UAM | IUBM Instituto Universitario Biología Molecular

INSTITUTO UNIVERSITARIO DE BIOLOGÍA MOLECULAR (IUBM)
UAM

INSTITUTE FOR MOLECULAR BIOLOGY-UAM

ANNUAL REPORT 2024

UAM Universidad Autónoma de Madrid

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Foreword by Federico Mayor Jr, director of IUBM-UAM

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

In 2024, the scientific staff of the IUBM-UAM comprised **72 permanent members,** including full professors ("catedráticos/as"), associated professors ("profesores/as titulares"), assistant professors ("profesores/as contratados doctor, profesores permanentes laborales and ayudantes doctor") and "Ramón y Cajal" and Talento junior researchers, who carry out their teaching in different UAM Departments (Molecular Biology, Biology, Neuroscience, Applied Physical Chemistry and Physics of Condensed Matter), plus one ascribed professor from Universidad Castilla-La Mancha. The IUBM-UAM members are distributed according to their research interests among the main Scientific Programs in which the CBM is structured: Genome Dynamics and Function (including Genome decoding and Genome maintenance and instability Research Units), Tissue and Organ Homeostasis (including Cell architecture and organogenesis and Cell-cell communication and inflammation Units), Physiological and Pathological Processes (including Molecular Neuropathology and Metabolic and signaling networks in disease Units) and Interactions with the environment (including Immune system development and function and Microbes in health and welfare Units). **52 staff members** of the IUBM-UAM **are principal or co-principal investigators** in research projects ongoing at the CBM. In addition, **9 postdoctoral fellows and circa 30 PhD students** were ascribed to the IUBM-UAM during 2024 as non-permanent members.

During 2024, the scientific personnel of the IUBM-UAM published **113 research articles** and directed **64 ongoing research projects**, funded by different national, European and international institutions. The research interests, publications, and funded projects of IUBM PIs are detailed in this Annual Report. It is also worth noting that, in addition to their active involvement in research, the IUBM-UAM members intensively participate in undergraduate and graduate teaching, and also in PhD programs related to their fields of investigation. In 2024, **12 doctoral theses** directed by members of the IUBM-UAM were presented and many more are ongoing.

On the 12th of December 2024 we held the third meeting of our External Scientific Advisory Board (ESAB), who made very helpful suggestions and reassuring comments regarding the activities of the IUBM. To encourage young investigators, the IUBM continued supporting in 2024 an Award to the best doctoral thesis presented at the CBM during this period, as well as awards for the best Oral Communication and the best Poster presented at the XI Workshop of Students & Posdocs organized by these students at the CBM. The IUBM also keeps organizing the outreach activity "Conoce el CBM" ("Get to know the CBM"), with the participation of circa 70 students of the second year of the Biochemistry grade, who can visit our facilities and learn about the research ongoing at the laboratories of IUBM investigators.

The CBM continues to develop the Severo Ochoa Centre of Excellence award 2023-2027 plan of activities, including the calls for recruitment of postdoctoral fellows, the implementation of PhD Advisory Commitee and CBMent Programs. CBM is organizing a major scientific event in September 2025 to commemorate its 50th anniversary. This will be a great opportunity for the CBM and the IUBM-UAM to consolidate its leadership in the biomedicine and molecular biology field.

Delivery of the **PINP AWARD TO THE BEST DOCTORAL THESIS** presented at the CBM during the year 2024. **Dr. Elena Moreno** and Prof. Beatriz López-Corcuera, Vice-Director of the CBM. December, 2024.

Delivery of the Best Oral Communication Award (**Javier Isoler), XI WORKSHOP STUDENTS & POSDOCS CBM.** Photo also includes Prof. María Yáñez-Mo, Secretary of IUBM-UAM, Prof. Beatriz López-Corcuera, Vice-Director CBM. November 2024.

Delivery of the Best Poster Award **(José García-Consuegra) XI WORKSHOP STUDENTS & POSDOCS CBM.** Photo also includes Prof. María Yáñez-Mo, Secretary of IUBM-UAM, Prof. Beatriz López-Corcuera, Vice-Director CBM and members of the Organizing Committee. November 2024.

CONOCE el CBMSO

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

Fecha: miércoles 14 de Febrero de 2024

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)
- Catalina Ribas (lab 304)
- Natalia Reglero (lab 304)
- Petronila Penela (lab 320)
- Marta Pereira/Beatriz Cubelos (lab 305)
- Aurelio Hidalgo (lab 108)
- David Ruano (lab 104) 11:30 h

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

IUBM-UAM Organization

Director

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

Scientific Secretary

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

External Scientific Advisory Board

- Prof. Antonio Zorzano Olarte. ***Universidad de Barcelona***
- Prof. Isabel Fariñas Gómez. ***Universidad de Valencia (until november 2024)***
- ***Prof. Isabel Fabregat Romero. IDIBELL. Barcelona. (fron december 2024)***
- Prof. Mª Ángela Nieto Toledano. ***Instituto de Neurociencias, Universidad Miguel Hernández (UMH)-CSIC***
- Prof. José Mª Valpuesta Moralejo. ***Centro Nacional de Biotecnología CSIC.***
- Prof. María Molina Martín. ***Universidad Complutense de Madrid.***

It is worth mentioning that the EASB member Prof. Isabel Fariñas was awarded this year the prestigious Premio Nacional de Investigación Santiago Ramón y Cajal. She was also designated as member of the Scientific Advisory Board of CSIC and thus decided to decline being a member of advisory boards of CSIC-related institutions. The IUBM-UAM then nominated Prof. Isabel Fabregat as a new member of the ESAB.

SCIENTIFIC STAFF IUBM-UAM 2024

➢ 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
FORMENTINI, LAURA
FRESNO ESCUDERO, MANUEL.
GÁMEZ ABASCAL, ALEJANDRA
GARCIA-ESCUDERO 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
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
PORLAN ALONSO, EVA
PORTILLA TUNDIDOR, YADILEYNI
PUCCIARELLI, Mª GRACIELA
RASTROJO LASTRAS, ALBERTO
REGLERO REAL, NATALIA
REMACHA MORENO, MIGUEL
REQUENA ROLANIA, JOSE MARIA
RIBAS NUÑEZ, CATALINA
RICHARD RODRIGUEZ, EVA
RODRIGUEZ GABRIEL, MIGUEL ANGEL
RODRIGUEZ POMBO, PILAR
RUANO GALLEGO, DAVID
RUIZ DESVIAT, LOURDES
RUIZ GOMEZ, ANA
SANTOS HERNÁNDEZ, JAVIER
SATRUSTEGUI GIL-DELGADO, JORGINA
SOTO ALVAREZ, MANUEL

STAMATAKIS ADRIANI, KONSTANTINOS
TRABA DOMÍNGUEZ, JAVIER
VALBUENA JIMÉNEZ, ALEJANDRO
VAQUERO LORENZO, CONCEPCIÓN
VILLA MORALES, MARIA
VENTOSO BANDE, IVAN
VIDA RUEDA, MARIA DEL CARMEN
YÁÑEZ MO, MARIA

- **Non-permanent postdoctoral members**

ALDUDO, JESUS
BOSCH REÑE, SANDRA
CECCHINI, DAVIDE AGOSTINO
COBOS FERNÁNDEZ, Mª ANGELES
FRANCOS QUIJORNA, ISAAC
GIMENO PÉREZ, MARIA
JARAÍZ RODRIGUEZ, MARIA DEL PILAR
LAINE MENÉNDEZ, SARA
LÓPEZ NIEVA, PILAR

- **PhD Students**

1. ALCOVER SÁNCHEZ, BERTA
2. ANDRÉS HERNÁIZ, RAQUEL DE
3. ASENSIO LÓPEZ, ALEJANDRO*
4. BARRIOS MUÑOZ, ANA LAURA
5. BENAYAS LÓPEZ, BEATRIZ
6. DE LA FLOR GARCÍA, MIGUEL
7. FULGENCIO COBIAN, ALEJANDRO
8. GALLEGO GARCÍA, DIANA*
9. GARCÍA GONZÁLEZ, DIEGO MARIN
10. HERREROS CABELLO, ALFONSO*
11. LÓPEZ FONSECA, CORAL*
12. MAROLDA, VIVIANA*
13. MARTINEZ BLANCO, ELENA*
14. MARTÍNEZ BONILLA, ADRIÁN
15. MERINO VALVERDE, JAVIER*
16. MORENO JIMÉNEZ, ELENA
17. MUÑOZ LÓPEZ, SARA
18. POLO NICOLI, SERGIO
19. RAMÍREZ CHUECA, ESTEBAN
20. RODRÍGUEZ RUBIO, MARINA
21. RUIZ GARCÍA, SARA
22. SANTOS, ROCÍO
23. SÁNCHEZ LIJARCIO, OBDULIA*

24. SOTO HEREDERO, GONZALO
25. STANCIC, BRINA
26. TERREROS RONCAL, JULIA
27. VELA MARTIN, LAURA
28. VEGA CUESTA, PATRICIA*

FINANCING AND BUDGET IUBM-UAM YEAR 2024

In addition to ongoing projects, in the year 2024 the members of the IUBM-UAM raised through competitive research projects circa **2.3 million euros (circa 455,000 euros in overheads).** According to the current 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 2024.

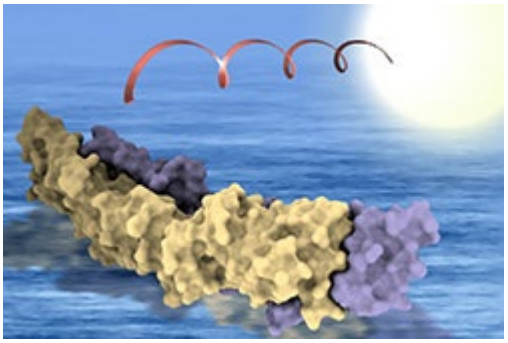
This budget was used for the following purposes:

Sponsorship of the PINP 2024 Award for the Best Doctoral Thesis 2024 in the CBMSO, Awards for the Best Oral Communication and the Best Poster in the XI WORKSHOP STUDENTS & POSDOCS CBMSO 2024, and "Conoce el CBMSO", February 2024.

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

SCIENTIFIC PROGRAMMES AND UNITS

Genome dynamics and function Programme



Genome decoding UNIT

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

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

- **Prof. Iván Ventoso Bande. Profesor Titular. Departamento de Biología Molecular.UAM.**
- **Prof. Miguel Ángel Rodríguez Gabriel. Profesor Titular. Departamento de BiologíaMolecular. UAM.**
- **Prof. Juan José Berlanga. Profesor Titular. Departamento de Biología Molecular.UAM.**
- **Prof. Margarita Cabrera Solans. Profesora Ayudante Doctora. 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 eIF2α 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 eIF2α 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

- **Nucleolar stress caused by arginine-rich peptides triggers a ribosomopathy and accelerates aging in mice.** Sirozh O, Saez-Mas A, Jung B, Sanchez-Burgos L, Zarzuela E, Rodrigo-Perez S, Ventoso I, Lafarga V, Fernandez-Capetillo O. **Molecular Cell.** 84, 1527-1540.e7. 2024.

- **Progressive alterations in polysomal architecture and activation of ribosome stalling relief factors in a mouse model of Huntington's disease.** Diaz-Lopez, Irene; Ventoso, Ivan; Fernandez, Jose-Jesus; Fernandez, Jose-Jesus; Martin-Solana, Eva; Fernandez-Fernandez, Maria Rosario; Fernandez-Fernandez, Maria Rosario. **Neurobiology of Disease,** 195, 106488, 2024.

- **Translational Control of Alphavirus-Host Interactions: Implications in Viral Evolution, Tropism and Antiviral Response.** Ventoso I, Berlanga JJ, Toribio R, Díaz-López I. **Viruses.** 2024 Jan 30;16(2):205.

Projects

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

Genetics and cell biology of cancer: T-cell lymphoblastic neoplasms
http://www.cbm.uam.es/jfpiqueras

- **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.**

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

- **PIM1 is a potential therapeutic target for the leukemogenic effects mediated by JAK/STAT pathway mutations in T-ALL/LBL.** Lahera A, Vela-Martín L, Fernández-Navarro P, Llamas P, López-Lorenzo JL, Cornago J, Santos J, Fernández-Piqueras J, Villa-Morales M. **NPJ Precis Oncol.** 2024 Jul 20;8(1):152.

- **The JAK3Q988P mutation reveals oncogenic potential and resistance to ruxolitinib.** Santos, Javier; Lahera, Antonio; Villa-Morales, María; Fernández-Piqueras, José; Vela-Martín, Laura. **Molecular Carcinogenesis**, 63, 5-10, 2024.

Regulation of gene expression in *Leishmania*

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

- **Prof. José Mª Requena Rolanía. Profesor Titular. Departamento de BiologíaMolecular. 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 immuno-pathological 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 (LiΔHSP70-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

- **A Proteogenomic Approach to Unravel New Proteins Encoded in the Leishmania donovani (HU3) Genome.** Adán-Jiménez J, Sánchez-Salvador A, Morato E, Solana JC, Aguado B, Requena JM**. Genes (Basel).** 2024 Jun 13;15(6):775.

- **Exploring the functionality and conservation of Alba proteins in Trypanosoma cruzi: A focus on biological diversity and RNA binding ability.** Matiz-González JM, Pardo-Rodriguez D, Puerta CJ, Requena JM, Nocua PA, Cuervo C**. Int J Biol Macromol**. 2024 Jun;272(Pt 2):132705.

- **Genetic Mechanisms Involved in Microbial Stress Responses.** Requena JM. **Genes (Basel).** 2024 Sep 27;15(10):1265.

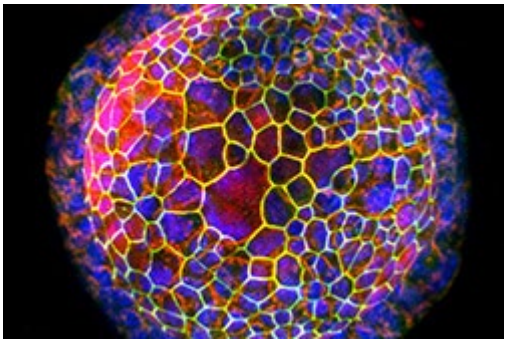
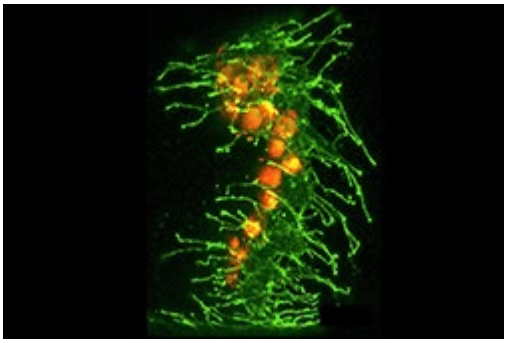
- **The Leishmania ribosome: more than passive mRNA translating machinery.** Requena JM**. Trends Biochem Sci**. 2024 Sep;49(9):754-756.

Projects

- Integrating OMICS data to decipher Leishmania gene organization and expression: clues for tackling leishmaniasis (Leish-OMICs). Agencia Estatal de Investigación. Ref. PID2020-117916RB-I00. PIs: Jose M. Requena & Begoña Aguado. Sep, 2021-2024

- CIBER en Área Enfermedades Infecciosas (CIBERINFEC). Instituto de Salud Carlos III. Ref. CB21/13/00018. PI: Javier Moreno. From 2022.

Tissue and organ homeostasis PROGRAMME

➢ Cell architecture & organogenesis UNIT

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).**

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 Ca2+/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.

Publications

- **INF2 formin variants linked to human inherited kidney disease reprogram the transcriptome, causing mitotic chaos and cell death.** Labat-de-Hoz L, Fernández-Martín L, Correas I, Alonso MA. **Cell Mol Life Sci**. 2024 Jun 25;81(1):279

- **Regulation of formin INF2 and its alteration in INF2-linked inherited disorders.** Labat-de-Hoz L, Jiménez MÁ, Correas I, Alonso MA. **Cell Mol Life Sci**. 2024 Nov 25;81(1):463.

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)**

Research summary:

The Drosophila wing originates from an epithelial tissue that grow by proliferation during larval development and differentiate 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 evolutionary conserved batteries of genes. The genetic and developmental analysis of the disc allow 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 10918 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 Towles-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 multitude of cancers, and the Drosophila Ras gene has been used to model cancer progression in flies. Using Crisper/Cas9 and homologous recombination we have generated Drosophila transgenic lines carrying altered versions of the fly and human Ras genes. We are characterizing the consequences of activating Ras mutations when the gene is expressed at normal levels in the wing, the ovary and the lymph gland. We expect to generate genetic

combinations in a background of endogenous activated Ras allowing us to model the formation and progression of tumors.

Thesis

- Patricia Vega Cuesta. Generación y caracterización de alelos mutantes Ras1V12 en el locus Ras1 de Drosophila. Directores. José Félix de Célis y Ana Ruiz Gómez. 2024.

Biophysics and systems biology

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

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

Research summary:

Our lab focuses on the study of the dynamics of developmental systems combing 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 experimental and computationally the dynamics of fluctuations in minimal networks motifs.

Publications

- **Cellular Compartmentalization as a Physical Regulatory Mechanism of Signaling Pathways.** Míguez, David G.; Fayad, Ahmed N.; Mazo-Durán, Diego**. Biophysica**. 4, 634-650.

- **Custom Automatic Segmentation Models for Medicine and Biology based on FastSAM.** Míguez, David G.; Pérez-Dones, Diego. **Wseas Transactions On Biology and Biomedicine,** 21, 373-384, 2024.

- **Cell proliferation and Notch signaling coordinate the formation of epithelial folds in the Drosophila leg.** Rodrıguez, Alonso; Foronda, David; Córdoba, Sergio; Felipe-Cordero, Daniel; Baonza, Antonio; Miguez, David G.; Estella, Carlos. **Development** (2024) 151 (8): dev202384.

- **An ETFDH-driven metabolon supports OXPHOS efficiency in skeletal muscle by regulating coenzyme Q homeostasis.** Herrero Martín, Juan Cruz; Salegi Ansa, Beñat; Álvarez-Rivera, Gerardo; Domínguez-Zorita, Sonia; Rodríguez-Pombo, Pilar; Pérez, Belén; Calvo, Enrique; Paradela, Alberto; Miguez, David G.; Cifuentes, Alejandro; Cuezva, José M.; Formentini, Laura. **Nature Metabolism** volume 6, pages209–225 (2024)

Projects

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

➢ Cell-cell communication and inflammation UNIT

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 BiologíaMolecular. 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

- **Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches** Welsh, Joshua A.; Goberdhan, Deborah C. I.; O'Driscoll, Lorraine; Buzas, Edit I.; Blenkiron, Cherie; Bussolati, Benedetta; Cai, Houjian; Di Vizio, Dolores; Driedonks, Tom A. P.; Erdbrügger, Uta; Falcon-Perez, Juan M.; Fu, Qing-Ling; Hill, Andrew F.; Lenassi, Metka; Lim, Sai Kiang; M˜y, G. Mahoney; Mohanty, Sujata; Möller, Andreas; Nieuwland, Rienk; Ochiya, Takahiro; Sahoo, Susmita; Torrecilhas, Ana C.; Zheng, Lei; Zijlstra, Andries; Abuelreich, Sarah; Bagabas, Reem; Bergese, Paolo; Bridges, Esther M.; Brucale, Marco; Burger, Dylan; Carney, Randy P. et al. **Journal of Extracellular Vesicles.** Volume13, Issue2 February 2024 e12404.

- **Molecular Determinants Involved in the Docking and Uptake of Tumor-Derived Extracellular Vesicles: Implications in Cancer.** Clares-Pedrero, Irene; Rocha-Mulero, Almudena; Palma-Cobo, Miguel; Cardeñes, Beatriz; Yáñez-Mó, María; Cabañas, Carlos**. Int. J. Mol. Sci.** 2024, 25(6), 3449**.**

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
- Vacunas basadas en exosomas miméticos PDC2021-121052-I00 (PRTR) 1.12.2021-31.11.2024. Principal Investigator: María Yáñez-Mo.

Thesis

- Beatriz Benayas López. Desarrollo y optimización de métodos cromatográficos para el aislamiento de vesículas extracelulares y su uso en biopsia líquida. Directora: María Yáñez-Mo. 2024.

Immunometabolism and Inflammation Lab

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

- **Prof. Elisa Carrasco. Profesora Ayudante Doctora. Departamento de Biología. UAM.**
- **Prof. Isaac Franco. Juan de la Cierva. Departameanto de Biología Molecular. 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

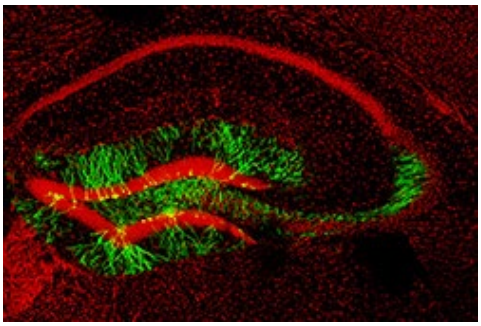
- **The effect of Fernblock® in preventing blue-light-induced oxidative stress and cellular damage in retinal pigment epithelial cells is associated with NRF2 induction.** Gallego-Rentero M, López Sánchez A, Nicolás-Morala J, Alcaraz-Laso P, Zhang N, Juarranz Á, González S, Carrasco E. The effect of Fernblock® in preventing blue-light-induced oxidative stress and cellular damage in retinal pigment epithelial cells is associated with NRF2 induction. **Photochemical & Photobiological Sciences.** 23, 1471-1484, 2024.

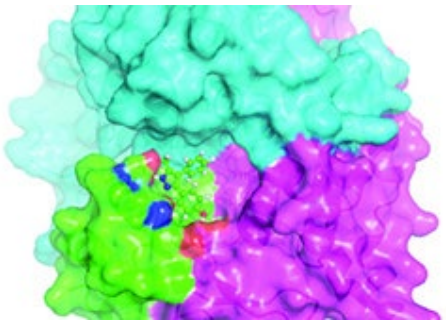
- **The m-TORC1 inhibitor Sirolimus increases the effectiveness of Photodynamic therapy in the treatment of cutaneous Squamous Cell Carcinoma, impairing NRF2 antioxidant signaling.** Nicolás-Morala J, Mascaraque-Checa M, Gallego-Rentero M, Barahona A, Abarca-Lachen E, Carrasco E, Gilaberte Y, González S, Juarranz Á**. Int J Biol Sci.** 2024 Aug 6;20(11):4238-4257.

Projects

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

PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES PROGRAMME





➢ Molecular Neuropathology UNIT

Pathogenic mechanisms of Alzheimer's disease

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

- **Prof. Mª Jesús Bullido Gómez-Heras. Profesora Titular. Departamento de BiologíaMolecular. UAM.**

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

- **Cholesterol Modulation Attenuates the AD-like Phenotype Induced by Herpes Simplex Virus Type 1 Infection**. Salgado B, Izquierdo B, Zapata A, Sastre I, Kristen H, Terreros J, Mejías V, Bullido MJ, Aldudo J. **Biomolecules**. 2024 May 20;14(5):603.

- **Connecting genomic and proteomic signatures of amyloid burden in the brain.** Puerta R, de Rojas I, García-González P, Olivé C, Sotolongo-Grau O, García-Sánchez A, García-Gutiérrez F, Montrreal L, Pablo Tartari J, Sanabria Á, Pytel V, Lage C, Quintela I, Aguilera N, Rodriguez-Rodriguez E, Alarcón-Martín E, Orellana A, Pastor P, Pérez-Tur J, Piñol-Ripoll G, de Munian AL, García-Alberca JM, Royo JL, Bullido MJ, Álvarez V, Real LM, Anchuelo AC, Gómez-Garre D, Larrad MTM, Franco-Macías E, Mir P, Medina M, Sánchez-Valle R, Dols-Icardo O, Sáez ME, Carracedo Á, Tárraga L, Alegret M, Valero S, Marquié M, Boada M, Juan PS, Cavazos JE, Cabrera A, Cano A; Alzheimer's Disease Neuroimaging Initiative.. **medRxiv** [Preprint]. 2024 Sep 6:2024.09.06.24313124.

- **Human in vivo evidence of associations between herpes simplex virus and cerebral amyloid beta load in normal aging.** Cantero JL, Atienza M, Sastre I, Bullido MJ. **Alzheimers Res Ther.** 2024 Apr 3;16(1):68.

- **A genome-wide association meta-analysis of all-cause and vascular dementia.** Fongang, Bernard; Sargurupremraj, Muralidharan; Jian, Xueqiu; Mishra, Aniket; Damotte, Vincent; de Rojas, Itziar; Skrobot, Olivia; Bis, Joshua C.; Fan, Kang-Hsien; Jacobsen, Erin; Li, Gloria Hoi-Yee; Yang, Jingyun; Alessandra, Bizzarro; Alessandra, Lauria; Hilal, Saima; Chong, Joyce Ruifen; Chai, Yuek Ling; Knol, M.J.; Concas, Maria Pina; Giorgia, Girotto; Riaz, Moeen; Yu, Chenglong; Guojonsson, Alexander; Lacaze, Paul; Naj, Adam C; Gireud-Goss, Monica; Wadop, Yannick N.; Soumare, Aicha; Bouteloup, Vincent; Gudnason, Vilmundur; Battista, Petronilla et al. **Alzheimers & Dementia.** Volume20, Issue9. September 2024. Pages 5973-599

- **X-chromosome-wide association study for Alzheimer's disease.** Le Borgne, Julie; Gomez, Lissette; Heikkinen, Sami; Amin, Najaf; Ahmad, Shahzad; Choi, Seung Hoan; Bis, Joshua; Grenier-Boley, Benjamin; Rodriguez, Omar Garcia; Kleineidam, Luca; Young, Juan; Tripathi, Kumar Parijat; Wang, Lily; Varma, Achintya; Campos-Martin, Rafael; van der Lee, Sven; Damotte, Vincent; de Rojas, Itziar; Palmal, Sagnik; Lipton, Richard; Reiman, Eric; McKee, Ann; De Jager, Philip; Bush, William; Small, Scott; Levey, Allan; Saykin, Andrew; Foroud, Tatiana; Albert, Marilyn; Hyman, Bradley; Petersen, Ronald; Younkin, Steven; Sano, Mary et al. **Molecular Psychiatry**. 2024.

Projects

- Cholesterol homeostasis and lysosome pathway in HSV-1 induced neurodegeneration and in Alzheimer's disease: Pathogenic mechanisms and biomarkers. PID2020-113921RB-I00. PI Bullido MJ & Frank-Garcia A. 01/09/2021-31/08/2024.

- Networked Center of Biomedical Research. Neurodegenerative diseases -CIBERNED- (https://www.ciberned.es/grupos/grupo-de-investigacion?id=28805)

- Hospital la Paz Institute for Health Research - IdiPaz. (http://www.idipaz.es) Group "Neurology and cerebrovascular diseases", PI E Díez-Tejedor

- Dementia Genetics Spanish Consortium (DEGESCO). Participant group. (https://www.ciberned.es/plataformas/degesco)

- European Alzheimer's Disease BioBank & International Genomics Alzheimer's Project (IGAP). Associated group. (https://consortiapedia.fastercures.org/consortia/igap/)

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

- **Role of palmitoylation on the neuronal glycine transporter GlyT2.** López-Corcuera, B.; Felipe, R.; Sarmiento-Jiménez, J. **J. Neurochem.** 168, 2056-2072, 2024.

Projects

- PID2020-119399RB-I00. The neuronal glycine transporter GlyT2 in pain and in hyperekplexia: pathological implications in development. Ministry of Science and Innovation. PI: B. López Corcuera. 2021-2024.

- CIVP20A6612, Fundación Ramón Areces. El transportador neuronal de glicina GlyT2 en hiperplexia: una patología glicinérgica del desarrollo. PI: B. López Corcuera. 01/05/2021 to 01/05/2024.
- 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.

Biology of human stem cells in translational neuroscience

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

- **Prof. Marta Pérez Pereira. Profesora Permanente Laboral. Departamento de BiologíaMolecular. UAM**

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

- **R-Ras1 and R-Ras2 regulate mature oligodendrocyte subpopulations.** 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. **Glia.** 2024 73(4):701-719.

- **The therapeutic use of clonal neural stem cells in experimental Parkinson´s disease.** Nelke A, García-López S, Caso JR, Pereira MP. **Stem Cell Res Ther.** 2024 Oct 9;15(1):356.

Projects

- OpenMIND (Opto-Electronic Neural Connectoid Model Implemented for Neurodegenerative Disease). GA-101047177. From 2022 to 2025.
- Cerebroides: desarrollo y complejidad. PID2020-118189RB-I00. Ministry of Science and Innovation. PI: M. Pérez-Pereira. 2021-Febrero 2025.

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 iPS 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.

Publications

- **Glial cell activation precedes neurodegeneration in the cerebellar cortex of the YG8-800 murine model of Friedreich ataxia.** Vicente-Acosta A, Herranz-Martín S, Pazos MR, Galán-Cruz J, Amores M, Loria F, Díaz-Nido J. **Neurobiol Dis**. 2024 Oct 1;200:106631.

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.

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+2) 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+2 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

- **HDAC4 Inhibits NMDA Receptor-mediated Stimulation of Neurogranin Expression**. de Andrés R, Martínez-Blanco E, Díez-Guerra FJ. **Mol Neurobiol. 2024** Nov 25.

Thesis

- Elena Martínez Blanco. Papel de Neurogranina en la regulación de la señalización de Calcio/Calmodulina y su impacto en la plasticidad neuronal. Director: Francisco Javier Díez Guerra. 2024.

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

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

- **Prof. Beatriz Cubelos Alvarez. Profesora Titular. Departamento deBiología Molecular. UAM.**

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

- **R-Ras1 and R-Ras2 regulate mature oligodendrocyte subpopulations.** 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. **Glia.** 2024 73(4):701-719.

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.

Thesis

- Berta Alcover Sánchez. Papel de R-Ras1 y R-Ras2 en la diferenciación y maduración oligodendrocitaria. Directora: Beatriz Cubelos. 2024

Tau function and dysfunctions in Alzheimer disease

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

- **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 Interina. Departamento de Anatomía, Histología y Neurociencias. UAM.**

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 GSK3β kinase, we have also investigated the effects of GSK3β 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

- **Hippocampal rejuvenation by a single intracerebral injection of one-carbon metabolites in C57BL6 old wild-type mice.** Antón-Fernández A, Cauchola RP, Hernández F, Ávila J. **Aging Cell.** 2025 Jan;24(1):e14365

- **In vivo cyclic overexpression of Yamanaka factors restricted to neurons reverses age-associated phenotypes and enhances memory performance.** Antón-Fernández A, Roldán-Lázaro M, Vallés-Saiz L, Ávila J, Hernández F. **Commun Biol.** 2024 May 24;7(1):631

- **Intron retention as a productive mechanism in human MAPT: RNA species generated by retention of intron 3.** Ruiz-Gabarre D, Vallés-Saiz L, Carnero-Espejo A, Ferrer I, Hernández F, Garcia-Escudero R, Ávila J, García-Escudero V. **EBioMedicine.** 2024 Feb;100:104953.

- **Protein tau phosphorylation in the proline rich region and its implication in the progression of Alzheimer's disease**. Merino-Serrais P, Soria JM, Arrabal CA, Ortigado-López A, Esparza MÁG, Muñoz A, Hernández F, Ávila J, DeFelipe J, León-Espinosa G. **Exp Neurol.** 2025 Jan;383:115049.

- **Role of folate receptor α in the partial rejuvenation of dentate gyrus cells: Improvement of cognitive function in 21-month-old aged mice.** Antón-Fernández A, Cuadros R, Peinado-Cahuchola R, Hernández F, Avila J. **Sci Rep.** 2024 Mar 22;14(1):6915.

- **The cellular prion protein does not affect tau seeding and spreading of sarkosyl-insoluble fractions from Alzheimer's disease.** Sala-Jarque J, Gil V, Andrés-Benito P, Martínez-Soria I, Picón-Pagès P, Hernández F, Ávila J, Lanciego JL, Nuvolone M, Aguzzi A, Gavín R, Ferrer I, Del Río JA. **Sci Rep.** 2024 Sep 16;14(1):21622.

Projects

- Neurorregeneración en la enfermedad de Alzheimer a través de la expresión de factores de pluripotencia in vivo. PID2020-113204GB-I00. PI Félix Hernández Pérez. MINECO. 1.9.2021-31.8.2024.

- 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

- Part of the Networking Research Center on Neurodegenerative Diseases (CIBERNED).

Molecular mechanisms of neurodegeneration

- **Prof. Juan Salvador Jiménez. Profesor Emérito. Departamento de Química Física Aplicada.UAM.**
- **Prof. María José Benítez Moreno. Profesora Titular. Departamento de Química FísicaAplicada. UAM.**
- **Prof. Mª José Pérez Alvarez. Profesora Titular. Departamento de Biología. UAM.**
  (in collaboration with different CBM laboratories)

Publications

- **The dynamics of oligodendrocyte populations following permanent ischemia promotes long-term spontaneous remyelination of damaged area.** Martín-Lopez G, Mallavibarrena PR, Villa-Gonzalez M, Vidal N, Pérez-Alvarez MJ. **Biochim Biophys Acta Mol Basis Dis.** 2024 Oct;1870(7):167270.

- **Pharmacological inhibition of mTORC1 reduces neural death and damage volume after MCAO by modulating microglial reactivity.** Villa-González M, Rubio M, Martín-López G, Mallavibarrena PR, Vallés-Saiz L, Vivien D, Wandosell F, Pérez-Álvarez MJ**. Biol Direct.** 2024 Apr 6;19(1):26

- **Transcriptomic alterations in APP/PS1 mice astrocytes lead to early postnatal axon initial segment structural changes.** Wandosell, Francisco; Garrido, Juan José; Ciorraga, María; Benitez, María José; Retana, Diana; Colmena, Inés; Ordoñez-Gutiérrez, Lara; Goméz, María José. **Cellular and Molecular Life Sciences**, 81, 444, 2024.

- **Transcriptomic alterations in APP/PS1 mice astrocytes lead to early postnatal axon initial segment structural changes.** Wandosell, Francisco; Garrido, Juan José; Ciorraga, María; Benitez, María José; Retana, Diana; Colmena, Inés; Ordoñez-Gutiérrez, Lara; Goméz, María José. **Cellular and Molecular Life Sciences**, 81, 444, 2024.

Adult neural stem cells: intrinsic and extrinsic factors that regulate their self-renewal and differentiation
https://www.cbm.uam.es/eporlan

- **Prof. Eva Porlan. Profesora Contratada Doctora. Departamento de BiologíaMolecular. UAM.**

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.

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).

Thesis

- López Fonseca, Coral. Efectos de la quinasa Plk1 en la regulación de factores de transcripción proneurales. Programa de Doctorado de Biociencias Moleculares. Directora: Eva Porlan. 2024.

Molecular basis of glutamatergic synapses
https://www.cbm.uam.es/fzafra

- **Prof. Francisco Zafra Gómez. Catedrático. Departamento de Biología Molecular.UAM.**

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.

Publications

- **Metabolic Rewiring and Altered Glial Differentiation in an iPSC-Derived Astrocyte Model Derived from a Nonketotic Hyperglycinemia Patient.** Arribas-Carreira L, Castro M, García F, Navarrete R, Bravo-Alonso I, Zafra F, Ugarte M, Richard E, Pérez B, Rodríguez-Pombo P. **Int J Mol Sci.** 2024 Feb 28;25(5):2814.

➢ Metabolic and Signaling Networks in Disease UNIT

Mitochondrial dysfunction in metabolic diseases

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

- **Prof. Eduardo Balsa. Profesor Permanente Laboral. Departamento de BiologíaMolecular. 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

- **Compensatory activity of the PC-ME1 metabolic axis underlies differential sensitivity to mitochondrial complex I inhibition.** Del Prado L, Jaraíz-Rodríguez M, Agro M, Zamora-Dorta M, Azpiazu N, Calleja M, Lopez-Manzaneda M, de Juan-Sanz J, Fernández-Rodrigo A, Esteban JA, Girona M, Quintana A, Balsa E**. Nat Commun. 2024 Oct 7;15(1):8682.**

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.

- RYC2018-024342-I (FSE). Ayuda Ramón y Cajal. IP: Eduardo Balsa. 2020-2024.

Physiopathology studies and therapeutical approaches in animal and cellular models of neurometabolic diseases
https://www.cbm.uam.es/lab220

- **Prof. Lourdes Ruiz-Desviat. Catedrática. Departamento de Biología Molecular. UAM.**
- **Prof. Eva Mª Richard Rodríguez. Profesora Titular. Departamento de BiologíaMolecular. UAM.**

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 Ca2+ 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 arrythmias. 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 casing inherited metabolic diseases.

Publications

- **Exploring RNA therapeutics for urea cycle disorders.** Richard E, Martínez-Pizarro A, Desviat LR. **J Inherit Metab Dis**. 2024 Nov;47(6):1269-1277.

- **Functional analysis of novel variants identified in cis in the PCCB gene in a patient with propionic acidemia.** Martínez-Pizarro A, Calmels N, Schalk A, Wicker C, Richard E, Desviat LR. **Gene.** 2024 Jan 30;893:147902.

- **Metabolic Rewiring and Altered Glial Differentiation in an iPSC-Derived Astrocyte Model Derived from a Nonketotic Hyperglycinemia Patient.** Arribas-Carreira L, Castro M, García F, Navarrete R, Bravo-Alonso I, Zafra F, Ugarte M, Richard E, Pérez B, Rodríguez-Pombo **P. Int J Mol Sci.** 2024 Feb 28;25(5):2814

- **PAH deficient pathology in humanized c.1066-11G>A phenylketonuria mice.** Martínez-Pizarro A, Picó S, López-Márquez A, Rodriguez-López C, Montalvo E, Alvarez M, Castro M, Ramón-Maiques S, Pérez B, Lucas JJ, Richard E, Desviat LR. **Hum Mol Genet.** 2024 Jun 5;33(12):1074-1089.

- **Regulating PCCA gene expression by modulation of pseudoexon splicing patterns to rescue enzyme activity in propionic acidemia.** Spangsberg Petersen US, Dembic M, Martínez-Pizarro A, Richard E, Holm LL, Havelund JF, Doktor TK, Larsen MR, Færgeman NJ, Desviat LR, Andresen BS. **Mol Ther Nucleic Acids.** 2023 Dec 13;35(1):102101.

- **Renal phenotyping in a hypomorphic murine model of propionic aciduria reveals common pathomechanisms in organic acidurias.** Desviat, Lourdes R.; Richard, Eva; Martinez-Pizarro, Ainhoa. **Scientific Reports,** 14, 30478, 2024.

- **Significance of utilizing in silico structural analysis and phenotypic data to characterize phenylalanine hydroxylase variants: A PAH landscape.** Himmelreich N, Ramón-Maiques S, avarrete R, Castejon-Fernandez N, Garbade SF, Martinez A, Desviat LR, Pérez B, Blau N. **Mol Genet Metab.** 2024 Jul;142(3):108514

- **Splice-Switching Antisense Oligonucleotides Correct Phenylalanine Hydroxylase Exon 11 Skipping Defects and Rescue Enzyme Activity in Phenylketonuria.** Desviat, Lourdes R.; Richard, Eva; Álvarez, Mar; Martínez-Pizarro, Ainhoa. **Nucleic Acid Therapeutics,** 34, 134-142, 2024.

- **The attenuated hepatic clearance of propionate increases cardiac oxidative stress in propionic acidemia.** Wang Y, Zhu S, He W, Marchuk H, Richard E, Desviat LR, Young SP, Koeberl D, Kasumov T, Chen X, Zhang GF. **Basic Res Cardiol**. 2024 Dec;119(6):1045-1062.

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.
- “Acidemia propiónica: impacto en el epigenoma y el proteoma en relación con el fenotipo cardiaco y neurológico”. Fundación Ramón Areces, XX concurso nacional para la adjudicación de ayudas a la investigación en ciencias de la vida y de la materia 2020 (May 2021-May 2024). PI: Eva María Richard Rodríguez.
- 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

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

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.

Molecular mechanisms of sex-differences in metabolism physiology and disease

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

- **Defective mitochondria remodelling in B cells leads to an aged immune response.** Martínez-Martín, Nuria; Martín-Belmonte, Fernando; Bovolenta, Elena R.; Cogliati, Sara; Cifuentes, Claudia; Prieto Carro, Cristina; González Martínez, Tamara; Guerra Rodriguez, Milagros; Ruiz García, Jonathan; Iborra-Pernichi, Marta; García-Consuegra, José; Velasco de la Esperanza, María; Estrada, Belén S.. **Nature Communications**, 15, 2569, 2024.

- **Early heart and skeletal muscle mitochondrial response to a moderate hypobaric hypoxia environment.** Cogliati, Sara; Aparisi, Ana Sagrera. **Journal of Physiology-London,** 602,5631-5641, 2024.

- **Effect of moderate hypobaric hypoxia on both heart and skeletal muscle during the first 24 hours of exposure**. Cogliati, Sara; Sagrera Aparisi, Ana. **Acta Physiologica**, 240, 34, 2024.

- **Sex differences in mitochondrial functions.** Cogliati, Sara. **Acta Physiologica,** 240, 19, 2024.

- **Sexual dimorphism on the acute effect of exercise in the morning vs. evening: A randomized crossover study.** Sevilla-Lorente R, Marmol-Perez A, Gonzalez-Garcia P, Rodríguez-Miranda N, 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. **J Sport Health Sci.** 2024 Dec 22:101021.

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 cardiaca durante la menopausia. CNS2023-143646 (PRTR). IP: Sara Cogliati. Ministerio. 2024-2026.

Translational Energy Metabolism

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

- **Prof. Laura Formentini. Profesora Titular. Departamento de BiologíaMolecular. 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

- **An ETFDH-driven metabolon supports OXPHOS efficiency in skeletal muscle by regulating coenzyme Q homeostasis.** Herrero Martín JC, Salegi Ansa B, Álvarez-Rivera G, Domínguez-Zorita S, Rodríguez-Pombo P, Pérez B, Calvo E, Paradela A, Miguez DG, Cifuentes A, Cuezva JM, Formentini L. **Nat Metab**. 2024 Feb;6(2):209-225.

- **Development of a Bmi1+ Cardiac Mouse Progenitor Immortalized Model to Unravel the Relationship with Its Protective Vascular Endothelial Niche.** Albericio G, Higuera M, Araque P, Sánchez C, Herrero D, García-Brenes MA, Formentini L, Torán JL, Mora C, Bernad A**. Int J Mol Sci.** 2024 Aug 13;25(16):8815.

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.

Patho-physiological implications of G protein-coupled receptors signaling networks
http://www.cbm.uam.es/fmayor

- **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 deBiología Molecular. UAM**
- **Dra. Carmen Vida. Profesora Ayudante Doctora. Departamento de Biología. UAM.**
- **Dra. Yadiely Portilla Tundidor. Profesora Ayudante Doctora. Departamento de Biologia Molecular UAM.**

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:

1. 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)
2. 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).
3. 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

- **GRK2-mediated AKT activation controls cell cycle progression and G2 checkpoint in a p53-dependent manner.** Rivas V, González-Muñoz T, Albitre Á, Lafarga V, Delgado-Arévalo C, Mayor F Jr, Penela P. **Cell Death Discov**. 2024 Aug 29;10(1):385.

- **The G-Protein-Coupled Receptor Kinase 2 Orchestrates Hair Follicle Homeostasis** Asensio, A. , Sanz-Flores, M., Liakath-Ali, K., Palacios-García, J., Paramio, J.M., García-Escudero, R.,Mayor jr, F., and Ribas, C. **bioXriv.** 2024. doi: 10.1101/2024.04.11.589052

- **Adrenergic modulation of neutrophil and macrophage functions: pathophysiological cues.**Vida, C, Portilla, Y., Murga, C. **Current Opinion In Physiology.** 41, 100780. 2024.

Projects

- European Union:H2020-MSCA Programme, Grant agreement 860229-ONCORNET2.0 (ONCOgenic Receptor Network of Excellence and Training) -Coordinator: Martine Smit, Amsterdam, F. Mayor Network group PI, 2020-2024.
- CIBER CARDIOVASCULAR, Instituto de Salud Carlos III, Group CB16/11/00278 (PI, F Mayor) 2017-2024.
- 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 2021-2024.
- PID2023-1467350B-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.

Thesis

- Viviana Marolda. Redes de Proteínas Asociadas a GRK2 en la Interacción de las Células de Cáncer de Mama con el Microambiente Tumoral. Directores: Federico Mayor Menéndez y Petronila Penela Márquez. 2024.

- Alejandro Asensio López. Papel de GRK2 en la homeostasis epidérmica. Directores: Federico Mayor Menéndez y Catalina Ribas Núñez. 2024.

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.

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

- **Protocol for volume correlative light X-ray and electron microscopy of endothelial cells in mouse tissue.** Reglero-Real N, Pérez-Gutiérrez L, Saleeb RS, Nourshargh S, Collinson L, Yoshimura A. **STAR Protoc.** 2024 Sep 20;5(3):103257

Proyects

- 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.

Calcium signalling in mitochondria and insulin/leptin signalling during ageing
http://www.cbm.uam.es/jsatrustegui

- **Prof. Jorgina Satrústegui. Profesora Emérita. Departamento de Biología Molecular.UAM.**
- **Prof. Beatriz Pardo. Profesora Titular Departamento de Biología Molecular. UAM (co-PI)**

- **Prof. Araceli del Arco. Profesora Titular Universidad de Castilla-La Mancha (co-PI)**
- **Prof. Laura Contreras Balsa. Profesora Permanente Laboral. Departamento de Biología Molecular. UAM.**
- **Prof. José Mª 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.Mg2+-Pi/SCaMCs. These carriers have Ca2+-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 Ca2+ 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 β-hydroxybutyrate (βOHB), 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 βOHB to Aralar-KO mice increases myelin protein levels and dopaminergic markers in these mice, suggesting βHB 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

- **A tribute to Sebastian Cerdan and his key contributions to brain metabolism.** Satrustegui, J; Larrubia, P Lopez. **Journal of Neurochemistry.** 168, 455-460. 2024.

- **Calcium-dependent mitochondrial Aspartate/Glutamate Carriers (AGCs), but not MCU, regulate proliferation in cells engaged in the Warburg effect**. Satrustegui, Jorgina; Gonzalez-Moreno, Luis. **Biochimica Et Biophysica Acta - Bioenergetics**, 1865, 89. 2024.

- **Neuronal hypoglycolysis sustains body health.** Pardo B. **Nat Metab.** 2024 Jul;6(7):1197-1199.

- **Small molecule transport across the mitochondrial inner membrane.** Satrustegui, Jorgina; Gonzalez-Moreno, Luis; Herrada-Soler, Eduardo. **Biochimica Et Biophysica Acta - Bioenergetics**, 1865, 89, 2024.

Projects

- Generation of a new human-like citrin-deficiency mouse model to study Citrin deficiency. CITRIN Foundation Research Grants. PIs: Laura Contreras & Araceli del Arco. 06/2022-10/2024
- 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 higado 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 Sanitara Fundación Jiménez Díaz (IIS FJD) as "Señalización mitocondrial del calcio" unit.

Cellular signaling networks in cancer (onco-resecel)

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

- **Prof. Petronila Penela Márquez. Profesora Titular. Departamento de BiologíaMolecular. UAM.**
- **Prof. Laura Nogués Vera. Profesora Ayudante Doctora. Departamento de Biologia Molecular UAM.**

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.

Publications

- **Engineered T cells secreting anti-BCMA T cell engagers control multiple myeloma and promote immune memory in vivo.** Orfao, Alberto; Mayado, Andrea; Jara, Maria; Penela, Petronila; Sanz, Laura; García-Ortiz, Almudena; Albitre, Ángela; Pérez-Pons, Alba. **Science Translational Medicine**, 16, eadg7962. 2024.

- **GRK2-mediated AKT activation controls cell cycle progression and G2 checkpoint in a p53-dependent manner.** Rivas V, González-Muñoz T, Albitre Á, Lafarga V, Delgado-Arévalo C, Mayor F Jr, Penela P. **Cell Death Discov**. 2024 Aug 29;10(1):385.

Projects

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

Thesis

- Viviana Marolda. Redes de Proteínas Asociadas a GRK2 en la Interacción de las Células de Cáncer de Mama con el Microambiente Tumoral. Directores: Federico Mayor Menéndez y Petronila Penela Márquez. 2024.

Translational medicine in inborn errors of metabolism and other rare genetic diseases
https://www.cbm.uam.es/bperez

- **Prof. Belén Pérez González. Catedrática. Departamento de Biología Molecular.UAM.**
- **Prof. Pilar Rodríguez Pombo. Profesora Titular. Departamento de BiologíaMolecular. UAM**

- **Prof. Alejandra Gámez Abascal. Profesora Titular. Departamento deBiología Molecular. UAM.**

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 techology as potential therapy.

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

Publications

- **An ETFDH-driven metabolon supports OXPHOS efficiency in skeletal muscle by regulating coenzyme Q homeostasis.** Herrero Martín JC, Salegi Ansa B, Álvarez-Rivera G, Domínguez-Zorita S, Rodríguez-Pombo P, Pérez B, Calvo E, Paradela A, Miguez DG, Cifuentes A, Cuezva JM, Formentini L. **Nat Metab**. 2024 Feb;6(2):209-225.

- **HepG2 PMM2-CDG knockout model: A versatile platform for variant and therapeutic evaluation**. Pérez, Belén; Gámez, Alejandra; Briso-Montiano, Álvaro; Gallego, Diana; Vilas, Alicia; Segovia-Falquina, Cristina; Soriano-Sexto, Alejandro; Martín-Martínez, Arturo; Ruiz-Montés, Vera. **Molecular Genetics and Metabolism**, 143, 108538, 2024.

- **Inborn errors of metabolism: solving old cases by combination of transcriptomic analysis and long-read sequencing.** Perez, Belen; Ugarte, Magdalena; Navarrete, Rosa; Leal, Fatima; Bravo-Alonso, Irene; Soriano-Sexto, Alejandro; Rodriguez, Pilar. **Journal of Human Genetics,** 32, 434, 2024.

- **Integration of multi-omics layers empowers precision diagnosis through unveiling pathogenic mechanisms on maple syrup urine disease**. 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. **J Inherit Metab Dis.** 2025 Jan;48(1):e12829

- **Metabolic Rewiring and Altered Glial Differentiation in an iPSC-Derived Astrocyte Model Derived from a Nonketotic Hyperglycinemia Patient.** Arribas-Carreira L, Castro M, García F, Navarrete R, Bravo-Alonso I, Zafra F, Ugarte M, Richard E, Pérez B, Rodríguez-Pombo P. **Int J Mol Sci.** 2024 Feb 28;25(5):2814.

- **Pathogenic variants of the coenzyme A biosynthesis-associated enzyme phosphopantothenoylcysteine decarboxylase cause autosomal-recessive dilated cardiomyopathy.** Ramon-Maiques, Santiago; Alvarez, Mar; Perez, Belen; Ugarte, Magdalena; Bravo-Alonso, Irene;

Rodriguez, Pilar; Arribas, Laura. **European Journal of Human Genetics,** 32, 433-434, 2024.

- **Transcriptomic analysis identifies dysregulated pathways and therapeutic targets in PMM2-CDG.** Pérez, Belén; Gámez, Alejandra; Gallego, Diana. **Biochimica Et Biophysica Acta - Molecular Basis of Disease,** 1870, 167163, 2024.

Projects

- Bridging the research and innovation gap for rare diseases in Europe by upgrading exellence 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

- Diana Gallego Martínez. Genómica funcional aplicada a la identificación de dianas terapéuticas en enfermedades metabólicas hereditarias. Directora: Belén Pérez González. 2024

- Obdulia Sánchez Lijarcio. Estrategia multiómica y de genómica funcional para la mejora del diagnóstico de enfermedades neurometabólicas. Directora: Belén Pérez González. 2024.

Cell communication in homeostasis and disease through new Gq-GPCR signaling nodes
https://www.cbm.uam.es/cribas

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

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

The G-Protein-Coupled Receptor Kinase 2 Orchestrates Hair Follicle Homeostasis Asensio, A. , Sanz-Flores, M., Liakath-Ali, K., Palacios-García, J., Paramio, J.M., García-Escudero, R.,Mayor jr, F., and Ribas, C. **bioXriv.** 2024. doi: 10.1101/2024.04.11.589052

Projects

- CIBER CARDIOVASCULAR, Instituto de Salud Carlos III, Group CB16/11/00278 (PI, F Mayor) 2017-2023.
- Participation in ERNEST (European Research Network on Signal Transduction) COST ACTION (European cooperation in Science and Technology)
- Redes de señalización de Galfaq en la homeostasis y comunicación celular: repercusión en disfunción endotelial e inflamación. PI22/00966. Instituto de Salud Carlos III. Principal investigator: 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.

Thesis

- Alejandro Asensio López. Papel de GRK2 en la homeostasis epidérmica. Directores: Federico Mayor Menéndez y Catalina Ribas Núñez. 2024.

Mitochondrial biology in immune modulation
www.cbm.uam.es/jtraba

- **Prof. Javier Traba Domínguez. Investigador Ramón y Cajal. Departamento deBiología 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 1β 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+), which activates sirtuin proteins, a group of enzymes possessing deacetylase activity that require NAD+ 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+-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+ synthesis in the salvage pathway, functions as a fasting mimetic and blunts monocyte/macrophage IL-1β 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-1β signaling are associated with psoriasis progression. Given our findings of the role of SIRT3 in immune-modulation, a question arising is whether NAD+ 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+ precursors blunt inflammation in a psoriatic mouse model via augmentation of mitochondrial function, fidelity and quality control programs.

Publications

- **Regulation of innate immune cell differentiation by mitochondrial nicotinamide adenine dinucleotide (NAD⁺) levels.** Traba, Javier; Oliva, Aurea; Rincon, Ruben. **Biochimica Et**

Biophysica Acta - Bioenergetics, 1865, 133, 2024.

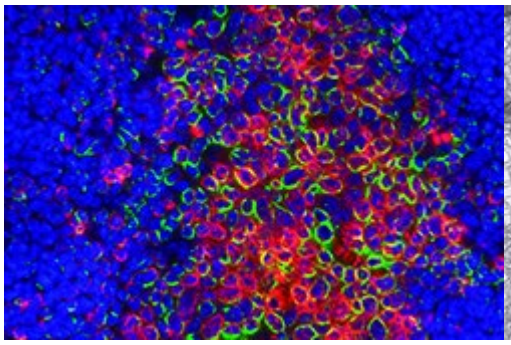
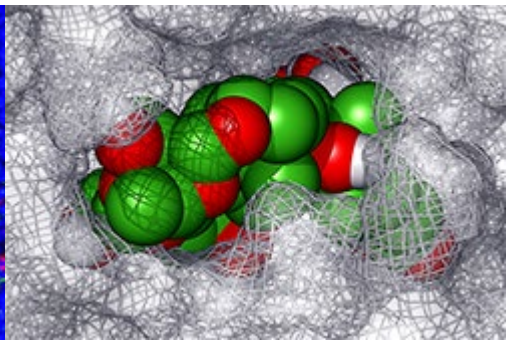
- **Uncovering a novel functional interaction between adult hepatic progenitor cells, inflammation and EGFR signaling during bile acids- induced injury.** Traba, J.; Calero-Perez, S.; Valverde, A. M. **Febs Open Bio,** 14, 468, 2024.

- **Vitamin-C-dependent downregulation of the citrate metabolism pathway potentiates pancreatic ductal adenocarcinoma growth arrest.** Traba, Javier; Cebrian, Arancha; Aguilera, Óscar; Meroño, Carolina. **Molecular Oncology**, 18, 2212-2233, 2024.

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.
- Regulación de la inmunidad innata y adaptativa por los niveles mitocondriales de nicotinamida adenina dinucleotido (NAD+). 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

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 Ayudante Doctor. Departamentode 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. PGF2α 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 PGF2α/Egr-1 mechanism. Moreover PGF2α induced TGFβ-PMEPA1 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

- **Assessment of molecular modulation by multifrequency electromagnetic pulses to preferably eradicate tumorigenic cells.** Piredda R, Martínez LGR, Stamatakis K, Martinez-Ortega J, Ferráz AL, Almendral JM, Revilla Y. **Sci Rep**. 2024 Dec 3;14(1):30150.

- **Discovery of circulating miRNAs as biomarkers of chronic Chagas heart disease via a small RNA-Seq approach.** Villar SR, Herreros-Cabello A, Callejas-Hernández F, Maza MC, Del Moral-Salmoral J, Gómez-Montes M, Rodríguez-Angulo HO, Carrillo I, Górgolas M, Bosch-Nicolau P, Molina I, Pérez-Molina JA, Monge-Maillo B, Bottasso OA, Beloscar J, Pérez AR, Fresno M, Gironès N. **Sci Rep.** 2024 Aug 9;14(1):18514.

- **Identification of Chagas disease biomarkers using untargeted metabolomics.** Fresno, Manuel; Gironès, Núria; Herreros-Cabello, Alfonso, **Scientific Reports**, 14, 187668, 2024.

- **NIK Is a Mediator of Inflammation and Intimal Hyperplasia in Endothelial Denudation-Induced Vascular Injury.** Baeza C, Ribagorda M, Maya-Lopez C, Fresno M, Sanchez-Diaz T, Pintor-Chocano A, Sanz AB, Carrasco S, Ortiz A, Sanchez-Niño MD. **International Journal of Molecular Sciences,** 25, 11473, 2024.

- **Quantitative Proteomic Analysis of Macrophages Infected with Trypanosoma cruzi Reveals Different Responses Dependent on the SLAMF1 Receptor and the Parasite Strain.** Herreros-Cabello A, Del Moral-Salmoral J, Morato E, Marina A, Barrocal B, Fresno M, Gironès N. **Int J Mol Sci**. 2024 Jul 8;25(13):7493.

- **Toll-like receptors ligand immunomodulators for the treatment congenital diaphragmatic hernia.** Vallejo-Cremades M, Merino J, Carmona R, Córdoba L, Salvador B, Martínez L, Tovar JA, Llamas MÁ, Muñoz-Chápuli R, Fresno M. **Orphanet J Rare Dis**. 2024 Oct 18;19(1):386.

Projects

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

Thesis

- Javier Merino Valverde. Lipopolisacáridos atípicos: estructura, actividad biológica y posibles aplicaciones clínicas. Director: Manuel Fresno Escudero. 2024.
- Alfonso Herreros Cabello. Aproximaciones ómicas para la biología y genética de Trypanosoma cruzi y la definición de biomarcadores en la enfermedad de Chagas. Directores. Manuel Fresno Escudero y

Núria Gironés Pujol.

Immunoregulatory mechanisms in the development of Chagas disease: translational applications

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

- **Prof. Núria Gironés Pujol. Profesor Titular. Departamento de Biología Molecular.UAM.**

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

- **Discovery of circulating miRNAs as biomarkers of chronic Chagas heart disease via a small RNA-Seq approach.** Villar SR, Herreros-Cabello A, Callejas-Hernández F, Maza MC, Del Moral-Salmoral J, Gómez-Montes M, Rodríguez-Angulo HO, Carrillo I, Górgolas M, Bosch-Nicolau P, Molina I, Pérez-Molina JA, Monge-Maillo B, Bottasso OA, Beloscar J, Pérez AR, Fresno M, Gironès N**. Sci Rep**. 2024 Aug 9;14(1):18514.

- **Identification of Chagas disease biomarkers using untargeted metabolomics.** Fresno, Manuel; Gironès, Núria; Herreros-Cabello, Alfonso, **Scientific Reports**, 14, 187668, 2024.

- **Quantitative Proteomic Analysis of Macrophages Infected with Trypanosoma cruzi Reveals**

Different Responses Dependent on the SLAMF1 Receptor and the Parasite Strain. Herreros-Cabello A, Del Moral-Salmoral J, Morato E, Marina A, Barrocal B, Fresno M, Gironès N. **Int J Mol Sci**. 2024 Jul 8;25(13):7493.

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.

Thesis

- Alfonso Herreros Cabello. Aproximaciones ómicas para la biología y genética de Trypanosoma cruzi y la definición de biomarcadores en la enfermedad de Chagas. Directores. Manuel Fresno Escudero y Núria Gironés Pujol.

Nitric Oxide and bioactive lipids signalling in the immune response
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 (NO2-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, NO2FA 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 NO2-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 NO2-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.

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

- **Herpes Simplex Virus type 1 inhibits autophagy in glial cells but requires ATG5 for the success of viral replication.** Ripa I, Andreu S, Josa-Prado F, Fernández Gómez B, de Castro F, Arribas M, Bello-Morales R, López-Guerrero JA**. Front Microbiol**. 2024 Jun 10;15:1411655.

- **Human Coronavirus 229E Uses Clathrin-Mediated Endocytosis as a Route of Entry in Huh-7 Cells.** Andreu S, Ripa I, López-Guerrero JA, Bello-Morales R. **Biomolecules**. 2024 Sep 29;14(10):1232.

- **Pseudorabies virus uses clathrin mediated endocytosis to enter PK15 swine cell line.** Andreu S, Agúndez C, Ripa I, López-Guerrero JA, Bello-Morales R. **Front Microbiol.** 2024 Feb 5;15:1332175

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

Biotechnology of probiotics and intestinal pathogens
Biotechnology of probiotics and intestinal pathogens - Centro de Biología Molecular Severo Ochoa

- **Prof. David Ruano Gallego. Investigador Ramón y Cajal. Departamento de Biología Molecular. UAM.**

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.

Publications

- **Immunoanalytical Detection of Conserved Peptides: Refining the Universe of Biomarker Targets in Planetary Exploration.** Mustieles-Del-Ser, Pedro; Ruano-Gallego, David; Parro, Víctor. **Anal. Chem**. 2024, 96, 12, 4764–4773.

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.

- 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

Biotechnology and genetics of extreme thermophiles

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

- **Prof. Mario Mencía Caballero. Profesor Titular. Departamento de Biología Molecular. UAM.**

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 PrimpoI 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 a 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 terephtalate 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

- **Differential requirement for RecFOR pathway components in Thermus thermophilus.** Gómez Campo CL, Abdelmoteleb A, Pulido V, Gost M, Sánchez-Hevia DL, Berenguer J, Mencía M. **Environ Microbiol Rep.** 2024 Jun;16(3):e13269.

Projects

- Nueva aproximación para la bioconversión sostenible de residuos plásticos en productos de alto valor añadido basada en microorganismos termófilos y síntesis enzimática. TED2021-130430B-C22 (PRTR). PI Mario Mencia. MINECO. 2022-2024.

- Desarrollo de un sistema biológico y de hardware para la evolución continua de proteínas en Thermus thermophilus para aplicaciones biotecnológicas. PID2022-137468OB-I00 (FEDER, UE). PI: M. Mencía. 1.9.2023-31.8.2026.

Bacterial cell envelope during preseptal growth
https://www.cbm.uam.es/mpazos

- **Prof. Manuel Pazos. Investigador Atracción Talento CAM. Departamento de Biología Molecular. UAM.**

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.

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.

SsDNA Virus Evolution, Pathogenesis and anti-cancer potential

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

- **Prof. José Mª Almendral del Río. Catedrático. Departamento de BiologíaMolecular. UAM.**
- **Prof. Alberto López-Bueno. Profesor Titular. Departamento de BiologíaMolecular. UAM.**

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 serveral 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 mutatnions 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 nonstrutural proteins and produce more viral genomes in U373 than the two parental strains, suggesting an enhanced oncotropism

Publications

- **Assembly of Structurally Simple Icosahedral Viruses.** Gil-Ranedo, Jon; López-Bueno, Alberto; Almendral, José M. **Sub-Cellular Biochemistry**, 105, 403-430. 2024.

- **Assessment of molecular modulation by multifrequency electromagnetic pulses to preferably eradicate tumorigenic cells.** Piredda R, Martínez LGR, Stamatakis K, Martinez-Ortega J, Ferráz AL, Almendral JM, Revilla Y. **Sci Rep**. 2024 Dec 3;14(1):30150.

- **VEGF-Virus Interactions: Pathogenic Mechanisms and Therapeutic Applications.** Sánchez-Martínez C, Grueso E, Calvo-López T, Martinez-Ortega J, Ruiz A, Almendral JM**. Cells.** 2024 Nov 4;13(21):1815.

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.

Molecular ecology of extreme environments
http://www.cbm.uam.es/ramils

- **Prof. Ricardo Amils Pibernat. Profesor Emérito. Departamento de BiologíaMolecular. 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

- **A concept for international societally relevant microbiology education and microbiology knowledge promulgation in society.** Bernal, Patricia; Udaondo, Zulema; Ramos, Juan Luis; Amils, Ricardo; Parro, Victor; Rojo, Fernando; Chavarría, Max; García, José Luis; Nikel, Pablo Iván. **Microbial Biotechnology**. 17, e14456. 2024.

- **Antioxidant and Emulsifying Activity of the Exopolymer Produced by Bacillus licheniformis.** Concepción, Abrusci; Ricardo, Amils. **International Journal of Molecular Sciences,** 25, 8249. 2024.

- **Association of Acidotolerant Cyanobacteria to Microbial Mats below pH 1 in Acidic Mineral Precipitates in Río Tinto River in Spain.** Gómez F, Rodríguez N, Rodríguez-Manfredi JA, Escudero C, Carrasco-Ropero I, Martínez JM, Ferrari M, De Angelis S, Frigeri A, Fernández-Sampedro M, Amils R. **Microorganisms.** 2024 Apr 19;12(4):829.

- **Continental scientific drilling and microbiology: (extremely) low biomass in bedrock of central Sweden.** Amils, Ricardo; Escudero, Cristina. **Biogeosciences**, 7, 1501, 2024.

- **Draft genome sequence of the deep-subsurface Ciceribacter sp. strain T2.26MG-112.2, a second Rhizobiaceae isolated from the Iberian Pyrite Belt at 492.6 mbs.** Martínez JM, García R, Leandro T, Amils R. **Microbiol Resour Announc**. 2024 May 9;13(5):e0050223.

- **Geomicrobiology of Río Tinto (Iberian Pyrite Belt): A Geological and Mineralogical Mars Analogue.** Amils, Ricardo**. Geomicrobiology: Natural and Anthropogenic Settings,** 123-150, 2024.

- **Halotolerant Endophytic Bacteria Priestia flexa 7BS3110 with Hg2+ Tolerance Isolated from Avicennia germinans in a Caribbean Mangrove from Colombia**. Soto-Varela ZE, Orozco Sánchez CJ, Bolívar-Anillo HJ, Martínez JM, Rodríguez N, Consuegra-Padilla N, Robledo-Meza A, Amils R. **Microorganisms**. 2024 Sep 7;12(9):1857.

- **Metal tolerance of Río Tinto fungi.** Oggerin M, Del Moral C, Rodriguez N, Fernandez-Gonzalez N, Martínez JM, Lorca I, Amils R. **Front Fungal Biol**. 2024 Oct 16;5:1446674.

- **Natural hydrogen in the energy transition: Fundamentals, promise, and enigmas.** Bobadilla, Luis F.; Amils, Ricardo; Odriozola, José A.; Blay, Vincent; Reina, Tomas Ramirez; Blay-Roger, Rubén. **Renewable & Sustainable Energy Reviews**, 189, 113888, 2024.

- **Immunoanalytical Detection of Conserved Peptides: Refining the Universe of Biomarker in Planetary Exploration.** Mustieles-Del-Ser, Pedro; Ruano-Gallego, David; Parro, Víctor **Chem**. 2024, 96, 12, 4764–4773.

Projects

- Decifering the metabolism of Fe(II) oxidation associated to the reduction of nitrate (NRFeOx) and its utilization for the bioremediation of nitrate contaminated waters. TED2021-129563B-I00 (2023-2024). PI: R. Amils.

- 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.

- TYPE III SECRETION SYSTEM EFFECTOR NETWORKS: ARTIFICIAL INTELLIGENCE APPLIED TO STUDY INTESTINAL BACTERIAL. RYC2021-031342-I (PRTR). IP: David Ruano. MInisterio. 2023-2025.

Yeast enzymes bioengineering to generate bioactive compounds
http://www.cbm.uam.es/MFernandezLobato

- **Prof. María Fernández Lobato. Catedrática. Departamento de Biología Molecular.UAM.**
- **Prof. Miguel Remacha Moreno. Catedrático. Departamento de Biología Molecular.UAM.**

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

- **Chitinous material bioconversion by three new chitinases from the yeast Mestchnikowia pulcherrima**. Plou, Francisco J.; Fernández-Lobato, María; Cervantes, Fadia V.; Míguez, Noa; Minguet-Lobato, Marina; Minguet-Lobato, Marina. **Microbial Cell Factories,** 23,31. 2024.

- **Enzymatic modification of dihydromyricetin by glucosylation and acylation, and its effect on the solubility and antioxidant activity.** Rodriguez-Garcia D, Uceda C, Barahona L, Ruiz-Nuñez M, Ballesteros AO, Desmet T, Sanz-Aparicio J, Fernandez-Lobato M, Gonzalez-Alfonso JL, Plou FJ. **Org**

Biomol Chem. 2024 Dec 17.

- **Insights into the transglucosylation activity of α-glucosidase from Schwanniomyces occidentalis.** Merdzo Z, Narmontaite E, Gonzalez-Alfonso JL, Poveda A, Jimenez-Barbero J, Plou FJ, Fernández-Lobato M. **Appl Microbiol Biotechnol**. 2024 Aug 17;108(1):443.

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.

- TED2021-129288B-C22: Simplification of the use of chitin-enriched waste for the enzymatic production of bioactive chitooligosaccharides. AEI- Projects oriented towards the ecological transition and the digital transition. 11/2022-10/2024. Principal Investigator: María Fernández.

- PDC2022-133134-C22: Scaling up the production of glycosidases to obtain modified flavonoids and their evaluation in biomedical applications. EAI-Proof of Concept Projects.11/2022-10/2024. Principal Investigator: María Fernández.

Thesis

- Marina Minguet Lobato. Novel Chitinases and Hyaluronidases: Discovery and Application in the Synthesis of Bioactive Oligosaccharides. Directora: María Fernández Lobato (autorizada diciembre 2024, defendida enero 2025)

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

- **Cryo-EM of human rhinovirus reveals capsid-RNA duplex interactions that provide insights into virus assembly and genome uncoating.** Valbuena, Alejandro; Mateu, Mauricio G.; Mata, Carlos P.; Rodríguez-Huete, Alicia; Castón, José R.; Castón, José R.; Gil-Cantero, David; Valiente, Luis. **Communications Biology**, 21, 373-384.2024.

- **Engineering and Bio/Nanotechnological Applications of Virus Particles.** Valbuena, Alejandro; Mateu, Mauricio G. **Sub-Cellular Biochemistry**, 105, 823-878, 2024.

- **Introduction: The Structural Basis of Virus Function.** Mateu, Mauricio G. **Sub-Cellular Biochemistry**, 105, 3-53, 2024.

- **Mechanical Properties of Viruses.** Mateu, Mauricio G. **Sub-Cellular Biochemistry**, 105, 629-691, 2024.

- **Single-Molecule Analysis of Genome Uncoating from Individual Human Rhinovirus Particles, and Modulation by Antiviral Drugs.** Valbuena A, Strobl K, Gil-Redondo JC, Valiente L, de Pablo PJ, Mateu MG. **Small.** 2024 Feb;20(6):e2304722

- **Structural Basis for Alternative Self-Assembly Pathways Leading to Different Human Immunodeficiency Virus Capsid-Like Nanoparticles.** Valbuena, Alejandro; Mateu, Mauricio G.; Abia, David; Gómez-Puertas, Paulino; Marcos-Alcalde, Íñigo; Domínguez-Zotes, Santos; Escrig, Judith. **Acs Nano,** 18, 27465-27478, 2024.

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 Virológica
- Global Virology Network
- Global Foot-and-Mouth Disease Research

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.**

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 (0-4ºC).

During these last two years, our experimental approach has relied on systems-level approaches to identify transcriptional and post-transcriptional regulatory networks at 4ºC. We performed transcriptomics analyses along the acclimation from 37ºC to 4ºC, 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 4ºC. 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.

Publications

- **Experimental evidence of d-glutamate racemase activity in the uncultivated bacterium Candidatus Saccharimonas aalborgensis.** Peñalver M, Paradela A, Palacios-Cuéllar C, Pucciarelli MG, García-Del Portillo F. **Environ Microbiol**. 2024

- **Kinetic and proteomic studies in milk show distinct patterns among major Listeria monocytogenes clones.** Espí-Malillos A, Palacios-Gorba C, López-Almela I, Ruiz-García P, López-Mendoza MC, García-Del Portillo F, Pucciarelli MG, Quereda JJ. **Microbes Infect**. 2024 Feb 10:105312.

- **Rli51 Attenuates Transcription of the Listeria Pathogenicity Island 1 Gene mpl and Functions as a Trans-Acting sRNA in Intracellular Bacteria.** Morón Á, Ortiz-Miravalles L, Peñalver M, García-Del Portillo F, Pucciarelli MG, Ortega AD. **Int J Mol Sci.** 2024 Aug 29;25(17):9380.

Ultrahigh-throughput discovery and engineering of enzymes for biotechnological applications
www.cbm.uam.es/ahidalgo

- **Prof. Aurelio Hidalgo Huertas. Profesor Titular. Departamento de BiologíaMolecular. 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 news hosts and methods for functional expression, compatible with enzymatic assays at high temperatures.

Publications

- **From accurate genome sequence to biotechnological application: The thermophile Mycolicibacterium hassiacum as experimental model.** Hidalgo, Aurelio; Gola, Susanne; Berenguer, José; Sánchez-Costa, Mercedes. **Microbial Biotechnology**, 17, e14290-e14290, 2024.

- **Thermostable in vitro transcription-translation compatible with microfluidic droplets.** Ribeiro ALJL, Pérez-Arnaiz P, Sánchez-Costa M, Pérez L, Almendros M, van Vliet L, Gielen F, Lim J, Charnock S, Hollfelder F, González-Pastor JE, Berenguer J, Hidalgo A. **Microb Cell Fact.** 2024 Jun 10;23(1):169.

Projects

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

PROJECTS ONGOING in 2024

Reference	Principal Investigator(s)	Title	Funding entity
2020-T1/BMD-19970	PAZOS DON PEDRO, MANUEL	Atracción del Talento	Madrid Regional Gov.
S2022/BMD-7209	MAYOR MENENDEZ, FEDERICO	INTEGRAMUNE-CM: SISTEMAS CELULARES Y MOLECULARES INTEGRADOS EN FISIOPATOLOGIA INMUNE-INFLAMATORIA	Madrid Regional Gov.
Y2020/BIO-6350	CARRASCO CERRO, ELISA	ESTRATEGIAS NUTRICIONALES DE PRECISIÓN PARA REACTIVAR EL SISTEMA INMUNE DETERIORADO COMO CONSECUENCIA DE LA EDAD, LA OBESIDAD O LA QUIMIOTERAPIA	Madrid Regional Gov.
101000560-RADICALZ-H2020-FNR-2020/H2020-FNR-2020-2	HIDALGO HUERTAS, AURELIO	RAPID DISCOVERY AND DEVELOPMENT OF ENZYMES FOR NOVEL AND GREENER CONSUMER PRODUCTS	European Union
101047177 — OpenMIND	PEREZ PEREIRA, MARTA	OPTO-ELECTRONIC NEURAL CONNECTOID MODEL IMPLEMENTED FOR NEURODEGENERATIVE DISEASE	European Union
101081957-BLUETOOLS-HORIZON-CL6-2022-CIRCBIO-01	HIDALGO HUERTAS, AURELIO	INNOVATIVE TOOLS FOR SUSTAINABLE EXPLORATION OF MARINE MICROBIOMES TOWARDS A CIRCULAR BLUE	European Union
818602-MARSFIRSTWATER-2018-COG	SANZ MARTIN, JOSE LUIS	THE PHYSICOCHEMICAL NATURE OF WATER ON EARLY MARS	European Union
H2020-MSCA PROGRAMME, GRANT AGREEMENT 860229-	MAYOR, FEDERICO	ONCORNET2.0 (ONCOgenic Receptor Network of Excellence and Training)	European Union
948478 MitoCure ERC-2020-STG	BALSA MARTINEZ, EDUARDO	MOLECULAR AND METABOLIC MECHANISMS UNDERLYING MITOCHONDRIAL DYSFUNCTION	European Union
956631 — CC-TOP — H2020-MSCA-ITN-2020	HIDALGO HUERTAS, AURELIO	C-C BOND FORMATION USING TOP PERFORMING ENZYMES	European Union
ERC-CoG-2020-101001916	LLORENS MARTIN, MARIA VICTORIA	HUMAN: INTERROGATING HUMAN ADULT HIPOCAMPAL NEUROGENESIS	European Union
Project 101160079 — BRIDGING-RD	PEREZ GONZALEZ, BELEN	Bridging the research and innovation gap for rare diseases in Europe by upgrading exellence of IMGGE	European Union
PR_EX_2022_01	BALSA MARTINEZ, EDUARDO	METABOLIC HETEROGENEITY AS A CRITICAL DETERMINAT OF MELANOMA METASTASIS PROJECT	CRIS Foundation
CONVENIO FJD	SANTOS HERNANDEZ, JAVIER	ANÁLISIS GENÓMICOS Y TRANSCRIPTOMICOS EN EL TRATAMIENTO PERSONALIZADO DE NEOPLASIAS	IIS-FJD Hospital
ION-ARPA	GARCIA ESCUDERO, VEGA	3' REPLACEMENT OF TAU MRNAS IN ALZHEIMER'S DISEASE BY A REPLICATIVE TRANS-SPLICING RIBOZYME-ION-ARPA	IONIS

CNS2023-143646 (PRTR)	COGLIATI, SARA	Descubrimiento de las vías mitocondriales relacionadas con la protección cardíaca del estradiol como tratamiento potencial para la insuficiencia cardiaca durante la menopausia	AEI- Spain
PDC2021-121052-I00 (PRTR)	YAÑEZ MO, MARIA	Vacunas basadas en exosomas miméticos	AEI- Spain
PDC2022-133134-C22 (PRTR)	FERNANDEZ LOBATO, MARIA	Escalado de la producción de glicosidasas para la obtención de flavonoides modificados y su evaluación en aplicaciones biomédicas	AEI- Spain
PDC2022-133147-I00 (PRTR)	MIGUEZ GOMEZ, DAVID	OSCAR, an Object Segmentation, Counter, Analysis Resource	AEI- Spain
PID2020-113204GB-I00	HERNANDEZ PEREZ, FELIX	Neurorregeneración en la enfermedad de Alzheimer a través de la expresión de factores de pluripotencia in vivo	AEI- Spain
PID2020-113921RB-I00	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 PATOGÉNICOS Y BIOMARCADORES	AEI- Spain
PID2020-114054RA-I00	COGLIATI, SARA	Dimorfismo sexual en el metabolismo de la glucosa: caracterización del papel mitocondrial.	AEI- Spain
PID2020-114499RB-I00	PARDO MERINO, BEATRIZ	Transportadores mitocondriales regulados por calcio: Papel de SCaMC3 y citrin en la señalización por calcio en el higado y de Aralar en la comunicación intercelular en el SNC	AEI- Spain
PID2020-117025RB-I00 (UAM)	HIDALGO HUERTAS, AURELIO	Búsqueda y mejora de 2desoxirribosil transferasas mediante métodos de ultra-alto rendimiento para la síntesis sostenible de nuevos análogos de nucleósido terapéuticos	AEI- Spain
PID2020-117218RB-I00	MAYOR MENENDEZ, FEDERICO	Redes de señalización de GRK2 y mecanismos moleculares de procesos patológicos	AEI- Spain
PID2020-117916RB-I00	REQUENA ROLANIA, JOSE MARIA	Integración de datos omicos para descifrar la organización y expresión génicas en Leishmania: pistas para enfrentar las leishmaniasis	AEI- Spain
PID2020-118189RB-I00	PEREZ PEREIRA, MARTA	Cerebroides: desarrollo y complejidad	AEI- Spain
PID2020-119399RB-I00	LOPEZ CORCUERA, BEATRIZ	EL TRANSPORTADOR NEURONAL DE GLICINA GlyT2 EN DOLOR Y EN HIPERPLEXIA. IMPLICACIONES PATOLÓGICAS EN DESARROLLO	AEI- Spain
PID2020-119627GB-I00	YAÑEZ MO, MARIA	Microdominios de membrana, exosomas, virus y vacunas	AEI- Spain
PID2021-123269OB-I00 (FEDER-UE)	CUBELOS ALVAREZ, BEATRIZ	Papel de R-Ras1 y R-Ras2 en la diferenciación y especificación oligodendrocitaria	AEI- Spain
PID2021-123389OB-I00 (FEDER-UE)	GIRONES PUJOL, NURIA	Papel del ligando del receptor SLAMF1 de Trypanosoma cruzi y de microRNAs durante la infección: aplicaciones en diagnóstico y terapia	AEI- Spain
PID2021-125844OB-I00 (FEDER-UE)	VENTOSO BANDE, IVAN	Reprogramación traduccional inducida por estrés en eucariotas y su influencia	AEI- Spain

		sobre la proteostasis celular. Mecanismos e impacto sobre	
PID2021-126973OB-I00 (FEDER-UE)	GARCIA MATEU, MAURICIO	Biomecánica y dinámica de virus humanos para el desarrollo de fármacos antivirales y materiales modificados por ingeniería de proteínas para usos biomédicos o nanotecnológicos	AEI- Spain
PID2022-136367OB-C32 (FEDER, UE)	FERNANDEZ LOBATO, MARIA	Producción y modificación funcional de glicoenzimas para la obtención sostenible de glicoderivados por transglicosilacion	AEI- Spain
PID2022-136607NB-I00 (FEDER, UE)	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	AEI- Spain
PID2022-136738OB-I00 (FEDER, UE)	FORMENTINI, LAURA	Disfunción de la actividad	AEI- Spain
PID2022-136810OB-I00 (FEDER, UE)	TRABA DOMINGUEZ, JAVIER	Regulación de la inmunidad innata y adaptativa por los niveles mitocondriales de nicotinamida adenina dinucleotido (NAD+).	AEI- Spain
PID2022-137238OB-I00 (FEDER, UE)	RUIZ DESVIAT, LOURDES	Enfermedades neurometabólicas raras: de la investigacion en nuevos modelos de enfermedad a terapias dirigidas	AEI- Spain
PID2022-137404OB-I00 (FEDER, UE)	BALSA MARTINEZ, EDUARDO	Descifrando el metabolismo mitocondrial como diana para la progresión tumoral y la metástasis.	AEI- Spain
PID2022-137468OB-I00 (FEDER, UE)	MENCIA CABALLERO, MARIO	Desarrollo de un sistema biológico y de hardware para la evolución continua de proteínas en Thermus thermophilus para aplicaciones biotecnológicas	AEI- Spain
PID2022-137487OB-I00 (FEDER, UE)	FRESNO ESCUDERO, MANUEL	Papel de TCFL5 en procesos de diferenciación, inmunosenescencia, inflamación y transtornos asociados al envejecimiento.	AEI- Spain
PID2022-137552OA-I00 (FEDER, UE)	REGLERO REAL, NATALIA	Desenmascarando nuevos papeles de los procesos de autofagia endotelial en la inflamación	AEI- Spain
PID2022-138782OA-I00 (FEDER, UE)	RUANO GALLEGO, DAVID	Descifrando las redes de efectores del Sistema de Secreción Tipo 3.	AEI- Spain
PID2022-140421NB-I00 (FEDER, UE)	MIGUEZ GOMEZ, DAVID	Interacción entre mecanismos físicos y moleculares en la regulación de la formación de la retina en vertebrados.	AEI- Spain
PID2022-140632NB-I00 (FEDER, UE)	LOPEZ GUERRERO, JOSE ANTONIO	Diseminación del virus herpes simplex tipo 1 en oligodendrocitos humanos: papel de la autofagia y del proteolípido MAL.	AEI- Spain
PID2022-140818OA-I00 (FEDER, UE)	PAZOS DON PEDRO, MANUEL	Bases moleculares de la inhibición de la división celular mediada por proteínas SPOR	AEI- Spain
PID2022-141799OB-I00 (FEDER, UE)	ALMENDRAL DEL RIO, JOSE MARIA	Reorientación de la Infección de Parvovirus hacia Procesos Celulares Determinantes del Cáncer Humano.	AEI- Spain
PID2022-143030OB-I00 (FEDER, UE)	DIAZ NIDO, JAVIER	Neurodegeneración en el cerebelo de modelos de ataxia de Friedreich: Bases moleculares y aproximaciones terapéuticas.	AEI- Spain
PID2023-146735OB-I00 (FEDER, UE)	MAYOR MENENDEZ, FEDERICO	lnteractomas del nodo GRK2 en señalización celular e implicaciones patológicas	AEI- Spain

PID2023-146837OB-I00 (FEDER, UE)	PARDO MERINO, BEATRIZ	Funciones de AGC1/Aralar en neuronas y OPCs en proliferación; mielinización, estado redox citosólico y niveles de aspartato	AEI- Spain
PID2023-146945NB-I00 (FEDER, UE)	PORLAN ALONSO, EVA	Dianas farmacológicos en las decisiones del destino de las células madre neurales: implicaciones para la regeneración	AEI- Spain
PID2023-148516OB-I00 (FEDER, UE)	COGLIATI, SARA	Estradiol y oxidación de ácidos grasos: entender su relación para proteger el corazón de la mujer posmenopáusica	AEI- Spain
PID2023-149460NB-I00 (FEDER, UE)	HERNANDEZ PEREZ, FELIX	Activación de transposones en modelos animales de la enfermedad de Alzheimer: implicación de la proteína tau	AEI- Spain
PID2023-149514OB-I00 (FEDER, UE)	YAÑEZ MO, MARIA	Vesículas extracelulares e inmunoterapia frente al cancer	AEI- Spain
PID2023-150608OB-I00 (FEDER, UE)	LOPEZ CORCUERA, BEATRIZ	PATOLOGÍAS DEL TRANSPORTADOR NEURONAL DE GLICINA GlyT2: HIPERPLEXIA Y DOLOR. IMPLICACIONES EN DESARROLLO	AEI- Spain
PID2023-152460NA-I00 (FEDER, UE)	SANTOS LOPEZ, ALFONSO	EVOLUCION DE MICROBIO Y DE ELEMENTOS GENETICOS MOVILES	AEI- Spain
RYC2018-024342-I (FSE)	BALSA MARTINEZ, EDUARDO	AYUDA RAMON Y CAJAL	AEI- Spain
RYC2018-026050-I (FSE)	TRABA DOMINGUEZ, JAVIER	AYUDA RAMÓN Y CAJAL (INMUNIDAD, INFECCION Y NUEVAS TERAPIAS)	AEI- Spain
RYC2021-031221-I (PRTR)	REGLERO REAL, NATALIA	RAMON Y CAJAL 2021	AEI- Spain
RYC2021-031342-I (PRTR)	RUANO GALLEGO, DAVID	TYPE III SECRETION SYSTEM EFFECTOR NETWORKS: ARTIFICIAL INTELLIGENCE APPLIED TO STUDY INTESTINAL BACTERIAL	AEI- Spain
RYC2022-037765-I (FSE+)	SANTOS LOPEZ, ALFONSO	UNDERSTANDING THE EVOLUTION OF ANTIBIOTIC RESISTANCE	AEI- Spain
TED2021-129288B-C22 (PRTR)	FERNANDEZ LOBATO, MARIA	Simplificación del aprovechamiento de desechos enriquecidos en quitina para la producción enzimática de quitooligosacaridos bioactivos	AEI- Spain
TED2021-129563B-I00 (PRTR)	AMILS PIBERNAT, RICARDO	DESCIFRANDO EL METABOLISMO DE LA OXIDACION DE FE(II) ASOCIADA A REDUCCION DE NITRATO (NRFEOX) Y SU UTILIZACION PARA LA BIORREMEDIACION DE AGUAS CONTAMINDAS CON NITRATOS.	AEI- Spain
TED2021-130430B-C22 (PRTR)	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.	AEI- Spain

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