESA"-UAM). 01/01/2023-31/12/2025.
- INTEGRAMUNE-CM. S-2022/BMD-7902. Coordinador F. Mayor. Comunidad de Madrid. 1.1.2023-31.12.2026.

## Mitochondrial biology in immune modulation

[www.cbm.uam.es/jtraba](http://www.cbm.uam.es/jtraba)

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- **Prof. Javier Traba Domínguez. Investigador Ramón y Cajal. Departamento de Biología Molecular. UAM.**
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## Research summary:

The mitochondria are essential organelles that carry out diverse functions in the eukaryotic cell. In addition to ATP production by oxidative phosphorylation, they participate in many pathways such as heat production, calcium signaling, detoxification of reactive oxygen species, synthesis of heme and other molecules, and regulation of cell death. Emerging functions include their role in the regulation of innate and adaptive immune responses, which happens largely by two mechanisms:

1) The mitochondria regulate immunometabolism, which studies how the metabolism of the immune cell changes when they are activated or differentiate into effector cell, and how those metabolic changes are essential for their effector function. For instance, M1 or proinflammatory macrophages in culture are largely glycolytic, whereas M2 or reparatory macrophages utilize oxidative phosphorylation to meet their ATP requirements.

2) During dysfunction, the mitochondria—due to their prokaryotic origin—can produce and release molecules (mitochondrial DNA, formyl peptides, etc.) that activate diverse routes of innate immune signaling, such as the NLRP3 inflammasome or the cGAS-STING pathway. This leads to the secretion of proinflammatory cytokines, including interleukin-1 $\beta$  or type I interferons.

The mitochondria thus play a key role in immune regulation. The overarching goal of our group is to study the role of the mitochondria in the modulation of innate and adaptive immune pathways.

We are particularly interested in how posttranslational modifications (PTMs) of mitochondrial proteins—such as lysine acetylation or succinylation—will regulate the activation and polarization of the macrophage. For this project, we focus on the roles of mitochondrial nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent deacetylases (like Sirtuin 3, SIRT3) or desuccinylases (like Sirtuin 5, SIRT5). Indeed, we have recently found that SIRT3 controls the secretion of type I interferons, which are antiviral molecules.

In the laboratory, we also study the role of mitochondrial metabolites, including adenine nucleotides (adenosine mono-, di- or triphosphate) or NAD<sup>+</sup>, in the activation and differentiation of macrophages and T lymphocytes. As transport of metabolites across the inner mitochondrial membrane is carried out by proteins of the Mitochondrial Carrier Family, we are altering the expression of mitochondrial carriers specific for those metabolites in immune cells, including SLC25A24/SCaMC-1, a calcium-dependent mitochondrial transporter for ATP-Mg/Pi, and SLC25A51/MCART1, the recently identified mitochondrial transporter for NAD<sup>+</sup>.

Since autoimmune or degenerative diseases are associated with imbalances in macrophage polarity or lymphocyte lineage differentiation, the study of how mitochondrial metabolites affect the differentiation of immune cells, and its potential modulation by compounds such as NAD<sup>+</sup> precursors, might be interesting for potential future therapies.

## Publications

- Han K, Singh K, Meadows AM, Sharma R, Hassanzadeh S, Wu J, Goss-Holmes H, Huffstutler RD, Teague HL, Mehta NN, Griffin JL, Tian R, Traba J, Sack MN. Boosting NAD preferentially blunts Th17 inflammation via arginine biosynthesis and redox control in healthy and psoriasis subjects. *Cell Rep Med.* 2023 Sep 19;4(9):101157. doi: 10.1016/j.xcrm.2023.101157. Epub 2023 Aug 15. PMID: 37586364; PMCID: PMC10518596.

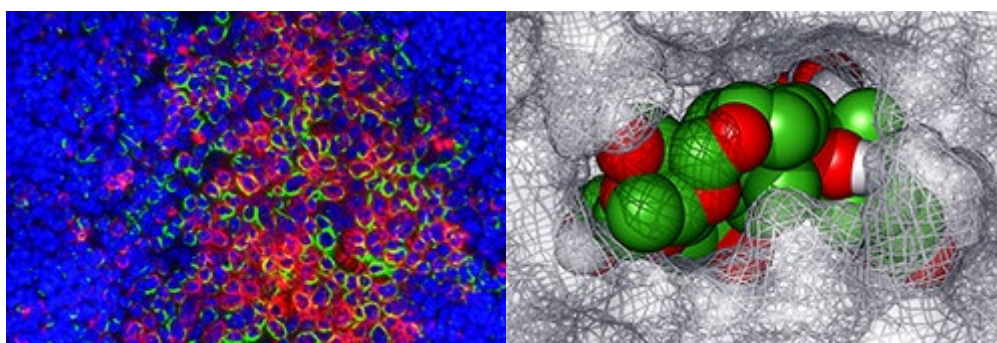
## Projects

- Regulación inmunometabólica a través de la proteína mitocondrial Sirtuina 3. PID2019-105665RA-I00, Agencia Estatal de Investigación. Principal Investigator: Javier Traba Domínguez. 01/06/2020-31/05/2023.
- Ramón y Cajal. Agencia Estatal de Investigación. RYC2018-026050-I, Principal Investigator: Javier

Traba Domínguez (Universidad Autónoma de Madrid). 01/09/2020-31/08/2025.

- Regulación de la inmunidad innata y adaptativa por los niveles mitocondriales de nicotinamida adenina dinucleotido (NAD<sup>+</sup>). PID2022-136810OB-I00 (FEDER, UE). PI: J. Traba. 1.9.2023-31.8.2026.

## INTERACTIONS WITH THE ENVIRONMENT PROGRAMME



### ➤ Immune system development and function UNIT

#### Immune Development and Inflammatory-mediated Diseases

<http://www.cbm.uam.es/manuel.fresno>

- **Prof. Manuel Fresno Escudero. Profesor Emérito 1.9.2023. Departamento de Biología Molecular. UAM.**
- **Prof. Konstantinos Stamatakis Andriani. Profesor Ayudante Doctor. Departamentode Biología Molecular. UAM.**

#### Research summary

Deletion of TCFL5, a bHLH transcription factor, drastically reduces the tumor properties of colon cancer cells. Interestingly, the 2 major isoforms, TCFL5\_E1/E8 and TCFL5\_E2b/E8 (CHA) had a different promoter and opposite functions, being TCFL5\_E2b/E8 protumoral function. TCFL5\_E1/E8 is essential for NFKB2 activity regulating the expression of anti-apoptotic genes as BCL2 whereas TCFL5\_E2b/E8 controls the expression of the pluripotency markers SOX2, NANOG and KLF4. We have identified some genes regulated by TCFL5\_E1/E8 and TCFL5\_E2b/E8 and established its role in some leukemias and in normal lymphopoiesis. TCFL5\_E2b/E8 expression was associated with greater severity in lymphoma and myeloma samples from patients. Using *Tcf15* deficient mice, we found *Tcf15* is required for the formation of germinal centers and differentiation of pro-B to pre-B cells by affecting the levels of SYK and BCR signalling, resulting in an inability to respond to stimuli and an increase in cell death. TCFL5 is also expressed during early mouse embryonic development, the preimplantation period and plays a role in the differentiation of embryonic cells to germline precursors by controlling the

expression of genes important in their differentiation, as shown in *Tcf15* deficient mice.

Toll-like receptors (TLRs) play a crucial role in pathogen recognition. However, signaling via TLR4 and TLR2 was different, as TLR2 ligands activated NF- $\kappa$ B and MAPKs earlier and exhibited a higher IL-10 /IL-12 ratio compared to TLR4 ligands. Furthermore, p38 MAPK is critical for IL-10 expression in response to TLR2 ligands, which triggers the macrophage change to a M2 and regulatory phenotype in contrast to the M1 phenotype induced by TLR4 activation. TRIF was required for IFN- $\beta$  induction and consequent expression of IL-12 in response to TLR2. Moreover, in vivo administration of TLR2 ligands exert a modulatory effect on cytokines with beneficial effects on the prevention of *Listeria* dissemination in a murine model of neonatal listeriosis.

TLR4 is considered the major receptor to recognize all LPSs. However, some atypical LPS's depart from the well-studied *E. coli* LPS and induce a TLR2-dependent inflammatory response in immune cells. Molecular docking analysis of *O. intermedium* LPS predicts a favorable formation of a TLR2/TLR4/MD-2 heterodimer, further confirmed by FRET. These imply that atypical LPSs may induce TLR4/TLR2 heterodimerization to decrease the bacteria activation of the innate immune system.

Finally, we were also working on Chagas' disease caused by *Trypanosoma cruzi* (see N. Gironès page) and contributed to understand some immunological aspects of COVID 19 infection (see corresponding page).

## Publications

- Biscari L, Maza MC, Farré C, Kaufman CD, Amigorena S, Fresno M, Gironès N, Alloatti A. Sec22b-dependent antigen cross-presentation is a significant contributor of T cell priming during infection with the parasite *Trypanosoma cruzi*. *Front Cell Dev Biol.* 2023 Mar 1;11:1138571. doi: 10.3389/fcell.2023.1138571. PMID: 36936692; PMCID: PMC10014565.
- Horndler L, Delgado P, Romero-Pinedo S, Quesada M, Balabanov I, Laguna-Goya R, Almendro-Vázquez P, Llamas MA, Fresno M, Paz-Artal E, van Santen HM, Álvarez-Fernández S, Olmo A, Alarcón B. Decreased breadth of the antibody response to the spike protein of SARS-CoV-2 after repeated vaccination. *Front Immunol.* 2023 Apr 3;14:1157263. doi: 10.3389/fimmu.2023.1157263. PMID: 37081876; PMCID: PMC10111966.
- Matamoros-Recio A, Merino J, Gallego-Jiménez A, Conde-Alvarez R, Fresno M, Martín-Santamaría S. Immune evasion through Toll-like receptor 4: The role of the core oligosaccharides from  $\alpha$ 2-Proteobacteria atypical lipopolysaccharides. *Carbohydr Polym.* 2023 Oct 15;318:121094. doi: 10.1016/j.carbpol.2023.121094. Epub 2023 Jun 9. PMID: 37479429
- Moneo-Corcuera D, Viedma-Poyatos Á, Stamatakis K, Pérez-Sala D. Desmin Reorganization by Stimuli Inducing Oxidative Stress and Electrophiles: Role of Its Single Cysteine Residue. *Antioxidants (Basel).* 2023 Aug 31;12(9):1703. doi: 10.3390/antiox12091703. PMID: 37760006; PMCID: PMC10525603.
- Pastor-Fernández A, Bertos AR, Sierra-Ramírez A, Del Moral-Salmoral J, Merino J, de Ávila AI, Olagüe C, Villares R, González-Aseguinolaza G, Rodríguez MÁ, Fresno M, Gironés N, Bustos M, Smerdou C, Fernandez-Marcos PJ, von Kobbe C. Treatment with the senolytics dasatinib/quercetin reduces SARS-CoV-2-related mortality in mice. *Aging Cell.* 2023 Mar;22(3):e13771. doi: 10.1111/accel.13771. Epub 2023 Jan 26. PMID: 36704839; PMCID: PMC10014049.
- Úbeda M, Maza MDC, Delgado P, Horndler L, Abia D, García-Bermejo L, Serrano-Villar S, Calvo C, Bastolla U, Sainz T, Fresno M. Diversity of immune responses in children highly exposed to SARS-CoV-2. *Front Immunol.* 2023 Mar 3;14:1105237. doi: 10.3389/fimmu.2023.1105237. PMID: 36936972; PMCID: PMC10020361.

## Projects

- Fresno Escudero, Manuel. TCFL5/CHA EN LA DIFERENCIACIÓN Y ACTIVACIÓN DE LINFOCITOS B Y T Y EN LA GENERACIÓN DE LEUCEMIAS. PIB2019-104760RB-100. Ministerio de Ciencia e Innovación. Julio 2020-Junio 2023.



- VALIDACIÓN DE DIANAS FARMACOLÓGICAS NEUROINFLAMATORIAS PARA EL TRATAMIENTO DEL DOLOR CRÓNICO. IP: Manuel Fresno. 20.9.2023-30.6.2024.
- Papel de TCFL5 en procesos de diferenciación, inmunosenescencia, inflamación y trastornos asociados al envejecimiento. PID2022-137487OB-I00 (FEDER, UE). IP. Manuel Fresno. 1.9.2023-31.8.2026
- Manuel Fresno Escudero. Jefe Grupo 12. Instituto de Investigaciones Sanitaria Princesa

## Thesis

Patricia Torres Gérica. Papel de la proteína Galectina-1 en el desarrollo del tejido adiposo y el metabolismo de los adipocitos. Programa de Doctorado en Biociencias Moleculares. Director: Manuel Fresno Escudero. 2023.

Teresa García Prieto. Las isoformas de Akt y TLR5 en la función de la barrer intestinal y la enfermedad inflamatoria intestinal. Programa de Doctorado en Biociencias Moleculares. Director: Manuel Fresno Escudero. 2023.

## Immunoregulatory mechanisms in the development of Chagas disease: translational applications.

<https://www.cbm.uam.es/ngirones>

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- **Prof. Núria Gironés Pujol. Profesor Titular. Departamento de Biología Molecular.UAM.**
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### Research summary:

During 2021 and 2022 the objectives of our research group were: (i) to further study the role of the SLAMF1 immune receptor in the infection *Trypanosoma cruzi*, the causative agent of Chagas disease; (ii) to evaluate the prognostic value of an isoform of TCFL5 (sCha) in Chagas disease patients; (iii) to study the effects of *T. cruzi* infection in cardiac remodeling; and (iv) to contribute to the understanding of *T. cruzi* mitochondrial genome, transcriptome and proteome.

### Scientific implications and relevance:

Some of the objectives are about to be reached, submitted for publication, or already published.

We pursued the research on the SLAMF1 immune receptor during infection using proteomics, and identified target genes that are being studied for their relevance in the context of the infection as therapeutic targets. We also studied the prognostic value of circulating miRNAs in Chagas disease patients, and the alterations in miRNA expression in macrophages infected with *T. cruzi*, and identified for the first time the presence of *T. cruzi* miRNAs in the infected culture that localize in extracellular vesicles (EVs).

We studied cardiac remodeling in the experimental mouse model of *T. cruzi* infection, and found overexpression of HCN4 channels, suggesting that arrhythmogenic treatments should be administered with caution in Chagas disease patients since they can have secondary effects (Rodríguez-Angulo H.O. et al. 2021).

We determined the complete genome of mitochondrial maxicircle and minicircles of *T. cruzi*. It was previously thought that minicircles were circular dsDNA composed of 4 repetitive elements, but using NGS sequencing we also found minicircles of 3, 2 and 1 repeats in the mitochondrial DNA. These findings are relevant because little is known about the role of the *T. cruzi* mitochondrial genome, and these findings may help to understand better the molecular biology of the parasite for fighting the infection (Callejas-Hernández F. et al. 2021).

Finally, we showed that autoantibodies against the immunodominant sCha (a TCFL5 isoform) epitope discriminate the risk of sudden death in chronic Chagas cardiomyopathy. Autoantibody levels correlated with the alterations found in 24h Holter ECG recording for the detection of arrhythmias and prevention of sudden death, and thus having a potential application as an alternative when Holter ECG is not available (Rodríguez-Angulo H.O. et al. 2021). We also collaborated in studies about the role of TCFL5 in spermatogenesis (Galán-Martínez J, Berenguer I. et al. 2022) and colorectal cancer (Galán-Martínez J., Stamatakis K. et al., 2022) with the research group of Dr. Manuel Fresno.

## Publications

- Biscari L, Maza MC, Farré C, Kaufman CD, Amigorena S, Fresno M, Gironès N, Alloatti A. Sec22b-dependent antigen cross-presentation is a significant contributor of T cell priming during infection with the parasite *Trypanosoma cruzi*. *Front Cell Dev Biol.* 2023 Mar 1;11:1138571. doi: 10.3389/fcell.2023.1138571. PMID: 36936692; PMCID: PMC10014565.
- Pastor-Fernández A, Bertos AR, Sierra-Ramírez A, Del Moral-Salmoral J, Merino J, de Ávila AI, Olagüe C, Villares R, González-Aseguinolaza G, Rodríguez MÁ, Fresno M, Gironés N, Bustos M, Smerdou C, Fernandez-Marcos PJ, von Kobbe C. Treatment with the senolytics dasatinib/quercetin reduces SARS-CoV-2-related mortality in mice. *Aging Cell.* 2023 Mar;22(3):e13771. doi: 10.1111/accel.13771. Epub 2023 Jan 26. PMID: 36704839; PMCID: PMC10014049.

## Projects

- Papel del ligando del receptor SLAMF1 de *Trypanosoma cruzi* y de microRNAs durante la infección: aplicaciones en diagnóstico y terapia. PID2021-123389OB-I00 (FEDER-UE). PI Nùria Gironés Pujol. MINECO. 2022-2025.

## Nitric oxide and bioactive lipids in the immune response

[www.cbm.uam.es/immune\\_NO\\_bioactive\\_lipids](http://www.cbm.uam.es/immune_NO_bioactive_lipids)

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- **Prof. Miguel Ángel Iñíguez Peña. Profesor Titular. Departamento de Biología Molecular. UAM.**
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## Research summary:

Nitric oxide (NO) and bioactive lipids as nitro-fatty acids (NO<sub>2</sub>-FA) or prostaglandins, are key mediators for maintaining cellular homeostasis, with an essential role in inflammation. Our research lines are dedicated to the study the role played by NO as well as nitro and oxo modified fatty acids in inflammation and in the activation and differentiation of T lymphocytes. We are currently studying the actions exerted by these agents on the activation of human T lymphocytes, analysing their involvement in the regulation of gene expression and activation of transcription factors. We are also interested in the analysis of chemotaxis, intercellular adhesion and the organization of adhesion and signalling receptors at the immune synapse. In addition, we are also examining the potential actions of these compounds on the selection of the adaptive immune response in human T lymphocytes.

NO is a key messenger in the pathogenesis of inflammation. In the immune system, NO has been considered to be a cytotoxic molecule associated with the response of phagocytic cells to pathogens as part of the first line of host defence against infection. However, NO can also regulate the adaptive immune response, linking innate and adaptive immunity. NO affects T helper cell differentiation and the effector functions of T lymphocytes,

and is a potential target for therapeutic manipulation. In the last years, our group has been interested in the study of the regulatory actions exerted by NO in T cell functions, focusing on protein S-nitrosylation and fatty acid nitro-alkylation, leading to the formation NO<sub>2</sub>-FA, as important post-translational modifications by which NO can act as a signalling molecule during T cell-mediated immunity.

Fatty acid oxidative modifications result in the production of bioactive lipids including prostaglandins and NO<sub>2</sub>-FA, important signalling molecules that can modulate the inflammatory process and the immune response. We are interested in the analysis of their influence on diverse parameters of T lymphocyte function, focusing on their effects on transcriptional activation and gene expression and their consequences on cell activation and differentiation. Their anti-inflammatory and immunomodulatory effects take place mainly through their ability to covalently modify transcriptional regulatory proteins and enzymes and to activate various nuclear and membrane receptors, finally modifying protein function and altering patterns of gene expression. Research on the molecular and cellular basis of the actions of electrophilic fatty acids in inflammation and the immune response, will contribute to the understanding of the potential therapeutic benefits of these compounds.

### Immunity and Viromics

[www.cbm.uam.es/antonio\\_alcami](http://www.cbm.uam.es/antonio_alcami)

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- **Prof. Alberto Rastrojo. Profesor Ayudante Doctor. Departamento de Biología. UAM. (Staff scientist with PI Dr. Antonio Alcamí, CBMSO-CSIC)**
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### Publications

- Archer SDJ, Lee KC, Caruso T, Alcami A, Araya JG, Cary SC, Cowan DA, Etchebehere C, Gantsetseg B, Gomez-Silva B, Hartery S, Hogg ID, Kansour MK, Lawrence T, Lee CK, Lee PKH, Leopold M, Leung MHY, Maki T, McKay CP, Al Mailem DM, Ramond JB, Rastrojo A, Šantl-Temkiv T, Sun HJ, Tong X, Vandenbrink B, Warren-Rhodes KA, Pointing SB. Contribution of soil bacteria to the atmosphere across biomes. *Sci Total Environ.* 2023 May 1;871:162137. doi: 10.1016/j.scitotenv.2023.162137. Epub 2023 Feb 10. PMID: 36775167.

### Microbes in health and welfare UNIT

#### Biotechnology and genetics of extreme thermophiles

<http://www.cbm.uam.es/jberenguer>

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- **Prof. José Berenguer Carlos. Catedrático. Departamento de Biología Molecular. UAM. Retired 31.8.2023.**
  - **Prof. Mario Mencía Caballero. Profesor Titular. Departamento de Biología Molecular. UAM.**
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#### Research summary:

The main objective of our group during this period has been to analyze the mechanisms of DNA transfer and

those acting as defense barriers in thermophilic bacteria that could render biotechnological applications. DNA transfer and repair is enhanced in thermal environments due to the strong selective factor appointed by high temperatures against replication fidelity that results in the selection of small genomes. For *Thermus thermophilus* (Tth), this selection has led to the evolution of a polyploid genome and the most efficient natural competence apparatus (NCA) so far described. In addition, Tth can exchange DNA by direct cell contacts using “transjugation”, a process in which a DNA donation apparatus (DDA) allows the ejection of DNA from a “donor” strain with the concomitant incorporation by a competent recipient mate through its NCA.

The main focus of our research in the last two years has been the analysis of the mechanisms involved in protection against the integration of environmental DNA (eDNA) in the genome. In this context we have studied the role of a DNA primase-polymerase (Ppol) encoded by mobile element ICETH2, as anti-eDNA barrier. We found that Ppol loss of function mutations increase dramatically the transformability of the cells with eDNA by 2-3 orders of magnitude, playing apparently a defensive role that is not active against DNA transferred by a mating pair in transjugation. This differential protective activity is similar to that provided by ThAgo, a homologue of the human Argonaute protein that uses DNA-DNA interference to cleave exogenous DNA entering the cells by transformation, suggesting a role for Ppol as putative generator of ssDNA guides for ThAgo. Further work of our group has shown the relevance of Ppol for plasmid stability and the existence of Ppol-independent mechanisms for the generation of ssDNA guides for ThAgo. Our most recent work has shown a deep imbrication of Ppol in DNA repair in Tth, keeping an unexpected equilibrium between its activity and that of the excinuclease AddAB, required to generate the 3' overhangs needed to repair dsDNA breaks by homologous recombination. In such equilibrium Ppol compensates for an apparently lethal overactivity of AddAB, in such a way that only addAB loss-of-function mutants survive to the inactivation of Ppol. Future work of the group will focus on the relation of HGT and recombination pathways and use this knowledge to develop new tools for the directed evolution of proteins in Tth.

### Publications

- Ribeiro AL, Sánchez M, Bosch S, Berenguer J, Hidalgo A. Stabilization of Enzymes by Using Thermophiles. *Methods Mol Biol.* 2023;2704:313-328. doi: 10.1007/978-1-0716-3385-4\_19. PMID: 37642853.
- Mencía M. Acid digestion and symbiont: Proton sharing at the origin of mitochondriogenesis?: Proton production by a symbiotic bacterium may have been the origin of two hallmark eukaryotic features, acid digestion and mitochondria: Proton production by a symbiotic bacterium may have been the origin of two hallmark eukaryotic features, acid digestion and mitochondria. *Bioessays.* 2023 Jan;45(1):e2200136. doi: 10.1002/bies.202200136. Epub 2022 Nov 14. PMID: 36373631.

### Projects

- NUEVAS HERRAMIENTAS DERIVADAS DE SISTEMAS PARA LA TRANSFERENCIA E INTERFERENCIA DE DNA DE BACTERIAS TERMÓFILAS. PID2019-109073RB-I00. PI José Berenguer Carlos. MINECO. 2020-2023.
- Nueva aproximación para la bioconversión sostenible de residuos plásticos en productos de alto valor añadido basada en microorganismos termófilos y síntesis enzimática. TED2021-130430B-C22 (PRTR). PI Mario Mencía. MINECO. 2022-2024.
- Desarrollo de un sistema biológico y de hardware para la evolución continua de proteínas en *Thermus thermophilus* para aplicaciones biotecnológicas. PID2022-137468OB-I00 (FEDER, UE). PI: M. Mencía. 1.9.2023-31.8.2026.

### Thesis

Carlos Verdú Cano. Nuevos conocimientos sobre mecanismos y barreras contra la transferencia horizontal de genes en *Thermus thermophilus*. Programa de Doctorado en Microbiología. Director. Mario Mencía Caballero. 2023.

## Bacterial cell envelope during preseptal growth

<https://www.cbm.uam.es/mpazos>

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- **Prof. Manuel Pazos. Investigador Atracción Talento CAM. Departamento de Biología Molecular. UAM.**
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### Research summary:

The research in the laboratory focuses on understanding the molecular mechanisms underpinning the biogenesis of the bacterial cell envelope of model and pathogenic gastrointestinal organisms (e.g. *Escherichia coli*) during preseptal growth, in the context of physiology and pathogenicity.

The peptidoglycan (PG) sacculus is an essential structural component of most bacterial cell envelopes, and its synthesis is one of the most frequently targeted process by antibiotics. Since the rise of antimicrobial resistance is making infections harder to treat, with special emphasis to those caused by Gram-negative bacteria due to their extra outer membrane barrier, it is crucial to understand how the cell envelope integrity is maintained during the bacterial cell cycle. The cell envelope integrity is essential for the physiology and pathogenicity of bacteria, and therefore both peptidoglycan and membrane synthesis machineries are coordinated and regulated to ensure the robust growth of the cell envelope.

Contrary to cell elongation and cell division, which have been studied in greater depth, the transition between both stages called preseptal growth remains poorly characterized. This switch involves the incorporation of new PG material at mid-cell before the septum is formed. In previous work we described the connection between the cytosolic FtsZ polymers and the PG synthases (PBP1A and PBP1B) through the partially redundant proteins ZipA and FtsA-FtsN. The disruption of both connections disables the incorporation of new preseptal PG, leading to non-viable filamented cells, identifying the preseptal PG growth as an essential process occurring prior cell division (Pazos *et al.* 2018, Nat Commun 9:5090). These results would answer the long-standing question about the mechanism by which single-point mutations in FtsA are able to bypass the requirement of ZipA for cell division and preseptal PG synthesis.

In addition, we described for the first time how the PG-binding SPOR proteins DamX and DedD are required for full functionality of the PG synthases PBP1A and PBP1B, and the lethal effect of an unbalanced DedD:DamX protein ratio (Pazos *et al.* 2020, mBio 11:e02796-20). SPOR domains are widely spread and conserved in bacterial proteins, making them promising target to interfere with bacterial cell envelope synthesis.

To accomplish our ultimate goal of identifying new potential antimicrobial targets, we aim to use a multidisciplinary approach combining genetics, biochemistry, cell biology and different microscopy techniques to characterize the molecular components and cell envelope features during this potentially vulnerable stage of the bacterial cell cycle.

### Projects

- Programa Atracción Talento. MANUEL PAZOS. 2022-2026: 2020-T1/BMD-19970 (CAM-UAM)
- Bases moleculares de la inhibición de la división celular mediada por proteínas SPOR. PID2022-140818OA-I00 (FEDER, UE). PI: M. Pazos. 1.9.2023-31.8.2026.

## SsDNA Virus Evolution, Pathogenesis and anti-cancer potential

<https://www.cbm.uam.es/jmalmendral>

- 
- Prof. José M<sup>a</sup> Almendral del Río. Catedrático. Departamento de Biología Molecular. UAM.
  - Prof. Alberto López-Bueno. Profesor Titular. Departamento de Biología Molecular. UAM.
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### Research summary:

We have focused our research over the last two years in reliably testing the anti-cancer capacity of the Minute Virus of Mice (MVM), a member of the *Parvoviridae*. In our recent report, we describe that human glioblastoma stem cells (GSCs), with patient-specific p53 mutants and p53-Ser15 phosphorylation, are selective targets for two MVM strains (p, i) that are non-pathogenic for humans. These MVM strains induced a DNA Damage Response (DDR) in GSCs growing as neurospheres and disrupted the architecture of GSC-derived brain tumors in orthotopic rodent models (see Figure 1A), showing promise for biosafe personalized therapy against human cancers with p53 deregulations.

Other major related issues being explored include attempting physical and chemotherapeutic treatments to overcome cellular innate responses of cancer cells against MVM infection, and targeting MVM infection to the tumour vasculature by engineering the MVM capsid with VEGF peptides. Further, major efforts are being dedicated to exploring evolutionary strategies to develop parvoviruses with improved anticancer properties by optimizing their cytotoxicity and replication capacity in human tumour cells. For this, we are exploring the phenotypic features of (i) naturally evolved MVM variants with distinct tropism and pathogenicity, (ii) chimeric viruses spontaneously emerging after coinfection with two MVM strains, and (iii) a collection of MVM mutants affected at the capsid domain recognizing sialic acid receptors that were obtained from directed evolution strategies (Figure 1B).

### Publications

- Mietzsch M, Qiu J, Almendral JM, Söderlund-Venermo M. Editorial: Parvoviruses: from basic research to biomedical and biotechnological applications. *Front Microbiol.* 2023 May 15;14:1194926. doi: 10.3389/fmicb.2023.1194926. PMID: 37256056; PMCID: PMC10225675.
- Calvo-López T, Grueso E, Sánchez-Martínez C, Almendral JM. Intracellular virion traffic to the endosome driven by cell type specific sialic acid receptors determines parvovirus tropism. *Front Microbiol.* 2023 Jan 23;13:1063706. doi: 10.3389/fmicb.2022.1063706. PMID: 36756201; PMCID: PMC9899843.

### Projects

- “Directed parvovirus evolution aimed at human cancer therapy”. PID2019-111146RB-I00. I+D+i Retos de Investigación 2019, Ministerio de Ciencia, Innovación y Universidades”. Principal investigators: A. López-Bueno and J.M. Almendral. Jun 2020-May 2023.
- Reorientación de la Infección de Parvovirus hacia Procesos Celulares Determinantes del Cáncer Humano. PID2022-141799OB-I00 (FEDER, UE). PI. J.M. Almendral. 1.9.2023-31.8.2026.

## Molecular Ecology of Extreme Environments

<http://www.cbm.uam.es/ramils>

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- Prof. Ricardo Amils Pibernat. Profesor Emérito. Departamento de Biología Molecular. UAM.
  - Prof. David Ruano Gallego. Investigador Ramón y Cajal. Departamento de Biología Molecular. UAM.
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### Research summary

This area of research has the following objectives:

-Geomicrobiology of the Iberian Pyrite Belt (IPB): characterization of the underground bioreactor responsible of the origin of the extreme conditions detected in the Río Tinto basin. This objective is developed in collaboration with Professor J.L. Sanz from the Department of Molecular Biology (UAM). The development of this objective aims to identify the microorganisms involved in the coupled operation of the C, H, N, S and Fe biogeochemical cycles in the deep subsurface of the IPB in the absence of light, their isolation, phenotypic and genotypic characterization, and their involvement in the oxidation of metal sulfides, mainly pyrite, in strict anaerobic conditions.

Acidophiles: conventional microbial ecology, molecular ecology, molecular biology and biotechnology of extreme acidic environments. This objective is mainly devoted to the exploration of the biotechnological applications (biomining, bioremediation, biomineralization and phytoremediation) of acidophilic organisms inhabiting the Tinto basin.

Characterization of extreme environments of astrobiological interest: Río Tinto and Iberian Pyrite Belt, Uyuni Salt Lake (Bolivia), Dallol in the Danakil depression (Ethiopia). This objective aims to characterize different extreme environments to evaluate the limits of life and the habitability in different planets and moons of the Solar System and from exoplanets.

### Publications

- Amils R, Escudero C, Oggerin M, Puente Sánchez F, Arce Rodríguez A, Fernández Remolar D, Rodríguez N, García Villadangos M, Sanz JL, Briones C, Sánchez-Román M, Gómez F, Leandro T, Moreno-Paz M, Prieto-Ballesteros O, Molina A, Tornos F, Sánchez-Andrea I, Timmis K, Pieper DH, Parro V. Coupled C, H, N, S and Fe biogeochemical cycles operating in the continental deep subsurface of the Iberian Pyrite Belt. *Environ Microbiol.* 2023 Feb;25(2):428-453. doi: 10.1111/1462-2920.16291. Epub 2022 Dec 9. PMID: 36453153; PMCID: PMC10107794. González-de la Fuente S, Requena JM, Aguado B. Datasets of Iso-Seq transcripts for decoding transcriptome complexity in four *Leishmania* species. *Data Brief.* 2023 Nov 20;52:109838. doi: 10.1016/j.dib.2023.109838. PMID: 38076479; PMCID: PMC10698239.
- Concepción Abrusci, Ricardo Amils, Enrique Sánchez-León. Biodegradation of Choline NTF<sub>2</sub> by *Pantoea agglomerans* in Different Osmolarity. *Characterization and Environmental Implications of the Produced Exopolysaccharide.* *Polymers (Basel).* 2023 Oct 3;15(19):3974. doi: 10.3390/polym15193974. PMID: 37836024; PMCID: PMC10575057.
- Daddaoua A, Álvarez C, Oggerin M, Rodríguez N, Duque E, Amils R, Armengaud J, Segura A, Ramos JL. Río Tinto as a niche for acidophilus enzymes of industrial relevance. *Microb Biotechnol.* 2023

- May;16(5):1069-1086. doi: 10.1111/1751-7915.14192. Epub 2023 Feb 7. PMID: 36748404; PMCID: PMC10128141.
- Escudero C, Amils R. Dark biosphere: Just at the very tip of the iceberg. *Environ Microbiol.* 2023 Jan;25(1):147-149. doi: 10.1111/1462-2920.16265. Epub 2022 Nov 9. PMID: 36307896; PMCID: PMC10100182.
  - Fairén AG, Rodríguez N, Sánchez-García L, Rojas P, Uceda ER, Carrizo D, Amils R, Sanz JL. Ecological successions throughout the desiccation of Tirez lagoon (Spain) as an astrobiological time-analog for wet-to-dry transitions on Mars. *Sci Rep.* 2023 Feb 8;13(1):1423. doi: 10.1038/s41598-023-28327-3. PMID: 36755119; PMCID: PMC9908944.
  - Hallsworth JE, Udaondo Z, Pedrós-Alió C, Höfer J, Benison KC, Lloyd KG, Cordero RJB, de Campos CBL, Yakimov MM, Amils R. Scientific novelty beyond the experiment. *Microb Biotechnol.* 2023 Jun;16(6):1131-1173. doi: 10.1111/1751-7915.14222. Epub 2023 Feb 14. PMID: 36786388; PMCID: PMC10221578.
  - Mateos G, Martínez-Bonilla A, Martínez JM, Amils R. Vitamin B<sub>12</sub> Auxotrophy in Isolates from the Deep Subsurface of the Iberian Pyrite Belt. *Genes (Basel).* 2023 Jun 26;14(7):1339. doi: 10.3390/genes14071339. PMID: 37510244; PMCID: PMC10378866.
  - Sánchez-León E, Huang-Lin E, Amils R, Abrusci C. Production and Characterisation of an Exopolysaccharide by *Bacillus amyloliquefaciens*: Biotechnological Applications. *Polymers (Basel).* 2023 Mar 21;15(6):1550. doi: 10.3390/polym15061550. PMID: 36987330; PMCID: PMC10056187.

## Projects

- Decifering the metabolism of Fe(II) oxidation associated to the reduction of nitrate (NRFeOx) and its utilization for the bioremediation of nitrate contaminated waters. TED2021-129563B-I00 (2023-2024). PI: R. Amils.
- Biodiversity characterization of the Río Tinto basin and the subsurface of the Iberian Pyrite Belt responsible of its origin, biotechnological applications. PID2019-104812GB-I00 (2020-2023). PI: R. Amils.
- Operación del bio-reactor subterráneo que da origen a las condiciones extremas del Río Tinto y las aplicaciones biotecnológicas de la biodiversidad de la Faja Pirítica Ibérica. PID2022-136607NB-I00 (FEDER, UE). PI: R. Amils. 1.9.2023-31.8.2026.
- Descifrando las redes de efectores del Sistema de Secreción Tipo 3. PID2022-138782OA-I00 (FEDER, UE). PI: D. Ruano. 1.9.2023-31.8.2026.

## Thesis

Enrique Marín Palma. Análisis de organismos de interés industrial en los documentos de patentes publicados por la Oficina Española de Patentes y Marcas en el período 2001-2021. Programa de Doctorado en Biociencias Moleculares. Director. Ricardo Amils Pibernat. 2023.

## Yeast enzymes bioengineering to generate bioactive compounds.

<http://www.cbm.uam.es/MFernandezLobato>

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- **Prof. María Fernández Lobato. Catedrática. Departamento de Biología Molecular.UAM.**



- **Prof. Miguel Remacha Moreno. Catedrático. Departamento de Biología Molecular.UAM.**
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### Research summary:

We work with microorganisms producing bioactive compounds for application in functional and nutraceutical food. We try to connect the generation of knowledge to the development of biotechnological applications. Basically, we focus on the characterization of enzymes producing new compounds, the analysis of their structural-functional determinants, their operational improvement using molecular biology tools, the characterization of the new molecules produced and the evaluation of their potential biological activity. We have designed methods to simplify protocols as the biocatalysts attachment to solid supports.

During the last years we have continued with the characterization and study of proteins from non-conventional yeast (included in genera as *Rhodotorula* and *Metschnikowia*) showing glycosyltransferase activity, applicable in the production of new heterooligosaccharides and glycoconjugate derivatives (basically glycosylated polyphenols) that may have prebiotic or antioxidant properties. We have also characterized new fungal chitinases that can hydrolyze different chitinolytic materials, waste from the industrial activity, to generate chitooligosaccharides with promising bioactive properties. In general, most of the characterized proteins are glycosyl hydrolases (GH) structurally included in families GH32, 31, 13 or 18. In fact, we resolved the 3D structure of the first yeast protein including in family GH32, assigned a function to the beta-sandwich domain that is present in all members of this family and proved that the oligomerization is directly involved in the substrate recognition and specificity. Recently we have found that some of the characterized enzymes can glycosylate compounds with aromatic rings such as hydroxytyrosol or phloretin, which confers them a special biotechnological interest. We have obtained numerous variants of enzymes that increase or alter the pattern of biosynthetic products. Isolated and characterized the formed products and optimized the biosynthetic reactions. We intend to extend our study to hydrolases including in other structural families, to increase and modify the transferase/biosynthetic activity of the enzymes studied, to scale up to industrial level the enzyme production and the products generated, as well as to validate the biological activity of the molecules obtained. Objectives included in those of the Glicoenz consortium (<http://www.glicoenz.org/p/glicoenz.html>).

### Projects

- Fundación Ramón Areces. XIX Concurso Nacional-Ciencias de la Vida y la Materia. Production of second-generation prebiotics and polyphenol glycosides. Validation of its bioactive properties for use in functional food. 04/2019-04/2023. Principal Investigator: María Fernández.
- PID2019-105838RB-C32. Prospecting and development of microbial enzymes to obtain new glycosylated compounds of pharmacological interest. MCI-Programa Estatal de Investigación, I+D+i-Orientada a los Retos de la Sociedad. 06/2020-05/2023. Principal Investigator: María Fernández.
- Producción y modificación funcional de glicoenzimas para la obtención sostenible de glicoderivados por transglicosilación. PID2022-137487OB-I00 (FEDER, UE). PI: M. Fernández-Lobato. 1.9.2023-31.8.2026.
- TED2021-129288B-C22: Simplification of the use of chitin-enriched waste for the enzymatic production of bioactive chitooligosaccharides. AEI- Projects oriented towards the ecological transition and the digital transition. 11/2022-10/2024. Principal Investigator: María Fernández.
- PDC2022-133134-C22: Scaling up the production of glycosidases to obtain modified flavonoids and their evaluation in biomedical applications. EAI-Proof of Concept Projects.11/2022-10/2024. Principal

Investigator: María Fernández.

## Thesis

David Piedrabuena Estrada. Producción sostenible de nuevos glicoconjugados con potenciales propiedades prebióticas mediante la  $\beta$ -fructofuranosidasa Ffase de *Schwanniomyces occidentalis* Programa de Doctorado en Biociencias Moleculares. Directora: María Fernández Lobato. 2023.

## Virus Engineering and Nanobiotechnology

<http://www.cbm.uam.es/mgmateu>

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- **Prof. Mauricio García Mateu. Catedrático. Departamento de Biología Molecular.UAM.**
  - **Prof. Alejandro Valbuena Jiménez. Profesor Ayudante Doctor. Departamento de Biología Molecular. UAM.**
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### Research summary:

Major research goals: We use protein engineering techniques and biochemical, biophysical and virological analyses to study the assembly, conformational stability and dynamics and physical properties of viruses, and their biological relevance (Mateu (ed.) (2013) *Structure and Physics of Viruses*, Springer 2013; new edition under way). Based on these studies, we aim at providing novel insights into key processes for viral infection, including virus morphogenesis, structural rearrangements and uncoating; and to provide guidelines and proof of concept for the application of this knowledge for the design of vaccines, antiviral drugs, biomaterials or modified nanoparticles for biomedical or bionanotechnological uses (see Mateu (2016). In *Protein-based Engineered Nanostructures*, Springer 2016, pp.83-120).

Scientific relevance and technological implications: Some major scientific contributions in the last years include: i) experimental evidence on the biological relevance of mechanical properties of viruses; ii) insights into the intimate relationship between virus mechanical elasticity and conformational dynamics at equilibrium; iii) detailed descriptions of virus capsid self-assembly routes, including the actual visualization in real time using high-speed atomic force microscopy of single molecules during capsid lattice assembly; iv) the discovery of the possibility to develop new antiviral drugs acting on the mechanical properties of viral particles; v) the genetic design of novel biomaterials with improved mechanical properties.

Some specific subjects that are currently being researched in our laboratory include: i) the relationship between the mechanics and dynamics of a virus capsid and virus assembly or genome uncoating; ii) the structural determinants of the mechanical properties of viruses; iii) the biological relevance of the mechanical properties of viruses; iv) the development of new antiviral drugs that modify the mechanical properties of viruses, and of mechanically resistant virus-based nanostructured materials.

### Publications

- Carrasco J, Antón R, Valbuena A, Pantoja-Uceda D, Mukhi M, Hervás R, Laurents DV, Gasset M, Oroz J. Metamorphism in TDP-43 prion-like domain determines chaperone recognition. *Nat Commun.* 2023 Jan 28;14(1):466. doi: 10.1038/s41467-023-36023-z. PMID: 36709343; PMCID: PMC9884275.
- Fuertes MA, López Mateos D, Valiente L, Rodríguez Huete A, Valbuena A, Mateu MG. Electrostatic Screening, Acidic pH and Macromolecular Crowding Increase the Self-Assembly Efficiency of the Minute Virus of Mice Capsid In Vitro. *Viruses.* 2023 Apr 25;15(5):1054. doi: 10.3390/v15051054. PMID:

37243141; PMID: PMC10224108.

- Luque D, Ortega-Esteban A, Valbuena A, Luis Vilas J, Rodríguez-Huete A, Mateu MG, Castón JR. Equilibrium Dynamics of a Biomolecular Complex Analyzed at Single-amino Acid Resolution by Cryo-electron Microscopy. *J Mol Biol.* 2023 Apr 15;435(8):168024. doi: 10.1016/j.jmb.2023.168024. Epub 2023 Feb 23. PMID: 36828271.
- Sánchez-Salvador A, González-de la Fuente S, Aguado B, Yates PA, Requena JM. Refinement of *Leishmania donovani* Genome Annotations in the Light of Ribosome-Protected mRNAs Fragments (Ribo-Seq Data). *Genes (Basel).* 2023 Aug Luque D, Ortega-Esteban A, Valbuena A, Luis Vilas J, Rodríguez-Huete A, Mateu MG, Castón JR. Equilibrium Dynamics of a Biomolecular Complex Analyzed at Single-amino Acid Resolution by Cryo-electron Microscopy. *J Mol Biol.* 2023 Apr 15;435(8):168024. doi: 10.1016/j.jmb.2023.168024. Epub 2023 Feb 23. PMID:36828271.
- Strobl K, Mateu MG, de Pablo PJ. Exploring nucleic acid condensation and release from individual parvovirus particles with different physicochemical cues. *Virology.* 2023 Apr;581:1-7. doi: 10.1016/j.virol.2023.01.010. Epub 2023 Feb 14. PMID: 36842268.
- Valbuena A, Strobl K, Gil-Redondo JC, Valiente L, de Pablo PJ, Mateu MG. Single-Molecule Analysis of Genome Uncoating from Individual Human Rhinovirus Particles, and Modulation by Antiviral Drugs. *Small.* 2023 Oct 8:e2304722. doi: 10.1002/smll.202304722. Epub ahead of print. PMID: 37806749.

## Projects

- Biomecánica y dinámica de virus humanos para el desarrollo de fármacos antivirales y materiales modificados por ingeniería de proteínas para usos biomédicos o nanotecnológicos. PID2021-126973OB-I00 (FEDER-UE). IP Mauricio García Mateu. MINECO. 2022-2025.
- Red Temática Nacional de Excelencia en Física Viroológica
- Global Virology Network
- Global Foot-and-Mouth Disease Research

## Regulation by RNA in the stress and virulence

<https://www.cbm.uam.es/mg.pucciarelli>

- **Prof. Graciela Pucciarelli. Profesora Titular. Departamento de Biología Molecular.UAM.**

## Research summary

*Listeria monocytogenes* is a foodborne bacterial pathogen that causes listeriosis, a severe disease mostly affecting pregnant women, elderly, and immunocompromised individuals as well as livestock. *L. monocytogenes* exhibits an outstanding capacity to tolerate widely used practices in the food industry that control microbial growth in food, including refrigeration. Our main objective is to understand the regulatory mechanisms and the adaptive strategies that allow *L. monocytogenes* to grow at refrigeration temperatures (0-4°C).

During these last two years, our experimental approach has relied on systems-level approaches to identify transcriptional and post-transcriptional regulatory networks at 4°C. We performed transcriptomics analyses along the acclimation from 37°C to 4°C, which showed the participation of transcriptional regulators and small non-coding regulatory RNAs (sRNAs) in two defined phases catalogued as early and late responses (Fig. 1A-B). We are currently characterizing the precise functional role of these regulators in cold adaptation and, in

addition, focusing on cell wall proteome changes occurring specifically at 4°C. The available data indicate that at least two surface proteins are produced only in cold. The next studies are designed to investigate the contribution of these proteins to the adaptive response and to characterize the mechanisms that control their expression.

We expect that the understanding of the regulatory mechanisms governing the *L. monocytogenes* capacity to tolerate cold temperature will provide the field with novel targets useful to prevent its growth in refrigerated food. These new antimicrobial preventive practices during food processing and storage will ultimately reduce the risk of *L. monocytogenes* infections in both humans and livestock.

### Ultrahigh-throughput discovery and engineering of enzymes for biotechnological applications

[www.cbm.uam.es/ahidalgo](http://www.cbm.uam.es/ahidalgo)

- **Prof. Aurelio Hidalgo Huertas. Profesor Titular. Departamento de Biología Molecular. UAM.**
- **Prof. Patricia Pérez-Arnáiz. Profesora Ayudante Doctora. Departamento de Biología Molecular. UAM:**

#### Research summary:

Microbial diversity is a vast reservoir of genetic information that can be valorized through industrial application, from biosynthetic gene clusters to novel enzyme catalysts. The synergy between new experimental discovery tools based on biology and those based on nanotechnologies are instrumental to find relevant genes faster and more efficiently, particularly enabling academic labs to undertake screening campaigns until now costly and limited to large enterprises.

In the HT Discovery lab, we develop methods to discover and engineer industrially relevant enzymes and biosynthetic gene clusters in the natural or artificial genetic diversity. One of the tools to discover new or improved enzymes are biological selections: inexpensive methods to find enzymes that couple the improved fitness of a protein to the survival of a biological host under selective pressure. In our group, we develop and apply biological selections to enhance the activity of enzymes with “unnatural” substrates relevant for the pharma and fine chemical industries and the stability of enzymes to withstand harsh conditions of industrial processes, such as the presence of organic cosolvents or high temperatures. Using such methods, we have developed selective and stable transferases in the frame of regional and national research grants. Subsequently, after suitable enzymes are found, we study the underlying rationale for their improved fitness, often using bioinformatic approaches, thus uncovering how and why enzymes function and ultimately, learning the language of proteins.

However, the complexity of cellular metabolism limits the applicability of biological selections. For this reason, we also work on screening methods, which involve individual enzymatic assays *in vitro* of each enzyme variant generated. To shorten this long, tedious and expensive process, droplet microfluidics enables the miniaturization of assays with throughput of kHz rates as well as a 1000x reduction of volume and assay costs. Moreover, microfluidics enables the conversion of general lab operations (additions, aliquoting, detection of a given property) into a particular chip design. Using ultrahigh-throughput screening, we have developed screening methods for esterases, KREDs, lyases and other enzymes in the EU-funded projects MetaFluidics, RadicalZ and CC-TOP. The enzymes discovered using these methods are not only located in unexplored regions of sequence space, but sometimes exhibited much coveted properties for subsequent engineering, such as catalytic promiscuity.

#### Publications

- Ribeiro AL, Sánchez M, Bosch S, Berenguer J, Hidalgo A. Stabilization of Enzymes by Using Thermophiles. *Methods Mol Biol.* 2023;2704:313-328. doi: 10.1007/978-1-0716-3385-4\_19. PMID: 37642853.

## Projects

- Innovative tools for sustainable exploration of marine microbiome innovative tools for sustainable exploration of marine microbiomes: towards a circular blue bioeconomy and healthier marine environments (HE-CL6, GA 101081957, BlueTools). European Commission. 01/12/2022-30/11/2026. Role: coordinator
- Rapid discovery and development of enzymes for novel and greener consumer products (H2020-SC2, GA 10100560 RadicalZ). European Commission. 01/06/2021- 31/05/2025. Role: coordinator
- C-C Bond Formation Using Top Performing Enzymes (MSCA-ITN, GA 956631 CC-TOP). European Commission. 01/02/2021- 31/01/2025.
- Búsqueda y mejora de 2 desoxirribosil transferasas mediante métodos de ultra-alto rendimiento para la síntesis sostenible de nuevos análogos de nucleósido terapéuticos. Ministerio de Ciencia e Innovación. (UltraNDTs, Project. PID2020-117025RB-I00). 01/09/2021- 31/08/2024.

## ➤ CULTURA CIENTÍFICA

- **Prof. José Antonio López Guerrero. Catedrático. Departamento de Biología Molecular. UAM.**

<https://www.cbm.uam.es/es/ciencia-y-sociedad/cultura-cientifica>

Science and technology are part of our cultural heritage and demand, or should, the attention of citizens. Within the Dissemination and Promotion of Scientific Culture program, the CBMSO participates in multiple activities. Among others: guided tours of the scientific-technical departments for pre-university students – an activity that has been carried out uninterruptedly for more than a quarter of a century and in which our Center is a pioneer in Spain; various courses for teaching professionals; specific programs such as the 4th ESO + company of the Community of Madrid, or the one for Finalist Students of the Spanish Biology Olympiad; various activities –talks, workshops- during the Science Week; participation in Fairs of Scientific Disclosure; scientific dissemination seminars in Centers, Colleges or Secondary Education Institutes –mainly during the celebration of Cultural Weeks-. Similarly, due to the excellence of its research and the scientific dissemination capacity of some of its members, the CBMSO has a long tradition of collaboration and participation in countless media, Press, Radio, Television or Digital Media

## Publications

- Andreu S, Ripa I, Bello-Morales R, López-Guerrero JA. Liposomal Lactoferrin Exerts Antiviral Activity against HCoV-229E and SARS-CoV-2 Pseudoviruses In Vitro. *Viruses.* 2023 Apr 15;15(4):972. doi: 10.3390/v15040972. PMID: 37112952; PMCID: PMC10142420.
- Andreu S, von Kobbe C, Delgado P, Ripa I, Buzón MJ, Genescà M, Gironès N, Del Moral-Salmoral J, Ramírez GA, Zúñiga S, Enjuanes L, López-Guerrero JA, Bello-Morales R. Dextran sulfate from *Leuconostoc mesenteroides* B512F exerts potent antiviral activity against SARS-CoV-2 *in vitro* and *in vivo*. *Front Microbiol.* 2023 May 3;14:1185504. doi: 10.3389/fmicb.2023.1185504. PMID: 37206325; PMCID: PMC10189130.

**Projects**

- DISEMINACIÓN DEL VIRUS HERPES SIMPLEX TIPO 1 EN OLIGODENDROCITOS HUMANOS: PAPEL DE LAS MICROVESÍCULAS Y DEL PROTEOLÍPIDO MAL. PID2019-110570GB-I00IP José Antonio López Guerrero. MINECO. 1.6.2020-31.5.2023.
- Diseminación del virus herpes simplex tipo 1 en oligodendrocitos humanos: papel de la autofagia y del proteolípido MAL. PID2022-140632NB-I00 (FEDER, UE). PI: J.A. López-Guerrero. 1.9.2023-31.8.2026-

## PROJECTS ONGOING in 2023

Reference	Title	Principal Investigator	Organisms
PI19/01155 (FEDER)	ENFOQUE CROSS-OMICO PARA EL DESCUBRIMIENTO DE LA BASE GENETICA DE ERRORES INNATOS DEL METABOLISMO Y PARA UNA INTERVENCION TERAPEUTICA PERSONALIZADA	PEREZ GONZALEZ, BELEN	FIS
PID2019-108674RB-I00	LA MITOCONDRIA Y SU DISFUNCIÓN EN PATOLOGÍA: PAPEL DE IF1	CUEZVA MARCOS, JOSE MANUEL	MINISTERIO
860229-ONCORN2.0-H2020-MSCA-ITN-2019	ONCOGENIC RECEPTOR NETWORK OF EXCELLENCE AND TRAINING 2.0' — 'ONCORN2.0' ('ACTION')	MAYOR MENENDEZ, FEDERICO	EUROPEO
PID2019-111338RB-I00	REGULACIÓN DEL METABOLISMO ENERGÉTICO EN EL CEREBRO: IMPLICACIONES PARA LA NEURODEGENERACIÓN EN LA ATAXIA DE FRIEDREICH	DIAZ NIDO, JAVIER	MINISTERIO
PID2019-104763RB-I00	NUEVOS REGULADORES FARMACOLÓGICOS DE LA NEUROGÉNESIS ADULTA Y LA REPROGRAMACIÓN DIRECTA: IMPLICACIONES PARA LA REGENERACIÓN	PORLAN ALONSO, EVA	MINISTERIO
PID2019-104760RB-I00	TCFL5/CHA EN LA DIFERENCIACIÓN Y ACTIVACIÓN DE LINFOCITOS B Y T Y EN LA GENERACIÓN DE LEUCEMIAS	FRESNO ESCUDERO, MANUEL	MINISTERIO
PID2019-104812GB-I00	CARACTERIZACIÓN DE LA BIODIVERSIDAD DE LA CUENCA DEL RÍO TINTO Y DEL SUBSUELO DE LA FAJA PIRÍTICA IBÉRICA QUE LO ORIGINA, APLICACIONES BIOTECNOLÓGICAS	AMILS PIBERNAT, RICARDO	MINISTERIO
PID2019-111146RB-I00	EVOLUCIÓN DIRIGIDA DE PARVOVIRUS PARA TERAPIA DE CANCER HUMANO	LOPEZ BUENO, ALBERTO	MINISTERIO
PID2019-109073RB-I00	NUEVAS HERRAMIENTAS DERIVADAS DE SISTEMAS PARA LA TRANSFERENCIA E INTERFERENCIA DE DNA DE BACTERIAS TERMÓFILAS	BERENGUER CARLOS, JOSE	MINISTERIO
PID2019-104241RB-I00	PAPEL DEL METABOLISMO MITOCONDRIAL SOBRE LA FISIOPATOLOGÍA DEL MÚSCULO ESQUELÉTICO: ROL DE LAS DESHIDROGENASAS FAD-DEPENDIENTES ASOCIADAS A LA FOSFORILACIÓN OXIDATIVA.	FORMENTINI, LAURA	MINISTERIO
PID2019-105344RB-I00	MECANISMOS RESPONSABLES DEL FENOTIPO PATOLÓGICO EN ENFERMEDADES NEUROMETABÓLICAS RARAS Y APROXIMACIONES TERAPÉUTICAS PERSONALIZADAS	RUIZ DESVIAT, LOURDES	MINISTERIO
PID2019-110570GB-I00	DISEMINACIÓN DEL VIRUS HERPES SIMPLEX TIPO 1 EN OLIGODENDROCITOS HUMANOS: PAPEL DE LAS MICROVESÍCULAS Y DEL PROTEOLÍPIDO MAL	LOPEZ GUERRERO, JOSE ANTONIO	MINISTERIO
PID2019-105838RB-C32	BÚSQUEDA Y DESARROLLO DE ENZIMAS MICROBIANAS APLICABLES A LA OBTENCIÓN DE NUEVOS COMPUESTOS GLICOSILADOS DE INTERÉS FARMACOLÓGICO	FERNANDEZ LOBATO, MARIA	MINISTERIO
PID2019-105665RA-I00	REGULACIÓN INMUNOMETABÓLICA A TRAVÉS DE LA PROTEÍNA MITOCONDRIAL SIRUIA 3	TRABA DOMINGUEZ, JAVIER	MINISTERIO
IND2019/BMD-17100	DOCTORADOS INDUSTRIALES CM 2019	YAÑEZ MO, MARIA	CM
948478 MitoCure ERC-2020-STG	MOLECULAR AND METABOLIC MECHANISMS UNDERLYING MITOCHONDRIAL DYSFUNCTION	BALSA MARTINEZ, EDUARDO	EUROPEO
956631 — CC-TOP — H2020-MSCA-ITN-2020	C-C BOND FORMATION USING TOP PERFORMING ENZYMES	HIDALGO HUERTAS, AURELIO	EUROPEO
101000560-RADICALZ-H2020-FNR-2020/H2020-FNR-2020-2	RAPID DISCOVERY AND DEVELOPMENT OF ENZYMES FOR NOVEL AND GREENER CONSUMER PRODUCTS	HIDALGO HUERTAS, AURELIO	EUROPEO

Y2020/BIO-6350	ESTRATEGIAS NUTRICIONALES DE PRECISIÓN PARA REACTIVAR EL SISTEMA INMUNE DETERIORADO COMO CONSECUENCIA DE LA EDAD, LA OBESIDAD O LA QUIMIOTERAPIA	CARRASCO CERRO, ELISA	CM
PID2020-113204GB-I00	Neurorregeneración en la enfermedad de Alzheimer a través de la expresión de factores de pluripotencia in vivo	HERNANDEZ PEREZ, FELIX	MINISTERIO
PID2020-117916RB-I00	Integración de datos omicos para descifrar la organización y expresión génicas en Leishmania: pistas para enfrentar las leishmaniasis	REQUENA ROLANIA, JOSE MARIA	MINISTERIO
PID2020-119627GB-I00	Microdominios de membrana, exosomas, virus y vacunas	YAÑEZ MO, MARIA	MINISTERIO
PID2020-114054RA-I00	Dimorfismo sexual en el metabolismo de la glucosa: caracterización del papel mitocondrial.	COGLIATI, SARA	MINISTERIO
PID2020-117025RB-I00 (UAM)	Búsqueda y mejora de 2desoxirribosil transferasas mediante métodos de ultra-alto rendimiento para la síntesis sostenible de nuevos análogos de nucleósido terapéuticos	HIDALGO HUERTAS, AURELIO	MINISTERIO
PID2020-114499RB-I00	Transportadores mitocondriales regulados por calcio: Papel de SCaMC3 y citrin en la señalización por calcio en el hígado y de Aralar en la comunicación intercelular en el SNC	PARDO MERINO, BEATRIZ	MINISTERIO
PID2020-113921RB-I00	HOMEOSTASIS DE COLESTEROL Y VÍA LISOSOMAL EN LA NEURODEGENERACIÓN INDUCIDA POR HSV-1 Y EN LA ENFERMEDAD DE ALZHEIMER: MECANISMOS PATOGENICOS Y BIOMARCADORES	BULLIDO GOMEZ-HERAS, MARIA JESUS	MINISTERIO
PID2020-117218RB-I00	Redes de señalización de GRK2 y mecanismos moleculares de procesos patológicos	MAYOR MENENDEZ, FEDERICO	MINISTERIO
PID2020-119399RB-I00	EL TRANSPORTADOR NEURONAL DE GLICINA GlyT2 EN DOLOR Y EN HIPERPLEXIA. IMPLICACIONES PATOLÓGICAS EN DESARROLLO	LOPEZ CORCUERA, BEATRIZ	MINISTERIO
CONVENIO INFLAPAIN	VALIDACIÓN DE DIANAS FARMACOLÓGICAS NEUROINFLAMATORIAS PARA EL TRATAMIENTO DEL DOLOR CRÓNICO	FRESNO ESCUDERO, MANUEL	ESTEVE PHARMACEUTICALS, S.A.
PDC2021-121052-I00 (PRTR)	Vacunas basadas en exosomas miméticos	YAÑEZ MO, MARIA	MINISTERIO
2020-T1/BMD-19970	Atracción del Talento	PAZOS DON PEDRO, MANUEL	CM
PID2021-126973OB-I00 (FEDER-UE)	Biomecánica y dinámica de virus humanos para el desarrollo de fármacos antivirales y materiales modificados por ingeniería de proteínas para usos biomédicos o nanotecnológicos	GARCIA MATEU, MAURICIO	MINISTERIO
PID2021-125844OB-I00 (FEDER-UE)	Reprogramación traduccional inducida por estrés en eucariotas y su influencia sobre la proteostasis celular. Mecanismos e impacto sobre	VENTOSO BANDE, IVAN	MINISTERIO
PID2021-123269OB-I00 (FEDER-UE)	Papel de R-Ras1 y R-Ras2 en la diferenciación y especificación oligodendrocitaria	CUBELOS ALVAREZ, BEATRIZ	MINISTERIO
PID2021-123389OB-I00 (FEDER-UE)	Papel del ligando del receptor SLAMF1 de Trypanosoma cruzi y de microRNAs durante la infección: aplicaciones en diagnóstico y terapia	GIRONES PUJOL, NURIA	MINISTERIO
101047177 — OpenMIND	OPTO-ELECTRONIC NEURAL CONNECTOID MODEL IMPLEMENTED FOR NEURODEGENERATIVE DISEASE	PEREZ PEREIRA, MARTA	EUROPEO
101081957-BLUETOOLS-HORIZON-CL6-2022-CIRCBIO-01	INNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE MICROBIOMINNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE MICROBIOMES:TOWARDS A CIRCULAR BLUE BIOECONOMY AND HEALTHIER MARINE ENVIRONMENTSINNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE MICROBIOMINNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE MICROBIOMES:TOWARDS A CIRCULAR BLUE BIOECONOMY AND HEALTHIER MARINE ENVIRONMENTS	HIDALGO HUERTAS, AURELIO	EUROPEO
PDC2022-133147-I00 (PRTR)	OSCAR, an Object Segmentation, Counter, Analysis Resource	MIGUEZ GOMEZ, DAVID	MINISTERIO



TED2021-130430B-C22 (PRTR)	Nueva aproximación para la bioconversión sostenible de residuos plásticos en productos de alto valor añadido basada en microorganismos termófilos y síntesis enzimática	MENCIA CABALLERO, MARIO	MINISTERIO
PDC2022-133134-C22 (PRTR)	Escalado de la producción de glicosidasas para la obtención de flavonoides modificados y su evaluación en aplicaciones biomédicas	FERNANDEZ LOBATO, MARIA	MINISTERIO
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TED2021-129563B-I00 (PRTR)	DESCIFRANDO EL METABOLISMO DE LA OXIDACION DE FE(II) ASOCIADA A	AMILS PIBERNAT, RICARDO	MINISTERIO
S2022/BMD-7209	INTEGRAMUNE-CM	MAYOR MENENDEZ, FEDERICO	CM
PR_EX_2022_01	METABOLIC HETEROGENEITY AS A CRITICAL DETERMINAT OF MELANOMA METASTASIS PROJECT	BALSA MARTINEZ, EDUARDO	FUND. CRIS
ION-ARPA	3' REPLACEMENT OF TAU MRNAS IN ALZHEIMER'S DISEASE BY A REPLICATIVE TRANS-SPLICING RIBOZYME-ION-ARPA	GARCIA ESCUDERO, VEGA	IONIS
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PID2022-140421NB-I00 (FEDER, UE)	Interacción entre mecanismos físicos y moleculares en la regulación de la formación de la retina de vertebrados	MIGUEZ GOMEZ, DAVID	MINISTERIO
PID2022-136810OB-I00 (FEDER, UE)	Regulación de la inmunidad innata y adaptativa por los niveles mitocondriales de nicotinamida adenina dinucleotido (NAD+)	TRABA DOMINGUEZ, JAVIER	MINISTERIO
PID2022-137404OB-I00 (FEDER, UE)	Descifrando el metabolismo mitocondrial como diana para la progresión tumoral y la metástasis	BALSA MARTINEZ, EDUARDO	MINISTERIO
PID2022-140818OA-I00 (FEDER, UE)	Bases moleculares de la inhibición de la división celular mediada por proteínas SPOR	PAZOS DON PEDRO, MANUEL	MINISTERIO
PID2022-137468OB-I00 (FEDER, UE)	Desarrollo de un sistema biológico y de hardware para la evolución continua de proteínas en Thermus thermophilus para aplicaciones biotecnológicas	MENCIA CABALLERO, MARIO	MINISTERIO
PID2022-138782OA-I00 (FEDER, UE)	Descifrando las redes de efectores del Sistema de Secreción Tipo 3	RUANO GALLEGO, DAVID	MINISTERIO
PID2022-137552OA-I00 (FEDER, UE)	Desenmascarando nuevos papeles de los procesos de autofagia endotelial en la inflamación	REGLERO REAL, NATALIA	MINISTERIO
PID2022-136367OB-C32 (FEDER, UE)	Producción y modificación funcional de glicoenzimas para la obtención sostenible de glicoderivados por transglicosilacion	FERNANDEZ LOBATO, MARIA	MINISTERIO
PID2022-137487OB-I00 (FEDER, UE)	Papel de TCFL5 en procesos de diferenciación, inmunosenescencia, inflamación y trastornos asociados al envejecimiento.	FRESNO ESCUDERO, MANUEL	MINISTERIO
PID2022-136607NB-I00 (FEDER, UE)	Operación del bio-reactor subterráneo que da origen a las condiciones extremas del Río Tinto y las aplicaciones biotecnológicas de la biodiversidad de la Faja Pirítica Ibérica	AMILS PIBERNAT, RICARDO	MINISTERIO
PID2022-141799OB-I00 (FEDER, UE)	Reorientación de la Infección de Parvovirus hacia Procesos Celulares Determinantes del Cáncer Humano	ALMENDRAL DEL RIO, JOSE MARIA	MINISTERIO
PID2022-136738OB-I00 (FEDER, UE)	Disfunción de la actividad mitocondrial en patología: la beta-oxidación de ácidos grasos en el mantenimiento de la homeostasia del organismo	FORMENTINI, LAURA	MINISTERIO
PID2022-137238OB-I00 (FEDER, UE)	Enfermedades neurometabólicas raras: de la investigación en nuevos modelos de enfermedad a terapias dirigidas	RUIZ DESVIAT, LOURDES	MINISTERIO
PID2022-140632NB-I00 (FEDER, UE)	Diseminación del virus herpes simplex tipo 1 en oligodendrocitos humanos: papel de la autofagia y del proteolípid MAL	LOPEZ GUERRERO, JOSE ANTONIO	MINISTERIO

## LIST OF PUBLICATIONS 2023

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