

# INSTITUTO UNIVERSITARIO DE BIOLOGÍA MOLECULAR (IUBM)

**UAM**

**INSTITUTE FOR MOLECULAR BIOLOGY-UAM**

## **ANNUAL REPORT 2025**



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## Foreword by María Yáñez-Mo, director of IUBM-UAM

The Instituto Universitario de Biología Molecular (IUBM) of the Universidad Autónoma de Madrid (UAM) was founded in 1971 under the leadership of Prof. Federico Mayor Zaragoza. Initially located in the Faculty of Sciences and closely linked to the Department of Molecular Biology, the Institute joined in September 1975 the newly created Center for Molecular Biology Severo Ochoa (CBM), established under the auspices of Prof. Severo Ochoa as a joint research center of the Spanish National Research Council (CSIC) and the UAM. Since then, the IUBM-UAM has brought together all UAM researchers working in CBM laboratories on topics related to molecular biology and biomedicine.

In November 2025, the directorship of the IUBM-UAM passed from Dr. Federico Mayor-Menéndez to me. I would like to express our sincere gratitude to Dr. Mayor for his dedicated leadership over the past eight years.

In 2025, the scientific staff of the IUBM-UAM comprised 73 permanent members, including full professors, associate professors, and assistant professors, as well as “Ramón y Cajal” and *Talento* junior researchers. Members of the Institute contribute to teaching across several UAM departments (Molecular Biology, Biology, Neuroscience, Applied Physical Chemistry, and Physics of Condensed Matter), and the IUBM-UAM also includes one affiliated professor from the University of Castilla–La Mancha.

IUBM-UAM researchers are organized along the Scientific Programs that structure the CBM: Genome Dynamics and Function, Tissue and Organ Homeostasis, Physiological and Pathological Processes, and Interactions with the Environment.

A total of 49 IUBM-UAM members served as principal or co-principal investigators of research projects active at the CBM. Additionally, 9 postdoctoral fellows and around 30 PhD students were affiliated with the Institute as non-permanent members. During 2025, IUBM-UAM researchers published **80 scientific articles** and led **74 research projects** funded by national, European, and international agencies. Detailed information on research interests, publications, and funded projects is provided throughout this Annual Report. The Institute also maintains a strong commitment to education at all levels: in 2025, **11 doctoral theses** supervised by IUBM-UAM members were defended, and many others are in progress.

Throughout this year, the CBM continued to implement the initiatives associated with its Severo Ochoa Centre of Excellence accreditation (2023–2027), including postdoctoral recruitment calls, internal collaboration grants program, the implementation of the PhD Advisory Committee and the CBMent Program, and the launch of the Center’s Communication and Innovation & Technology Transfer Offices. In September 2025, we celebrated the *CBM Cincuentenario Golden Jubilee Symposium: “Fifty Years of Discovery”*. These celebrations not only honored our history and achievements but also highlighted the promising future of our research and the strength of our collaborations. As the central event, we hosted a high-profile institutional ceremony and scientific symposium featuring speakers distinguished with major international awards, including Nobel Prizes, BBVA Foundation Frontiers of Knowledge Awards, and Lasker Awards, reinforcing the leadership of the IUBM-UAM in biomedicine and molecular biology.

The IUBM-UAM also carried out specific institutional activities, including the funding of the Award for the Best Doctoral Thesis defended at the CBM in 2025, as well as prizes for the Best Oral Communication and Best Poster at the XI Workshop of Students & Postdocs—initiatives aimed at supporting young researchers and enhancing the visibility of the Institute within the Center. The IUBM also continued the outreach activity “*Conoce el CBM*” (“Get to Know the CBM”), through which around 70 second-year Biochemistry students visited our facilities and learned about the research conducted in the laboratories of IUBM investigators.

Finally, in December we inaugurated a new tradition of scientific excellence by holding the **1st Federico Mayor Zaragoza Memorial Lecture**, delivered by Prof. Aurora Martínez (University of Bergen, UiB).

## Activities IUBM-UAM 2025



Delivery of the **PINP AWARD TO THE BEST DOCTORAL THESIS** presented at the CBM during the year 2025. **Dr Claudia Rodríguez López** and Prof. Beatriz López-Corcuera, Vice-Director of the CBM. December, 2025.



Delivery of the Best Oral Communication Award (**Victor Manuel Cruz**), XII WORKSHOP STUDENTS & POSDOCS **CBM**. Photo also includes Profs. Federico Mayor-Menendez and María Yáñez-Mo, Director and Secretary of IUBM-UAM, and Prof. Beatriz López-Corcuera, Vice-Director CBM and members of the Organizing Committee. November 2025.



Delivery of the Best Poster Award (**Alicia González Moya**) XII WORKSHOP STUDENTS & POSDOCS CBM. Photo also includes Profs. Federico Mayor-Menendez and María Yáñez-Mo, Director and Secretary of IUBM-UAM and Prof. Beatriz López-Corcuera, Vice-Director CBM. November 2025.

## CONOCE el CBMSO

### Actividad dirigida a los alumnos del segundo curso del grado de Bioquímica

**Fecha:** miércoles 12 de Febrero de 2025

**10:00** -Aula Ramón Areces Bienvenida y breve presentación general del CBMSO  
(10 min, Federico Mayor, director del IUBM-UAM)

**10:10 h** Breve introducción (4-5 diapositivas) de los proyectos de investigación por parte de cada uno de los distintos grupos participantes (6 min máximo por cada uno de los 10 investigadores).

#### Orden de intervención:

- Laura Formentini (lab 326) /Sara Cogliati (lab 326)
- Irene García Higuera (lab 320)
- Eva Porlan (lab 306)
- Natalia Reglero (lab 304)
- Petronila Penela (lab 320)
- Aurelio Hidalgo (lab 108)
- David Ruano (lab 104) 11:30 h
- Natalia Reglero (lab 304)
- Javier Traba (lab 321)
- Patricia Pérez (lab 108)
- Cristina Murga (lab 320)
- María Yáñez-Mo (lab 412)
- Laura Contreras (lab 321)
- Catalina Ribas (lab 304)

Cada grupo de 5-6 alumnos se encontrará con su profesor/a asignado en el aula Areces y se dirigirá a su laboratorio, donde durante 40-60 minutos podrán visualizar alguna actividad experimental concreta que se esté llevando a cabo en el laboratorio y/o ver un determinado equipo científico, etc.

**12:30 horas:** Fin de la actividad

## Director

- ✚ Prof. Federico Mayor Menéndez. *Universidad Autónoma de Madrid (until December 2025).*
- ✚ Prof. María Yáñez Mo. *Universidad Autónoma de Madrid (since December 2025)*

## Scientific Secretary

- ✚ Prof. María Yáñez Mo. *Universidad Autónoma de Madrid (until December 2025)*
- ✚ Prof. Sara Cogliati. *Universidad Autónoma de Madrid (since December 2025)*

## External Scientific Advisory Board

- ✚ Prof. Antonio Zorzano Olarte. *Universidad de Barcelona*
- ✚ Prof. Isabel Fabregat Romero. *IDIBELL. Barcelona. (from december 2024)*
- ✚ Prof. M<sup>a</sup> Ángela Nieto Toledano. *Instituto de Neurociencias, Universidad Miguel Hernández (UMH)-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 2025**➤ **Permanent members**

ALMENDRAL DEL RIO, JOSE MARIA  
AMILS PIBERNAT, RICARDO.  
ARCO MARTÍNEZ, ARACELI  
BALSA MARTÍNEZ, EDUARDO  
BENITEZ MORENO, MARIA JOSÉ  
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  
DIAZ NIDO, JAVIER  
DIEZ GUERRA, FRANCISCO JAVIER  
FERNÁNDEZ LOBATO, MARÍA  
FORMENTINI, LAURA  
FRESNO ESCUDERO, MANUEL.  
GÁMEZ ABASCAL, ALEJANDRA  
GARCIA-ESCUDEO BARRERAS, VEGA  
GARCIA MATEU, MAURICIO  
GARCÍA-HIGUERA, IRENE  
GIRONES PUJOL, NURIA  
HERNANDEZ PÉREZ, FÉLIX  
HIDALGO HUERTAS, AURELIO  
IÑIGUEZ PEÑA, MIGUEL ANGEL  
JIMÉNEZ MARTÍNEZ, JUAN SALVADOR  
LOPEZ BUENO, ALBERTO  
LOPEZ CORCUERA, BEATRIZ  
LOPEZ GUERRERO, JOSE ANTONIO  
MAYOR MENENDEZ, FEDERICO  
MARTÍNEZ LOZANO, JOSÉ MANUEL  
MENCÍA CABALLERO, MARIO  
MÍGUEZ GÓMEZ, DAVID  
MURGA MONTESINOS, CRISTINA  
NAVARRO LÉRIDA, INMACULADA  
NOGUÉS VERA, LAURA  
PAZOS DON PEDRO, MANUEL  
PARDO MERINO, BEATRIZ  
PENELA MARQUEZ, PETRONILA  
PÉREZ ALVAREZ, MARIA JOSÉ  
PÉREZ ARNÁIZ, PATRICIA

PEREZ GONZALEZ, BELEN  
PÉREZ PEREIRA, MARTA  
PINAL SEOANE, NOELIA  
PORLAN ALONSO, EVA  
PORTILLA TUNDIDOR, YADILEYNI  
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  
SOTO ALVAREZ, MANUEL  
SATRÚSTEGUI GIL-DELAGO, JORGINA  
STAMATAKIS ADRIANI, KONSTANTINOS  
TRABA DOMÍNGUEZ, JAVIER  
VALBUENA JIMÉNEZ, ALEJANDRO  
VAQUERO LORENZO, CONCEPCIÓN  
VILLA MORALES, MARIA  
VENTOSO BANDE, IVAN  
VIDA RUEDA, MARIA DEL CARMEN  
YÁÑEZ MO, MARIA  
ZAFRA GÓMEZ, FRANCISCO

*\*Retired 2025.*

➤ **Non-permanent postdoctoral members**

ALDUDO, JESUS  
GIMENO PÉREZ, MARIA  
JARAÍZ RODRIGUEZ, MARIA DEL PILAR  
LAINE MENÉNDEZ, SARA  
LÓPEZ NIEVA, PILAR

➤ **PhD Students**

ANDRÉS HERNÁIZ, RAQUEL DE  
ASENSIO LÓPEZ, ALEJANDRO  
BARRIOS MUÑOZ, ANA LAURA  
DE ANDRÉS HERNÁIZ, MIGUEL  
DE LA FLOR GARCÍA, MIGUEL  
GARCÍA GONZÁLEZ, DIEGO MARIN  
MARTINEZ BLANCO, ELENA

MARTÍNEZ BONILLA, ADRIÁN

MUÑOZ LÓPEZ, SARA

RAMÍREZ CHUECA, ESTEBAN

RODRIGUEZ RUBIO, MARINA

ROMERO CARRAMIÑANA, INÉS

RUIZ GARCÍA, SARA

SOTO HEREDERO, GONZALO

STANCIC, BRINA

TERREROS RONCAL, JULIA

VERDÚ CANO, CARLOS

VELA MARTIN, LAURA

## ✚ FINANCING AND BUDGET IUBM-UAM YEAR 2025

In the year 2025 the members of the IUBM-UAM raised through research projects circa **2.5 million euros, corresponding circa of 525.000 euros in overheads**. According to the current agree 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 4,100 euros for the year 2025.

This budget was used for the following purposes:

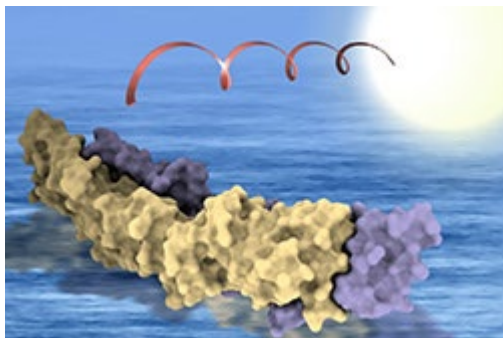
**Sponsorship** of the PINP 2025 Award for the Best Doctoral Thesis 2025 in the CBMSO, Awards for the Best Oral Communication and the Best Poster in the XI WORKSHOP STUDENTS & POSDOCS CBMSO 2025, and “Conoce el CBMSO”, February 2025.

**Sponsorship** of 1<sup>st</sup> Memorial Lecture Prof. Prof. Federico Mayor Zaragoza, December 2025.

**Equipment:** Acquisition of laboratory materials for practical classes for undergraduate and postgraduate students.

## SCIENTIFIC PROGRAMMES AND UNITS

### ✚ Genome dynamics and function Programme



#### ➤ Genome decoding UNIT

##### 1. 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 BiologíaMolecular. UAM.
- Prof. Juan José Berlanga. Profesor Titular. Departamento de Biología Molecular.UAM.
- Prof. Margarita Cabrera Solans. Profesora Permanente Laboral. Departamento de Biologia Molecular. UAM.

#### Research summary

We have identified the ES6S region of 40S ribosomal subunit as the gateway for mRNA entry and 43S-PIC scanning during translation initiation. 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. Blocking ES6S region differentially affected translation of mRNAs encoding some proto-oncogenes (H-Ras, CCND3, ODC-1, etc.), genes involved in signal transduction with long and structured 5'UTR mRNAs and also some viral mRNAs. We are currently evaluating the ES6S region as a target for antitumoral and antiviral molecules.

More recently, we found that the differential effect of the non-structural protein 1 (NSP1) of SARS-CoV-2 on translation depends on the composition of 5' UTR and codon usage bias of target mRNA. Our data suggest the existence of two mechanisms for the recruitment of mRNA to the 40S subunit (threading and slotting) and a functional interaction between the speed of elongation (codon bias) and translation initiation. We are also looking at the implications of our results for the molecular evolution of SARS-CoV-2 and other human respiratory viruses.

We continue to study the molecular and functional links among stress response, translational reprogramming and cellular homeostasis. Thus, we found that preventing eIF2 $\alpha$  phosphorylation in yeast not only impaired stress response, but also accelerated aging by a mechanism that involves proteostasis and autophagy disruption. We have identified some genes involved in proteasome activity whose expression is regulated by eIF2 $\alpha$  phosphorylation. We are characterizing the role of these genes in key processes regulating proteostasis such as protein aggregation, autophagy, mitophagy and how they can affect cell longevity.

## Publications

- Berlanga JJ, Matamoros T, Pulido MR, Sáiz M, Bayón MN, Toribio R, Ventoso I. **The differential effect of SARS-CoV-2 NSP1 on mRNA translation and stability reveals new insights linking ribosome recruitment, codon usage, and virus evolution.** *Nucleic Acids Res.* 2025 Mar 20;53(6):gkaf261. doi: 10.1093/nar/gkaf261. PMID: 40193709; PMCID: PMC11975289.
- Ventoso I. **Codon Usage Bias in Human RNA Viruses and Its Impact on Viral Translation, Fitness, and Evolution.** *Viruses.* 2025 Sep 6;17(9):1218. doi: 10.3390/v17091218. PMID: 41012646; PMCID: PMC12474380.

## 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.

## 2. 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 neoplasms (T-ALL/LBL) are a type of aggressive hematological cancer derived from immature T-cells, mostly affecting children and adolescent boys. Current treatments consist of high-dose multi-agent chemotherapy followed by hematopoietic stem cell transplantation in standard-high risk patients. Cure rates reach up to 90% among pediatric patients but only 48% in adults, and they are associated with acute and long-term toxicity. In addition, 20-40% of patients experience a relapse or do not respond to first-line treatments, then showing a dismal prognosis with survival rates below 10% and very limited therapeutic options. These weaknesses in the clinical management of T-ALL/LBL patients need to be addressed. The lack of clinical features or molecular markers that can accurately allocate T-ALL/LBL patients to a specific risk stage at the time of diagnosis argues, at least in part, for the toxicity associated with the treatment.

On the other hand, no targeted treatments against the main alterations identified T-ALL/LBL are currently available in the clinical setting and since the approval of nelarabine in 2005 no pharmacological inhibitors have been approved for relapsed/refractory (R/R) T-ALL/LBL patients. All this

highlights two unmet needs: 1) a more refined stratification of T-ALL/LBL patients according to their potential risk, which would lead to improved cure rates and reduced toxicity; and 2) the development of targeted treatments against the main alterations affecting T-ALL/LBL patients, which would contribute to lowering chemotherapy doses to avoid late effects and would offer a therapeutic option for R/R patients. Our group is trying to contribute to solve these two issues. Using genomic, transcriptomic and clinical data from patients, therapy prioritization algorithms based on the patient's omics characteristics, together with molecular approaches to validate our hypotheses, we explore the genetic and molecular alterations in patients to identify molecular markers that are predictive of poor response to treatment and that can be obtained at diagnosis. In addition, we aim to identify potential therapeutic targets amenable to pharmacological intervention. As members of Fundación Jiménez Díaz Health Research Institute, our research involves the active participation of our colleagues from the Haematology and Pathologic Anatomy services. For years, we have been working closely together to assign a clinical significance to our molecular results. With our research, we expect to contribute to a better clinical management of this disease, with a better identification of high-risk patients to guide their treatment, and with an enhanced efficacy of current therapies in a relevant fraction of patients whose targeted treatment is nowadays an unmet need. Ultimately, this would contribute to increase the cure rates for T-ALL/LBL patients.

### Publications

- Lahera A, Vela-Martín L, Fernández-Navarro P, López-Lorenzo JL, Cornago J, Llamas P, Fresno M, Santos J, Villa-Morales M. **Improved identification of T-ALL paediatric patients with low MRD but poor prognosis using a transcriptional signature.** Br J Haematol. 2025 Nov;207(5):2147-2152. doi: 10.1111/bjh.70118. Epub 2025 Aug 27. PMID: 40859815; PMCID: PMC12624190.

### Proyectos

- ANÁLISIS GENÓMICOS Y TRANSCRIPTÓMICOS EN EL TRATAMIENTO PERSONALIZADO DE NEOPLASIAS LINFOBLÁSTICAS DE CELULAS T. CONVENIO FUNDACIÓN JIMÉNEZ DÍAZ. IP: JAVIER SANTOS HERNÁNDEZ. ISS-FJD.
- ¿Cómo mejorar el resultado clínico de los pacientes de T-ALL/LBL? Propuesta de terapias dirigidas contra la hiperactivación de la señalización de STAT5 PID2024-160114OB-I00. IP: MARÍA C. VILLA. MINISTERIO.

### Thesis

Sara Ruiz García. El papel del ARN largo no codificante MALAT1 en las neoplasias de células T precursoras. Directores: Javier Santos Hernández y M<sup>a</sup> Pilar López Nieva.

### 3. Regulation of gene expression in *Leishmania*

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

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- 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.
- 

### Research summary

Protists of the *Leishmania* genus include species causing severe diseases in humans, i.e. leishmaniasis. Moreover, *Leishmania* species are the subject of fundamental interest regarding the evolution of gene regulatory mechanisms, as these organisms have put aside transcriptional regulation. There is currently no acceptable vaccine for preventing leishmaniasis and treatment options are limited. The research activity of our group is focused on studying, on the one hand, genome organization and gene expression in this parasite, and, on the other hand, the immunopathological outcomes associated with the infections caused by this parasite. Our aim is contributing knowledge for the development of new methods of controlling this parasitosis.

Massive sequencing techniques have become routine tools in our group for studying molecular mechanisms of gene expression in this parasite. These tasks are being done in close collaboration with Dr Begoña Aguado (head of the Genomics & Massive Sequencing service at CBMSO). Our group has generated new assemblies, improving previous ones, for the genomes of prototypical *Leishmania* species like *L. infantum*, causative agent of visceral leishmaniasis in Spain and other countries around the Mediterranean basin, and *L. braziliensis*, causing mucocutaneous leishmaniasis in South America. For hosting this information, which is actively curated, a web page was created: <http://leish-esp.cbm.uam.es>. Furthermore, we are using massive RNA sequencing (RNA-seq) for the annotation of transcriptomes of several *Leishmania* species and to study changes in gene expression. Thus, RNA-seq was used to determine genes involved in parasite resistance against the drugs currently available for treatment of human leishmaniasis. Additionally, we are looking for regulatory cis-elements, often found in the 3' untranslated regions (UTRs) of mRNAs, associated with RNA-binding proteins (RBPs), as key players in the regulation of gene expression.

Another area of active research, headed by Dr Manuel Soto, is aimed to the study of *Leishmania* – host immune response interactions, towards the development of prophylactic tools for preventing *Leishmania* infection. In this regards, a genetically modified-*Leishmania* mutant line (*Li*ΔHSP70-II) is being analyzed as a promising vaccine; its inoculation induces memory and effector T cell responses against *Leishmania* able to control subsequent challenges. Finally, as members of the Tropical Diseases network, our group is engaged in collaborative research activities with different national health institutions.

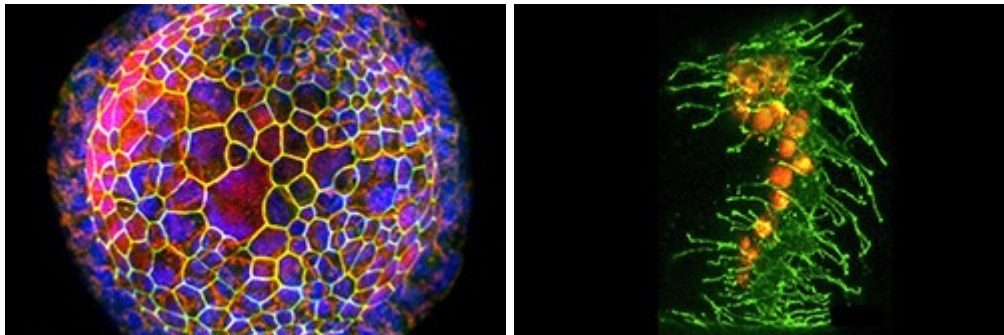
## Publications

- Martín-Sánchez J, Requena JM, Gállego M, Jiménez M, Molina R, Nguewa P, Morillas-Márquez F, Pérez-Victoria JM, Monge-Maillo B, Morales-Yuste M, Marín C. **Agreement Document for the Study of Leishmaniasis from a One Health Approach in Spain**. *Trop Med Infect Dis*. 2025 Sep 18;10(9):269. doi: 10.3390/tropicalmed10090269. PMID: 41003580; PMCID: PMC12474016.

## 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.
- Integración de datos ómicos en conjuntos de datos de acceso abierto y desarrollo de herramientas bioinformáticas como ayuda para el control de la leishmaniasis. PID2024-159768OB-I00. IP: JOSÉ M<sup>a</sup> REQUENA. MINISTERIO.
- 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

#### 1. Cell polarity.

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

- Prof. Isabel Correas Hornero. Catedrática. Departamento de Biología Molecular.UAM. (Co-PI with Dr. Miguel Alonso, CSIC-CBM). Retired September 2025.

#### Research summary

Formins are a family of proteins crucial for the formation of linear actin polymers. While most formins, like mDia1, are regulated by Rho GTPases, INF2 stands out as it is uniquely regulated by Ca<sup>2+</sup>/calmodulin interaction with its N-terminal extension. INF2 plays a pivotal role in controlling microtubule modifications implicated in degenerative diseases and cancer. Mutations in INF2 lead to specific degenerative hereditary diseases affecting the kidney (focal and segmental glomerulosclerosis) and peripheral nerves (Charcot-Marie-Tooth disease). Investigating the molecular mechanisms behind pathogenic INF2-induced cell degeneration is a current focus of our research.

The MAL family of integral membrane proteins includes seven highly hydrophobic members. A characteristic of these proteins is their presence in condensed membrane subdomains or rafts associated with specialized membrane traffic and cell signaling pathways. Specifically, we found three MAL family members (MAL, MAL2, and MYADM) playing vital roles in these processes. Analyzing large-scale genomic datasets, we've identified strong correlations between the expression levels of MAL-family members and prognosis in diverse types of cancer, including those affecting the breast, kidney, lung, pancreas, and endometrium.

The primary cilium, which is a non-motile appendage of the plasma membrane, orchestrates crucial signaling pathways related to cell proliferation, differentiation, survival, and migration. Dysfunctions in the primary cilium are linked to various human developmental and degenerative disorders, which are collectively known as ciliopathies. Our group has discovered the role of the midbody remnant (MBR) in promoting primary cilium biogenesis. This role involves a physical connection between the midbody remnant and the plasma membrane, which allow the transfer of specialized membranes from the MBR to be used by the centrosome for the assembly of the ciliary membrane. Our work establishes a tripartite link between the three major microtubule-based organelles —the centrosome, the MBR and the primary

cilium. This novel insight enhances our understanding of the process of primary ciliogenesis and, hopefully, will contribute to explaining the ciliary defects in some ciliopathies.

## 2. Cell signalling during imaginal development in *Drosophila*

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

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

The *Drosophila* wing originates from an epithelial tissue that grows by proliferation during larval development and differentiates in the pupal stage into a wing and part of the thorax of the fly. Cell proliferation and differentiation are common processes in multicellular tissues, and they are directed by evolutionarily conserved batteries of genes. The genetic and developmental analysis of the wing disc allows us to address experimentally different aspects of epithelial biology.

We are carrying out three research projects. The first project involves the analysis of the requirements of *Drosophila* genes in the wing. We grouped the 14,000 *Drosophila* genes into 16 functional groups and screened UAS-RNAi lines targeting 10,918 of these genes. We classified the resulting phenotypes into morphological classes affecting the size, pattern or differentiation of the wing and correlate 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 Toures-Brokes disease and Okihiro syndrome. We have identified a minimal DNA response element for Spalt through the analysis of the regulatory region of one of its downstream genes. 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 a multitude of cancers, and the *Drosophila* Ras gene has been used to model cancer progression in flies. Using Crispr/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.

### Publications

- Vega-Cuesta P, Pulido D, Abia D, Herrera S, Lopez-Varea A, Ruiz-Gómez A, Fernández-Freire P, Peropadre A, de Celis JF. A *Drosophila* ecdysone-deficient model to assess the endocrine disruptor activity of Bisphenol A. *Ecotoxicol Environ Saf.* 2025 Jul 15;300:118483. doi:

10.1016/j.ecoenv.2025.118483. Epub 2025 Jun 10. PMID: 40499484.

### 3. Mechanisms of Tumorigenesis in *Drosophila*

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

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- **Prof. Noelia Pinal Seosana . Profesora Ayudante Doctora. Departamento de Biología.UAM. (Staff scientist with PI Dr. Ginés Morata, CSIC-CBM)**
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#### Research summary:

Nowadays, our work is focused on the study of cellular senescence, a fascinating phenomenon involved in inflammation and tumorigenesis, which has been described in vertebrate cells. We have recently found that *Drosophila* senescent cells possess the same features as those of vertebrates. We are making full use of the sophisticated *Drosophila* genetic technology to describe the genetic modifications of senescent cells and their interactions with surrounding cells.

### 4. Biophysics and systems biology

<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:

Our lab focuses on the study of the dynamics of developmental systems combining experimental, theoretical and computational tools. Our main interests are:

- **Regulation of stem cell differentiation during developmental processes**

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. We combine *in vivo* and *in silico* approaches to understand how the wiring of the pathways determines the role of the proteins that regulate the differentiation of neurons. We also study how the interplay between mode and rate of division of stem cells is orchestrated. To do that, we use *in toto* microscopy combined with theoretical tools and algorithms developed in the lab to quantify the effect of key regulators in the balance between proliferation and differentiation during vertebrate neurogenesis.

- **Nonlinear regulation in pathways and its impact on disease treatment**

Small molecule inhibitors display significant potential as treatment for diseases that involve the deregulation of signal transduction pathways. These inhibitors are developed based on their target specificity and binding affinity. We focus on the fact that the numerous signaling proteins and feedback loops in signaling pathways strongly influence the efficiency of pharmacological treatment. The existence of several regulatory positive and negative feedback loops either creates complex dose-responses, desensitization to periodic treatments, or modulation of the drug effect in combinatorial treatments. Our experiments show that the effect of inhibitors strongly depends on the architecture of the targeted

pathway, and a detailed characterisation of these nonlinear effects can be useful when designing optimal treatment strategies.

- **Stochasticity and effect of perturbations in biological networks**

Biological networks control cellular behaviour both at the intracellular and at intercellular level. These highly interconnected networks need to perform in the continuously fluctuating and changing cellular microenvironment. Disruption of these networks often leads to aberrant cell behaviour and disease. This leads to some broad questions that we try to address in the lab at different levels: How can these highly nonlinear biological networks integrate and process information? How can they operate robustly in the presence of noise and fluctuations? What are the mechanisms at the network level underlying the adaptation to the different sources of extrinsic and intrinsic noise? To answer these questions, we use a synthetic biology approach to analyse experimentally and computationally the dynamics of fluctuations in minimal networks motifs.

### Publications

- Sonustun B, Vahsen BF, Ledesma-Terrón M, Li Z, Tuffery L, Xu N, Calder EL, Jungverdorben J, Weber L, Zhong A, Míguez DG, Monetti M, Zhou T, Giacomelli E, Studer L. **Telmisartan is neuroprotective in a hiPSC-derived spinal microtissue model for C9orf72 ALS via inhibition of neuroinflammation.** Stem Cell Reports. 2025 Jul 8;20(7):102535. doi: 10.1016/j.stemcr.2025.102535. Epub 2025 Jun 19. PMID: 40541176; PMCID: PMC12277806.
- Ledesma-Terrón M, Pérez-Dones D, Mazo-Durán D, Navarro-Martinez G, Gíron GG, Míguez DG. **Object Stitching by Clustering of Adjacent Regions for accurate quantification of three-dimensional tissues.** J Cell Sci. 2025 Sep 15;138(18):jcs264316. doi: 10.1242/jcs.264316. Epub 2025 Sep 26. PMID: 40879476.

### Projects

- 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.
- OSCAR, an Object Segmentation, Counter, Analysis Resource. PDC2022-133147-I00. IP: DAVÍD MÍGUEZ. MINISTERIO.

### Thesis

Diego Pérez Dones. Object Statistical Clustering of Adjacent Regions: A 3D tool to localize cell types in crowded environments. Director: David Míguez Gómez. Programa de Doctorado de Biociencias Moleculares. Universidad Autónoma de Madrid.

## ➤ Cell-cell communication and inflammation UNIT

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

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

- Prof. María Yáñez-Mo. Profesora Titular. Departamento de Biología Molecular. UAM.

## Research summary:

Our research team is dedicated to advancing the understanding of tetraspanin-enriched nanodomains, specialized membrane structures crucial in cell adhesion and migration processes. In addition, tetraspanin proteins are highly prevalent on extracellular vesicles (EVs), shuttles for bioactive proteins, lipids, and RNAs, unveiling novel pathways for intercellular communication.

Our investigations aim to unravel the intricate mechanisms underlying EV biogenesis and their subsequent uptake by recipient cells. Within our group we also pioneer innovative approaches for EV isolation, detection and quantification for their use in liquid biopsy in personalized medicine. Moreover, we are at the forefront of engineering synthetic exosome mimetics, harnessing tetraspanin-based tools as therapeutic tools to replicate and enhance natural cellular processes.

## Publications

- Rodriguez-Baili MC, Palma-Cobo M, Prucca CG, Yáñez-Mó M, Gil GA. **Intercellular communication between extracellular vesicles from conditioned macrophages and breast cancer cells drives endocrine therapy resistance.** *Front Cell Dev Biol.* 2025 Jun 3;13:1548724. doi: 10.3389/fcell.2025.1548724. PMID: 40567500; PMCID: PMC12188363.
- Palma-Cobo M, Toribio V, Morales J, López-Martín S, Enrich C, Lu A, Yáñez-Mó M. **Genome-Wide CRISPR/Cas9 Screening Identifies the COMMANDER Recycling Complex as a Key Player in EV Uptake.** *J Extracell Vesicles.* 2025 Sep;14(9):e70166. doi: 10.1002/jev2.70166. PMID: 40985903; PMCID: PMC12456102.
- Adamo G, Amarantos I, Arzimanoglou I, Bergese P, Bongiovanni A, Bussolati B, Cauda V, Chiari M, Garinis GA, Giebel B, Guazzi P, Jurga M, Neri C, Ohlsson P, Rohde E, Sales G, Trapani I, Vader P, Vainio S, Wauben MHM, Yáñez-Mó M, Zarovni N. **Spotlight on innovation: key insights from the extracellular vesicle cluster meeting at the European Innovation Council.** *Cytotherapy.* 2026 Jan;28(1):101976. doi: 10.1016/j.jcyt.2025.08.008. Epub 2025 Aug 31. PMID: 41137847.
- Benayas B, Sánchez-Herrero E, Robado de Lope L, Morales J, López-Martín S, Provencio M, Valés-Gómez M, Romero A, Yáñez-Mó M. **Optimized size exclusion chromatography demonstrates that extracellular vesicles are the key RNA carriers of ALK translocations in non-small cell lung cancer cell line secretome and patient plasma.** *Extracell Vesicles Circ Nucl Acids.* 2025 Jun 18;6(2):310-323. doi: 10.20517/evcna.2025.14. PMID: 40852597; PMCID: PMC12367459.

## 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.
- Vesículas extracelulares e inmunoterapia frente al cancer. PID2023-149514OB-I00 (FEDER, UE). Proyectos I+D Generación de Conocimiento. Principal Investigator: María Yáñez-Mó. 01/09/2024-31/08/2027

## 2. Immunometabolism and Inflammation Lab

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

- **Prof. Elisa Carrasco. Profesora Ayudante Doctora. Departamento de Biología. UAM.**

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

### Research summary

We have been pioneers proposing that the immune system, particularly T cells, controls tissue senescence and the onset of age-related diseases. We are now investigating how the immune system contributes to systemic senescence as well as to the general aging process. Would the rejuvenation of the immune system compartment suffice to delay organismal aging or at least some of its manifestations? An affirmative response to this question might have vast consequences for improving healthy aging.

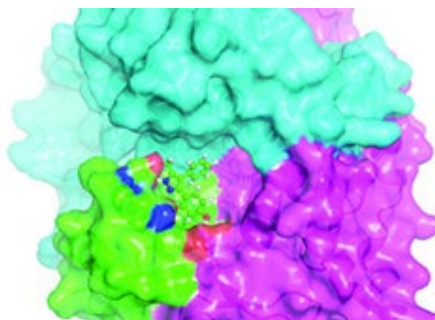
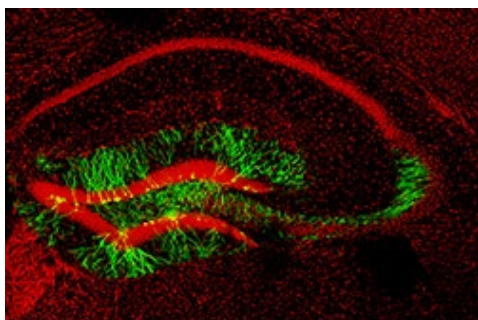
### Publications

- Soto-Herederó G, Gabandé-Rodríguez E, Carrasco E, Escrig-Larena JI, Gómez de Las Heras MM, Delgado-Pulido S, Francos-Quijorna I, Blanco EM, Fernández-Almeida Á, Abia D, Rodríguez MJ, Fernández-Díaz CM, Álvarez-Flores MB, Ramírez de Molina A, Jung S, Del Sol A, Zorita V, Sánchez-Cabo F, Torroja C, Mittelbrunn M. **KLRG1 identifies regulatory T cells with mitochondrial alterations that accumulate with aging.** Nat Aging. 2025 May;5(5):799-815. doi: 10.1038/s43587-025-00855-9. Epub 2025 Apr 30. PMID: 40307497; PMCID: PMC12092250.
- Gómez de Las Heras MM, Carrasco E, Pérez-Manrique M, Inohara N, Delgado-Pulido S, Fernández-Almeida Á, Gálvez-Castaño MI, Francos-Quijorna I, Simó C, García-Cañas V, Escrig-Larena JI, Aranda JF, Soto-Herederó G, Gabandé-Rodríguez E, Blanco EM, Días-Almeida J, Núñez G, Mittelbrunn M. **CD4 T cell therapy counteracts inflammaging and senescence by preserving gut barrier integrity.** Sci Immunol. 2025 Aug;10(110):eadv0985. doi: 10.1126/sciimmunol.adv0985. Epub 2025 Aug 1. PMID: 40749035; PMCID: PMC7618201.
- Gallego-Rentero M, Botella LM, Mascaraque M, Nicolás-Morala J, Albiñana V, Abarca-Lachen E, Gilaberte Y, González S, Juarranz Á, Carrasco E. **N-acetylcysteine and raloxifene boost photodynamic therapy against cutaneous squamous cell carcinoma by decreasing TGFβ1 secreted by cancer-associated fibroblasts.** Int J Biol Sci. 2025 Apr 28;21(7):3164-3182. doi: 10.7150/ijbs.106642. PMID: 40384860; PMCID: PMC12080389.

### Projects

- Reprogramación epigenética como estrategia para revertir el deterioro de la función cutánea en ratones con deficiencia mitocondrial específica de células T. SI4/PJI/2024-00166. IP: ELISA CARRASCO. COMUNIDAD DE MADRID.

## 🚩 PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES PROGRAMME



### ➤ Molecular Neuropathology UNIT

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#### 1. 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

To identify genes and mechanisms involved in the neurodegeneration characteristic of Alzheimer's disease (AD), we developed cell models that reflect different aspects of the pathogenesis of the disease. These models allow us to identify new genes/functions associated with AD, which could be therapeutic targets for the disease. To do this, we analyze differential gene expression in the models and develop genetic association studies and biomarkers in clinical samples. In recent years, we have focused on models of herpes simplex virus 1 (HSV-1) infection that present characteristic markers of AD, including alterations in the trafficking, metabolism and proteolysis of the amyloid precursor protein (APP), as well as in the phosphorylation of the tau protein.

The study of the lysosome autophagy pathway in these models indicates that HSV-1, especially in the presence of oxidative stress, profoundly affects the final stages of the pathway, causing an increase in lysosomal content accompanied by a significant reduction in the activity of different cathepsins and in the degradation of lysosomal substrates. The evidence that another alpha-herpesvirus with neurotropic properties, HSV-2, induces the same neurodegeneration markers as HSV 1, supports the possible involvement of various infectious agents like as herpesviruses in AD-associated neurodegeneration.

The results of the functional and genetic/biomarker association studies developed so far support the hypothesis that lysosomal function failure could constitute a relevant mechanism in HSV-1-induced neurodegeneration and, in general, in AD type neurodegeneration, so our group is focused on the study of this functional pathway. Currently, we are developing more complex cell models, based on human NPCs, to validate our previous findings in a more physiological environment and delve deeper into the mechanisms involved.

In addition, we participate in several collaborative projects. The most numerous are those aimed to study the genetic architecture of AD, within the framework of the Spanish Consortium for Dementia Genetics (DEGESCO) and the international consortia EADB and IGAP, which continue to reveal new factors and relevant functions in the pathogenesis of this disease.

## Publications

- Akdeniz BC y cols. **Polygenic Hazard Score for Predicting Age-associated Risk of Alzheimer's Disease in European Populations: Development and Validation.** medRxiv [Preprint]. 2025 Jul 28;2025.07.28.25332293. doi: 10.1101/2025.07.28.25332293. PMID: 40766162; PMCID: PMC12324
- Bracher-Smith M y cols. **Machine learning in Alzheimer's disease genetics.** Nat Commun. 2025 Jul 22;16(1):6726. doi: 10.1038/s41467-025-61650-z. PMID: 40691194; PMCID: PMC12280214.
- Le Borgne J, y cols. **X-chromosome-wide association study for Alzheimer's disease.** Mol Psychiatry. 2025 Jun;30(6):2335-2346. doi: 10.1038/s41380-024-02838-5. Epub 2024 Dec 4. PMID: 39633006; PMCID: PMC12092188.
- Nicolas A, y cols. **Transferability of European-derived Alzheimer's disease polygenic risk scores across multiancestry populations.** Nat Genet. 2025 Jul;57(7):1598-1610. doi: 10.1038/s41588-025-02227-w. Epub 2025 Jun 18. PMID: 40533518; PMCID: PMC12283339.
- Puerta R, y cols. **Alzheimer's Disease Neuroimaging Initiative. Linking genomic and proteomic signatures to brain amyloid burden: insights from GR@ACE/DEGESCO.** Funct Integr Genomics. 2025 Mar 25;25(1):73. doi: 10.1007/s10142-025-01581-6. PMID: 40133566; PMCID: PMC11937198.
- García-González P y cols. **A Spanish-Portuguese GWAS of progressive supranuclear palsy reveals a novel risk locus in NFASC.** Eur J Hum Genet. 2025 Jul;33(7):960-965. doi: 10.1038/s41431-025-01872-3. Epub 2025 May 16. PMID: 40379966; PMCID: PMC12229675.
- Thomassen JQ y cols. **APOE stratified genome-wide association studies provide novel insights into the genetic etiology of Alzheimer's disease.** medRxiv [Preprint]. 2025 May 9;2025.05.07.25327065. doi: 10.1101/2025.05.07.25327065. PMID: 40385391; PMCID: PMC12083631.
- Cruchaga C y cols. **GWAS meta-analysis of CSF Alzheimer's disease biomarkers 18,948 individuals reveal novel loci and genes regulating lipid metabolism, brain volume and autophagy.** Res Sq [Preprint]. 2025 May 21;rs.3.rs-6597595. doi: 10.21203/rs.3.rs-6597595/v1. PMID: 40470240; PMCID: PMC12136742.

## Projects

- PAPEL DE LA NEUROINFLAMACIÓN Y LA HOMEOSTASIS DE COLESTEROL EN LA NEURODEGENERACIÓN INDUCIDA POR HSV-1 EN MODELOS HUMANOS NEURALES AVANZADOS EN 3D PID2020-113921RB-I00. IP: MARIA JESÚS BULLIDO. PID2024-155549OB-I00: IP: MARÍA JESÚS BULLIDO.
- HOMEOSTASIS DE COLESTEROL Y VÍA LISOSOMAL EN LA NEURODEGENERACIÓN INDUCIDA POR HSV-1 Y EN LA ENFERMEDAD DE ALZHEIMER: MECANISMOS PATOGENICOS Y BIOMARCADORES . PID2020-113921RB-I00. IP: MARIA JESÚS BULLIDO.
- Networked Center of Biomedical Research. Neurodegenerative diseases -CIBERNED-  
Annual Report 2025 –Institute for Molecular Biology UAM- IUBM

(<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/>)

## 2. Physiopathological aspects 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

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.

### Publications

- Sarmiento-Jiménez J, Felipe R, Núñez E, Ferrando-Muñoz A, Benito-Muñoz C, Gago F, Vázquez J, Camafeita E, Clement E, Wilson B, López-Corcuera B. **A New GlyT2 Variant Associated with Hyperekplexia**. Int J Mol Sci. 2025 Jul 14;26(14):6753. doi: 10.3390/ijms26146753. PMID: 40725001; PMCID: PMC12295724.

## Projects

- PATOLOGÍAS DEL TRANSPORTADOR NEURONAL DE GLICINA GlyT2: HIPERPLEXIA Y DOLOR. IMPLICACIONES EN DESARROLLO. PID2023-150608OB-I00 (FEDER, UE). Ministry of Science and Innovation. PI: B. López Corcuera. 2024-2027.

### 3. Biology of human stem cells in translational neuroscience

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

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

Research in animal models of neurodegenerative diseases has demonstrated that stem cells elicit beneficial effects through mechanisms such as brain plasticity, rather than mere cell replacement. However, responses varied significantly across species, underscoring the need for human-specific studies due to the unique characteristics of the human brain.

Our group investigates the biology of stem cells as a source of human neurons and as a therapeutic tool in animal models of neurological disorders, including Parkinson's disease. To explore human neuron responses, we focus on generating A9 dopaminergic neurons, which are critically affected in Parkinson's disease. We have explored various culture surfaces and found that both material composition and surface topography at nano and micro scales play crucial roles in developing innovative culture systems.

Building on these findings, our efforts are directed towards developing human brain organoids to better understand complex neuronal circuits and diverse neuron phenotypes. In alignment with efforts to minimize the use of laboratory animals for basic research and to expand our knowledge of human neural tissue biology, we have enhanced cerebral organoids with improved features for patterning studies, thereby enhancing their utility in preclinical research.

Current endeavors include refining scaffold designs by integrating materials and topographies validated in 2D cultures, harnessing their abilities to promote neuronal growth and support electrical conductivity. As brain organoids mature, the lack of glial cell support presents a challenge, prompting initiatives to introduce oligodendrocytes (OLs) derived from human stem cells. These OLs are intended to survive, mature, and potentially myelinate the neuronal networks within organoids, thereby enhancing their functional maturity.

In summary, our research aims to advance stem cell therapies through a nuanced understanding of human neuron responses, culminating in the development of sophisticated brain organoid models that faithfully replicate human brain complexity. These models enable detailed studies on neurological disorders and facilitate the exploration of therapeutic interventions.

## Publications

- Alcover-Sanchez B, Garcia-Martin G, Paleo-García V, Quintas A, Dopazo A, Gruart A, Delgado-García JM, de la Villa P, Wandosell F, Pereira MP, Cubelos B. **R-Ras1 and R-Ras2 regulate mature oligodendrocyte subpopulations.** *Glia*. 2025 Apr;73(4):701-719. doi: 10.1002/glia.24643. Epub 2024  
Annual Report 2025 –Institute for Molecular Biology UAM- IUBM

Nov 19. PMID: 39558879; PMCID: PMC11845848.

- Ulecia-Morón, C.; Bris, Á.G.; MacDowell, K.S.; Cerveró-García, P.; Madrigal, J.L.M.; García-Bueno, B.; Pereira, M.P.; Leza, J.C.; Caso, J.R. **Chronic mild stress dysregulates autophagy, membrane dynamics, and lysosomal status in frontal cortex and hippocampus of rats.** Eur. Neuropsychopharmacol. 2025. 94: 24-35. DOI: 10.1016/j.euroneuro.2025.02.005.

## Projects

- Cerebroides: desarrollo y complejidad. PID2020-118189RB-I00. IP: MARTA PÉREZ PEREIRA. MINISTERIO.
- NANOPLATFORMS FOR NEUROSCIENCE. 101169352-NeuroNanotech-MSCA-2023-DN-01. IP: MARTA PÉREZ PEREIRA. PROYECTO EUROPEO.

## 4. Neuronal repair and molecular therapy in neurodegeneration: spinocerebellar ataxias

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

### Research summary:

Friedreich's ataxia is a neurogenetic, autosomal recessive 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 can serve as a very useful model for other degenerative diseases in which mitochondrial dysfunction also plays a very important role.

In the context of Friedreich's ataxia, we have developed different neural cell models to study the molecular mechanisms of the neurodegenerative process triggered by frataxin deficiency. These studies have allowed us to identify processes such as iron-sulfur centre deficiency, a decrease in some mitochondrial respiratory chain complexes, the generation of reactive oxygen species, increased DNA damage, activation of the p53 protein, and activation of apoptosis as crucial elements in neurodegeneration. In addition, we have demonstrated an additional, very important role of astrocyte activation that contributes to the neurodegenerative process through neuroinflammatory and neurotoxic processes.

Furthermore, we are also using our cellular models to test possible therapeutic strategies with an emphasis on finding molecules (drugs or genes) capable of compensating for the functional deficits induced by frataxin deficiency or capable of efficiently increasing frataxin expression. In particular, we are paying special attention to neurotrophic factors and drugs capable of stimulating the production and/or signalling of these factors. Our group has been the first to discover that brain-derived neurotrophic factor (BDNF) has the ability to inhibit neurodegeneration induced by frataxin deficiency. We have also found that SAG, an agonist of the SHH pathway, decreases the activation of frataxin-deficient astrocytes and the secretion of proinflammatory cytokines.

Our group has also been a pioneer in the development of gene therapy strategies for Friedreich's ataxia by introducing correct copies of the frataxin gene through the administration of herpesviral vectors carrying the cDNA or the complete genomic "locus" of frataxin. Currently our group is focused on the characterization of neurodegeneration in the cerebellum of a new mouse model of Friedreich's ataxia. This mouse model will also be very useful for testing possible therapeutic strategies.

In collaboration with the group of Dr. Tiago Fernandes and Dr. Joaquim Cabral, from the Institute of Bioengineering of the University of Lisbon, we are also exploring the generation of human cerebellar organoids as a new experimental model of Friedreich's ataxia. For this purpose we are using iPSC cells derived from fibroblast biopsies from healthy subjects and patients with Friedreich's ataxia. In the area of transfer, our group has had research contracts with the biopharmaceutical company Minoryx evaluating possible drugs in our Friedreich's ataxia models.

Our group also collaborates with the Federation of Ataxias of Spain (FEDAES) by disseminating advances in research among patients and family members. In addition to our research activity, we are strongly committed to improving and innovating the teaching/learning of Biomedicine, the dissemination of advances in biomedical research and its bioethical and social implications.

## Projects

- 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.

### 5. Molecular basis of neuronal plasticity

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

- **Prof. Francisco Javier Díez-Guerra. Catedrático. Departamento de Biología Molecular. UAM.**

## Research summary:

Memories are encoded by long-term changes in synaptic efficiency and connectivity. An in-depth knowledge of the molecular basis of synaptic regulation is fundamental to decipher the mechanisms involved in the formation of memories. Our group studies the cellular and molecular mechanisms that modulate the plasticity of neural networks, with the aim of finding molecular targets and effective strategies to improve cognitive performance. Synaptic activity triggers intracellular calcium (Ca<sup>2+</sup>) oscillations that locally modulate several signaling pathways. Calmodulin (CaM), a protein that binds calcium, translates these oscillations into intracellular signaling events. Its availability and activity are locally regulated by proteins such as neurogranin (Ng), very abundant in the post-synaptic environment, which sequesters CaM in a Ca<sup>2+</sup> and phosphorylation dependent manner. We use several preparations including primary cultures of dissociated neurons to understand the role of Ng in events of synaptic plasticity, such as those associated with hebbian plasticity (Long Term Potentiation -LTP- and Long Term Depression -LTD) and homeostatic plasticity (synaptic scaling).

For that we use a combination of biochemical, molecular biology, electrophysiology, advanced microscopy and other imaging techniques. Since Ng levels and cognitive performance are positively correlated in the human brain, we are interested to understand the mechanisms underlying the regulation of Ng transcription and its local translation in dendrites. We propose Ng as a molecular target for strategies designed to prevent, treat or alleviate conditions and pathologies associated to impaired cognitive function. We justify this objective on the following premises. First, Ng function is quite restricted to its action in the brain. Thus, Ng deficiency in mice does not cause apparent anatomical or physiological abnormalities, but severe cognitive impairments. And second, targeting Ng expression to improve cognition is very likely devoid of

side-effects, since Ng expression is tightly regulated in space and time (only expressed in the postnatal forebrain) and specifically associated to cognitive performance. In summary, a broader and deeper understanding of the role of Ng and other CaM-sequestering proteins in the mechanisms of neuronal plasticity will contribute to the development of newer therapies to improve the cognitive function and quality of life of aging individuals and patients suffering from neurological diseases.

## Publications

- Rapún J, Pérez-Martín S, Cámara-Checa A, San José G, Núñez-Fernández R, Crespo-García T, Hoban A, Rubio-Alarcón M, Martínez-Blanco E, Tamargo J, Díez- Guerra FJ, López B, Gómez R, González A, Delpón E, Caballero R. **Two concurrent mechanisms are responsible for the  $\text{Na}^+$  increase produced by dapagliflozin and empagliflozin in healthy and heart failure cardiomyocytes.** *Biomed Pharmacother.* 2025 May;186:117984. doi: 10.1016/j.biopha.2025.117984. Epub 2025 Mar 17. PMID: 40101587.
- de Andrés R, Martínez-Blanco E, Díez-Guerra FJ. **HDAC4 Inhibits NMDA Receptor- mediated Stimulation of Neurogranin Expression.** *Mol Neurobiol.* 2025 May;62(5):5609-5628. doi: 10.1007/s12035-024-04598-3. Epub 2024 Nov 25. PMID: 39581920.
- Martínez-Blanco E, de Andrés R, Baratas-Álvarez L, Díez-Guerra FJ. **CaMK2rep: A Highly Sensitive Genetically Encoded Biosensor for Monitoring CaMKII Activity in Mammalian Cells.** *Anal Chem.* 2025 Sep 23;97(37):20275-20290. doi: 10.1021/acs.analchem.5c03227. Epub 2025 Sep 14. PMID: 40947561; PMCID: PMC12461680.

## 6. Molecular mechanisms of Oligodendrocyte-Neuron interaction & pathologies associated with myelin

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

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

In our laboratory, we focus on studying the neurological component of demyelinating pathologies, with a specific emphasis on investigating the molecular mechanisms responsible for myelination processes in the Central Nervous System (CNS). We know that proper myelination is crucial for the correct transmission of nerve impulses. In the CNS, oligodendrocytes play a fundamental role in myelinating neuronal axons, a complex process involving multiple cellular interactions. Diseases resulting from improper myelination, such as Multiple Sclerosis or leukodystrophies, currently lack effective treatments.

Therefore, understanding the molecular mechanisms responsible for oligodendrocyte maturation and how oligodendrocyte-neuron interaction is established is crucial for advancing the study of these myelin diseases. Our group has demonstrated the importance of R-Ras1 and R-Ras2 GTPases, essential proteins in oligodendrocyte differentiation and survival, as well as in maintaining energy homeostasis.

Our experimental models, lacking R-Ras1 and/or R-Ras2, faithfully reproduce the symptomatic characteristics of myelin diseases, suggesting that they could be used as models for the development of

new treatments based on the neurological component. Overall, our work seeks to shed light on the molecular processes underlying demyelinating pathologies and open new avenues for the development of effective therapies.

### Publications

- Alcover-Sanchez B, Garcia-Martin G, Paleo-García V, Quintas A, Dopazo A, Gruart A, Delgado-García JM, de la Villa P, Wandosell F, Pereira MP, Cubelos B. **R-Ras1 and R-Ras2 regulate mature oligodendrocyte subpopulations.** *Glia*. 2025 Apr;73(4):701-719. doi: 10.1002/glia.24643. Epub 2024 Nov 19. PMID: 39558879; PMCID: PMC11845848.
- Esteban-Ortega, G.M.; Garcia-Martin, G.; Cubelos, B. **Novel Animal Models for Multiple Sclerosis: R-Ras GTPases in Myelin Pathophysiology.** *Biomolecules*- 2025, 15, DOI 10.3390/biom15091309

### 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.
- La interacción entre R-Ras e integrina regula la diferenciación oligodendrocitaria. PID2024-160510OB-I00. IP: BEATRIZ CUBELOS.

### 7. Tau function and dysfunctions in Alzheimer disease

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

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- **Prof. Félix Hernández Pérez. Catedrático. Departamento de Biología Molecular.UAM. (Co-PI with Dr. Jesús Avila, CSIC-CBM)**
  - **Prof. Vega García-Escudero. Profesora Contratada Doctora. Departamento de Anatomía, Histología y Neurociencias. UAM.**
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### Research summary:

Tau is a neuronal protein that plays a direct or indirect role in various neuronal functions. Dysfunctions in tau can lead to neurodegenerative disorders, known as tauopathies, with Alzheimer's disease being the most significant. Tau's functions are influenced by its subcellular localization and its binding to specific neuronal components. Our objective is to analyze these known tau functions and explore potential new ones.

We have examined the structural and functional differences between human and mouse tau proteins, focusing on an extra amino acid sequence unique to human tau, which plays a role in axonal transport of certain proteins. Additionally, we have studied the mechanism responsible for extracellular tau secretion and tau's involvement in localizing NMDA extrasynaptic receptors. Given that tau is a phosphoprotein primarily modified by the GSK3 $\beta$  kinase, we have also investigated the effects of GSK3 $\beta$  overexpression in neuronal cells. In Dr. Hernández's group, we analyzed tau's presence in glial cells (oligodendrocytes, astrocytes, and microglia) and discovered that various cell surface receptors may facilitate interactions between extracellular tau and neurons or glial cells.

Our group has collaborated extensively with other research teams, both within and outside of the CBM, on topics related to Alzheimer's disease, other neurodegenerative disorders, and aging. Regarding aging, we have documented the rejuvenation of certain aged granule neurons in the hippocampal region following expression of reprogramming (Yamanaka) factors.

## Publications

- Vallés-Saiz L, Domene-Serrano I, Picher AJ, Pérez M, García-Escudero V, Hernández F, Avila J. **Structure and function of Full-length Tau**. PLoS One. 2025 Oct 31;20(10):e0335251. doi: 10.1371/journal.pone.0335251. PMID: 41171737; PMCID: PMC12578172.
- Vallés-Saiz L, Abdelkader-Guillén A, Ávila J, Hernández F. **Retrotransposon Protein L1 ORF1p Expression in Aging Central Nervous System**. Int J Mol Sci. 2025 May 4;26(9):4368. doi: 10.3390/ijms26094368. PMID: 40362605; PMCID: PMC12072369.
- Domene-Serrano I, Cuadros R, García-Escudero V, Vallejo-Bedia F, Santa-María I, Vallés-Saiz L, Hernandez F, Avila J. Shapeshifter W-Tau Peptide Inhibits Tau Aggregation and Disintegrates Paired Helical Filaments. Biochemistry. 2025 Apr 15;64(8):1841-1851. doi: 10.1021/acs.biochem.4c00809. Epub 2025 Mar 26. PMID: 40140976; PMCID: PMC12004447.
- Avila J, Hernández F, Perry G. **Amyloid and tau pathologies cross-talk to promote Alzheimer's disease: novel mechanistic insights**. Neuroscience. 2025 Aug 30;582:58-62. doi: 10.1016/j.neuroscience.2025.07.025. Epub 2025 Jul 17. PMID: 40683523.
- Merino-Serrais P, Soria JM, Arrabal CA, Ortigado-López A, Esparza MÁG, Muñoz A, Hernández F, Ávila J, DeFelipe J, León-Espinosa G. **Protein tau phosphorylation in the proline rich region and its implication in the progression of Alzheimer's disease**. Exp Neurol. 2025 Jan;383:115049. doi: 10.1016/j.expneurol.2024.115049. Epub 2024 Nov 8. PMID: 39522802.
- Anton-Fernandez A, Domene-Serrano I, Cuadros R, Peinado-Cahuchola R, Sanchez- Pece M, Hernandez F, Avila J. **Peptide Family Promotes Brain Cell Rejuvenation and Improved Cognition through Peripheral Delivery**. ACS Omega. 2025 Mar 31;10(13):13236-13250. doi: 10.1021/acsomega.4c10849. PMID: 40224410; PMCID: PMC11983169.
- Anton-Fernandez, A.; Cauchola, R.P.; Hernández, F.; Avila, J. **Hippocampal rejuvenation by a single intracerebral injection of one-carbon metabolites in C57BL6 old wild-type mice**. Aging Cell. 2025. 24. DOI: 10.1111/accel.14365
- Anton-Fernandez, A.; Ruiz de Alegría, Á.; Mariscal-Casero, A.; Roldán-Lázaro, M.; Peinado-Cauchola, R.; Avila, J.; Hernández, F. **Partial reprogramming by cyclical overexpression of Yamanaka factors improves pathological phenotypes of tauopathy mouse model of human Alzheimer's disease**. Progress in Neurobiology 2025. 247. DOI: 10.1016/j.pneurobio.2025.102743.
- Domene-Serrano, I.; Cuadros, R.; García-Escudero, V.; Vallejo-Bedia, F.; Santa-María, I.; Vallés-Saiz, L.; Hernández, F.; Avila, J. Shapeshifter **W-Tau Peptide Inhibits Tau Aggregation and Disintegrates Paired Helical Filaments**. Biochemistry 2025. 64: 1841-1851. DOI: 10.1021/acs.biochem.4c00809

## Projects

- Activación de transposones en modelos animales de la enfermedad de Alzheimer: implicación de la proteína tau. PID2023-149460NB-I00 (FEDER, UE). PI Félix Hernández Pérez. MINECO. 1.9.2024-31.8.2027.

- Activación de transposones en modelos animales de la enfermedad de Alzheimer: implicación de la proteína tau. PID2023-149460NB-I00: IP: FÉLIX HERNÁNDEZ PÉREZ.
- 3' REPLACEMENT OF TAU MRNAS IN ALZHEIMERS DISEASE BY A REPLICATIVE TRANS-SPLICING RIBOZYME-ION-ARPA. ION-ARPA. IP: GARCIA ESCUDERO, VEGA. IONIS.
- Part of the Networking Research Center on Neurodegenerative Diseases (CIBERNED).

## 8. 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.**  
(in collaboration with different CBM laboratories)
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## Publications

- Villa-Gonzalez, M.; García-Juan, M.; Ordóñez-Gutiérrez, L.; Pérez-Álvarez, M.J.; Jurado, F.W. **HIF-1 $\alpha$  downregulates the APP protein after oxygen and glucose deprivation in the APP<sup>swE</sup>/PSEN1 mouse model of Alzheimer's disease-** Neurochem. Inter. 2025, 183. DOI: 10.1016/j.neuint.2024.105923

## Adult neural stem cells: 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:

The principal investigator (Dr. Eva Porlan) is a beneficiary of the Ramón y Cajal program, and has established a novel and independent line of research in the CBMSO, since 2016. This line focuses on the study of intrinsic and extrinsic factors that regulate the quiescence-proliferation switch and the mode of division of mammalian adult neural stem cells (NSC), and how these factors contribute to the maintenance of NSCs in their natural dwelling reservoirs, the neurogenic niches. The subependymal zone (also known as the subventricular zone) is the most prolific neurogenic niche in adult rodents, where residing stem cells generate large numbers of immature neurons that migrate into the olfactory bulb, where they differentiate into different types of interneurons. In a society of demographic change like is our own, a research challenge is the search for druggable targets to mobilize NSCs at their endogenous niches in order to activate stem cells that are mainly quiescent to divide and generate differentiated and functional progeny. This strategy holds promise to promote regenerative responses in physiological ageing, brain lesions or similar pathological situations, and appears as a very attractive venue for the future of cell replacement therapies. We are currently exploring the potential of targets whose biological activity are susceptible of pharmacological modulation for enhancing NSC transition into proliferation and neurogenic output, both during homeostasis and in damage-regeneration paradigms in the adult brain.

## Publications

- Sebastián-Serrano Á, Simón-García A, Santos-Galindo M, Sánchez-Carralero MP, H-Alcántara A, Clemente C, Pose-Utrilla J, Campanero MR, Porlan E, Lucas JJ, Iglesias T. **Down-regulation of neuroprotective protein kinase D in Huntington's disease.** Cell Death Dis. 2025 Jun 3;16(1):418. doi: 10.1038/s41419-025-07688-9. PMID: 40461488; PMCID: PMC12134097.

## Projects

- Dianas farmacológicas en las decisiones del destino de las células madre neurales: implicaciones para la regeneración. PID2023-146945NB-I00 (FEDER, UE). IP: Eva Porlan. Ministerio. 2024-2027.
- Instituto de Investigación Hospital Universitario La Paz "Hospital La Paz Institute for Health Research" (IdiPAZ).

### 9. Molecular basis of glutamatergic synapses

<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:

The work of our laboratory is dedicated to understanding the molecular mechanisms of neurotransmission, particularly the role played by neurotransmitter transporters in this process. These proteins, primarily located in presynaptic neurons and glial cells that surround synaptic structures, control the residence time of neurotransmitters in the synapse and, therefore, play a role in controlling neuronal excitability. We have conducted studies on the regulation and structure-function relationships of various transporters, such as the glial glutamate transporters (GLT-1 and GLAST), glycine transporters GlyT1 (mainly glial, though with neuronal isoforms) and GlyT2 (neuronal), the GABA transporter (GAT-1, mainly neuronal), and the dopamine transporter (DAT1, neuronal). Each transporter not only has a specific cellular localization but also a subcellular one, achieved through specific trafficking mechanisms that we also investigate. Since intracellular trafficking is regulated by interactions with other proteins, our laboratory has conducted studies on the composition of the interactomes of various transporters using proteomics techniques (proximity labeling). We are also interested in genetic alterations in the genes of these transporters, which produce defective proteins either in their transport mechanism or in their intracellular trafficking. For example, in a recent study, we found a pathogenic variant of the SLC6A1 gene (variant G307R) that encodes a defective form in the GABA transport mechanism by GAT-1 and is associated with a form of developmental and epileptic encephalopathy (DEE). We have described that treatment with pharmacochaperones could improve the activity of this and other pathogenic variants of GAT-1, which is of interest for patients affected by DEEs.

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

### 1. Mitochondrial dysfunction in metabolic diseases

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



- **Prof. Eduardo Balsa. Profesor Permanente Laboral. Departamento de Biología Molecular. UAM.**

#### Research summary:

Mitochondria are unique and complex organelles that perform essential functions in many aspects of cell biology. 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. The Balsa laboratory seeks to understand the basic molecular components that regulate mitochondrial function and integrate this knowledge in the context of human physiology and disease.

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 how cancer cells adapt to unfavoured tumour microenvironments by rewiring their mitochondrial metabolism to enable tumour growth and survival.

#### Publications

- Zamora-Dorta M, Laine-Menéndez S, Abia D, González-García P, López LC, Fernández-Montes P, Calvo E, Vázquez J, Enríquez JA, Balsa E. **Time-resolved mitochondrial screen identifies regulatory components of oxidative metabolism.** EMBO Rep. 2025 Jun;26(12):3045-3074. doi: 10.1038/s44319-025-00459-9. Epub 2025 Apr 29. PMID: 40301572; PMCID: PMC12187934.

#### 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 DETERMINAT 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.
- Explorando las Interacciones metabólicas entre neuronas y astrocitos en la neurodegeneración Inducida por disfunción: CNS2024-154370. IP: EDUARDO BALSA.
- Descubriendo el impacto de las alteraciones metabólicas inducidas por el envejecimiento en la microglía.. LABAE259022BALS. IP: EDUARDO BALSA. AECC.

2. **Physiopathology studies and therapeutical approaches in animal and cellular models of neurometabolic diseases**

3.

<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

The group belongs to CIBER Rare Diseases (CIBERER) and to Health Research Institute Hospital La Paz (IdiPAZ) and actively collaborates with Centro de Diagnóstico de Enfermedades Moleculares (CEDEM, Science Faculty, UAM). 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. Our projects represent translational research with the aim of generating and characterizing animal and cellular models relevant for specific diseases, to be used as research tools to understand the molecular and physiopathological mechanisms responsible for disease, to analyse potential biomarkers for prognosis and follow-up and to identify new therapeutic targets. The ultimate aim is to develop personalized therapies, both mutation specific approaches, such as gene editing and antisense oligonucleotides, as well as pharmacological therapies with antioxidant compounds and mitochondrial activators, performing preclinical studies in the specific disease models.

The research group has ample experience in the generation of iPSCs from patients' fibroblasts and their differentiation to neuronal precursors, astrocytes and cardiomyocytes, relevant cell lineages for the diseases under study. We have also extensively used gene editing CRISPR/Cas9 technology to generate cellular (hepatoma cells, iPSCs) and animal (mouse) models of disease, both knock-out or knock-in with patient specific mutations.

One line of research involves the analysis of the physiopathological mechanisms underlying PA, one of the most frequent organic acidemias in which we have demonstrated, using a mouse model, that mitochondrial dysfunction, oxidative stress and miRNAs dysregulation contribute to the multiorganic complications of the disease. We have revealed alterations in Ca<sup>2+</sup> mishandling, associated to elevated ROS levels and higher SERCA2a oxidation rate, along with dysregulation of specific cardiomiRs, as mechanisms involved in the development of PA associated cardiomyopathies. Studies in iPSCs-derived cardiomyocytes confirm these alterations, with PA cardiomyocytes exhibiting greatly depressed cell excitability and an increased risk of arrhythmias. In iPSCs-derived PA astrocytes we observe altered mitochondrial function, miRNAs deregulation and astrogliosis.

For many years the group has studied the molecular genetics of different inherited metabolic diseases, with a special emphasis on missense and splicing variants. We have characterized the molecular mechanism of many of these variants using different eukaryotic and prokaryotic expression systems and splicing reporter minigenes. We have developed methods for modulation of splicing using antisense oligonucleotides, having successfully corrected splicing defects in cellular models of different diseases. Ongoing studies involve the use of gene editing approaches (CRISPR/Cas, base editors) to permanently correct in vitro and in vivo specific variants causing inherited metabolic diseases.

### Publications

- Cámara-Checa, A.y cols (Richard, E). **Propionic Acidemia-Induced Proarrhythmic Electrophysiological Alterations in Human iPSC-Derived Cardiomyocytes**. J. Inherited Metabolic Annual Report 2025 –Institute for Molecular Biology UAM- IUBM

Dis. 2025. 48. DOI: 10.1002/jimd.70030.

- Cavazza, A. y cols (Richard, E). **Advanced delivery systems for gene editing: A comprehensive review from the GenE-HumDi COST Action Working Group**. Molecular Therapy Nucleic Acids. 2025. 36. DOI: 10.1016/j.omtn.2025.102457.
- García-Tenorio, E.M.; Álvarez, M.; Gallego-Bonhomme, M.; Desviat, L.R.; Richard, E. **Novel CRISPR-Cas9 iPSC knockouts for PCCA and PCCB genes: advancing propionic acidemia research**. Human Cell. 2025. 38. DOI: 10.1007/s13577-025-01193-z

## Projects

- 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.
- A European Training Programme to Foster the Full Therapeutic Potential. EFFECT GA 101. IP: LOURDES RUIZ-DESVIAT. PROYECTO EUROPEO.
- 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

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; hence, nearly all plasma and serum proteins are glycoproteins. This co-translational modification widens the functional spectra of proteins by at least one magnitude order. Glycan biosynthesis is more significantly affected by disease states than by protein production. Glycomics, therefore hold considerable promise specifically as disease markers. The nonlinear and non-template-based biosynthesis of glycans makes a head-to-head comparison of glycomics to proteomics not technically possible, and a complex structural analysis of glycome is necessary to get a glycomic profile.

The group has devoted the last five years to assembling, implementing and validating 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 Neurocisticercosis 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 diseases from which we have clinically defined cohorts (Chagas disease, Leishmaniasis and Neurocysticercosis). From our previous studies on total 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.

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

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

- **Prof. Sara Cogliati. Profesora Permanente Laboral. Departamento de Biología Molecular. UAM.**

#### Research summary

It is evident that women and men, female and male animals, are biologically different, resulting from genetic, epigenetic, hormonal, and environmental factors. However, the progress in the understanding of the sex-specific physio-pathology is still marginal. Therefore, it is not surprising that such a limited comprehension of the molecular mechanisms hampers the development of appropriate therapeutic strategies.

Our laboratory aims to understand the molecular mechanisms underlying metabolic sex-differences in health and disease, explicitly exploring mitochondria's role as the central hub where all metabolic functions converge.

We are currently addressing the role of mitochondria leading to a sex-specific response to heart failure and glucose metabolism. Our studies capitalize on in vivo and in vitro analysis combining biochemistry approaches to omics techniques.

#### Publications

- Sevilla-Lorente R, Marmol-Perez A, Gonzalez-Garcia P, Rodríguez-Miranda MLN, Riquelme-Gallego B, Aragon-Vela J, Martinez-Gálvez JM, Molina-Garcia P, Alcantara JMA, Garcia-Consuegra J, Cogliati S, Salmeron LM, Huertas JR, Lopez LC, Ruiz JR, Amaro-Gahete FJ. **Sexual dimorphism on the acute effect of exercise in the morning vs. evening: A randomized crossover study.** J Sport Health Sci. 2025 Dec;14:101021. doi: 10.1016/j.jshs.2024.101021. Epub 2024 Dec 22. PMID: 39716617; PMCID: PMC11930212.
- Zhang, F.; París-Ogáyar, M.; Artiga, Á.; Hernando, J.; Villar-Alvarez, E.; Lorenzo, J.; Salegi Ansa, B.; Cogliati, S.; Formentini, L.; Haro-Gonzalez, P.; Ruíz-Molina, D.; Otaegui, J.R.; Roscini, C.; Jaque, D. A Chromatic **Nanoswitcher for Thermal Monitoring of Cell Metabolism.** Advanced Functional Materials. 2025. 35, DOI 10.1002/adfm.202418813

#### 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.
- Estradiol y oxidación de ácidos grasos: entender su relación para proteger el corazón de la mujer

posmenopáusica. PID2023-148516OB-I00 (FEDER, UE). IP: Sara Cogliati. MINECO. 2024-2027.

- Descubrimiento de las vías mitocondriales relacionadas con la protección cardíaca del estradiol como tratamiento potencial para la insuficiencia cardíaca durante la menopausia. CNS2023-143646 (PRTR). IP: Sara Cogliati. Ministerio. 2024-2026.

## 5. Translational Energy Metabolism

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

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

### Research summary

During the past years, our research has been focused on understanding how mitochondrial energy metabolism contributes to the integration of cellular functions, leading to the onset and progression of various pathologies. Complex regulatory mechanisms enable mitochondrial metabolism to meet cellular demands, which go beyond ATP production. We have demonstrated that mitochondrial oxidative phosphorylation also plays additional roles in controlling cell immunity and inflammation (Formentini L. et al., Cell Reports, 2017, PMID: 28494869) and regulating intra- and inter-cellular oncogenic signals (Nuevo-Tapioles, C. et al., Nature Communications, 2020, PMID: 32681016). Impaired mitochondrial function also significantly affects adipose tissue and skeletal muscle lipid species and metabolism (Formentini L et al., Diabetologia, 2017, PMID: 28770317; Sanchez-Gonzalez C et al, EMBO J. 2020, PMID: 32488939). Interestingly, these metabolic disturbances impair ROS and calcium signaling, leading to profound changes in muscle structure (Sanchez-Gonzalez C et al, Cell Death and Disease 2022, PMID: 32488939), thus emerging as key hallmarks of myopathies. Very recently, we have demonstrated the existence of a metabolon in skeletal muscle, aimed at integrating nutrient catabolism with mitochondrial efficiency (Nat Metabolism 2024, doi: 10.1038/s42255-023-00956-y).

### Current Aims

One of the main goals of my research line, supported by PID2022-136738OB-I00 national funding and Fundación Ramón Areces, is to further investigate mitochondrial metabolism in pathophysiology. Using two conditional and tissue-specific mouse models with impaired mitochondrial activity (dysfunctional oxidative phosphorylation mice, LowOXPHOS mice; dysfunctional fatty acid oxidation mice, LowFAO mice), our research group is elucidating how different mitochondrial dysfunctions, environmental factors, and diets impact metabolism at the cellular, tissue, and organismal levels. We aim to identify the aspects of mitochondrial activity that limit cell homeostasis and understand which products of metabolism are essential for proper organism function, as well as how cells obtain or transform them in physiological tissue environments. This knowledge is crucial for exploiting mitochondrial metabolism for therapeutic purposes in the field of cancer and ageing.

### Publications

- Morin E, Doumard E, Hartnell LM, Salegi Ansa B, Leduc-Gaudet JP, Quillien A, Nakhle J, Ethuin S, Goudounèche D, Payré B, Soldan V, Balor S, Mattout A, Rouquette J, Dubois L, Sengenès C, Planat V, Casteilla L, Yart A, Dray C, Aligon J, Ferrucci L, Duchesne É, Hussain SNA, Gouspillou G, Formentini L, Mourier A, Baris OR, Valet P, Parpex H, Monsarrat P, Vigneau M, Pradère JP. **EMito-Metrix enables automated evaluation of mitochondrial morphology across species.** Nat Metab. 2025 Nov;7(11):2179-2182. doi: 10.1038/s42255-025-01400-z. PMID: 41094017.
- Zhang, F.; París-Ogáyar, M.; Artiga, Á.; Hernando, J.; Villar-Alvarez, E.; Lorenzo, J.; Salegi Ansa, B.; [Annual Report 2025 –Institute for Molecular Biology UAM- IUBM](#)

Cogliati, S.; Formentini, L.; Haro-Gonzalez, P.; Ruíz-Molina, D.; Otaegui, J.R.; Roscini, C.; Jaque, D. **A Chromatic Nanoswitcher for Thermal Monitoring of Cell Metabolism. Advanced Functional Materials.** 2025. 35. DOI: 10.1002/adfm.202418813

## Projects

- Disfunción de la actividad mitocondrial en patología: la beta-oxidación de ácidos grasos en el mantenimiento de la homeostasia del organism. PID2022-137238OB-I00 (FEDER, UE). PI: Laura Formentini. 1.9.2023-31.8.2026.
- MICROBIOMINNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE MICROBIOMES:TOWARDS A CIRCULAR BLUE BIOECONOMY AND HEALTHIER MARINE ENVIRONMENTS. 101167421-UNION-HORIZON-MSCA-2023-DN-0. IP: LAURA FORMENTINI. PROYECTO EUROPEO.

## 6. 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. Profesora Ayudante Doctora. Departamento de Biología. UAM.**
  - **Dra. Yadiely Portilla Tundidor. Profesora Ayudante Doctora. Departamento de Biología Molecular UAM.**
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## Research summary:

The complex intercommunication among cell types in their specific tissue environment or via organ crosstalk is essential for homeostasis, while alterations in such interplays lead to pathological situations. The aim of our group is to better understand the role of key signaling nodes in the maladaptive rewiring of cellular communication pathways in disease, with emphasis on G protein-coupled receptor kinase 2 (GRK2) hub. GRK2 levels are altered in humans in prevalent cardiovascular and metabolic pathologies and in certain tumors. Therefore, understanding the molecular basis of such changes in GRK2 expression and its functional impact on cellular processes is critical to assess the feasibility of GRK2 as a useful diagnostic biomarker and/or of new therapeutic strategies based on the modulation of the activity, levels or specific interactions of this protein. In addition to its canonical role as GPCR regulator, GRK2 can directly interact with and/or phosphorylate non-GPCR components of transduction cascades. Our laboratory has pioneered the research on the characterization of different GRK2 interactomes, unveiled new mechanisms of regulation of GRK2 activity, expression and protein stability, uncovered new GRK2 substrates and interacting proteins, and first reported the participation of GRK2 in several relevant cellular processes and patho-physiological situations (angiogenesis, breast cancer, hypertension, cell cycle, cell migration, cardiac and whole-body insulin resistance). By using cellular and mouse models with altered GRK2 dosage (including tamoxifen-induced, tissue-specific deficient and/or mutant knock-in mice), we aim to gain insight on the stimuli and

mechanisms triggering changes in GRK2 expression/functionality, on the impact of altering GRK2 in disease initiation and/or progression, and on the phenotypic integration of canonical and non-canonical GRK2 functions, both cell type- and tissue microenvironment-specific, in pathological conditions.

The main lines of research of our group are the following:

3. Study the role of GRK2 in the integration of tumor microenvironment (TME) cues in breast cancer. We investigate connections among tumor microenvironment stresses (such as hypoxia or stiffness), chemokine and growth factor-receptors and GRK2 interactors in the rewiring of breast cancer cells leading to metastatic features (in collaboration with P. Penela CBM lab)
4. Evaluate the impact of altering GRK2 functionality in epidermal homeostasis and keratinocyte-immune cells crosstalk. We are exploring how GRK2 deletion in keratinocytes affects the skin immune cell landscape, barrier function, skin-microbiome interaction and hair follicle homeostasis, leading to enhanced susceptibility to inflammatory diseases and squamous cell carcinomas (in collaboration with C. Ribas CBM lab).
5. Investigate the role of GRK2 in inflammation caused by Western Diets, high in saturated fats and free sugars, and its pathophysiological consequences. Specifically, we study the influence of GRK2 in myeloid cells on macrophage polarization processes and the molecular mechanisms involved, as well as the dynamics of early neutrophil infiltration in adipose tissue and the different infiltrating phenotypic subpopulations and tissular damage that can be found after diet. These research objectives involve active collaborations with other PIs of our CBMSO Unit, as well as our participation in international and national networks (European ITN, CIBER Cardiovascular (CIBER-CV, ISCIII), the INTEGRAMUNE Madrid Biomedicine network), and our affiliation to the Instituto de Investigación Sanitaria La Princesa.

## Publications

- Asensio A, Sanz-Flores M, Liakath-Ali K, Romo-Gallo A, Palacios-García J, Paramio JM, García-Escudero R, Mayor F Jr, Ribas C. **The G-Protein-Coupled Receptor Kinase 2 Orchestrates Hair Follicle Homeostasis.** *J Invest Dermatol.* 2025 Sep 8:S0022-202X(25)02417-0. doi: 10.1016/j.jid.2025.08.040. Epub ahead of print. PMID: 40930461.

## Projects

- INTEGRAMUNE-CM. S-2022/BMD-7902. Coordinador. Comunidad de Madrid. 1.1.2023-31.12.2026.
- Interactomas del nodo GRK2 en señalización celular e implicaciones patológicas. PID2023-146735OB-I00 (FEDER, UE). IP: Federico Mayor Menéndez y Cristina Murga Montesinos. Ministerio. 2024-2027.
- 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). Agencia Estatal de Investigación (AEI), Spain 2021-abril 2025.
- PID2023-146735OB-I00. GRK2 interactomes in cellular signalling and disease (GRK2INTER). Agencia Estatal de Investigación (AEI), Spain. Principal Investigator (PI): Federico Mayor Jr. and Cristina Murga (co-PI).2024 -2027.
- Impact of Nutritional Stress on Sepsis Aggravation: Therapeutic Potential of Biomimetic Nanoparticles. SI4/PJI/2024-00172. IP: VIDA RUEDA, MARIA DEL CARMEN. COMUNIDAD DE MADRID.

## 6. Vascular inflammation and autophagy

[Vascular inflammation and autophagy - Centro de Biología Molecular Severo Ochoa](#)

**Prof. Natalia Reglero Real. Investigadora Ramón y Cajal. Departamento de Biología Molecular.**

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### Research summary:

Inflammation is at the basis of a plethora of diseases with very different aetiological origins. Although this immune reaction plays a paramount role during host survival and tissue repair, inflammation must be tightly regulated to avoid excessive tissue damage and the instigation of inflammatory diseases. For instance, uncontrolled recruitment of immune cells from blood vessels to injured tissues, as well as dysregulated vascular leakage, can lead to the development of numerous pathologies, including highly prevalent cardiovascular, metabolic and infectious conditions as well as tumour progression. Therefore, understanding the mechanisms through which the vasculature becomes dysfunctional during pathological inflammation is an area of extremely forefront research interest.

In recent years, autophagy, a metabolic, cytoplasmic quality control and general homeostatic process, has emerged as a central regulator of immune functions. So far, most of this evidence derives from immune cell-autonomous control of inflammation, with autophagy regulating the survival, differentiation, polarization and inflammatory mediator generation of diverse immune cell subsets. Crucially, our group has demonstrated that autophagy processes in endothelial cells, the portal governing the entry of leukocytes and macromolecules into tissues, are essential to limit neutrophil tissue recruitment during acute inflammation and associated tissue damage. However, the molecular mechanisms and nature of the autophagy processes regulating this phenomenon is still unknown. Hence, the main goal of our emerging laboratory is to decipher the molecular mechanisms through which endothelial cell autophagy pathways shape the inflammatory response with the aim of identifying new therapeutic approaches for the regulation of inflammatory disorders. Collectively, we aim to explore the initiating factors, molecular characteristics and pathophysiological relevance of endothelial autophagy processes during acute and chronic inflammation as well as ageing-associated pathologies.

### Publications

- Reglero-Real N, Rolas L, Nourshargh S. **Ageing microvasculature: Effects on immune cell trafficking and inflammatory diseases.** *J Exp Med.* 2025 Jul 7;222(7):e20242154. doi: 10.1084/jem.20242154. Epub 2025 Jun 2. PMID: 40455014; PMCID: PMC12128883.

### Proyectos

- RYC2021-031221-I (PRTR). Ayuda Ramón y Cajal. IP: Natalia Reglero. 2023-2027.
- Desenmascarando nuevos papeles de los procesos de autofagia endotelial en la inflamación- PID2022-137552OA-I00 (FEDER, UE). IP: Natalia Reglero Real. MINECO. 2023-2026.

## 7. Calcium signalling in mitochondria and insulin/leptin signalling during ageing

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

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- **Prof. Jorgina Satrustegui. 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 Permanente Laboral. Departamento de Biología Molecular. UAM.
- Prof. José M<sup>a</sup> Carrascosa Baeza. Catedrático. Departamento de Biología Molecular. UAM.

### Research summary:

Our interests are understanding calcium regulation of mitochondrial function by way of the calcium-dependent mitochondrial carriers of aspartate-glutamate/AGCs, components of the malate aspartate shuttle (MAS), or ATP.Mg<sup>2+</sup>-Pi/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. Our aim is to study the role of citrin/AGC2 in liver in the mitochondrial response to Ca<sup>2+</sup> mobilizing agonists.

Deficiency in Aralar/AGC1 is a rare disease with impaired neurodevelopment, epilepsy and hypomyelination. We have explored treatments for Aralar deficiency and found that  $\beta$ -hydroxybutyrate ( $\beta$ OHB), the main metabolic product of ketogenic diets, is able to overcome the defect in basal and workload-stimulated respiration in Aralar-deficient neurons and partially reverts their failure to produce aspartate and NAA. In vivo administration of  $\beta$ OHB to Aralar-KO mice increases myelin protein levels and dopaminergic markers in these mice, suggesting  $\beta$ HB administration as a potential treatment in Aralar deficiency.

However, whether the defect in myelination of the Aralar-KO mouse is due to the lack of aralar in neurons or oligodendrocytes is unclear. Our present aim is to generate neuron or oligodendrocyte-specific Aralar KO to address these issues.

Citrin deficiency is a urea cycle disorder with different manifestations. Citrin/AGC2 is mainly expressed in liver. In the frame of the Citrin Foundation, we are exploring the exogenous expression of Aralar, which has low expression in normal liver, as possible therapy for Citrin deficiency. We have generated Citrin-KO mice carrying liver-specific Aralar transgene and are studying the effect of the transgene in recovering liver MAS activity and other traits of Citrin deficiency reproduced in Citrin-KO mice.

An ongoing COVID-19 project (CvK), is aimed at developing a therapy against COVID-19 symptoms with the use of senolytics, which would selectively eliminate organisms' senescent cells.

### Publications

- Díaz-Rullo J, González-Moreno L, Del Arco A, González-Pastor JE. **Decoding the general role of tRNA queuosine modification in eukaryotes**. Sci Rep. 2025 Jan 2;15(1):345. doi: 10.1038/s41598-024-83451-y. PMID: 39747999; PMCID: PMC11695743.

### Projects

- Funciones de AGC1/Aralar en neuronas y OPCs en proliferación; mielinización, estado redox citosólico y niveles de aspartate. PID2023-146837OB-I00 (FEDER, UE). IP: Beatriz Pardo. Ministerio.

2024-2027.

- 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.

## Thesis

Luis González Moreno. Regulación de la función mitocondrial por calcio en células proliferativas: papeles de los transportadores mitocondriales regulados por calcio. Directores: Beatriz Pardo Merino y Araceli del Arco Martínez. Programa de Doctorado de Biociencias Moleculares. Universidad Autónoma de Madrid.

## 8. 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.**
  - **Prof. Laura Nogués Vera. Profesora Ayudante Doctora. Departamento de Biología Molecular UAM.**
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## Research summary:

Breast cancer is a disease of high prevalence with around 25,000 new diagnoses in Spain each year. Its incidence is much higher in the developed world, suggesting that the western lifestyle with unhealthy dietary habits (excessive caloric intake, overweight, obesity) and chronic stress states (adrenergic overstimulation) may influence the onset and progression of this disease.

The histopathological variety and molecular heterogeneity of breast tumors (luminal subtypes, triple negative, ERBB2), together with genomic instability and intra-tumoral cellular diversity, are factors that make difficult to achieve efficient treatments. In breast cancer, the main altered proteins responsible for genomic instability and heterogeneity are ATM kinase, Brca1 ligase and the tumor suppressor transcription factor p53 together with its negative regulator Mdm2 ligase. Although in ~ 80% of ductal breast carcinomas p53 is restrained by the activation/amplification of Mdm2 or by the deactivation of positive regulators such as ATM, therapies based on these targets are not yet satisfactory.

However, the identification of molecular dependencies in certain types of breast cancer has improved the treatment of patients with ERBB2(Her2) + or luminal tumors by using drugs directed against the HER2 tyrosine kinase receptor or the estrogen receptor (ER). However, in “triple negative” tumors (TNBCs) (negative for the steroid receptor (ER), progesterone (PR) and ERBB2 receptor) there are no clearly identified dependencies, and the treatments are not sufficiently effective. Another important problem is the emergence of resistance in luminal, Her2 and triple negative breast cancers, in parallel to the heterogeneity due to genomic instability and tumor metabolic reprogramming.

The objective of our group is to identify, as potential multifunctional therapeutic targets, signaling nodes that cooperate with oncogenes in the acquisition of tumor capacities (angiogenesis, proliferation, invasion or metastasis) or that block the activity of tumor suppressors, being able to alter the cellular homeostasis.

Results of our laboratory suggest that intertwined alterations of the serine-threonine kinase GRK2 and the Mdm2 ligase are key for cell-autonomous malignant transformation, as well as in the interplay of the

transformed cell with the tumor micro-environment and the systemic condition of the patient. Our results indicate that these proteins modulate each other differently in normal epithelial cells and in tumor cells, responding in different ways to signals that stimulate adrenergic receptors and other G-protein coupled receptors (GPCR) or growth factor tyrosine kinase receptors (RTK).

In this context, our research aims to characterize the role of these nodes (GRK2 and Mdm2), as the relevant proteins phosphorylated and ubiquitinated by them, in a) diverse cellular processes such as cell cycle control and cell division, differentiation, energy metabolism or senescence, which are key in maintaining a normal cell behavior; b) in the consequences of hormonal (adrenergic, estrogenic) and metabolic stress on genomic stability; and c) in pro-tumoral stroma remodeling by analyzing the pathological angiogenesis and fibrosis that facilitate tumor growth and dissemination.

## Projects

- INTEGRAMUNE-CM. S-2022/BMD-7902. Coordinador F. Mayor. Comunidad de Madrid. 1.1.2023-31.12.2026.
- Targeting Metabolic Invasive Phenotype to Overcome immunotherapy Resistance of metastatic melanoma. MetaPhOR. SI4/PJI/2024-00219. IP: LAURA NOGUÉS. COMUNIDAD DE MADRID.

## 9. 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:

Our group aims to apply the knowledge gained from basic research to clinical practice and improve the diagnosis, prevention, and treatment of inherited metabolic diseases (IMD). These diseases are prevalent, affecting 1 in every 800 newborns and belong to the largest groups of rare diseases. High-throughput genomic sequencing has helped us discover new gene-pathology associations in IEM. However, we propose a new approach to overcome the limitations of current technologies in identifying specific genetic causes of the disease. Our plan involves using third-generation sequencing, metabolomics, transcriptomics, and epigenomics to detect long repetitive elements, copy number alterations, structural variations, and epigenetic defects in DNA or RNA. We will also use a functional genomics platform to understand the clinical impact of genetic defects.

Our second objective is to research advanced therapeutic strategies using biocompatible nanoparticles loaded with small chemical compounds, repositioning drugs, RNA therapy, or therapeutic proteins. We are developing preclinical liver and brain organoid platforms obtained through human iPSC differentiation to evaluate potential drugs. We will edit, activate, or inhibit genes using CRISPR to generate models and to explore this technology as potential therapy.

Finally, we aim to identify new therapeutic targets and biomarkers by integrating multi-omics data into computational models.

## Publications

- Tejedor JR, Soriano-Sexto A, Beccari L, Castejón-Fernández N, Correcher P, Sainz-Ledo L, Alba-Linares JJ, Urdinguio RG, Ugarte M, Fernández AF, Rodríguez-Pombo P, Fraga MF, Pérez B. **Integration of multi-omics layers empowers precision diagnosis through unveiling pathogenic mechanisms on maple syrup urine disease.** J Inherit Metab Dis. 2025 Jan;48(1):e12829. doi: 10.1002/jimd.12829. Epub 2024 Dec 10. PMID: 39659154; PMCID: PMC11670297.
- Soriano-Sexto A, Sánchez-Lijarcio O, Beccari L, Castejón-Fernández N, Leal F, Alcaide P, de la Morena-Barrio B, Bahílo-Curises MDP, Correcher P, Hencke-Tresbach R, López L, Martín-Hernández E, Yahyaoui R, Ugarte M, Rodríguez-Pombo P, Pérez B. **Expanding the genetic landscape of inherited metabolic diseases using long-read sequencing and transcriptomic profiling.** Eur J Hum Genet. 2026 Jan 26. doi: 10.1038/s41431-025-01995-7. Epub ahead of print. PMID: 41588148.
- Pascoal C, Granjo P, Mexia P, Gallego D, Adubeiro Lourenço R, Sharma S, Pérez B, Castro-Caldas M, Grosso AR, Dos Reis Ferreira V, Videira PA. **Unraveling the biological potential of skin fibroblast: responses to TNF- $\alpha$ , highlighting intracellular signaling pathways and secretome.** Immunol Lett. 2025 Dec;276:107057. doi: 10.1016/j.imlet.2025.107057. Epub 2025 Jul 4: 40619104
- M.A. Martínez Olmos, E. Venegas Moreno, M. Morales Conejo, L. Ceberio Hualde, B. Pérez, M. de Tallo Forga, F.J. Pérez-Sádaba, P. Correcher Medina. **Clinical characteristics and management of Spanish adult patients with phenylketonuria.** Rev Clin Esp. 2025 Oct; 225(8):502356. doi: 10.1016/j.rceng.2025.40850348
- Elena Martín-Hernández y cols (B. Pérez). **Understanding the natural history and the effects of current therapeutic strategies on urea cycle disorders: insights from the UCD Spanish registry.** Nutrients. 2025 Mar 28;17(7):1173. doi: 10.3390/nu17071173. PMID: 40218931

## Projects

- Bridging the research and innovation gap for rare diseases in Europe by upgrading excellence of IMGGE. Project 101160079 — BRIDGING-RD. IP: Belén Pérez. Comisión Europea. 2024-2027.
- Belen Pérez is Head of a CIBERER group (CB06/07/0004) and a IdiPAZ group

## Thesis

Alejandro Soriano Sexto. La molécula de RNA en diagnóstico y terapia de precisión. Directora. Belén Pérez González. Programa de Doctorado de Biociencias Moleculares. Universidad Autónoma de Madrid.

### 10. Cell communication in homeostasis and disease through new Gq-GPCR signaling nodes

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

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- Prof. Catalina Ribas Núñez. Catedrática. Departamento de Biología Molecular. UAM.
  - Prof. Inmaculada Navarro. Profesora Permanente Laboral. Departamento de Biología Molecular. UAM.
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## Research summary

Cell-cell communication and the interactions that occur between them are a key aspect in the maintenance of cellular homeostasis, regulating individual cellular processes and intercellular relationships. When cells do not interact properly or incorrectly decode molecular messages, a pathological process is triggered.

**The main objective of our group** is to understand the functional impact, at the cellular and organismal level, of new interactions of important G protein-coupled receptor (GPCR) signaling nodes, relevant in the maintenance of cellular homeostasis (eg. Gαq and GRK2), and how changes in them can affect the progression of pathologies, using cell and animal models with altered expression/activity of these proteins, as well as patient samples or animal models of disease. We will focus particularly on the functional impact of these new interactions and their modulation by accessory proteins (such as GRKs, AGS, RGS, caveolin, Ric8), on cell death processes, **integration of nutrient sensing/autophagy signals, and endothelial dysfunction in the development of inflammatory/metabolic pathologies and cancer.**

The Gαq interactome has expanded considerably with the description of new effectors and our group has contributed to this, through the identification of a new interaction region in Gαq, different from the classic effector binding region. This non-canonical Gαq signaling has turned out to be relevant in the development of cardiovascular pathologies and, furthermore, recent results have revealed the novel role of Gαq as a central modulator of mTORC1, contributing to the regulation of the autophagic process and thus to the maintenance of cell homeostasis, depending on nutrients fluctuations. These new Gαq interaction networks appear to be important in the regulation of endothelial function. Furthermore, Gαq is known to interact with various cytoskeletal components as well as important membrane microdomain organizers, suggesting the existence of signaling complexes that might be limited to specific subcellular environments.

In turn, we have also revealed a relevant role of one of the main regulators of these Gq-GPCR signaling pathways, GRK2, in the maintenance of the epithelial phenotype of stratified epithelia and demonstrated how its absence contributes to the development and malignancy of oral carcinomas (HNSCC), also revealing an important role of this kinase in epidermal homeostasis and in its inflammatory response.

To deepen a better understanding of the contribution of these signaling nodes to cellular communication between different cell types, both under physiological and pathological conditions, regulating exosome trafficking/autophagy, endothelial dysfunction/angiogenesis and extracellular matrix remodeling (including: normal or activated fibroblasts (CAF), endothelial cells, immune system cells and/or tumor cells), taking into account their respective secretomes, will contribute to the development of more effective therapies in inflammatory/metabolic and tumor contexts.

Some of these research objectives imply active collaborations with other members of our Unit at the CBMSO, as well as through CIBER Cardiovascular (CIBER-CV, ISCIII), Network of Biomedicine Integramune, (Comunidad de Madrid), as well as our affiliation to the Institute of Sanitary Research La Princesa.

## Publications

- Asensio A, Sanz-Flores M, Liakath-Ali K, Romo-Gallo A, Palacios-García J, Paramio JM, García-Escudero R, Mayor F Jr, Ribas C. **The G-Protein-Coupled Receptor Kinase 2 Orchestrates Hair Follicle Homeostasis.** J Invest Dermatol. 2025 Sep 8:S0022-202X(25)02417-0. doi: 10.1016/j.jid.2025.08.040. Epub ahead of print. PMID: 40930461.

## Projects

- Participation in ERNEST (European Research Network on Signal Transduction) COST ACTION (European cooperation in Science and Technology)
- Redes de señalización de Galfa 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.

## 11. Mitochondrial biology in immune modulation

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

- **Prof. Javier Traba Domínguez. Profesor Permanente Laboral. Departamento de Biología Molecular. UAM.**

### Research summary:

Mitochondria are known as the powerhouses of the cell, and yet their functions are much more complex. In addition to energy conversion, they are also involved in heat production, calcium signaling and storage, signaling through and detoxification of reactive oxygen species (ROS), synthesis of heme and other molecules, and regulation of cell death. Emerging functions of the mitochondria in disease include their role as damage-associated molecular patterns (DAMPs), which are important for innate and adaptive immune activation. In this context, release of mitochondrial components of bacterial origin, such as mitochondrial DNA, may activate several pathways that lead to the secretion of pro-inflammatory cytokines (Fig. 1), a phenomenon called sterile inflammation. Among them, the most studied pathway is the NLRP3 inflammasome, a cytosolic multiprotein complex that senses the presence oxidized mitochondrial DNA (mtDNA) in the cytosol (and thus acts as a sensor for mitochondrial dysfunction) and in turn activates caspase-1, an enzyme that cleaves other proteins, including the precursors of the inflammatory cytokines interleukin 1 $\beta$  and interleukin 18, as well as the pyroptosis inducer Gasdermin D, into active mature peptides. The NLRP3 inflammasome thus plays a central role in immunity as an inflammatory response initiator and is associated with a broad range of degenerative diseases associated with aging, including Alzheimer's, asthma, gout, ischemia/reperfusion, hypertension, diabetes or psoriasis.

Mitochondria are also being recognized as important nutrient-sensing organelles which functionally adapt in a nutrient-dependent manner. Nutrient restriction leads to activation of several pathways and to higher levels of intracellular nicotinamide adenine dinucleotide (NAD<sup>+</sup>), which activates sirtuin proteins, a group of enzymes possessing deacetylase activity that require NAD<sup>+</sup> as a cosubstrate to function, and thus are considered metabolic and energy sensors.

Our research has shown that nutrient restriction blunted the activation of the inflammasome in macrophages, and that this effect depended partially on the activation of the NAD<sup>+</sup>-dependent mitochondrial deacetylase enzyme Sirtuin 3 (SIRT3). The mechanism of action of SIRT3 is very intriguing: by modulating the acetylation status and activity of mitochondrial superoxide dismutase (SOD2), and thus mitochondrial ROS levels, it finely controls the extrusion of oxidized mtDNA into the cytosol, where it acts as an NLRP3 agonist (Fig. 2). In addition, we have found that nicotinamide riboside (NR), an intermediate precursor of NAD<sup>+</sup> synthesis in the salvage pathway, functions as a fasting mimetic and blunts monocyte/macrophage IL-1 $\beta$  production and reduces T helper 1 (Th1) and 17 (Th17) cell activation.

Interestingly, a mouse model of psoriasis, a chronic inflammatory skin disease linked to hyperactivation of Th17 cells, displayed downregulation of the SIRT3 gene and decreased mitochondrial SOD2 activity, and thus can be considered a functional SIRT3 knockdown. The downregulation of this gene might be involved in the hyperinflammatory phenotype observed in some of its tissues. It is also known that NLRP3 inflammasome activation and IL-1 $\beta$  signaling are associated with psoriasis progression. Given our findings

of the role of SIRT3 in immune-modulation, a question arising is whether NAD<sup>+</sup> precursors could mimic caloric restriction effects and ameliorate an inflammatory disease. Psoriasis, a prototypic Th17 disease, appears to be an appealing candidate disease to test this hypothesis.

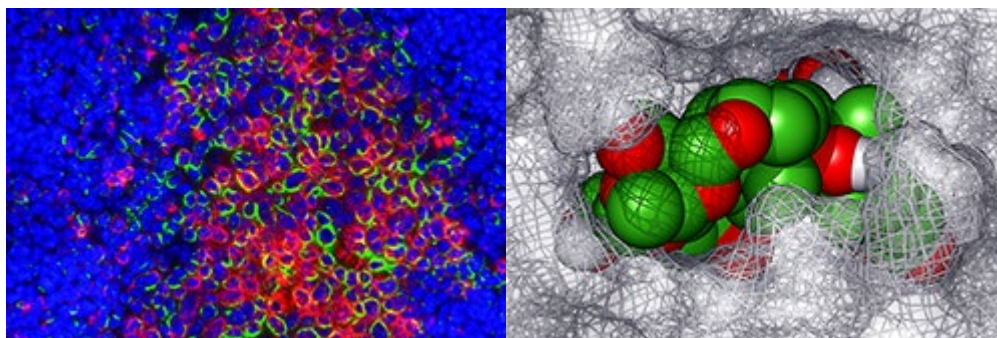
The main lines of research of our group are the following:

Expand our studies into the fundamental role of mtDNA in innate inflammatory pathways regulated by the mitochondrial protein SIRT3, the main deacetylase in the mitochondria. Evaluate whether NAD<sup>+</sup> precursors blunt inflammation in a psoriatic mouse model via augmentation of mitochondrial function, fidelity and quality control programs.

## Projects

- 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.
- SLC25A51: EL TRANSPORTADOR MITOCONDRIAL DE NICOTINAMIDA ADENINA DINUCLEOTIDO (NAD<sup>+</sup>) COMO NUEVO REGULADA. CNS2024-154366. IP: JAVIER TRABA. MINISTERIO.
- 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

#### 1. Regulation and function of proinflammatory mediators and their involvement in immune 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 Permanente Laboral. Departamento de Biología Molecular. UAM.

#### Research summary

We analyzed the involvement of Toll-like receptors (TLR)/NFAT/Cyclooxygenase (Cox)-2/prostaglandins (PGs) in the immune system and inflammatory pathologies as Obesity, Cancer and Sepsis. PGF<sub>2</sub>α negatively regulates adipocyte differentiation through transcription factor NFAT. Moreover, NFATc4 deficiency plays a key role in obesity and fatty acid metabolism. Cox-2 inhibitors reduce cancer but have side effects. As an alternative, we have analyzed genes regulated by Cox2 that may provide a protooncogenic advantage. Among those, we identified, mPGES1 is involved in increased growth and induced through a PGF<sub>2</sub>α/Egr-1 mechanism. Moreover PGF<sub>2</sub>α induced TGFβ-PMEDA1 pathway, which is a critical mediator of epithelial plasticity and ovarian carcinoma progression. Dual-specificity phosphatase 10 (Dusp10) controls stress response to serum deprivation and confluence arrest and binds and dephosphorylates Yes-associated protein 1 (YAP) in colorectal cancer progression.

TCFL5, initially cloned by us as CHA, is a member of the bHLH transcription factor family. We found that human TCFL5 gene locus is a complex with 4 isoforms. Besides, we performed interactome analysis of all TCFL5 isoforms. The 2 major isoforms, TCFL5 and CHA, will result from alternative promoter usage and differential transcription, rather than from gene splicing. We have confirmed binding to those promoters of Notch1, Egr1 and c-Myc. We found that CHA isoform, but not TCFL5 can bind to c-Myc and repressed its transcriptional activity in several cancer cell lines. Notch1 can bind to TCFL5 promoter and induce TCFL5 isoform. On the contrary, c-Myc can induce both TCFL5 and CHA transcription. We have also defined a set of genes regulated by TCFL5/CHA in leukemia cell lines and established its role in the prognosis and development of B-and T-acute lymphoblastic leukemia and in normal hematopoiesis.

The protozoan parasite, *Trypanosoma cruzi* causes Chagas' disease. We addressed the impact of *T. cruzi* genetic variability in the clinical outcome and immunopathology of the disease. We addressed the role that T cell CD4+ subsets, myeloid subclasses including myeloid-derived suppressor cells (MDSC) have in the immunopathogenesis with special focus on myocarditis, both in animal models and in patients, which differ depending of the infecting strain. To address this enormous complexity we used a system biology multiomic approaches including genomics, transcriptomic, metabolomics, etc. We have found many metabolic, miRNA and mRNA transcription alterations in *T. cruzi* infection suggesting a stressful condition in the heart. Serum miRNAs are excellent Biomarkers of Chagas' disease progression. Besides, we defined Slamf1 as a new *T. cruzi* receptor.

## Publications

- Callejas-Hernández F, Herreros-Cabello A, Poveda C, Maza MC, Mares JF, Santos-Peñaloza DK, Fresno M, Gironès N. **RNA Sequence Analysis in Macrophages Infected With *Trypanosoma cruzi*: Focus on TLR2 and TLR7, Iron Metabolism, and Extracellular Matrix Biosynthesis.** J Infect Dis. 2025 Jul 11;231(6):e1102-e1113. doi: 10.1093/infdis/jiaf074. PMID: 39948431; PMCID: PMC12247843.
- Lahera A, Vela-Martín L, Fernández-Navarro P, López-Lorenzo JL, Cornago J, Llamas P, Fresno M, Santos J, Villa-Morales M. **Improved identification of T-ALL paediatric patients with low MRD but poor prognosis using a transcriptional signature.** Br J Haematol. 2025 Nov;207(5):2147-2152. doi: 10.1111/bjh.70118. Epub 2025 Aug 27. PMID: 40859815; PMCID: PMC12624190.
- Herreros-Cabello, A.; Callejas-Hernández, F.; Fresno, M.; Gironès, N. **Mitochondrial DNA Structure in *Trypanosoma cruzi* Pathogens.** 2025. 14. DOI: 10.3390/pathogens14010073
- Herreros-Cabello, A.; Callejas-Hernández, F.; Gironès, N.; Fresno, M. ***Trypanosoma cruzi*: Genomic Diversity and Structure .** Pathogens. 2025. 14, DOI: 10.3390/pathogens14010061.
- Cuesta, N.; Staniszewska, A.D.; Moreno, C.; Punzón, C.; Fresno, M. **NF-κB-Inducing Kinase Is Essential for Effective c-Rel Transactivation and Binding to the IL12b Promoter in Macrophages.** Biology. 2025. 14. DOI: 10.3390/biology14010033.
- Santi-Rocca, J.; Martín-García, D.F.; Lorca-Alonso, I.; la González-de la Fuente, S.; Aguado, B.; Bonner, M.; Amard, V.; Amiot, P.; Bar, C.; Berbon, V.; Berkani, N.; Burke, A.; Cartagena, I.; Chatard, J.-M.; Coutayar, C.; Depraz, G.; Morales, I.; Popa, N.; Regniers, S.; Rissoan, T.; Robert, C.; Tremoureux, A.; Verdy, M.; Fresno, M.; Gironès, N. **Microbial Complexes in Subgingival Plaque: A Bacterial Meta-Taxonomic Study.** J. Clin. Periodontol. 2025. 52, 983-998. DOI: 10.1111/jcpe.14138

## Projects

- 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

## Thesis

Manuel Montero Gómez de las Heras. El papel de los linfocitos T en la integridad de la barrera intestinal: implicaciones para la inflamación relacionada con el envejecimiento, la senescencia y la multimorbilidad asociada a la edad. Directores: María Mittelbrum Herrero y Manuel Fresno Escudero. Programa de Doctorado de Biociencias Moleculares. Universidad Autónoma de Madrid.

## 2. 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:

Chagas disease caused by *Trypanosoma cruzi* affects approximately 7 million people in Latin America. Furthermore, blood transfusion and organ transplantation are health problems in countries receiving migrants from endemic areas. Cardiac pathology is the most serious and characteristic manifestation and a future incidence of between 6,000 and 30,000 cases of Chagas cardiomyopathy is estimated in Spain. Chagas disease is a neglected tropical disease for which there is no effective treatment for the chronic phase of the disease or reliable prognostic markers. Our research aims to understand how immunopathology is generated focusing on the immunoregulatory mechanisms mediated by myeloid suppressor cells (MDSCs). MDSCs are immature myeloid cells that expand in tumor processes, trauma, and infections. They are characterized by the expression of inducible nitric oxide synthase (iNOS) and arginase 1 (ARG1) that use the substrate L-arginine for the production of inflammatory mediators such as nitric oxide (NO) with antimicrobial effect, and with proliferative and tissue repairing effects, respectively. In this context, we have observed that infection by the parasite causes the expansion of MDSCs and a drastic reduction in the levels of L-arginine, which inhibits the proliferation of T cells and RNS, including nitric oxide (NO) produced by the iNOS. Supplementation with L-arginine in infected mice produced a decrease in mortality and an improvement in the clinical score of the mice and could be used in combination therapy.

Related to the above, the immune receptor SLAMF1, a regulator of the production of reactive oxygen species (ROS) by NADPH oxidase 2 (NOX2), inhibits the production of ROS in a manner dependent on the parasite strain, so the inhibition of the interaction of SLAMF1 with it could be the basis of a new therapy. To do this we use “Omic” tools such as Genomics, Transcriptomics, Proteomics, and Metabolomics, these studies have led us to identify which pathways are important in the immune response against the parasite, as well as the role of microRNAs as biomarkers and in the regulation of gene expression in the host cell.

Our interest in the translational application of our research leads us to maintain scientific collaborations with Spanish and foreign groups, basic and clinical, to identify new therapeutic targets and new prognostic biomarkers necessary for treating and monitoring patients.

### Publications

- Callejas-Hernández F, Herreros-Cabello A, Poveda C, Maza MC, Mares JF, Santos-Peñaloza DK, Fresno M, Gironès N. **RNA Sequence Analysis in Macrophages Infected With *Trypanosoma cruzi*: Focus on TLR2 and TLR7, Iron Metabolism, and Extracellular Matrix Biosynthesis.** J Infect Dis. 2025 Jul 11;231(6):e1102-e1113. doi: 10.1093/infdis/jiaf074. PMID: 39948431; PMCID: PMC12247843.
- Herreros-Cabello, A.; Callejas-Hernández, F.; Fresno, M.; Gironès, N. **Mitochondrial DNA Structure in *Trypanosoma cruzi* Pathogens.** 2025. 14. DOI: 10.3390/pathogens14010073
- Herreros-Cabello, A.; Callejas-Hernández, F.; Gironès, N.; Fresno, M. ***Trypanosoma cruzi*: Genomic Diversity and Structure .** Pathogens. 2025. 14, DOI: 10.3390/pathogens14010061.

- Santi-Rocca, J.; Martín-García, D.F.; Lorca-Alonso, I.; la González-de la Fuente, S.; Aguado, B.; Bonner, M.; Amard, V.; Amiot, P.; Bar, C.; Berbon, V.; Berkani, N.; Burke, A.; Cartagena, I.; Chatard, J.-M.; Coutayar, C.; Depraz, G.; Morales, I.; Popa, N.; Regniers, S.; Rissoan, T.; Robert, C.; Tremoureaux, A.; Verdy, M.; Fresno, M.; Gironès, N. **Microbial Complexes in Subgingival Plaque: A Bacterial Meta-Taxonomic Study**. J. Clin. Periodontol. 2025. 52, 983-998. DOI: 10.1111/jcpe.14138

## 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.

### 3. Nitric Oxide and bioactive lipids signalling in the immune response

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

- **Prof. Miguel Ángel Iñíguez Peña. Profesor Titular. Departamento de BiologíaMolecular. UAM.**

#### Research summary:

Nitric oxide (NO) and bioactive lipids as nitro-fatty acids (NO<sub>2</sub>-FA) or prostaglandins (PGs), are key mediators in a variety of physiological and pathological processes, with an essential role in inflammation. Recent studies indicate that both mediators can play an important role in the modulation of the immune response. Our research lines are dedicated to the study the role played by NO, NO<sub>2</sub>FA and PGs in inflammation and in the activation and differentiation of T lymphocytes, analysing their involvement in the regulation of gene expression and activation of transcription factors triggered from the T cell receptor.

We are also interested in the analysis of other parameters of activation such as chemotaxis, intercellular adhesion and the organization of adhesion and signalling receptors at the immune synapse. The analysis of the actions exerted by these agents in the activation and function of human T lymphocytes will allow us to determine their role in the modulation of the immune response.

1. Nitric oxide and adaptive immunity 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. By targeting signalling molecules, 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, nitration of fatty acids and nitro-alkylation of proteins by NO<sub>2</sub>-FA, as important post-translational modifications by which NO can act as a signalling molecule during T cell-mediated immunity.

2. Actions of bioactive lipids in inflammatory processes. Fatty acid oxidative modifications result in the production of bioactive lipids, which display a variety of actions in pathophysiological processes. These compounds include PGs and NO<sub>2</sub>-FA, important signalling molecules that can modulate the inflammatory process and the immune response. To this end, we analyse 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 in the immune response, will contribute to the understanding of the potential therapeutic benefits of these compounds.

#### 4. Neurovirología y Terapia Génica Asociadas A Herpesvirus

[JOSE ANTONIO LOPEZ GUERRERO - Universidad Autónoma de Madrid](#)

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

#### Research summary:

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

- Galdo-Torres D, Andreu S, Caballero O, Hernández-Ruiz I, Ripa I, Bello- Morales R, López-Guerrero JA. **Immune Modulatory Effects of Vitamin D on Herpesvirus Infections.** *Int J Mol Sci.* 2025 Feb 19;26(4):1767. doi: 10.3390/ijms26041767. PMID: 40004230; PMCID: PMC11855552.
- Andreu S, Galdo-Torres D, Ripa I, Caballero O, Bello-Morales R, López- Guerrero JA. **From HSV-2 to HSV-1: A change in the epidemiology of genital herpes.** *J Infect.* 2025 Nov;91(5):106636. doi: 10.1016/j.jinf.2025.106636. Epub 2025 Oct 20. PMID: 41115532.
- Andreu S, Tang K, Zhou J, Pino-Peco G, López-Carrobles N, Bello-Morales R, Galdo-Torres D, Zhang L, Gago F, López-Guerrero JA, Liu X, Zhan P, Menéndez- Arias L. **Discovery of a Baloxavir-Inspired Endonuclease Inhibitor That Prevents Herpes Simplex Virus 1 Replication in Cell Culture and In Vivo.** *Adv Sci (Weinh).* 2025 Nov;12(42):e08006. doi: 10.1002/advs.202508006. Epub 2025 Sep 15. PMID: 40948202; PMCID: PMC12622528.
- Ripa I, Andreu S, Galdo D, Caballero O, Bello-Morales R, López-Guerrero JA. **Polyclonal LC3B Antibodies Generate Non-Specific Staining in the Nucleus of Herpes Simplex Virus Type 1-Infected Cells: Caution in the Interpretation of LC3 Staining in the Immunofluorescence Analysis of Viral Infections.** *Int J Mol Sci.* 2025 Jul 11;26(14):6682. doi: 10.3390/ijms26146682. PMID: 40724934; PMCID: PMC12294389.

## Projects

- 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

### 5. Biotechnology of probiotics and intestinal pathogens

[Biotechnology of probiotics and intestinal pathogens - Centro de Biología Molecular Severo Ochoa](#)

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- **Prof. David Ruano Gallego. Investigador Ramón y Cajal. Departamento de Biología Molecular. UAM.**
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The intestine plays a crucial role in our body, not only in absorbing nutrients from the food we eat but also in hosting a complex network of interactions involving intestinal enterocytes (cells lining the intestine), microbiome bacteria (microorganisms living in the gut), and the immune system. Changes in these factors can disrupt the stability of these interactions, allowing harmful bacteria to invade the intestine and cause diseases.

In our research laboratory, we focus on studying how pathogenic bacteria utilize a specialized mechanism called the Type 3 Secretion System to infect the intestine and evade the immune system's defenses. These bacteria employ specific proteins known as effector proteins, which establish a network of interactions critical for their infection process. Our goal is to unravel this network of protein interactions to gain a better understanding of how infections occur and how the immune system responds to different infection strategies. To achieve this, we have created mutant strains of these pathogenic bacteria. We then use these mutants to infect mice and observe the effects they have on the intestine. This allows us to gain insights into the mechanisms behind infection and immunity.

Furthermore, we aim to harness the power of probiotics for biotechnological applications in the field of biomedicine. Using advanced techniques from synthetic biology, we intend to develop methods for manipulating strains of bacteria that were previously not well-understood. These particular bacterial strains have the potential to serve as indicators of good health and offer protection against intestinal diseases. Our research seeks to boost the capabilities of these probiotics as valuable tools for improving human health.

## Projects

- 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.
- DESARROLLO DE UN NUEVO METODO DIAGNOSTICO DEL SOBRECRECIMIENTO BACTERIANO. CPP2024-011348. IP: DAVID RUANO. MINISTERIO.
- TYPE III SECRETION SYSTEM EFFECTOR NETWORKS: ARTIFICIAL INTELLIGENCE APPLIED TO STUDY INTESTINAL BACTERIAL. RYC2021-031342-I (PRTR). IP: David Ruano. MInisterio. 2023-2025.

## Microbes in health and welfare UNIT

### 1. Biotechnology and genetics of extreme thermophiles

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

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- Prof. Mario Mencía Caballero. Profesor Titular. Departamento de Biología Molecular. UAM.
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#### Research summary:

As a way to be able to harness evolution in a biotechnology workhorse, such as *Thermus thermophilus* is, we want to understand the processes that contribute to the genome plasticity of this organism such as, mechanisms of horizontal gene transfer, defense mechanisms against those and genome repair pathways and their mutual interactions. The main defense systems we are currently studying are the Argonaute programmable nuclease, the DNA primase-polymerase Primpol and the AddAB complex (equivalent to RecBCD). The recombinational repair pathways we are studying are RecFOR, RecJ and HerA-NurA. The analysis of these routes also show the strategies utilized by an extreme thermophile to cope with the DNA damage caused by the high temperatures. Following this we are developing a new system for continuous culture, induced diversity generation and selection of improved variants in an iterative automated process. The new systems we are developing will be used for the discovery of thermostable proteins and in the isolation of thermostable variants of enzymes that could better respond to the requirements for industrial biocatalysts or in other applications in the field of Molecular Biology, such as gene edition. And on the same line, we are testing the possibilities of this organism in plastic (polyethylene terephthalate and polystyrene) residue degradation and metabolization, to try to generate a possible solution to the problem of the plastic waste

accumulation in the world.

Also sharing the evolution theme, I am interested in the early evolutionary events that led to the split of Bacteria and Archaea in the first place and the emergence of Eukarya in a second stage. As for the split Bacteria-Archaea I posit a divergence based on the proton gradient and the key and unaltered differences between the archaeal membranes and those of bacteria. Differences eventually translated to mitochondria and eukaryotes. Regarding the emergence of eukaryotes, according to my theory, the pivotal event would be the association of a protophagocytic organism (derived from asgard archaea) with an alpha-proteobacteria that enabled the acidic digestion process to appear and this was to be critical for the emergence of phagocytosis, mitochondria, and eventually the rest of eukaryotic features.

#### Publications

- Blesa, A.; Sánchez-Costa, M.; Berenguer, J. **The PulE ATPase is required for twitching motility and DNA donation during *Thermus thermophilus* transjugation.** *Int. Microbiol.* 2025, 28:1047-1055. DOI: 10.1007/s10123-024-00598-4

#### Projects

- 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.
- 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. IP: MARIO MENCÍA CABALLERO.

## 2. 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:

A major and essential structural component of the cell envelope of most bacteria is the peptidoglycan sacculus, and its synthesis is by far the most antibiotic-targeted process. In Gram-negative bacteria, the thin and net-like peptidoglycan layer is surrounded by an asymmetric and hydrophobic lipid bilayer (the outer membrane), which acts as a permeability barrier against external agents like many clinically used antibiotics. During the bacterial cell cycle both peptidoglycan and membrane biogenesis machineries are coordinated and regulated to ensure the robust growth of the cell envelope and the viability of the cell. Contrary to cell elongation and cell division, the transition between both stages called preseptal growth – synthesis of cell envelope at the division site before septation – remains poorly characterized.

The research in the laboratory focuses on understanding the molecular mechanisms regulating the biogenesis of the bacterial cell envelope of Gram-negative bacteria, using gastrointestinal pathogenic organisms. Using a multidisciplinary approach combining genetics, biochemistry, cell biology and different microscopy techniques we aim to identify and characterize the protein interactions and their impact on the peptidoglycan enzymatic activities, the mechanical and structural properties of the cell envelope, and the impact on virulence.

### Publications

- Hernandez-Rocamora V, Martorana AM, Belloso A, Ballesteros D, Zaccaria M, Perez AJ, Iorga BI, Abia D, Gray J, Breukink E, Xiao J, Pazos M, Polissi A, Vollmer W. **A novel peptidoglycan deacetylase modulates daughter cell separation in E. coli.** bioRxiv [Preprint]. 2025 Feb 19:2025.02.18.638797. doi: 10.1101/2025.02.18.638797. Update in: PLoS Genet. 2025 Sep 5;21(9):e1011626. doi: 10.1371/journal.pgen.1011626. PMID: 40027703; PMCID: PMC11870482.
- Gonzalez-Garcia, M.C.; Ballesteros, D.; Hernandez, J.J.; Pazos, M.; Rodríguez, I.; Requejo-Isidro, J.; Flors, C. **Exploring bacteria–surface interactions with a fluorescent membrane tension probe.** Proc. Nat. Acad. Sci. 2025 122, DOI: . 10.1073/pnas.2512977122

### 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.
- Atracción Talento. 2020-T1/BMD-19970. IP: M. Pazos. Comunidad de Madrid. 2022-2026.

### 3. 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 investigate the molecular biology of ssDNA viruses, with special emphasis in virus members of the Parvoviridae, to understand their evolution patterns, mechanisms underlying pathogenicity, and oncolytic potential against human cancer.

#### Pathogenicity.

In these studies, we combine mice infections with sequence analysis of the parvovirus Minute Virus of Mice (MVM) genetic variants arising at precise stages of the caused diseases. The evolutionary capacity of this virus in response to immune and adaptive pressures is monitored by genome sequencing. This allows at certain cases to localize the selected amino acid changes at defined functional domains of the 3-D capsid structure.

#### Parvovirus MVM life cycle.

The preferent infection capacity of cancer cells (oncolysis) by MVM is being addressed by an in-depth analysis of the virus life cycle steps in human cancer cells, aimed at identifying regulators and precise molecular interactions at each major virus life cycle stage. Hence, we demonstrated that capsid assembly proceeds as trimeric intermediates that translocate through the nuclear envelope at the S phase of the cell cycle, and this nuclear transport competence relies on the phosphorylation at specific sites of the protein subunits mediated by the Raf-1 kinase (MAPK route) commonly deregulated in cancer cells.

One aspect of MVM life-cycle regulation of particular interest for its oncolytic capacity is the dependence of S-phase on the transport of capsid subunits, and thus on the nuclear assembly of the virus. This coupling is relevant for understanding parvovirus pathogenesis and tropism for proliferative cells. Its disturbance may determine viral persistence in host tissues.

#### Anti-cancer applications of the parvovirus MVM.

The anti-cancer therapeutic potential of the MVM was shown by its capacity to infect and eliminate cancer stem cells obtained from glioblastoma patients (the most aggressive brain tumor) implanted in the brain of rodent models. In neurospheres the MVM targets its cytotoxic action exclusively against those cells that have altered both innate responses and the central regulator p53 by mutation or aberrant phosphorylation, in a patient-dependent manner. These results raise hopes for a new personalized and biosafe medicine, based on viruses that selectively infect malignant stem cells, that could be used in therapies against this devastating type of cancer and against others carrying deregulated p53 signaling.

Other ongoing approaches in our lab to enhance MVM oncolysis tackle re-targeting the virus to the neovascularization process required for tumor growth. We are engineering different domains of MVM capsid with heterologous peptides blocking VEGF, to either induce antibodies that may reduce

tumor growth, or to drive the tropism of the virus specifically to VEGF-R expressing vascular cells supporting the tumor vascularization.

### **MVM evolution confers advantageous anti-glioblastoma properties.**

We are attempting to increase MVM tropism for cancer cells through multiple experimental strategies: (i). Under natural evolution in mice, MVM variants arise that contain amino acid changes in a “dimple” at the 2-fold axis of symmetry of the capsid. Some of them modulate the binding affinity for the sialic acid (sia) cell receptor and show improved infectivity of glioblastoma cells. The molecular basis of this enhanced onco-tropism is related to an important effect of the sia-type contacts on the endocytic traffic of the virion. (ii) We have developed several directed evolution strategies in vitro, based on the generation of MVM libraries by mutagenesis (error-prone PCRs or saturation of precise codons) of the cellular receptor binding site and subsequent adaptation to glioblastoma cells through serial passages. The goal is to retarget MVM capsids toward sialoglycans preferentially expressed in glioblastoma cell lines. Some of the recombinant viruses engineered with the selected mutations replicate and propagate better than the wild type virus in the U373 glioblastoma cell line. (iii) Finally, we are fostering genetic recombination between the MVMp and MVMi strains by high multiplicity of co-infection of permissive cells. Oncotropic chimeric viruses emerged spontaneously in these cultures and are subjected to selection in U373 cells. One of the resulting viruses displays chimeric nonstructural proteins and produce more viral genomes in U373 than the two parental strains, suggesting an enhanced oncotropism

### **Publications**

- Calvo-López T, Grueso E, Sánchez-Martínez C, Almendral JM. **Correction: Intracellular virion traffic to the endosome driven by cell type specific sialic acid receptors determines parvovirus tropism.** Front Microbiol. 2025 Jul 2;16:1640264. doi: 10.3389/fmicb.2025.1640264. Erratum for: Front Microbiol. 2023 Jan 23;13:1063706. doi: 10.3389/fmicb.2022.1063706. PMID: 40673143; PMCID: PMC12263578.
- Segovia JC, Ramírez JC, Río P, Lotufo CM, López-Bueno A, Calvo-López T, Lamana ML, Sandoñis V, Balas A, Bautista JM, Abad P, Azcárate IG, Lopez Lorenzo JL, Jalilian FA, Amini R, Kinnunen PM, Jokelainen P, Mohanraj U, Söderlund-Venermo M, Almendral JM. **A presumed mouse parvovirus with overlooked high toxicity for human primitive CD34+ hematopoietic precursors in vitro and in bone marrow-humanized mice.** Microbiol Spectr. 2025 Oct 27;13(12):e0233925. doi: 10.1128/spectrum.02339-25. Epub ahead of print. PMID: 41143413; PMCID: PMC12671093

### **Projects**

- 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.
- Fabricación y bioseguridad preclínica de parvovirus de ratón para la terapia de tumores cerebrales humanos. PDC2025-166224-I00. IP: ALMENDRAL DEL RIO, JOSE MARIA

### **4. Molecular ecology of extreme environments**

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

- **Prof. Ricardo Amils Pibernat. Profesor Emérito. Departamento de Biología Molecular. UAM.**
- **Prof. José Manuel Martínez Lozano. Profesor Ayudante Doctor. Departamento de Biología Molecular. UAM.**

## Research summary

This area of research has the following objectives:

- Acidophiles: conventional microbial ecology, molecular ecology, molecular biology and biotechnology of extreme acidic environments (biomining, specific metal sequestering, biomineralization and phytoremediation). This objective is mainly interested in the exploration of biotechnological applications of acidophiles, most of them related with the recovery of metals from minerals or from contaminated waters.
- Geomicrobiology of the Iberian Pyrite Belt (IPB) subsurface: characterization of the underground bioreactor responsible of the extreme acidic conditions detected in the Río Tinto basin. The development of this objective allowed to identify the microorganisms involved in the biogeochemical cycles (C, N, S, Fe) operating in the subsurface of the IPB. Nitrate reducing microorganisms have been identified as responsible of oxidizing ferrous iron in strict anaerobic conditions, facilitating the chemical attack to the high concentration of metal sulfides existing in the IPB, generating the extreme conditions detected in the Tinto basin.
- Geomicrobiological characterization of extreme environments as habitability models of astrobiological interest: The following ecosystems are studied: Río Tinto, Spain (Mars analogue); Uyuni salt lake, Bolivia (Europa analogue); Tirez hypersaline lagoon, Spain (Europa analogue) and Dallol in the Danakil depression, Ethiopia (Mars analogue). This objective aims to characterize different extreme environments as models for life in different planets and moons of the solar system. This research is interested in knowing the limits of life characterizing analogue ecosystems in our planet as preparation of future space exploration missions.

## Publications

- Sabroso E, Martínez JM, Sánchez-León E, Rodríguez N, Amils R, Abrusci C. **Production and Characterisation of an Exopolysaccharide by *Vreelandella titanicae* Zn11\_249 Isolated from Salar Uyuni (Bolivia)**. *Polymers* (Basel). 2025 Aug 30;17(17):2362. doi: 10.3390/polym17172362. PMID: 40942280; PMCID: PMC12431424.
- Durán-Sequeda DE, Soto-Valera ZE, Pizarro Castañeda R, Torres MJ, Tobias LS, Vergel C, Quintero Line AP, Bolívar-Anillo HJ, Amils R, Iglesias-Navas MA. **Increased Drought Stress Tolerance in Maize Seedlings by *Bacillus paralicheniformis* Halotolerant Endophytes Isolated from *Avicennia* Germinants**. *Plants* (Basel). 2026 Jan 4;15(1):143. doi: 10.3390/plants15010143. PMID: 41515088; PMCID: PMC1278813
- Sabroso E, Abrusci C, Rodríguez N, Amils R, Martínez JM. **Genomic analysis of a novel isolate *Vreelandella Titanicae* sp. Zn11\_249 from the chaotropic environment Salar de Uyuni (Bolivia)**. *BMC Genomics*. 2026 Jan 16;27(1):181. doi: 10.1186/s12864-025-12431-x. PMID: 41540327; PMCID: PMC12892813.
- Hallsworth JE, Udaondo Z, Pedrós-Alió C, Höfer J, Benison KC, Lloyd KG, Cordero RJB, de Campos CI, 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.
- Bottaro M, Abramov S, Amils R, Straub D, Kühnel S, Mollenkopf M, Kleindienst S, Obst M, Kappler M. **Impact of pH and salinity fluctuations on oxidation of Fe(II) by nitrate-reducing microorganisms enriched from the reduced tidal sediment of an extreme acidic river (Río Tinto, Spain)**. *FEMS Microbiol Ecol*. 2025 Sep 22;101(10):fiae083. doi: 10.1093/femsec/fiae083. PMID: 40880130; PMCID: PMC12475565.

- Cai Q, Zhao W, Wang J, Yang G, Amils R, Martínez JM, Mateos G, Carrasco-Ropero I, Wu J, Xu M. **cooperation mechanism between *Bacillus thuringiensis* and *Citrobacter freundii* that enhance cadmium biomineralization.** J Hazard Mater. 2025 May 5;488:137354. doi: 10.1016/j.jhazmat.2025.137354. Epub 2025 Jan 25.
- PMID: 39889604.
- Oggerin M, Del Moral C, Rodriguez N, Fernandez-Gonzalez N, Martínez JM, Lorca I, Amils R. **Metal tolerance of Río Tinto fungi.** Front Fungal Biol. 2024 Oct 16;5:1446674. doi: 10.3389/ffunb.2024.1446674. PMID: 39479218; PMCID: PMC11521807.
- Rivas-Santisteban J, Martínez JM, Escudero C, Hernández-Antolín R, Cid-Barri L, Ellis GJ, Domingo Sánchez C, Sobrino F, Amils R. **Metagenomic analysis of heavy water-adapted bacterial communities.** Microb Genom. 2025 May;11(5):001414. doi: 10.1099/mgen.0.001414. PMID: 40438915; PMCID: PMC12171019.

## Projects

- 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.
- DESCIFRANDO EL METABOLISMO DE LA OXIDACION DE FE(II) ASOCIADA A REDUCCION DE NITRATO (NRFOX) Y SU UTILIZACION PARA LA BIORREMEDIACION DE AGUAS CONTAMINADAS CON NITRATOS. TED2021-129563B-I00. IP: RICARDO AMILS.

## Thesis

Adrián Martínez Bonilla. Oxidación anaerobia de hierro por microorganismos aislados del subsuelo profundo de la Faja Pirítica Ibérica. Directores: Ricardo Amils Pibernat y Cristina Escudero Parada. Programa de Microbiología. Universidad Autónoma de Madrid.

## 5. 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 of biotechnological interest, mainly fungi and yeasts, producers of bioactive compounds. We try to connect the generation of knowledge to the development of biotechnological applications. Basically we focus on the characterization of new enzymes producing bioactive compounds, the analysis of their structural-functional determinants, the operational improvement using molecular biology tools and in obtaining and characterization of new molecules with potential industrial utility. We have patented in different countries the industrial applicability of most proteins characterized and designed methods for their attachment to solid supports.

During the last years we have been characterizing and studying several fungi and non-conventional yeast

proteins (from genera *Xanthophyllomyces*, *Schwanniomyces*, *Rhodotorula*, etc.) showing glycosyltransferase activity, and applicable in the production of sugars with prebiotic properties. All are glycosylhydrolases (GH) structurally included in family GH32, 31, 13 or 18. Indeed, we have resolved the 3-D 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. We have obtained numerous enzymatic variants that increase or alter the biosynthetic product patterns. Recently we have found that some of the characterized enzymes can glycosylate compounds with aromatic rings such as the hydroxytyrosol or pterostilbene (both antioxidants), which confers them a special biotechnological interest. 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 or give new uses to the molecules obtained. Objectives included in those of the consortia [Glicoenz](#), [Fish4Fish](#) and a project founded by the Fundación Ramon Areces (XIX Concurso Nacional-Ciencias de la Vida y la Materia).

### Publications

- Minguet-Lobato M, Fernández-García Á, Jiménez-Ortega E, Cervantes FV, Sánchez-Pozo P, Plou FJ, Sanz-Aparicio J, Fernández-Lobato M. **Structural- mechanistic insights and performance engineering of chitinase MpChit35 for tailored chito-oligosaccharide production.** Int J Biol Macromol. 2025 Sep;322(Pt 1):146538. doi: 10.1016/j.ijbiomac.2025.146538. Epub 2025 Aug 6. PMID: 40763848.
- Martínez-Ranz M, Kidibule PE, Jiménez-Ortega E, Valcárcel J, Vázquez JA, Sanz-Aparicio J, Fernández-Lobato M. **Boosting Biocatalytic Efficiency: Engineering of Chitinase Chit33 with Chitin and Cellulose Binding Domains for Sustainable Chitin Conversion.** J Agric Food Chem. 2025 May 7;73(18):11121-11131. doi: 10.1021/acs.jafc.4c10364. Epub 2025 Apr 25. PMID: 40279401; PMCID: PMC12129251

### Projects

- Producción y modificación funcional de glicoenzimas para la obtención sostenible de glicoderivados por transglicosilacion. PID2022-137487OB-I00 (FEDER, UE). PI: M. Fernández-Lobato. 1.9.2023-31.8.2026.
- Producción y modificación funcional de glicoenzimas para la obtención sostenible de glicoderivados por transglicosilacion. PID2022-136367OB-C32. IP: MARÍA FERNÁNDEZ LOBATO.
- Simplificación del aprovechamiento de desechos enriquecidos en quitina para la producción enzimática de quitoooligosacaridos bioactivos. TED2021-129288B-C22: IP: MARÍA FERNÁNDEZ LOBATO.

### Thesis

Marina Minguet Lobato. Novel Chitinases and Hyaluronidases: Discovery and Application in the Synthesis of Bioactive Oligosaccharides. Directores: Francisco J. Plou Gasca y María Fernández Lobato. Programa de Microbiología. Universidad Autónoma de Madrid.

## 6. Virus engineering and Nanobiotechnology

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

- Prof. Mauricio García Mateu. Catedrático. Departamento de Biología Molecular.UAM.
- Prof. Alejandro Valbuena Jiménez. Profesor Ayudante Doctor. Departamento de Biología Molecular. UAM.

## Research summary:

Major research goals: We use protein engineering techniques and biochemical, biophysical and virological analyses to study assembly, conformational stability and dynamics and physical properties of viruses, and their biological relevance (Mateu (ed.) (2013) *Structure and Physics of Viruses*, Springer 2013; Mateu (2013) *Arch.Biochem.Biophys.* 531,65-79). Based on these studies, we aim also at the design and analysis of genetically and/or structurally modified viral particles for the development of biomedical and bionanotechnological applications (Mateu (2016). In *Protein-based Engineered Nanostructures*, Springer 2016, pp.83-120).

Scientific relevance and technological implications: In-depth knowledge of certain key processes for viral infection, including virus morphogenesis, structural rearrangements and uncoating; application of this knowledge for the design of vaccines, antiviral drugs, biomaterials and modified nanoparticles for biomedical or bionanotechnological uses.

Some recent results: i) The combined use of atomic force microscopy (AFM) and electron microscopy allowed us to experimentally determine for the first time the reversible pathway and intermediates of assembly and disassembly of a structurally simple spherical virus (Fig.1). ii) Using mutational analysis and the determination of mechanical properties of virus particles by AFM we have discovered a relationship between genetic changes that alter the mechanical stiffness of virus particles and changes in the propensity of the latter to undergo conformational changes related to the infection process (Fig.2). iii) we have characterized the structure, dynamics and mechanical properties of a bidimensional nanocoating made by self-assembly of the HIV capsid protein on a solid matrix. These and other studies by our group have implications for a better understanding of processes essential for viral infection, the design of new antivirals that may inhibit these processes, and the development of nanoparticles and bidimensional biomaterials with improved mechanical properties for applications such as targeted drug delivery or tissue regeneration.

## Publications

- Valiente L, Riomoros-Barahona V, Gil-Redondo JC, Castón JR, Valbuena A, Mateu MG. **A RNA Dodecahedral Cage Inside a Human Virus Plays a Dual Biological Role in Virion Assembly and Genome Release Control.** *J Mol Biol.* 2025 Feb 1;437(3):168922. doi: 10.1016/j.jmb.2024.168922. Epub 2024 Dec 24. PMID: 39725271.
- Escrig J, Gil-Redondo JC, Valbuena A, Mateu MG. **Engineering mechanical strength and resistance to fatigue of a nanostructured protein material through genetic removal of electrostatic repulsions.** *Nanoscale.* 2025 Sep 11;17(35):20157-20168. doi: 10.1039/d5nr02490k. PMID: 40828143.
- Gil-Redondo JC, Valiente L, Riomoros-Barahona V, Valbuena A, Mateu MG. **Human Rhinovirus B14 with Non-functional Drug-binding Pockets Recovers Infectivity through Stereochemically Constrained Mutations that Restore Capsid Flexibility.** *J Mol Biol.* 2025 Sep 1;437(17):169260. doi: 10.1016/j.jmb.2025.169260. Epub 2025 May 30. PMID: 40451500.

## 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

## Thesis

Luis Valiente Martínez-Sicluna. Determinantes estructurales de ensamblaje, estabilidad y desencapsidación del rinovirus humano. Directores: Mauricio García-Mateu y Alejandro Valbuena Jiménez. Programa de Doctorado de Biociencias Moleculares. Universidad Autónoma de Madrid.

Judith Escrig Traver. Nuevos estudios sobre el ensamblaje, las propiedades mecánicas y la dinámica de la cápsida del virus de la inmunodeficiencia humana. Directores: Mauricio García-Mateu y Alejandro Valbuena Jiménez. Programa de Doctorado de Biociencias Moleculares. Universidad Autónoma de Madrid.

### 7. RNA-based control of *Listeria* adaptation to stress and virulence

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

- Prof. Graciela Pucciarelli. Profesora Titular. Departamento de Biología Molecular.UAM. (retired december 2025).

## 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.

## Thesis

Marcos Peñalver Medina. Estudio evolutivo de la pared celular en bacterias con diferentes estilos de vida. Directores: María Graciela Pucciarelli Morrone y Francisco García del Portillo. Programa de Doctorado de Biociencias Moleculares. Universidad Autónoma de Madrid.

## 8. 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 protein 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, enabling especially academic labs to undertake screening campaigns until now costly and limited to large enterprises.

In our laboratory, we make use of both biological selections or ultrahigh-throughput screening based on droplet microfluidics to find rare genes and enzymes of interest in the natural or man-made diversity. Biological selections couple the improved fitness of a protein to the survival of a biological host under selective pressure. Using these and other methods for protein engineering, we have developed “thermostable” and soluble variants of enzymes for biocatalysis, such as esterases, dehalogenases and aldolases and fluorescent proteins.

However, the complexity of cellular metabolism limits the application of biological selections. Microfluidics enables the miniaturization of assays with throughput of kHz and a 1000x reduction in volume and costs. Therefore, droplet microfluidics achieves throughputs typical of biological selections with none of their complexity. Within the H2020 project MetaFluidics, in our laboratory, we have implemented a fluorescence-based microfluidic sorting platform and assays to find stable hydrolases in thermal environments as well as other relevant enzymes for biocatalysis. This has entailed developing new hosts and methods for functional expression, compatible with enzymatic assays at high temperatures.

### Publications

- Blas-Muñoz L, Orrego AH, Hofmeister M, Martínez-Salvador J, Ortega C, Rondón Berrio V, Díaz-Rullo J, Finnigan J, Charnock S, Fessner WD, González-Pastor JE, Hidalgo A. **A Microfluidics-Based Ultrahigh-Throughput Screening Unveils Diverse Ketoreductases Relevant to Pharmaceutical Synthesis.** *Anal Chem.* 2025 Sep 30;97(38):20698-20706. doi: 10.1021/acs.analchem.5c01029. Epub 2025 Sep 16. PMID: 40957694; PMCID: PMC12489886.
- Lorente-Arévalo Á, Gimeno-Pérez M, Ortega C, Finnigan J, Charnock S, Hidalgo A. **Ultrahigh-throughput screening assay for PET-degrading enzymes.** *Methods Enzymol.* 2025;714:489-503. doi: 10.1016/bs.mie.2025.01.021. Epub 2025 Jan 31. PMID: 40288854.

### 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.
- Sustainable exploration and biodiscovery of novel products and processes from extreme aquatic microbiomes to expedite the circular bioeconomy. 101182278 (XTREAM). IP: AURELIO HIDALGO. PROYECTO EUROPEO.
- ULTRAHIGH-THROUGHPUT EXPLORATION OF METAGENOMIC SEQUENCE SPACE TO DISCOVER AND ENGINEER NOVEL BIOCATALYSTS AND BIOACTIVE COMPOUNDS. HORIZON-MSCA-2024-DN-01-MetaExplore (101226425). IP: AURELIO HIDALGO. PROYECTO EUROPEO.

## PROJECTS ONGOING in 2025

Referencia Proyecto	Responsable Proyecto	TÍTULO	Organismo financiador
PDC2025-166224-IOO	ALMENDRAL DEL RIO, JOSE MARIA	Fabricación y bioseguridad preclínica de parvovirus de ratón para la terapia de tumores cerebrales humanos	MINISTERIO
PID2022-141799OB-IOO	ALMENDRAL DEL RIO, JOSE MARIA	Reorientación de la Infección de Parvovirus hacia Procesos Celulares Determinantes del Cáncer Humano	MINISTERIO
PID2022-136607NB-IOO	AMILS PIBERNAT, RICARDO	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	MINISTERIO
TED2021-129563B-IOO	AMILS PIBERNAT, RICARDO	DESCIFRANDO EL METABOLISMO DE LA OXIDACION DE FE(II) ASOCIADA A REDUCCION DE NITRATO (NRFE0X) Y SU UTILIZACION PARA LA BIORREMEDIACION DE AGUAS CONTAMINADAS CON NITRATOS	MINISTERIO
948478 MitoCure ERC-2020-STG	BALSA MARTINEZ, EDUARDO	MOLECULAR AND METABOLIC MECHANISMS UNDERLYING MITOCHONDRIAL DYSFUNCTION	EUROPEO
CNS2024-154370	BALSA MARTINEZ, EDUARDO	Explorando las Interacciones metabólicas entre neuronas y astrocitos en la neurodegeneración Inducida por disfunción	MINISTERIO
LABAE259022BALS	BALSA MARTINEZ, EDUARDO	Descubriendo el impacto de las alteraciones metabólicas inducidas por el envejecimiento en la microglía que	AECC
PID2022-137404OB-IOO	BALSA MARTINEZ, EDUARDO	Descifrando el metabolismo mitocondrial como diana para la progresión tumoral y la metástasis	MINISTERIO
PR_EX_2022_01	BALSA MARTINEZ, EDUARDO	METABOLIC HETEROGENEITY AS A CRITICAL DETERMINAT OF MELANOMA METASTASIS PROJECT	FUND. CRIS
PID2020-113921RB-IOO	BULLIDO GOMEZ-HERAS, MARIA JESUS	HOMEOSTASIS DE COLESTEROL Y VÍA LISOSOMAL EN LA NEURODEGENERACIÓN INDUCIDA POR HSV-1 Y EN LA ENFERMEDAD DE ALZHEIMER: MECANISMOS PATOGENICOS Y BIOMARCADORES	MINISTERIO
PID2024-155549OB-IOO	BULLIDO GOMEZ-HERAS, MARIA JESUS	PAPEL DE LA NEUROINFLAMACIÓN Y LA HOMEOSTASIS DE COLESTEROL EN LA NEURODEGENERACIÓN INDUCIDA POR HSV-1 EN MODELOS HUMANOS NEURALES AVANZADOS EN 3D	MINISTERIO
SI4/PJI/2024-00166	CARRASCO CERRO, ELISA	Reprogramación epigenética como estrategia para revertir el deterioro de la función cutánea en ratones con deficiencia mitocondrial específica de células T	CM
CNS2023-143646	COGLIATI, SARA	Descubrimiento de las vías mitocondriales relacionadas con la protección cardíaca del estradiol como tratamiento potencial	MINISTERIO
PID2020-114054RA-IOO	COGLIATI, SARA	Dimorfismo sexual en el metabolismo de la glucosa: caracterización del papel mitocondrial.	MINISTERIO
PID2023-148516OB-IOO	COGLIATI, SARA	Estradiol y oxidación de ácidos grasos: entender su relación para proteger el corazón de la mujer posmenopáusia	MINISTERIO
PID2021-123269OB-IOO	CUBELOS ALVAREZ, BEATRIZ	Papel de R-Ras1 y R-Ras2 en la diferenciación y especificación oligodendrocitaria	MINISTERIO
PID2024-160510OB-IOO	CUBELOS ALVAREZ, BEATRIZ	La interacción entre R-Ras e integrina regula la diferenciación oligodendrocitaria	MINISTERIO
PID2022-143030OB-IOO	DIAZ NIDO, JAVIER	Neurodegeneración en el cerebelo de modelos de ataxia de Friedreich: Bases moleculares y aproximaciones terapéuticas	MINISTERIO
PDC2022-133134-C22	FERNANDEZ LOBATO, MARIA	permiten la progresión de las metástasis cerebrales	MINISTERIO

PID2022-136367OB-C32	FERNANDEZ LOBATO, MARIA	Producción y modificación funcional de glicoenzimas para la obtención sostenible de glicoderivados por transglicosilación	MINISTERIO
TED2021-129288B-C22	FERNANDEZ LOBATO, MARIA	Simplificación del aprovechamiento de desechos enriquecidos en quitina para la producción enzimática de quitooligosacaridos bioactivos	MINISTERIO
101167421-UNION-HORIZON-MSCA-2023-DN-01	FORMENTINI, LAURA	MICROBIOMINNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE MICROBIOMES:TOWARDS A CIRCULAR BLUE BIOECONOMY AND HEALTHIER MARINE ENVIRONMENTS	EUROPEO
PID2022-136738OB-100	FORMENTINI, LAURA	Disfunción de la actividad	MINISTERIO
PID2022-137487OB-100	FRESNO ESCUDERO, MANUEL	Papel de TCFL5 en procesos de diferenciación, inmunosenescencia, inflamación y trastornos asociados al envejecimiento	MINISTERIO
ION-ARPA	GARCIA ESCUDERO, VEGA	3' REPLACEMENT OF TAU MRNAS IN ALZHEIMERs DISEASE BY A REPLICATIVE TRANS-SPLICING RIBOZYME-ION-ARPA	IONIS
PID2021-126973OB-100	GARCIA MATEU, MAURICIO	Biomecánica y dinámica de virus humanos para el desarrollo de fármacos antivirales y materiales modificados por ingeniería de proteínas	MINISTERIO
PID2021-123389OB-100	GIRONES PUJOL, NURIA	Papel del ligando del receptor SLAMF1 de Trypanosoma cruzi y de microRNAs durante la infección: aplicaciones en diagnóstico y terapia	MINISTERIO
PID2020-113204GB-100	HERNANDEZ PEREZ, FELIX	Neurorregeneración en la enfermedad de Alzheimer a través de la expresión de factores de pluripotencia in vivo	MINISTERIO
PID2023-149460NB-100	HERNANDEZ PEREZ, FELIX	Activación de transposones en modelos animales de la enfermedad de Alzheimer: implicación de la proteína tau	MINISTERIO
101000560-RADICALZ-H2020-FNR-2020/H2020-FNR-2020-2	HIDALGO HUERTAS, AURELIO	RAPID DISCOVERY AND DEVELOPMENT OF ENZYMES FOR NOVEL AND GREENER CONSUMER PRODUCTS	EUROPEO
101081957-BLUETOOLS-HORIZON-CL6-2022-CIRCBIO-01	HIDALGO HUERTAS, AURELIO	INNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE	EUROPEO
101182278 (XTREAM)	HIDALGO HUERTAS, AURELIO	Sustainable exploration and biodiscovery of novel products and processes from extreme aquatic microbiomes to expedite the circular bioeconomy	EUROPEO
956631 — CC-TOP — H2020-MSCA-ITN-2020	HIDALGO HUERTAS, AURELIO	C-C BOND FORMATION USING TOP PERFORMING ENZYMES	EUROPEO
HORIZON-MSCA-2024-DN-01- MetaExplore (101226425)	HIDALGO HUERTAS, AURELIO	ULTRAHIGH-THROUGHPUT EXPLORATION OF METAGENOMIC SEQUENCE SPACE TO DISCOVER AND ENGINEER NOVEL BIOCATALYSTS AND BIOACTIVE COMPOUNDS	EUROPEO
PID2020-119399RB-100	LOPEZ CORCUERA, BEATRIZ	EL TRANSPORTADOR NEURONAL DE GLICINA GlyT2 EN DOLOR Y EN HIPERPLEXIA. IMPLICACIONES PATOLÓGICAS EN DESARROLLO	MINISTERIO
PID2023-150608OB-100	LOPEZ CORCUERA, BEATRIZ	PATOLOGÍAS DEL TRANSPORTADOR NEURONAL DE GLICINA GlyT2: HIPERPLEXIA Y DOLOR. IMPLICACIONES EN DESARROLLO	MINISTERIO
PID2022-140632NB-100	LOPEZ GUERRERO, JOSE ANTONIO	Diseminación del virus herpes simplex tipo 1 en oligodendrocitos humanos: papel de la autofagia y del proteolípido MAL	MINISTERIO
PID2020-117218RB-100	MAYOR MENENDEZ, FEDERICO	Redes de señalización de GRK2 y mecanismos moleculares de procesos patológicos	MINISTERIO
PID2023-146735OB-100	MAYOR MENENDEZ, FEDERICO	Interactomas del nodo GRK2 en señalización celular e implicaciones patológicas	MINISTERIO

S2022/BMD-7209	MAYOR MENENDEZ, FEDERICO	INTEGRAMUNE-CM: COMITÉ DE GESTION DE PROGRAMA: SISTEMAS CELULARES Y MOLECULARES INTEGRADOS EN FISIOPATOLOGIA INMUNE-INFLAMATORIA	CM
PID2022-137468OB-I00	MENCIA CABALLERO, MARIO	Desarrollo de un sistema biológico y de hardware para la evolución continua de proteínas en <i>Thermus thermophilus</i> para aplicaciones biotecnológicas	MINISTERIO
TED2021-130430B-C22	MENCIA CABALLERO, MARIO	Nueva aproximación para la bioconversión sostenible de residuos plásticos en productos de alto valor añadido basada en microorganismos termófilos y síntesis enzimática	MINISTERIO
PDC2022-133147-I00	MIGUEZ GOMEZ, DAVID	OSCAR, an Object Segmentation, Counter, Analysis Resource	MINISTERIO
PID2022-140421NB-I00	MIGUEZ GOMEZ, DAVID	Interacción entre mecanismos físicos y moleculares en la regulación de la formación de la retina de vertebrados	MINISTERIO
SI4/PJI/2024-00219	NOGUES VERA, LAURA	Targeting Metabolic Invasive Phenotype to Overcome immunotherapy Resistance of metastatic melanoma. MetaPhOR	CM
PID2020-114499RB-I00	PARDO MERINO, BEATRIZ	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	MINISTERIO
PID2023-146837OB-I00	PARDO MERINO, BEATRIZ	Funciones de AGC1/Aralar en neuronas y OPCs en proliferación; mielinización, estado redox citosólico y niveles de aspartato	MINISTERIO
2020-T1/BMD-19970	PAZOS DON PEDRO, MANUEL	Atracción del Talento	CM
PID2022-1408180A-I00	PAZOS DON PEDRO, MANUEL	Bases moleculares de la inhibición de la división celular mediada por proteínas SPOR	MINISTERIO
Project 101160079 — BRIDGING-RD	PEREZ GONZALEZ, BELEN	Bridging the research and innovation gap for rare diseases in Europe by upgrading excellence of IMGGE	EUROPEO
101047177 — OpenMIND	PEREZ PEREIRA, MARTA	OPTO-ELECTRONIC NEURAL CONNECTOID MODEL IMPLEMENTED FOR NEURODEGENERATIVE DISEASE	EUROPEO
PID2020-118189RB-I00	PEREZ PEREIRA, MARTA	Cerebroides: desarrollo y complejidad	MINISTERIO
Project: 101169352- NeuroNanotech-MSCA-2023-DN-01	PEREZ PEREIRA, MARTA	NANOPLATFORMS FOR NEUROSCIENCE	EUROPEO
PID2023-146945NB-I00	PORLAN ALONSO, EVA	Dianas farmacológicas en las decisiones del destino de las células madre neurales: implicaciones para la regeneración	MINISTERIO
PID2022-1375520A-I00	REGLERO REAL, NATALIA	Desenmascarando nuevos papeles de los procesos de autofagia endotelial en la inflamación	MINISTERIO
RYC2021-031221-I	REGLERO REAL, NATALIA	RAMON Y CAJAL 2021	MINISTERIO
PID2020-117916RB-I00	REQUENA ROLANIA, JOSE MARIA	Integración de datos omicos para descifrar la organización y expresión génicas en <i>Leishmania</i> : pistas para enfrentar las leishmaniasis	MINISTERIO
PID2024-159768OB-I00	REQUENA ROLANIA, JOSE MARIA	Integración de datos ómicos en conjuntos de datos de acceso abierto y desarrollo de herramientas bioinformáticas como ayuda para el control de la leishmaniasis	MINISTERIO
CPP2024-011348	RUANO GALLEGO, DAVID	DESARROLLO DE UN NUEVO METODO DIAGNOSTICO DEL SOBRECRECIMIENTO BACTERIANO	MINISTERIO
PID2022-1387820A-I00	RUANO GALLEGO, DAVID	Descifrando las redes de efectores del Sistema de Secreción Tipo 3	MINISTERIO
RYC2021-031342-I	RUANO GALLEGO, DAVID	RAMON Y CAJAL 2021	MINISTERIO
EFFECT GA 101	RUIZ DESVIAT, LOURDES	A European Training Programme to Foster the Full Therapeutic Potential of	EUROPEO

PID2022-1372380B-I00	RUIZ DESVIAT, LOURDES	Enfermedades neurometabólicas raras: de la investigación en nuevos modelos de enfermedad a terapias	MINISTERIO
CONVENIO FJD	SANTOS HERNANDEZ, JAVIER	ANÁLISIS GENÓMICOS Y TRANSCRIPTÓMICOS EN EL TRATAMIENTO PERSONALIZADO DE NEOPLASIAS LINFOBLÁSTICAS DE CELULAS T	IIS-FJD
CSN-UAM	SANTOS HERNANDEZ, JAVIER	CONSEJO SEGURIDAD NUCLEAR	CSN
PID2023-152460NA-I00	SANTOS LOPEZ, ALFONSO	EVOLUCION DE MICROBIO Y DE ELEMENTOS GENETICOS MOVILES	MINISTERIO
RYC2022-037765-I	SANTOS LOPEZ, ALFONSO	RAMON Y CAJAL 2022	MINISTERIO
CNS2024-154366	TRABA DOMINGUEZ, JAVIER	SLC25A51: EL TRANSPORTADOR MITOCONDRIAL DE NICOTINAMIDA ADENINA DINUCLEOTIDO (NAD+) COMO NUEVO REGULAD	MINISTERIO
PID2022-1368100B-I00	TRABA DOMINGUEZ, JAVIER	Regulación de la inmunidad innata y adaptativa por los niveles mitocondriales de nicotinamida	MINISTERIO
RYC2018-026050-I (FSE)	TRABA DOMINGUEZ, JAVIER	RAMON Y CAJAL 2018	MINISTERIO
PID2021-1258440B-I00	VENTOSO BANDE, IVAN	Reprogramación traduccional inducida por estrés en eucariotas y su influencia sobre la proteostasis celular. Mecanismos e impacto sobre	MINISTERIO
SI4/PJI/2024-00172	VIDA RUEDA, MARIA DEL CARMEN	Impact of Nutritional Stress on Sepsis Aggravation: Therapeutic Potential of Biomimetic Nanoparticles	CM
PID2024-1601140B-I00	VILLA MORALES, MARIA CONSUELO	¿Cómo mejorar el resultado clínico de los pacientes de T-ALL/LBL? Propuesta de terapias dirigidas contra la hiperactivación de la señalización de STAT5.	MINISTERIO
PID2023-1495140B-I00	YAÑEZ MO, MARIA	Vesículas extracelulares e inmunoterapia frente al cancer	MINISTERIO

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<b>PROGRAMA DE DOCTORADO DE BIOCENCIAS MOLECULARES</b>					
<b>Primer apellido</b>	<b>Segundo apellido</b>	<b>Nombre</b>	<b>Título de la tesis Castellano</b>	<b>Nombre Director 1</b>	<b>Nombre Director 2</b>
Soriano	Sexto	Alejandro	La molécula de RNA en diagnóstico y terapia de precisión	Perez Gonzalez, Maria Belen	
González	Moreno	Luis	Regulación de la función mitocondrial por calcio en células proliferativas: papeles de los transportadores mitocondriales regulados por calcio	Pardo Merino, Beatriz	del Arco Martínez, Araceli
Valiente	Martínez-Sicluna	Luis	Determinantes estructurales de ensamblaje, estabilidad y desencapsidación del rinovirus humano	Garcia Mateu, Mauricio	Valbuena Jimenez, Alejandro
Escrig	Traver	Judith	Nuevos estudios sobre el ensamblaje, las propiedades mecánicas y la dinámica de la cápsida del virus de la inmunodeficiencia humana	Garcia Mateu, Mauricio	Valbuena Jimenez, Alejandro
Montero	Gómez de las Heras	Manuel	El papel de los linfocitos T en la integridad de la barrera intestinal: implicaciones para la inflamación relacionada con el envejecimiento, la senescencia y la multimorbilidad asociada a la edad	Mittelbrum Herrero, Maria	Fresno Escudero, Manuel
Pérez	Dones	Diego	Object Statistical Clustering of Adjacent Regions: A 3D tool to localize cell types in crowded environments.	Miguez Gomez, David	
Ruiz	García	Sara	El papel del ARN largo no codificante MALAT1 en las neoplasias de células T precursoras	Santos Hernandez, Fco. Javier	Lopez Nieva, Maria Pilar
Peñalver	Medina	Marcos	Estudio evolutivo de la pared celular en bacterias con diferentes estilos de vida	Pucciarelli Morrone, Maria Graciela	García del Portillo, Francisco
<b>PROGRAMA DE DOCTORADO DE MICROBIOLOGÍA</b>					
<b>Primer apellido</b>	<b>Segundo apellido</b>	<b>Nombre</b>	<b>Título de la tesis Castellano</b>	<b>Nombre Director 1</b>	<b>Nombre Director 2</b>
Martínez	Bonilla	Adrián	Oxidación anaerobia de hierro por microorganismos aislados del subsuelo profundo de la Faja Pirítica Ibérica	Amils Pibernat, Ricardo	Escudero Parada, Cristina
Minguet	Lobato	Marina	Novel Chitinases and Hyaluronidases: Discovery and Application in the Synthesis of Bioactive Oligosaccharides	Plou Gasca, Francisco José	Fernandez Lobato, Maria

## PUBLICATIONS 2025

Authors	Title	Year	Publication	Volume	Page start	Page end	DOI
Akdeniz BC y cols (Bullido, M.J).	Polygenic Hazard Score for Predicting Age-associated Risk of Alzheimer's Disease in European Populations: Development and Validation.	2025	medRxiv [Preprint]				10.1101/2025.07.28.25332293
Alcover-Sanchez, B.; Garcia-Martin, G.; Paleo-García, V.; Quintas, A.; Dopazo, A.; Gruart, A.; Delgado García, J.M.; de la Villa, P.; Wandosell, F.; Pereira, M.P.; Cubelos, B.	R-Ras1 and R-Ras2 regulate mature oligodendrocyte subpopulations	2025	GLIA	73	701	719	10.1002/glia.24643
Andreu S, Tang K, Zhou J, Pino-Peco G, López-Carroles N, Bello-Morales R, Galdo-Torres D, Zhang L, Gago F, López-Guerrero JA, Liu X, Zhan P, Menéndez- Arias L.	Discovery of a Baloxavir-Inspired Endonuclease Inhibitor That Prevents Herpes Simplex Virus 1 Replication in Cell Culture and In Vivo.	2025	Adv Sci (Weinh)	12	e08006		10.1002/advs.202508006
Andreu, S.; Galdo-Torres, D.; Ripa, I.; Caballero, O.; Bello-Morales, R.; López-Guerrero, J.A.	From HSV-2 to HSV-1: A change in the epidemiology of genital herpes	2025	<u>J. Infect.</u>	91			10.1016/j.jinf.2025.106636
Anton-Fernandez A, Domene-Serrano I, Cuadros R, Peinado-Cahuchola R, Sanchez-Peche M, Hernandez F, Avila J.	Peptide Family Promotes Brain Cell Rejuvenation and Improved Cognition through Peripheral Delivery.	2025	ACS Omega	10	13236	13250	
Anton-Fernandez, A.; Cauchola, R.P.; Hernández, F.; Avila, J.	Hippocampal rejuvenation by a single intracerebral injection of one-carbon metabolites in C57BL6 old wild-type mice	2025	Aging Cell	24			10.1111/accel.14365
Anton-Fernandez, A.; Domene-Serrano, I.; Cuadros, R.; Peinado-Cahuchola, R.; Sanchez-Peche, M.; Hernández, F.; Avila, J.	Peptide Family Promotes Brain Cell Rejuvenation and Improved Cognition through Peripheral Delivery	2025	ACS Omega	10	13236	13250	10.1021/acsomega.4c10849
Anton-Fernandez, A.; Ruiz de Alegría, Á.; Mariscal-Casero, A.; Roldán-Lázaro, M.; Peinado-Cauchola, R.; Avila, J.; Hernández, F.	Partial reprogramming by cyclical overexpression of Yamanaka factors improves pathological phenotypes of tauopathy mouse model of human Alzheimer's disease	2025	Progress in Neurobiology	247			10.1016/j.pneurobio.2025.102743
Asensio, A.; Sanz-Flores, M.; Liakath-Ali, K.; Romo-Gallo, A.; Palacios-García, J.; Paramio, J.M.; Garcia-Escudero, R.; Mayor, F.; Ribas, C.	The G-Protein-Coupled Receptor Kinase 2 Orchestrates Hair Follicle Homeostasis	2025	J. Invest. Dermatol.				10.1016/j.jid.2025.08.040
Avila, J.; Hernández, F.; PERRY, G.	Amyloid and tau pathologies cross-talk to promote Alzheimer's disease: novel mechanistic insights	2025	Neuroscience	582	58	62	10.1016/j.neuroscience.2025.07.025

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Berlanga, J.J.; Matamoros, T.; Pulido, M.R.; Sáiz, M.; Bayón, M.N.; Toribio, R.; Ventoso, I.	The differential effect of SARS-CoV-2 NSP1 on mRNA translation and stability reveals new insights linking ribosome recruitment, codon usage, and virus evolution	2025	Nucleic Acids Res.	53			10.1093/nar/gkaf261
Blas-Muñoz L, Orrego AH, Hofmeister M, Martínez-Salvador J, Ortega C, Rondón Berrio V, Díaz-Rullo J, Finnigan J, Charnock S, Fessner WD, González-Pastor JE, Hidalgo A.	A Microfluidics-Based Ultrahigh -Throughput Screening Unveils Diverse Ketoreductases Relevant to Pharmaceutical Synthesis.	2025	Anal Chem	97	20698	20706	10.1021/acs.analchem.5c01029
Blesa, A.; Sánchez-Costa, M.; Berenguer, J.	The PulE ATPase is required for twitching motility and DNA donation during <i>Thermus thermophilus</i> transjugation	2025	Int. Microbiol.	28	1047	1055	10.1007/s10123-024-00598-4
Bottaro, M.; Abramov, S.; Amils, R.; Straub, D.; Kühnel, S.; Mollenkopf, M.; Kleindienst, S.; Obst, M.; Kappler, A.	Impact of pH and salinity fluctuations on oxidation of Fe(II) by nitrate-reducing microorganisms enriched from the reduced tidal sediment of an extreme acidic river (Río Tinto, Spain)	2025	FEBS Microbiol Ecology	101			10.1093/femsec/fiaf083
Bracher-Smith, M y cols (Bullido, M.J).	Machine learning in Alzheimer's disease genetics	2025	Nat. Commun.	16			10.1038/s41467-025-61650-z
Cai, Q.; Zhao, W.; Wang, J.; Yang, G.; Amils, R.; Martínez, J.M.; Mateos, G.; Carrasco-Ropero, I.; Wu, J.; Xu, M.	A cooperation mechanism between <i>Bacillus thuringiensis</i> and <i>Citrobacter freundii</i> that enhances cadmium biomineralization	2025	Journal of Hazardous Materials	488			10.1016/j.jhazmat.2025.137354
Callejas-Hernández, F.; Herreros-Cabello, A.; Poveda, C.; Maza, M.C.; Mares, J.F.; Santos-Peñaloza, D.K.; Fresno, M.; Gironès, N.	RNA Sequence Analysis in Macrophages Infected With <i>Trypanosoma cruzi</i> : Focus on TLR2 and TLR7, Iron Metabolism, and Extracellular Matrix Biosynthesis	2025	J. Infect. Dis	231	e1102	e1113	10.1093/infdis/jiaf074
Calvo-López, T.; Grueso, E.; Sánchez-Martínez, C.; Almendral, J.M.	Correction: Intracellular virion traffic to the endosome driven by cell type specific sialic acid receptors determines parvovirus tropism (Frontiers in Microbiology, (2023), 13, (1063706), 10.3389/fmicb.2022.1063706)	2025	Frontiers in Microbiol.	16			10.3389/fmicb.2025.1640264
Cámara-Checa, A.y cols (Richard, E)	Propionic Acidemia-Induced Proarrhythmic Electrophysiological Alterations in Human iPSC-Derived Cardiomyocytes	2025	J. Inherited Metabolic Dis.	48			10.1002/jimd.70030

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Díaz-Rullo, J.; González-Moreno, L.; del Arco Martínez, A.; González-Pastor, J.E.	Decoding the general role of tRNA queuosine modification in eukaryotes	2025	Sci. Rep.	15			10.1038/s41598-024-83451-y
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García-Tenorio, E.M.; Álvarez, M.; Gallego- Bonhomme, M.; Desviat, L.R.; Richard, E.	Novel CRISPR-Cas9 iPSC knockouts for PCCA and PCCB genes: advancing propionic acidemia research	2025	Human Cell	38			10.1007/s13577-025- 01193-z
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