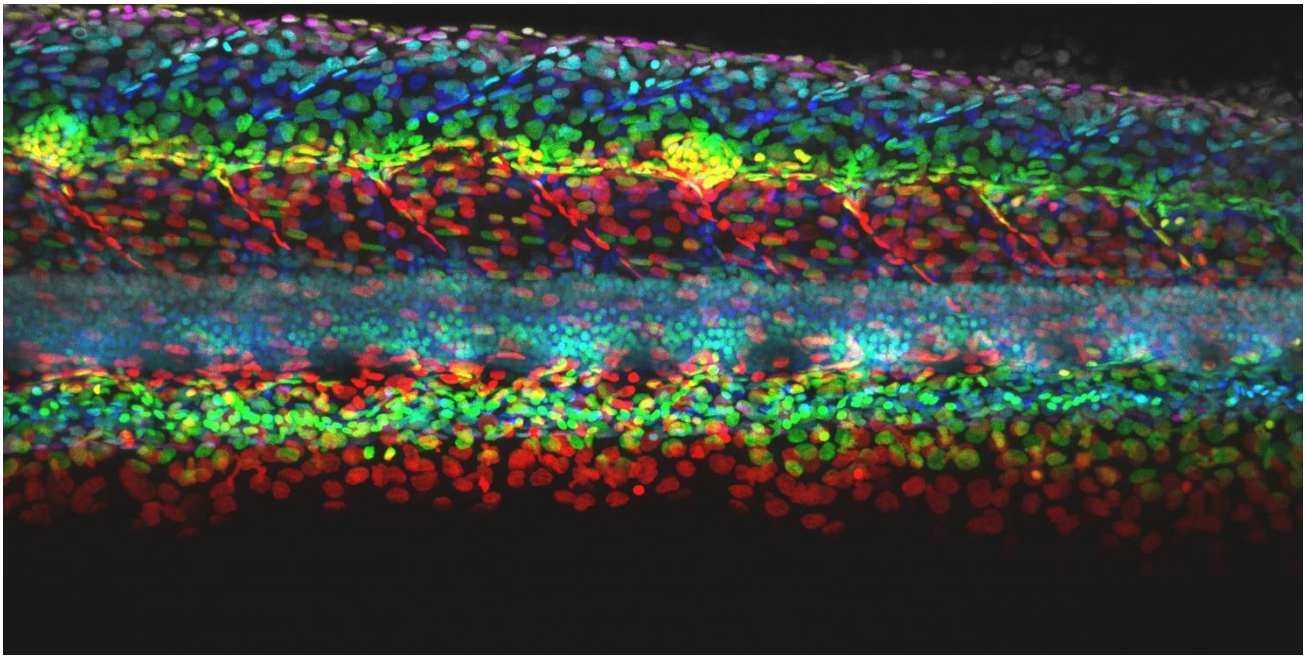
Centro
Andaluz
de Biología
del Desarrollo

Annual Report 2025



EXCELENCIA MARÍA DE MAEZTU

AGENCIA ESTATAL DE INVESTIGACIÓN

Junta de Andalucía

UNIVERSIDAD PABLO DE OLAVIDE SEVILLA

CSIC

CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

CABD Annual Report 2025

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Cover: Zebrafish larva 3.5 days post fertilization. Visualization of nuclei and slow and fast muscle fibres (Authors: José María Urbano and Ariadna Crespo).

CABD Activities 2025

The Andalusian Centre for Developmental Biology (*Centro Andaluz de Biología del Desarrollo*, CABD) is devoted to investigating the architecture and function of living organisms. Since its foundation in 2003, the CABD has grown steadily and is widely recognised as a centre of scientific excellence. The success of the centre is reflected by two consecutive ***María de Maeztu*** (MdM) **Unit of Excellence** awards from the Spanish *Agencia Estatal de Investigación* (2017-2021, 2022-2025). The centre hosts 30 established groups and 4 emerging groups that investigate fundamental aspects of development, genetics, cell biology and microbiology. Many of the processes studied at the CABD are relevant to human health, and several CABD groups collaborate closely with clinicians and patient associations to explore biomedical perspectives.

Two **new group leaders** and one **junior group leader** were appointed in 2025. New incorporations of pre- and postdoctoral researchers, as well as staff to scientific platforms, service facilities and administration raised the CABD personnel to 291 by the end of 2025. This number includes 53 undergrad students (mainly B.Sc., M.Ms. and FP students) and visitors, reflecting the extensive CABD efforts in training of early career scientists. The personnel are contracted by the Spanish National Research Council (CSIC) and the Pablo de Olavide University (UPO) in roughly equal numbers whereas institutional support is also provided by the Andalusian Regional Government (Junta de Andalucía). Group Leader Francisca Martínez was selected for the prestigious **EMBO Young Investigator Programme**, bringing the number of former and current CABD EMBO YIPs to 5. The academic activities of CABD personnel in 2025 included a significant number of lectures, practical classes, planning as well as supervision of students at B.Sc., M.Sc., and Ph.D. level: 79 theses were successfully defended at the CABD in 2025.

Funding for **22 new research projects** was obtained through competitive calls from national and international agencies, worth a total of ~7.0 million euros. CABD researchers were also involved in multiple contracts to foster collaborations between public and private entities through for instance the newly started spinoff company **ONESTX** that was awarded 1.4 million euros from the Spanish Research Agency to develop clinical trials with Alzheimer patients. The scientific productivity of the CABD in terms of publications amounted to **93 peer-reviewed articles and book chapters** and ~5,300 citations during 2025, mostly with open access in leading journals and with the participation of numerous scientists from international institutions. This reflects the open and collaborative spirit of CABD researchers, which is also evident from the many contributions to congresses and the organization of large scientific events, such as the “III Meeting of the European Network EURESTOP” and the “Danio-ReCODE Marie Skłodowska-Curie Network Meeting” celebrated in Seville in January and September, respectively. Moreover, the CABD is very active in science dissemination with tailored events for a variety of audiences across age and educational backgrounds.

2025 was the fourth year of the CABD’s strategic plan “***Decision Making in Cell Collectives across Scales***” (DMC3). The overarching objective of DMC3 is to understand how cell collectives have evolved and how they are organized to generate and maintain complex living organisms. To achieve a complete picture, the objective is approached at cellular, organismal, and ecological level using a variety of computational, genomics, proteomics and imaging techniques. The strategic plan is organized around five central questions and from the individual group reports included in the following pages, it is evident that many interesting answers are being discovered for each of them. Some CABD groups host associated scientists with independent projects, some of which are included in this report.

One of the central questions in DMC3 deals with the relationship that regulatory and structural changes in the genome have with **evolutionary innovations** (“Q1”). This has been addressed in

several studies in 2025. Evolutionary innovations often emerge not from the creation of entirely new genes, but through the **rewiring and repurposing of conserved gene expression programmes**, a process termed "developmental systems drift". For instance, comparative single-cell analyses of bat wing development revealed that the transformation of forelimbs into wings involves the evolutionary reuse of a proximal limb programme—specifically the transcription factors *MEIS2* and *TBX3*—in the distal tissue of the embryo. Similarly, while the core transcription factors regulating eye development are conserved between *Drosophila* and the hoverfly *Episyrphus balteatus*, there is substantial variation in their regulatory interactions and the distribution of **cis-regulatory elements (CREs)**. These CREs orchestrate the spatiotemporal regulation of transcriptional programmes, and their functional diversification is a primary driver of morphological evolution. Small changes in enhancer sequences can lead to **heterochrony**, such as temporal shifts in *Otd* expression that account for differences in ommatidial size between species. Furthermore, computational frameworks like FANTASIA showed that protein functional similarities can be decoupled from classical sequence conservation, revealing how structural and regulatory genomic changes allow biological functions to self-organize and emerge across distant taxa. High-quality diploid genome assemblies are increasingly used to resolve these regulatory dynamics, providing a clearer picture of how genomic variation translates into the remarkable phenotypic diversity seen in nature.

Another central question relates to the coordinated use of gene regulatory networks between neighbouring cells and organs (“Q2”). Cells communicate their physiological and developmental states across space and time through sophisticated **inter-organ signalling axes** to maintain systemic homeostasis. A striking example is the role of **macrophage-derived Dpp** (a BMP2/4 homolog), which acts as a systemic regulator during dietary stress. When larvae are exposed to a high-sugar diet, macrophages sense this environmental change and secrete Dpp, which signals the prothoracic gland to inhibit the synthesis of the steroid hormone ecdysone, thereby prolonging development to ensure the organism reaches an optimal size. Another dimension of this communication is the **"male pre-mating response"** in *Drosophila*, where the brain's perception of female sexual pheromones triggers metabolic changes across the fat body and gonads, mobilizing energy reserves like glycogen and lipids to prepare for reproduction. On a different scale, local mitochondrial stress in neurons is communicated through a **neuron–glia–intestine signalling axis**, which scales local perturbations into coordinated organismal responses that influence longevity and adaptation. This spatial coordination is also evident during tissue morphogenesis, where cells must harmonize gene regulatory networks with their neighbours to ensure robust developmental outcomes. Furthermore, horizontal gene transfer in microbial communities allows horizontally acquired genes to integrate into distinct regulatory and metabolic networks, effectively harmonizing gene circuits across different cellular contexts.

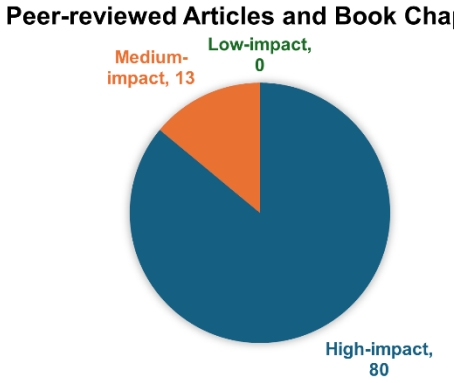
The capacity of cells to sense and respond to changes in their environment represents the third central question: which are the underlying mechanisms and what role do they play in cell collectives’ behaviour (“Q3”)? Studies at the CABD described in 2025 how cells continuously sense and respond to environmental and mechanical cues, often coordinating these responses to drive **collective cell behaviours**. Mechanically, cells interpret information such as the **pulsatile contractions of the yolk** to activate morphogenetic movements like epiboly during gastrulation. Similarly, the balance between internal mechanical forces and those exerted by the **extracellular matrix (ECM)** is essential for cell shape changes; for example, a localized reduction in integrin-dependent adhesion is sufficient to trigger basal epithelial tissue folding. In response to chemical stressors like hydroxyurea (HU), cells undergo a striking **structural remodelling** involving perinuclear ER expansion and the clustering of nuclear pore complexes (NPCs). This phenotype, triggered by thiol stress, activates specific proteostatic mechanisms in both the ER and cytoplasm to manage misfolded proteins. In microbial

environments, bacteria sense cues to regulate individual traits, such as polar flagellar assembly, as well as collective transitions like **starvation-induced biofilm dispersal**. Complex microbial consortia demonstrate collective adaptation by rapidly re-organizing their genetic information—often via plasmids and transposable elements—to degrade pollutants like ibuprofen. Such collective decisions are heavily influenced by environmental pressures, including antibiotic stress, which drives the emergence of adaptive traits and the integration of new resistance determinants within the community.

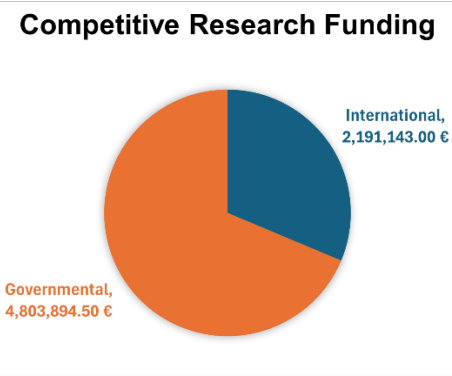
The **spatial organization of the genome** within the nucleus and its physical boundaries are critical regulators of gene expression and cellular resilience (“Q4”). CABD researchers study the **cohesin complex**, which is a central player in this architecture, organizing chromatin hubs and maintaining the 3D genome structure necessary for proper development and genomic stability. The physical integrity of the nuclear boundary is maintained by proteins like **BAF (Barrier to Autointegration Factor)**; mutations in BAF, such as those found in Nestor-Guillermo Progeria Syndrome (NGPS), lead to growth retardation and skeletal defects by disrupting the rate and fidelity of protein synthesis. Within the nucleus, structural tethers such as **Lem2** anchor telomeres to the nuclear periphery, a spatial arrangement essential for fungal pathogenesis. Furthermore, the nucleus exhibits dynamic physical changes during development, such as the formation of a novel "interkinetic envelope" that surrounds chromosomes between meiotic divisions in oocytes. Mechanical stress also directly impacts the nucleus, where environmental pressures like **thiol stress** can force the physical separation of the inner and outer nuclear membranes and the reorganization of nuclear speckles. These speckles play a vital role in splicing regulation and the reprogramming of embryonic stem cells towards totipotency. Ultimately, these structural features ensure that the genome remains correctly organized to respond to internal and external cues.

The fifth question relates to energy constrains and metabolic states and the role they play in tissue morphogenesis, aging and disease (“Q5”). Several CABD groups focus on the biogenesis and function of mitochondria, an organelle that is central to these processes, using a variety of models, including yeast, nematodes, flies, fish, mice and organoids as well as cells derived from human patients. The **EMC complex** acts as a critical transmembrane chaperone that maintains **membrane fluidity** by facilitating sterol homeostasis (specifically ergosterol); its deficiency leads to rigid membranes, impaired mitochondrial respiration, and respiratory failure. This link between lipid composition and aerobic energy production is vital for survival during quiescence. Metabolism also influences homeostasis via **epigenetic regulation**; for example, the nutrient **biotin** can increase histone biotinylation to reactivate the inactive X chromosome, restoring the expression of the *WDR45* gene and correcting bioenergetic defects in neurodegenerative BPAN cells. Energy availability is particularly decisive in the development of the human nervous system, as seen in **brain organoids** where neuronal differentiation processes are shaped by metabolic constraints. In aging, energetic shifts are often coordinated with transcription and alternative splicing, as observed in the *Drosophila* ovarian stem cell niche where factors like **Smu1** are necessary for niche homeostasis. Furthermore, mitochondrial perturbations in neurons influence systemic aging by triggering organismal stress responses. This metabolic-dependent regulation is often mediated by enzymes like **histone deubiquitinases**, which modulate stress responses based on the cell's energetic state, highlighting the pervasive role of metabolism in shaping the aging process and disease susceptibility.

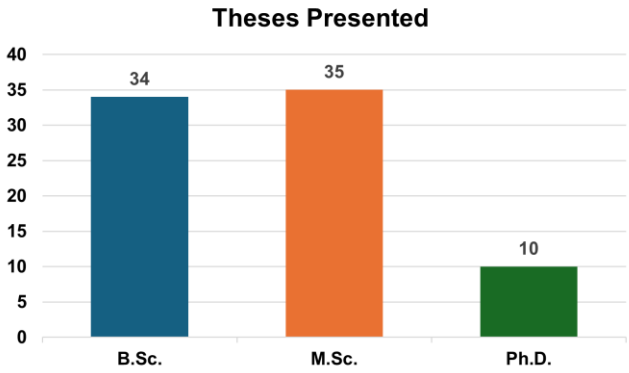
CABD Facts & Figures 2025



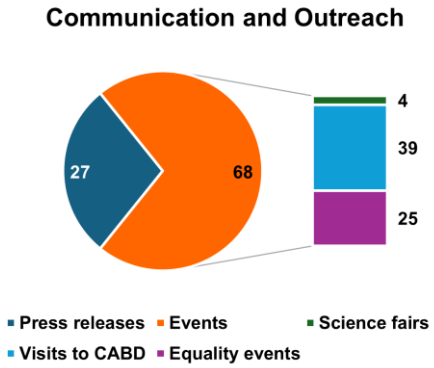
We published 93 peer-reviewed articles and book chapters in 2025. Of these, 80 (86%) were classified as high-impact by the CSIC and 13 (14%) as medium-impact. Co-authors from foreign institutions contributed to 65 (70%) of the publications.



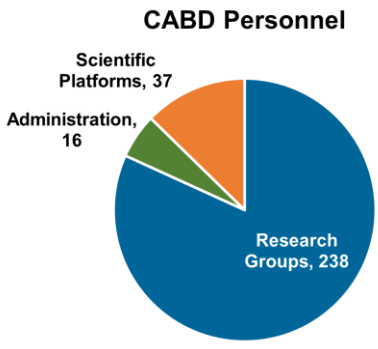
The CABD obtained 22 grants from competitive funding schemes: 20 from the Spanish Government, 1 from the European Commission and 1 from the European Research Council.



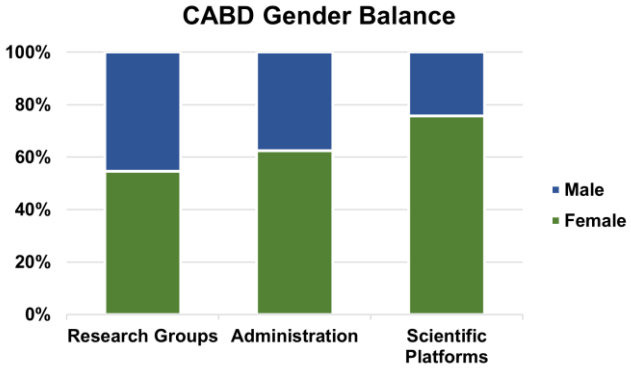
A total of 79 theses were presented in 2025. The majority represented M.Sc. projects (44%), followed by B.Sc. projects (43%) and doctoral theses (13%).



We were in contact with more than 3500 persons across all ages – mainly school and high school students – through 68 outreach events in 2025.



Most CABD personnel are associated to Research Groups (82%), whereas 13% and 5% work in Scientific Platforms and Administration, respectively.



The majority of CABD personnel are women in the three categories: in total 168 females (58%) versus 123 males (42%).

Summer School on Genetic Research Models

Sol Sotillos (Establishment of Cell polarity and its Relationship to Signalling), Ana Fernández Miñán (Functional Genomics Facility), Laura Tomás Gallardo (Dorothy Hodgkin Proteomics and Biochemistry Facility)

Summary of activities:

Summer School in “Olavide en Carmona: Modelos genéticos en investigación, de la bacteria al ratón (I y II)” July 14-25 de julio.

This is a two weeks theoretical/practical course that provides an initial exposure to the most commonly used genetic model organisms in life science research: bacteria, yeast, *Caenorhabditis elegans*, *Drosophila melanogaster*, zebrafish, chick, and mouse. The objective is to offer a broad, integrative overview of these different model systems, emphasizing their experimental advantages and limitations through the application of various molecular and cell biology techniques, including RNA interference (RNAi), fluorescent immunohistochemistry and in vivo fluorescence imaging, and recombinant protein production, among others. The course is inspired by internationally renowned benchmarks, such as the Developmental Biology course at Institut Curie/Sorbonne University (Paris) and the Embryology course at the Marine Biological Laboratory (Woods Hole, Massachusetts). This course is designed for undergraduate students in Biology, Biotechnology, and related disciplines, as well as for postgraduate students (Master’s level and pre- and postdoctoral researchers). Participants gained an initial introduction to the most widely used techniques across different model organisms and learned their practical applications. The course was delivered by research staff from the Andalusian Centre for Developmental Biology (CABD), providing students with access to a nationally and internationally recognized research institute in developmental biology (the only one of its kind in Spain) where all these model systems are studied concurrently. Methodological training was complemented by theoretical lectures, ensuring that participants acquired a comprehensive theoretical and practical foundation in model systems. This training does not only strengthen their academic profile but may also assist them in defining their scientific objectives and even their future career paths. This course was partially funded by MdM DMC3 as part of its objectives.

Reference:

https://www.europapress.es/andalucia/noticia-investigadora-reivindica-upo-inversion-visibilidad-ciencia-basica-salva-vidas-no-perciba-20250717105257



Cell Division Control

Juan Jiménez

Summary of activities:

Using fission yeast as an eukaryotic cell model, we analyze genes required for the control of cell growth and division (collaborative project with Victor Alvarez). Through the analysis of the Oca3/Emc2 gene, early identified in our lab, we demonstrate that misfolded proteins, over-produced both directly and indirectly in EMC mutant cells, accumulate in the mitochondrial matrix resulting in mitochondrial defects, a phenotype that resembles mitochondrial disfunctions described in certain human diseases.

In a second research line (collaborative project with Andrés Garzón), we observed that flor yeast, the only wild Saccharomyces yeast free of Totivirus, can maintain these viruses when ectopically infected. In nature, infection only occurs through sexual reproduction. We suggest that the sexual isolation of flor yeast in their wild environment may be behind this Totivirus-free condition.

Finaly, the use of AnaBlast (an algorithm developed with Antonio Perez Pulido) allowed the identification of putative coding roles of tRNAs before ribosomes existed, driving me to propose a revolutionary hypothesis about the origin of life in earth.

Projects: Plan Nacional PGC 2023/00279/001 - *Totivirus en el campo, el lagar y el laboratorio. Conocimiento básico y aplicaciones*. PIs: A. Garzón and J. Jiménez

Ph D Thesis: Modesto Berraquero Pérez. *El papel de EMC en la homeostasis de membrana y función mitocondrial*. 2025. Directors: Juan Jiménez and Victor Alvarez-Tallada.

Teaching: I am engaged of teaching Genetics (both Spanish and English subjects), and participated in the “Olavide en Carmona” 2025 course “*Aromas de los vinos de Sevilla. Historia, tradición e innovación*”

Two highlights:

Ltc1 localization by EMC regulates cell membrane fluidity to facilitate membrane protein biogenesis. Berraquero M, Tallada VA, Jimenez J. iScience. 2025 Mar;28(3):112096. DOI: 10.1016/j.isci.2025.112096.

Jimenez, J. Earth, a planetary PCR machine to create life, or the brief history of a tRNA. *Discov Life* 55, 17 (2025). https://doi.org/10.1007/s11084-025-09691-8. (highlighted in https://scientias.net/la-tierra-la-maquina-planetaria-de-pcr-que-creo-la-vida/ and the podcast https://www.youtube.com/watch?v=jbKPXyXbi-g)



Daily temperature cycles of earth could have function as a PCR machine to generate an RNA-like hairpin, the first Darwinian “living molecule”.

Nuclear Dynamics in Cell and Developmental Biology

Peter Askjaer

Summary of activities:

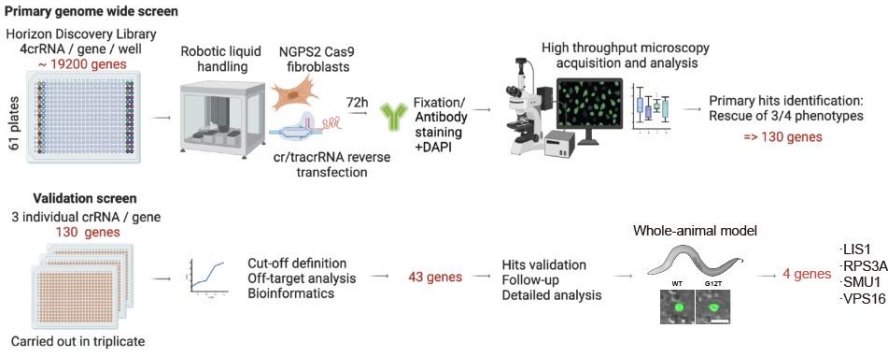
We recently developed a model of Nestor-Guillermo Progeria Syndrome (NGPS) in the nematode *Caenorhabditis elegans* (https://doi.org/10.1038/s44318-024-00261-8). NGPS is caused by a single amino acid substitution at position 12 (A12T) of the human nuclear envelope protein BAF (Barrier to Autointegration Factor). NGPS leads to growth retardation and severe skeletal defects, but the underlying mechanisms are unknown. In collaboration with the group of Dr. Delphine Larrieu (University of Cambridge, UK), we performed a genome-wide CRISPR screen combined with semi-automated high throughput microscopy, identifying 43 genes that rescued multiple cellular phenotypes in fibroblasts from NGPS patients. The hits are enriched for genes involved in protein synthesis, protein and RNA transport and osteoclast formation and were validated in our whole-organism *C. elegans* model. We further confirmed that BAF A12T can disrupt protein synthesis rate and fidelity, which could contribute to premature aging in patients. This reinforces the current hypothesis that loss of cellular homeostasis observed in both premature and physiological aging might occur through similar mechanisms. Our work highlights the power of multiparametric genome-wide suppressor screens to identify genes enhancing cellular resilience in premature aging and provide insights into the biology underlying progeria-associated cellular dysfunction.

We also collaborated with the groups of Dr. Julien Dumont (Institut Jacques Monod, Paris) and Dr. Antonio Miranda-Vizuete (Instituto de Biomedicina de Sevilla) in two studies that identified a novel membrane structure in meiosis and a connection between transsulfuration and redox homeostasis, respectively.

Two highlights:

An interkinetic envelope surrounds chromosomes between meiosis I and II in *C. elegans* oocytes. El Mossadeq L, Bellutti L, Le Borgne R, Canman JC, Pintard L, Verbavatz JM, Askjaer P, Dumont J. J Cell Biol. 2025 Mar 3;224(3):e202403125. doi: 10.1083/jcb.202403125.

A multiparametric anti-aging CRISPR screen uncovers a role for BAF in protein synthesis regulation. Breusegem SY, Houghton J, Romero-Bueno R, Fragoso-Luna A, Kentistou KA, Ong KK, Janssen AFJ, Bright NA, Riedel CG, Perry JRB, Askjaer P, Larrieu D. Nat Commun. 2025 Feb 16;16(1):1681. doi: 10.1038/s41467-025-56916-5.



Overview of screen in NGPS fibroblasts and nematodes to identify potential therapeutic targets to treat progeria.

Programmed Dell Death during Development and Disease

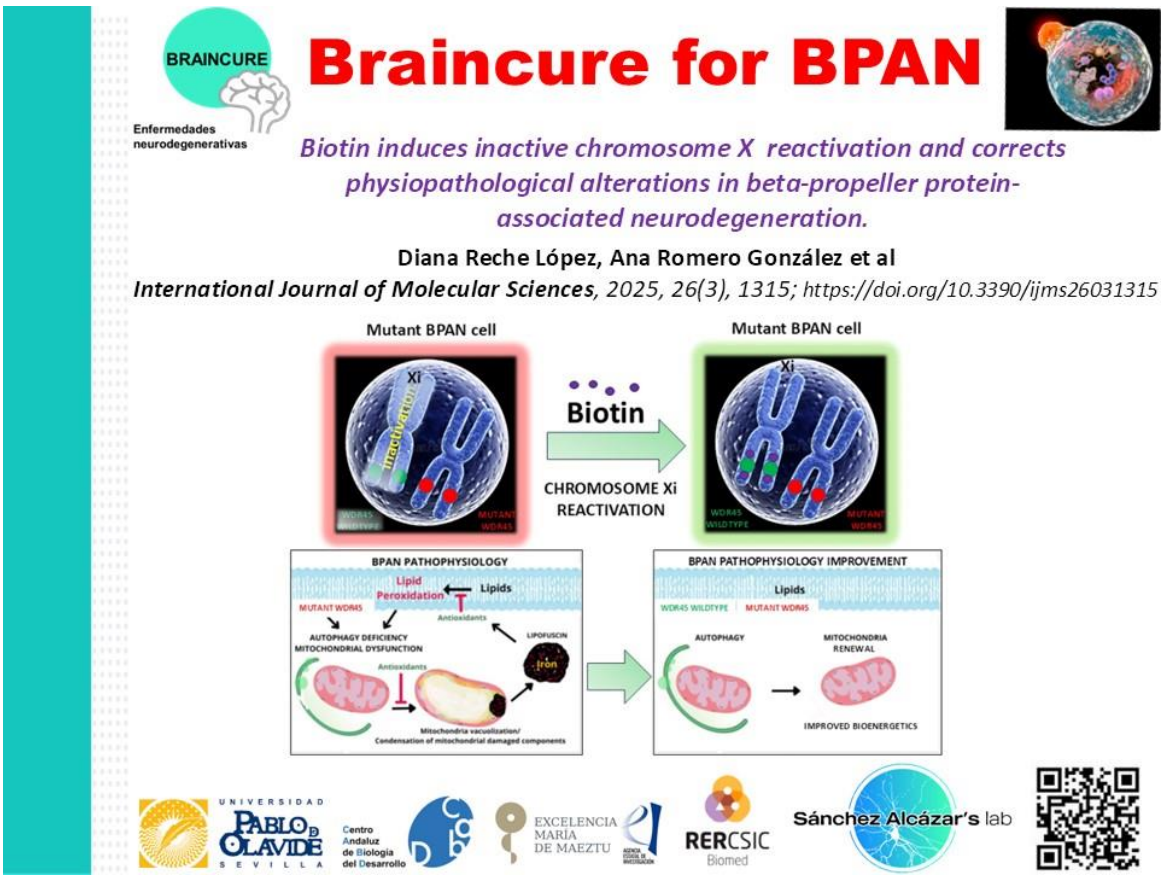
José Antonio Sánchez Alcázar

Summary of activities:

The group has continued its work in understanding the pathophysiological mechanisms and the search for therapeutic approaches in rare genetic diseases. It is worth noting that we collaborate in the clinical trials on KAT6A syndrome and mitochondrial diseases that are being carried out at the Virgen Macarena University Hospital in Seville. This research is aligned with the question Q5 of the DMC3 Strategic Plan - the relevance of energy constrains in collective cell decisions.

Highlight:

Biotin Induces Inactive Chromosome X Reactivation and Corrects Physiopathological Alterations in Beta-Propeller-Protein-Associated Neurodegeneration. Reche-López D, Romero-González A, Álvarez-Córdoba M, Suárez-Carrillo A, Cilleros-Holgado P, Piñero-Pérez R, Gómez-Fernández D, Romero-Domínguez JM, López-Cabrera A, González-Granero S, García-Verdugo JM, Sánchez-Alcázar JA. Int J Mol Sci. 2025 Feb 4;26(3):1315. doi: 10.3390/ijms26031315.



Control of Epithelial Morphogenesis in Vertebrates

Juan Ramón Martínez Morales

Summary of activities:

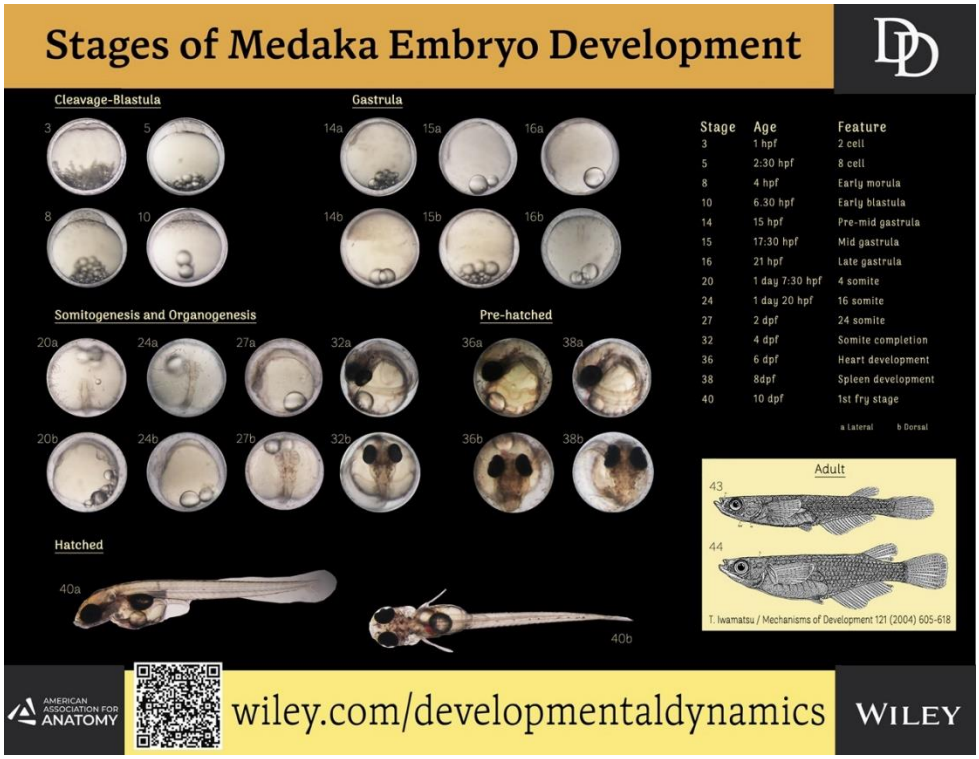
2025 has been again a transition year in the lab, with several publications to be released during 2026. Interesting results have been generated within the two main research lines/running grants in the laboratory. Both are very related with the objectives Q1 and Q3 of the MdM proposal.

a) **ProgRet-ITN**. (In collaboration with Juan Tena; H2020-MSCA-ITN-2022 (ID:101120562): In the frame of this project Sofia Manzo (DC) has generated reference RNAseq, ATACseq and Hi-Ci datasets for the retina in the aging model killifish; both in wild type and retinal dystrophy genetic models generated in the laboratory. In addition, the publication "Single-cell multiomics identifies key nodes and cis-regulatory elements of the networks specifying the eye domains in zebrafish. Macho et al 2026" has been deposited in BioRxiv and submitted for publication.

b) **MechaChrom**. Mechanical regulation of chromatin and transcription during tissue morphogenesis. MINECO. REF: PID2023-152286NB-I00. This proposal tackles how mechanical information is interpreted in the context of the gastrulating embryo. Cielo Centola (FPI) has identified a Yap-dependent key role for the pulsatile contractions of the yolk in the activation of the morphogenetic movements that direct epiboly and axis formation during gastrulation in the medaka embryo.

Highlight:

Insights and emerging perspectives from the 2025 Medaka PI/ERC IndiGene meeting: Heidelberg 22-24th July 2025. Acemel RD, Bobe J, Centanin L, Centola C, Chhabra S, Loosli F, Bhandari R, Vázquez-Marin J, Zilova L, Birney E, Wittbrodt J, Martinez-Morales JR. *Developmental Dynamics*. Accepted Dec 2025. Meeting report linked to the publication of the medaka developmental stages poster:



Stem Cell Behaviour in their Niches and Epithelial Morphogenesis

Acaimo González Reyes

Summary of activities:

2025 witnessed the publication of two research lines related to i) ageing in the *Drosophila* female germline stem cell (GSC) niche (Even-Ross et al., *Nature Communications*, 2025) and to ii) the signalling necessary to form a working female gonad during *Drosophila* development (Rosales-Nieves et al., *PLoS Genetics*, 2025).

We had reported that a number of genes involved in calcium signalling and the splicing factor *mbl* showed significant changes during ageing. This year we have characterized in detail the calcium transients detected in control niche cells of varying agess and found statistically significant differences between young and old cells. We also generated *mbl*-RNAi flies and studied calcium transients in *mbl* knock downs, observing significant differences with the controls. In addition, manipulation of genes involved in calcium metabolism and signalling (i.e., SERCA, GluRII and calmodulin) gave mutant phenotypes for some of them.

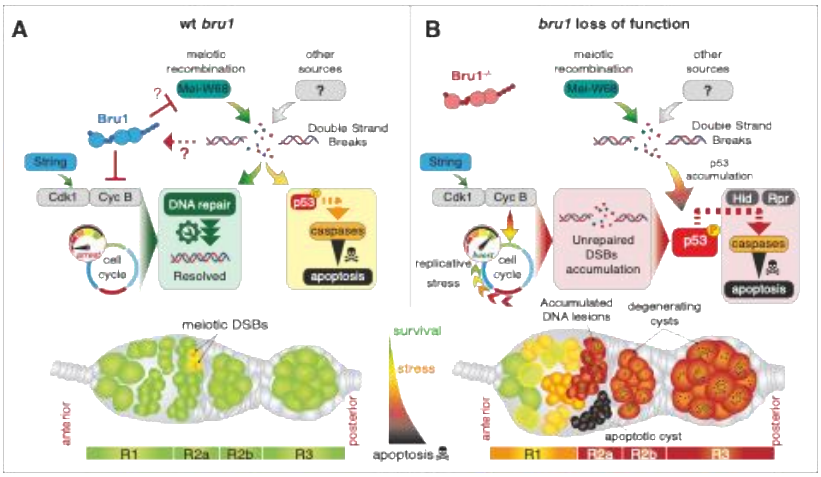
We have also devoted some energy to define the functions that the gene *bruno 1 (bru1*; it encodes for a translational repressor) has during early oogenesis. We have submitted a paper in which we demonstrate that *bru1* contributes to the mitosis-to-meiosis transition and prevents excess DNA damage and apoptosis in the germline. Our results thus reveal an essential role for *bru1* in the protection of germline integrity.

Our research on the ageing of a stem cell niche and on the molecular characterisation of gametogenesis fall within the MdM DMC3 Questions 3 and 5.

Two highlights:

Drosophila ovarian stem cell niche ageing involves coordinated changes in transcription and alternative splicing. Even-Ros D, Huertas-Romero J, Marín-Menguiano M, Nusspaumer G, Borge M, Irimia M, Zurita F, González-Reyes A. Nat Commun. 2025 Mar 16;16(1):2596. doi: 10.1038/s41467-025-57901-8.

ETS transcription factor pointed controls germline survival in Drosophila. Rosales-Nieves AE, Marín-Menguiano M, López-Onieva L, Garrido-Maraver J, González-Reyes A. PLoS Genet. 2025 Aug 25;21(8):e1011809. doi: 10.1371/journal.pgen.1011809.



Schematic model for Bru1 function in the gemarium.

Bacteriophages and their Relationship with CRISPR-Cas and other Defence Systems in Bacteria

Antonio J. Pérez Pulido

Summary of activities:

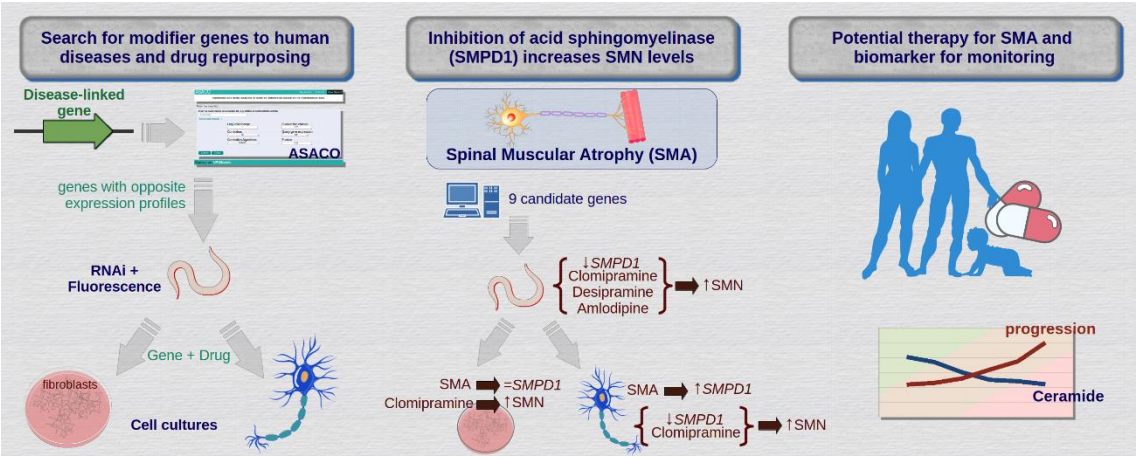
Our group is interested in studying bacteriophage-bacteria relationships using computational biology, with a particular focus on the evolution and dynamics of defense systems such as CRISPR-Cas systems. This year, we published the defensome of the bacterium *Acinetobacter baumannii* and discovered that its most prevalent clonal group lacks restriction-modification systems, which it replaces with Ssp systems based on phosphorothioate modifications. We also discovered the genome of a new strain of *A. guillouiae* in the assembly of a mite. Finally, in a multidisciplinary collaboration, we have associated sphingolipid metabolism with the rare disease Spinal Muscular Atrophy for the first time and proposed a possible drug for its treatment.

All of this has been complemented by six additional publications, including collaborations and an article derived from a Master's Thesis for the Master's Degree in Advanced Bioinformatics Analysis at Pablo de Olavide University..

Two highlights:

The evolutionary replacement of restriction-modification by Ssp antiviral systems is associated with the distribution of prophages in the major clonal group of Acinetobacter baumannii. Moreno-Rodríguez A, Rubio A, Garzón A, Smani Y, Pérez-Pulido AJ. mBio. 2025 Sep 10;16(9):e0213525. doi: 10.1128/mbio.02135-25.

Inhibition of acid sphingomyelinase increases SMN levels and connects sphingolipid metabolism to Spinal Muscular Atrophy. Brokate-Llanos AM, Beltran M, Garzón A, Garcera A, Miralles MP, Celma-Nos F, Campoy-López A, Soler RM, Muñoz MJ, Pérez-Pulido AJ. Biomed Pharmacother. 2025 Nov;192:118610. doi: 10.1016/j.biopha.2025.118610.



Graphical abstract of Brokate et al. (2025) Inhibition of acid sphingomyelinase increases SMN levels and connects sphingolipid metabolism to Spinal Muscular Atrophy

Genetic Regulation of Aging in *Caenorhabditis elegans*

Manuel J. Muñoz

Summary of activities:

The group's research has primarily focused on work bridging basic science and technology transfer, as traditionally pursued. Our investigations have centred on utilizing the nematode *Caenorhabditis elegans* as a platform for disease model generation, identification of novel therapeutic candidates, and understanding drug mechanisms of action. This year, we completed experiments and published findings on a C. elegans model of spinal muscular atrophy (SMA) and identified drugs that improve both the nematode model and neuronal cell cultures from SMA patients. This multidisciplinary collaboration involved the bioinformatics group at CABD (directed by Antonio Pérez-Pulido) and the University of Lleida team (directed by Rosa Soler), who conducted cellular assays (DOI: 10.1016/j.biopha.2025.118610). The intellectual property was protected through a 2024 patent, and the work was published in Biomedicine and Pharmacotherapy (Q1, IF 7.5). Additionally, in collaboration with the Institute of Materials Science, we studied the toxic effects of nanoparticles designed for therapeutic applications (DOI: 10.1002/adom.202501422). With the Institute of Fats, we identified food by-product extracts with biological activity that ameliorate neurodegenerative disease models in C. elegans (DOI: 10.3390/foods14061048). The group is a promoter of the spin-off Olavide Neuron STX, aimed at advancing STX64 to clinical trials, funded by private and public capital. Our research group currently receives funding to elucidate the drug's mechanism of action in C. elegans (MICIN. PID2024-161733OB-I00). In addition, we established a new Spin Off company called ArcoS Recombine, aimed at producing recombinant proteins using an innovate system. The company has already secured private capital funding.

Two highlights:

Inhibition of acid sphingomyelinase increases SMN levels and connects sphingolipid metabolism to Spinal Muscular Atrophy. Brokate-Llanos AM, Beltran M, Garzón A, Garcera A, Miralles MP, Celma-Nos F, Campoy-López A, Soler RM, Muñoz MJ, Pérez-Pulido AJ. Biomed Pharmacother. 2025 Nov;192:118610. doi: 10.1016/j.biopha.2025.118610.

Cr3+-Doped γ- and β-Gallium Oxide Nanoprobes for Bioimaging: Synthesis, Persistent Luminescence, and Biocompatibility. Arroyo E, Monje-Moreno JM, Torres-Herrero B, et al. Adv. Optical Mater. 13, no. 28 (2025): e01422. https://doi.org/10.1002/adom.202501422

The graphical abstract on the previous page illustrates the pipeline of the work published by the group in collaboration with the group of Antonio Perez and Rosa Soler. The interdisciplinary team afford the identification of new putative drugs to treat Spinal Muscular Atrophy. The workflow implies a bioinformatic analysis, search of candidates in an *C. elegans* model developed by the group and validation in neuronal patient cells.

Mitotic Spindle Nucleation and Coordination with the Cell Cycle

Víctor Álvarez Tallada

Summary of activities:

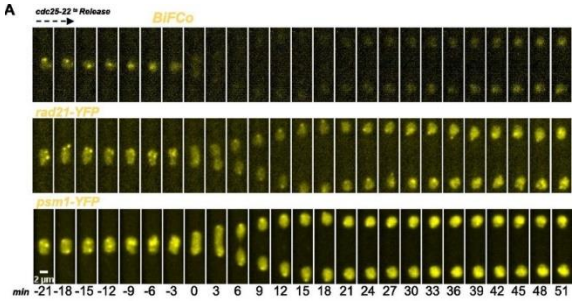
Our main research line deals with the regulation of ɣ-tubulin complex in the transition to enter into mitosis. We have identified key phosphorylation residues to license mitotic spindle firing in prophase. We are working in the identification of kinases and phosphatases involved in the regulation of these sites.

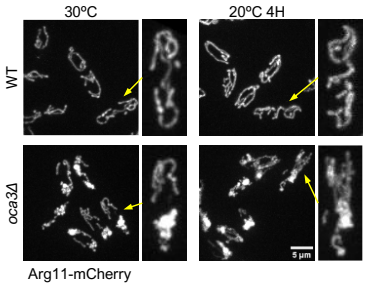
On other research lines we are working with cohesin complex in eukaryotes, which is essential to keep genome architecture, organising chromatin within the nucleus and regulating gene expression. We have developed a novel strategy as a proof of concept in fission yeast to track the assembled cohesin complex by fluorescence microscopy in living cells but excluding the signal of its individual proteins. This allows the quantification of cohesin loading in living cells in different genetic backgrounds, environment alterations, developmental stages etc. Based on these data and according to institute´s DMC3 Strategic plan, we are collaborating with Dr. James Castelli's group (UPO/CSIC collaboration) to implement this tool in drosophila and using it to study the role of cohesin in development, gene regulation and evolutionary conservation of factors necessary for the maintenance of genomic stability that we have identified in our studies in fission yeast. This may also be used as a good model to study genetic diseases such as cohesinopathies and cancer. We are sharing a predoc student supported by an FPI grant from Maria de Maeztu program within our institute to bring together the best of both worlds. In addition, over this year we have publish two works that demonstrate that the EMC complex is essential for membrane protein biogenesis and mitochondrial function in fission yeast. Specifically, EMC facilitates the localization of Lam6/Ltc1, which regulates ergosterol homeostasis and membrane fluidity. EMC deficiency leads to ergosterol overaccumulation, rigid membranes, impaired mitochondrial respiration, and reduced quiescence survival. Remarkably, these defects—including respiratory failure and cold sensitivity—are rescued by inhibiting ergosterol biosynthesis or using membrane-fluidizing agents like Tween 20, highlighting the critical link between membrane lipid composition and aerobic energy production.

Two highlights:

Specific Dynamic Interactions Between Proteins in Fission Yeast. Gonzalez-Martin E, Tallada VA. Bimolecular Fluorescence Complementation as a Tool to Study Methods Mol Biol. 2025;2862:103-120. doi: 10.1007/978-1-0716-4168-2_8.

Ltc1 localization by EMC regulates cell membrane fluidity to facilitate membrane protein biogenesis. Berraquero M, Tallada VA, Jimenez J. iScience. 2025 Feb 24;28(3):112096. doi: 10.1016/j.isci.2025.112096.





Nuclear Architecture and Dynamics

Rafael R. Daga and Silvia Salas Pino

Summary of activities:

In 2025, our group published three research articles that align with the objectives of MdM DMC3, particularly Q1 and Q3. One study expands on our recent iScience publication on the proteasome stress response to protein-folding stress, presenting a novel methodological framework to analyse proteasome assembly, composition, and activity. A second study demonstrates that hydroxyurea (HU), a widely used anticancer drug, induces thiol stress, a finding with potential relevance for personalized medicine. In addition, we collaborated with Alfonso Fernández on a manuscript addressing the relationship between nuclear architecture and gene expression. In terms of training activities, two PhD students from the group, Ana Sánchez and María Expósito, successfully deposited their doctoral theses. Furthermore, Álvaro Mendoza and Paola Gallardo joined the laboratory supported by an FPU fellowship and a Postdoctoral Talent grant from the Junta de Andalucía, respectively, strengthening the group's research capacity.

The laboratory has also actively participated in outreach activities. In parallel, as university professors, we have contributed extensively to undergraduate and postgraduate teaching within the Genetics area: Genética Molecular and Molecular Genetics (BSc in Biotechnology); Ingeniería Genética (BSc in Biotechnology), Genética Humana (BSc in Human Nutrition and Dietetics); Estrategias para la generación de Nuevos Fármacos; Bases Celulares y Moleculares del Cáncer; Métodos Prácticos en el Estudio de Patologías; Modelos Animales en Biotecnología (MSc).

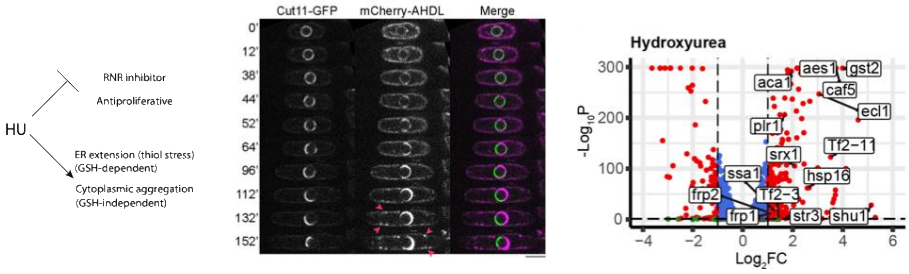
Ongoing project: Deciphering new proteostatic mechanisms in yeast. Ministerio de Ciencia e Innovación, Ref.: PID2024-160582OB-I00 Project period: 01/09/2025 – 31/08/2028

Collaborations: Alfonso Fernández (IBFG, Salamanca); Elena Hidalgo (Pompeu Fabra U, Barcelona); Fred Chang (UCSF, USA); Alejandro Díaz Moscoso (IIQ, Seville); Manuel Bernal (Málaga U); Ana Rojas (CABD); Antonio Pérez Pulido (UPO/CABD).

Two highlights:

Protocol for the analysis of proteasome activity, assembly state, and composition in fission yeast extracts using native gels. Ruiz-Romero G, Daga RR, Salas-Pino S. STAR Protoc. 2025 Dec 4;6(4):104233. doi: 10.1016/j.xpro.2025.104233.

Hydroxyurea induces an oxidative stress response that triggers ER expansion and cytoplasmic protein aggregation. Sánchez-Molina A, Bernal M, Posligua-García JD, Pérez-Pulido AJ, de Cubas L, Hidalgo E, Valdivieso MH, Salas-Pino S, Daga RR. PLoS Biol. 2025 Nov 19;23(11):e3003493. doi: 10.1371/journal.pbio.3003493



HU cause thiol stress. HU induces perinuclear ER extension which result in NPCs clusterization and cytoplasmic protein aggregation. ER expansion is caused by defective protein folding, is GSH dependent and can be suppressed by protein synthesis inhibitor puromycin, while cytoplasmic aggregation is GSH-independent and can be prevented by inhibition of protein synthesis with cycloheximide. Transcriptomic analysis shows that HU stress response differs from canonical UPR.

Macrophage Axis in Inter-Organ Physiology

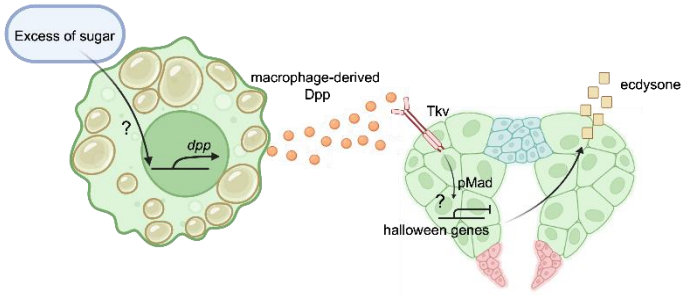
Sergio Juárez Carreño

Summary of activities:

In 2025 my group started at the CABD. In these few months we have been focussed to finish a previous manuscript started in Barcelona at the IRB. Briefly, we discovered by transcriptomic and genetics analysis that macrophage-derived Dpp (BMP2/4 human homolog) is up-regulated and secreted to inhibit the ecdysone synthesis under High- sugar diet (HSD) during development. Dpp inhibits ecdysone synthesis via BMP pathway activation in the prothoracic gland under high-sugar conditions, thereby controlling systemic growth and final size of the organism. Our findings highlight a novel role for macrophage-derived Dpp as a crucial inter-organ signaling molecule that, beyond its morphogen activity, mediates sterol hormone synthesis during dietary stress such as HSD. This work identifies them as promising therapeutic targets for metabolic and developmental disorders. This research is related to the third research question (Q3) of the MdM project, as it examines how the environment modulates macrophage behaviour to sustain systemic homeostasis

Highlight:

A systemic role of macrophage-derived BMP2/4 homolog Dpp in regulating sterol hormone synthesis under dietary stress. Juarez-Carreño S*, Milán M*. bioRxiv; 2025. DOI: 10.1101/2025.09.10.675304.
* corresponding authors



The current model describes how macrophage-secreted Dpp regulates ecdysone biosynthesis and developmental progression under conditions of diet-induced stress, primarily through its receptor Thickveins (Tkv) expressed in the prothoracic gland.

Molecular Evolution of Microbial Interactions Lab (MolEMI Lab)

Tanja Dapa

Summary of activities:

Throughout 2025, the MolEMI lab continued our core research on the host-microbe coevolution between the gut microbiota and the mammalian host. We focus on the synergistic relationship between the host and a bacterial key member of this community, *Bacteroides thetaiotaomicron*. Specifically, in the line with DMC3, we aim to decipher how regulatory changes in the bacterial genome influence the coevolutionary path and the complex interplay between the microbiota, the intestine, and the host's immune response. Working at the cutting edge of this field, we have established a method to study bacterial evolution using a new mouse line at the Andalusian Center for Developmental Biology (CABD-UPO-CSIC): the C57BL/6J-Rag1^{em10Lutzy}/J strain. These immunocompromised mice lack an adaptive immune response, providing a unique model for our observations.

Our team, currently consisting of Tanja Dapa (PI of the lab) and second-year PhD student Inmaculada Mena Guzman, was also joined by two undergraduate students who contributed significantly to the project this year.

In addition to our research, the MolEMI lab is also very dedicated to outreach activities. We participated during educational visits at the CABD, we took part in the "Speed Dating with Researchers" event at CaixaForum Seville during the European Researchers' Night (La Noche Europea de l@s Investigador@s), we hosted workshops at nearby public schools for the International Day of Women and Girls in Science, and many more.

Two highlights:

Organization of "The First Meeting of the Sevillian School of Microbiology (ESM)". 12/06/2025. Centro Andaluz de Biología del desarrollo, Sevilla.

Attendance as a speaker at the "Iberian EvoMG PI meeting". 8-10 October 2025, CRG, Barcelona, Spain.

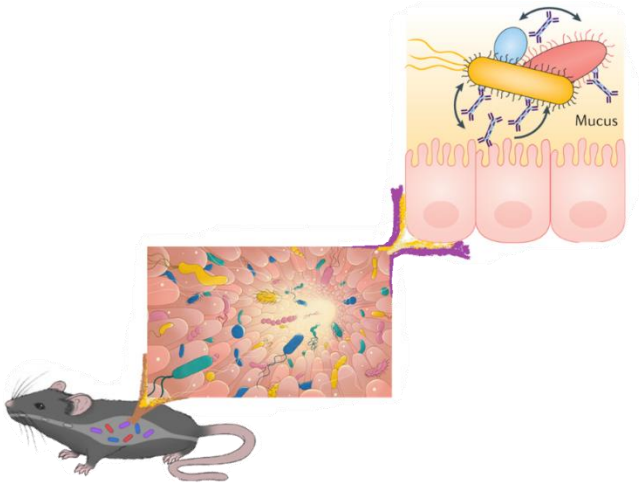


Illustration representing the current line of research of MolEMI Lab. Host-microbe interaction withing the mammalian intestine.

(© Joana C. Carvalho; © PMID: 34862512).

Vertebrate Development and Evolution

Javier Lopez-Rios and Gretel Nusspaumer

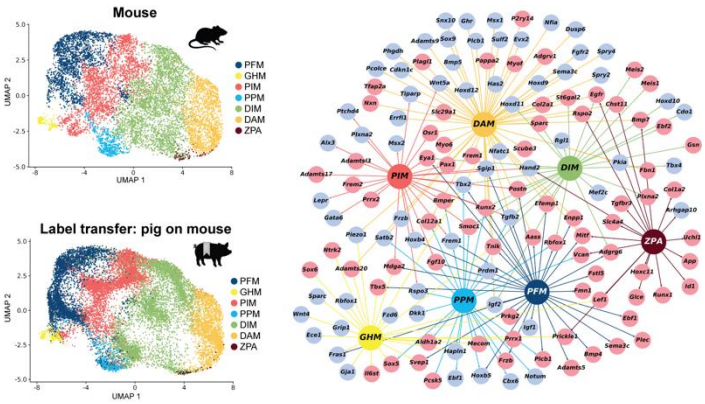
Summary of activities:

During 2025, we continued our studies on the morphological evolution of the limb skeleton. In particular, we developed several approaches that allow us to compare single-cell transcriptomic and epigenomic datasets from homologous organs in different species. For instance, we optimized methods such as SCENIC+ to reconstruct the topology of gene regulatory networks during mouse and pig limb development in specific cell populations. These approaches allowed us to identify expression and regulatory changes in the morpho-regulatory patterning systems of the artiodactyl limb bud along the proximo-distal (e.g., distal FGF sensing) and the anterior-posterior (e.g., HH signaling) axes, in comparison to the mouse. For example, we identified that *FGFR2* expression is specifically downregulated in the handplate progenitors of the pig limb bud in comparison to the mouse, which provides a causal explanation for the distal expansion of the expression of the BMP antagonist *GREM1*, a hypothesis supported by limb culture experiments. We also applied these single-cell methods for network inference to the study of Ewing sarcoma, with the aim of identifying the cell of origin of this rare and malignant bone tumor. Finally, we also optimized a murine model of neonatal sepsis and we have started to characterize its consequences in the bone marrow at the single-cell level to identify interactions between the mesenchymal and hematopoietic compartments.

Two highlights:

Epigenomic signatures of cis-regulatory elements in the developing mouse and pig forelimb. Sospedra-Arrufat I, Martínez-García PM, Gil-Gálvez A, Alcaina-Caro A, Tena JJ, Nusspaumer G, Lopez-Rios J. Sci Data. 2025 Apr 10;12(1):598. doi: 10.1038/s41597-025-04946-5.

Range extender mediates long-distance enhancer activity. Bower G, Hollingsworth EW, Jacinto SH, Alcantara JA, Clock B, Cao K, Liu M, Dziulko A, Alcaina-Caro A, Xu Q, Skowronska-Krawczyk D, Lopez-Rios J, Dickel DE, Bardet AF, Pennacchio LA, Visel A, Kvon EZ. Nature. 2025 Jul;643(8072):830-838. doi: 10.1038/s41586-025-09221-6.



Divergent gene expression between mouse and pig limb buds in specific mesenchymal cell populations as revealed by scRNA-seq analysis.

Computational Biology and Bioinformatics

Ana M Rojas Mendoza and Ildefonso Cases

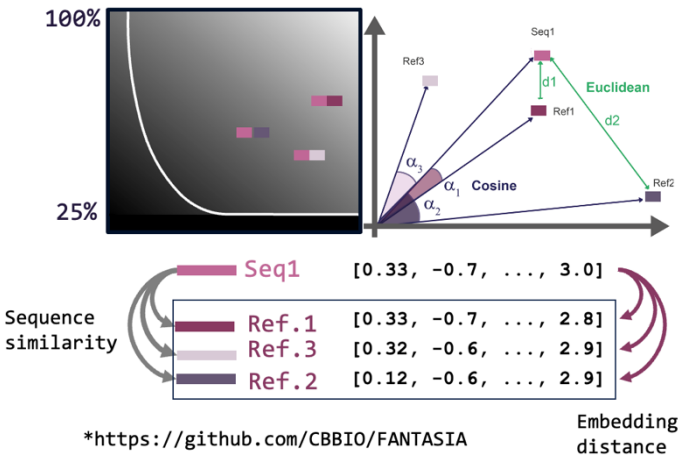
Summary of activities:

In 2025, the group research focused on **advancing computational** and **Artificial Intelligence-based** approaches to understand how biological function emerges and self-organizes across molecular, cellular, and evolutionary scales. A central achievement was the **development of protein language model-based frameworks for large-scale functional annotation**, with particular emphasis on the functional dark proteome[1]. Through FANTASIA, we demonstrated that protein embeddings capture latent functional organization that is often decoupled from classical sequence conservation, revealing emergent functional similarities across distant taxa. This work is particularly relevant for understanding how regulatory and structural changes in genomes relate to evolutionary innovation and to pathological functional variants that are not readily identifiable by conventional approaches. In parallel, we contributed to theoretical and computational analyses of the structural evolution of Gene Ontology[2], showing how biological knowledge and functional descriptors organize into modular and hierarchical structures that mirror increasing biological complexity. These results provide a systems-level perspective on how gene functions and regulatory programs become coordinated across biological contexts, from individual genes to interacting networks. Several ongoing projects integrate protein functional prediction with conformational plasticity, multifunctionality, and nuclear organization, contributing to a mechanistic understanding of how cells sense internal and external cues and incorporate this information into self-organized regulatory states. By linking molecular properties to higher-order organization, these activities connect genome-encoded information with cellular behaviour in space and time. These developments generated significant outreach and media impact, including national radio interviews (RNE: “A Hombros de Gigantes”), and press coverage focused on the use of artificial intelligence to uncover hidden biological functions, contributing to the societal visibility of computational biology.

Two highlights:

FANTASIA leverages language models to decode the functional dark proteome across the animal tree of life. Martínez-Redondo GI, Perez-Canales FM, Carbonetto B, Fernández JM, Barrios-Núñez I, Vázquez-Valls M, Cases I, Rojas AM, Fernández R. Commun Biol. 2025 Aug 14;8(1):1227. doi: 10.1038/s42003-025-08651-2.

Structural Changes in Gene Ontology Reveal Modular and Complex Representations of Biological Function. Valverde S, Vidiella B, Martínez-Redondo GI, Duran-Nebreda S, Fernández R, Bombarely A, Rojas AM, Bentley RA. Mol Biol Evol. 2025 Jun 4;42(6):msaf148. doi: 10.1093/molbev/msaf148.



Conceptual overview of FANTASIA, an AI-based system that uses protein language model embeddings to infer functional similarity beyond sequence conservation. By exploiting geometric relationships in embedding space, FANTASIA reveals emergent functional organization across proteins and species. The system is supported by national and European funding and has received media attention, including radio interviews on the use of AI in biology.

3D Genomics

Darío Jesús Lupiáñez García

Summary of activities:

In 2025, our group continued investigating gene regulation and 3D genome organization, with a focus on developmental and evolutionary processes. Supported by the European Research Council (ERC) and the Agencia Estatal de Investigación (AEI), we explored enhancer–promoter communication, sex determination mechanisms, and chromatin hub dynamics, addressing questions central to the goals of the MdM DMC3.

Key publications include a comparative single-cell study elucidating mechanisms of bat wing formation (Schindler et al., Nature Ecology & Evolution, 2025) and a study demonstrating that gonadal sex and temperature independently influence germ cell differentiation in turtles (Hatkevich et al., PNAS, 2025). These works highlight how genomic regulatory changes can coordinate cellular behaviours across space and time, linking structural genome organization to developmental outcomes, and advancing our understanding of self-organization principles.

Beyond research, our group actively contributed to the scientific community and public outreach. I continued serving on the director boards of the Sociedad Española de Genética (SEG) and the Sociedad Española de Biología del Desarrollo (SEBD). Together with Aurora Ruiz Herrera (University of Barcelona), I organized the X Curso Nacional de Genética, focused on novel strategies to read, interpret, and modify the genome (Figure 1). Our group also participated in national and international networks, including Conexion Genoma, R2G, and DFG SPP 2403. These contributions to science and dissemination were recently recognized with the Gold Medal of the City of Algeciras.

Two highlights:

X Curso Nacional de Genética (14-19 septiembre 2025, La Cristalera, Madrid): https://segenetica.es/curso/cng2025/

Gold Medal of the City of Algeciras: https://www.algeciras.es/es/detalle-de-noticia/Landaluce-hace-entrega-de-la-insignia-de-la-ciudad-a-Dario-Lupianez/



Epigenomics in Disease and Aging

Juan J. Tena, Christina Paliou and Martin Franke

Summary of activities:

During 2025, our laboratory has participated in 8 publications, some of them particularly relevant for the objectives of MdM DMC3. Importantly, two members of the team were awarded with Ramón y Cajal fellowships in the last years, and during 2025 they secured funding from Ministerio de Ciencia, Innovación y Universidades and CSIC (4 projects). We have also contributed to several projects in collaboration with national and international groups, like the study of dorsoventral pattern of the vertebrate limb, with Prof. Marian Ros, or the study of retinal hereditary diseases for the International Training Network ProgRet. These two projects are particularly relevant for the objectives of MdM DMC3.

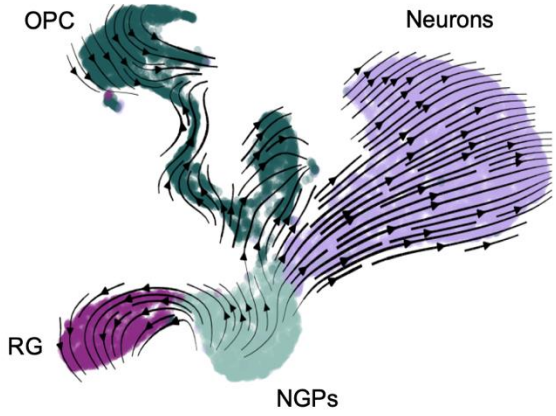
We have incorporated an Associated Professor from UPO University, Pedro M. Martínez, into the group, becoming one of the few groups in the institute with members from both institutions, CSIC and UPO, and contributing to their total integration at CABD.

Finally, we carried out some teaching activities in Master's and undergraduate courses, and participated in several outreach activities, like 'Ciencia en el cole' and 'Sábados científicos en familia".

Two highlights:

Defence of the Doctoral Project "Central regulator genes integrate signaling pathways ensuring robust embryonic development", by Marta Moreno Oñate, in June 2025.

Neotenic transcriptomic features in the adult turquoise killifish brain. Burgos-Ruiz AM, Naranjo S, del Valle Hernández-Pérez M, et al. bioRxiv; 2025. DOI: 10.1101/2025.03.24.645095.



RNA-velocity analysis suggests that non-glial progenitors (NGPs) give rise to different cells in the killifish brain: radial glia (RG), oligodendrocyte progenitor cells (OPCs) and neurons.

Evolution of Organogenetic Gene Networks

James C.-G. Hombría

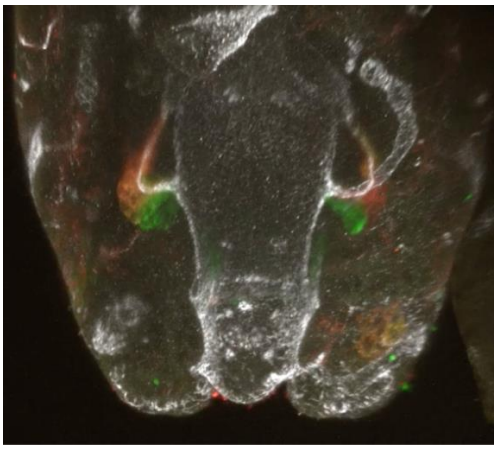
Summary of activities:

We have described one of the most extreme cases of organ divergence in nature. Taking advantage of the metameric nature of the *Drosophila* larva, we have shown that from a group of homologous cells present in the same position in all cephalic and trunk segments, three morphologically and functionally distinct organs develop: the tracheae, the cephalic endoskeleton to which the muscles that move the masticatory organs are attached (the tentorium), and the two glands that synthesize the hormones that control molting and larval metamorphosis (the *corpora allata* and the prothoracic glands).

The tracheae are tubules develop in each trunk segment from an ectodermal primordium that invaginates and branches without losing its epithelial character. The tubules from adjacent segments merge forming the gas exchange tubular network. In the intercalary, maxillary and labial cephalic segments, the homologous cells invaginate in a similar way, but a group of cells in the maxilla and labium activate the snail gene which induces their epithelial to mesenchymal transition (EMT) and activate their migration towards the dorsal abdomen. These cells will give rise to the *corpora allata* and the prothoracic glands. The remaining homologous cells of these three cephalic primordia that have not experimented an EMT, fuse forming tubular structures attached to the external epithelium similar to what the tracheae do in the trunk segments. This epithelial tubular structure locally activates the stripe gene, becoming the tendon to which the masticatory muscles anchor. We have shown that by manipulating Hox gene expression, we can transform the trachea into tentorium and vice versa.

Highlight:

Divergent origin of the insect cephalic endoskeleton and the trachea from a homologous metameric structure. Barcenilla-Merino D, Sánchez-Higueras C, Hombría JC. Curr Biol. 2025 Sep 8;35(17):4165-4177.e4. doi: 10.1016/j.cub.2025.07.041.



Dorsal view of a Drosophila larval head stained with anti-aPKC showing the tubular anterior tentorium stained in green and the posterior tentorium in red.

Gene Regulation and Evolution

Francisca Martínez Real

Summary of activities:

In 2025, our group reached several important milestones. One of my PhD students from Germany, Magdalena Schindler, co-supervised with my former postdoctoral mentor, successfully defended her PhD thesis. In parallel, we published her second paper as first author and with me as senior author, in Nature Ecology & Evolution, completing a project initiated several years ago. In this work, we uncovered how the reuse of pre-existing and conserved gene expression programmes contributes to evolutionary innovations, such as wing development in bats. That same year, a new experimental PhD student joined our group at the CABD, funded by an FPI fellowship. Together with a previously recruited computational PhD student, this has consolidated a balanced wet-dry team, enabling us to address evolutionary questions from complementary perspectives. Our main goal is to understand how evolutionary changes in the genome translate into changes in gene regulation, ultimately driving the remarkable phenotypic diversity observed in nature. To this end, we study regulatory evolution both genome-wide and at specific loci by combining single-cell omics, deep-learning approaches, synthetic genomics, and interspecies transgenic models. Both PhD students actively strengthened their training during 2025 by participating in advanced courses, including the “X Curso Nacional de Genética” and the “III Principles of Evolution Course: Biology through Time and Organizational Levels”. We have also presented our work at several international meetings, for instance at the Symposium of Vertebrate Genome Evolution organized by the Louis-Jeantet Foundation in Geneva, where I was invited by renowned scientists in the field, highlighting the international visibility of our research. In addition, in 2025 I successfully passed the highly competitive selection process to become a member of the EMBO Young Investigator Programme, an achievement from which the entire group will benefit through enhanced networking, training, and funding opportunities.

Two highlights:

Comparative single-cell analyses reveal evolutionary repurposing of a conserved gene programme in bat wing development. Schindler M, Feregrino C, Aldrovandi S, Lo BW, Monaco AA, Ringel AR, Morales AE, Zehnder T, Behncke RY, Glaser J, Barclay A, Andrey G, Kragesteen BK, Hägerling R, Haas SA, Vingron M, Ulitsky I, Marti-Renom MA, Hechavarria J, Fasel N, Hiller M, Lupiáñez DG, Mundlos S, Real FM. Nat Ecol Evol. 2025 Sep;9(9):1626-1642. doi: 10.1038/s41559-025-02780-x.

Membership in the EMBO Young Investigator Programme. This appointment also recognizes our entire research group as an EMBO-YIP lab, opening opportunities for funding, training courses, access to facilities, as well as support for conference attendance and research internships for all group members.

New EMBO Young Investigators EMBO

	Name	Research project	Affiliation	Location
	Francisca Martínez Real	Molecular basis of evolutionary innovation: a synthetic genomics approach	Centro Andaluz de Biología del Desarrollo	Seville, ES

Press release from EMBO announcing new members of the EMBO YIP

Fungal and Yeast Biotechnology

José Ignacio Ibeas Corcelles

Epigenetic Regulation of Virulence in Plant Pathogenic Fungi

Ramón Ramos Barrales

Summary of activities:

Following our 2024 publication in New Phytologist regarding the role of Row protein family in plant pathogenesis, we have focused on the spatial dynamics of the fungal genome and the standardization of proteomic techniques. Our research into nuclear architecture was selected for an oral presentation at the 17th European Conference on Fungal Genetics (ECFG17) in Dublin (March 2025). Ramón Ramos Barrales delivered the talk titled: "Lem2-mediated tethering of telomeres to the nuclear periphery is essential for *Ustilago maydis* pathogenesis." This work identifies the protein Lem2 as a critical structural tether that organizes the nucleus, allowing fungal penetration into the plant. This research aligns with Question 4 of the DMC3 Strategic Plan: *"How do nuclear organization and nuclear membrane dynamics regulate gene expression, as well as cellular growth and behaviour?".*

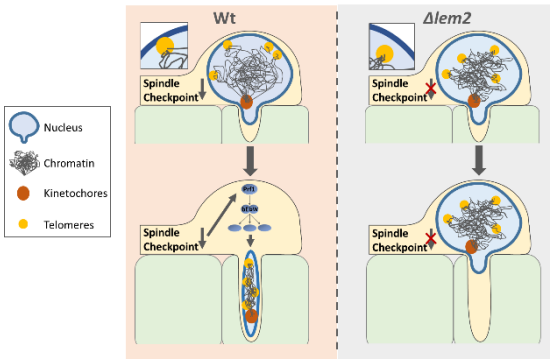
In addition, we have contributed to the lab protocol series Methods in Molecular Biology, published by Springer Nature. Our chapter, titled "Protein extraction methods in *Ustilago maydis*" is currently in press. This publication provides the scientific community with optimized, reproducible protocols for isolating high-quality protein fractions from *Ustilago maydis*, overcoming a significant technical hurdle in the study of fungal pathogens.

Two highlights:

International Conference Presentation: Oral Communication at ECFG17, Dublin, 2025.

Book Chapter: "Protein extraction methods in *Ustilago maydis*." *Methods in Molecular Biology*, Springer Nature (In press).

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Model of the role of Lem2 in pathogenesis.

Biotechnology of Industrial and Artisan Fermentations. Competitivity Factors in Microbial Communities and their Application

Andrés Garzón

Summary of activities:

In 2025, our research group has made progress in the implementation of our project from the Knowledge Generation Program, which focuses on the role of yeast killer elements in intraspecific competition interactions across various yeast life stages (natural environment, fermentations, and biofilm formation). We have a PhD student and a lab technician conducting research on this topic. Our activities are well focussed on Q3 question of of MdM DMC3. We have analysed the natural diversity of this system in wild yeasts to uncover recombination dynamics link to sexual reproduction that had been previously unnoticed, that will be published soon. We are currently extending this analysis to yeast biofilms communities assaying possible biotechnological applications.

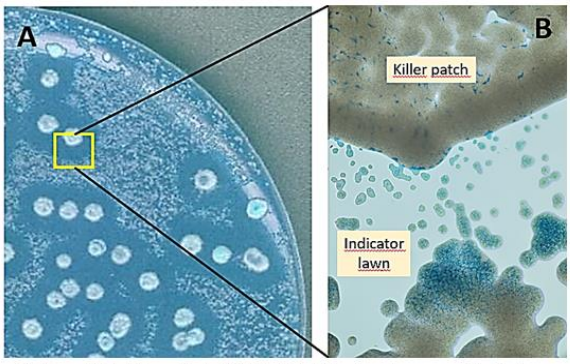
We maintain our applied science focus through ongoing collaborations with two companies, Bodegas Gonzalez Palacios and Bodegas Salado. We are writing research collaboration agreements with both. We have organized a summer university course where we have explained our scientific applied science projects.

We continue to sustain productive collaborations with the research groups of Juan Jimenez, Antonio Pérez-Pulido and Manuel Muñoz. These collaborations have resulted in three publications and a patent application still under evaluation.

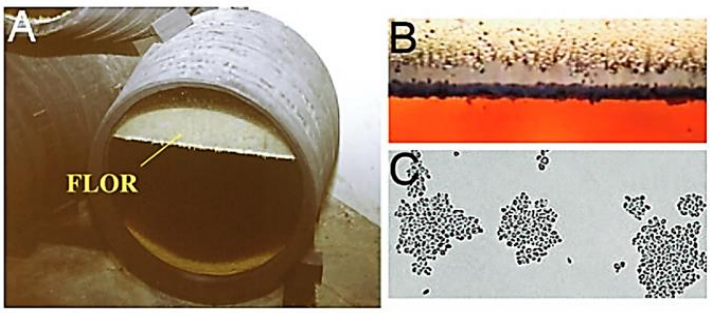
Two highlights:

The evolutionary replacement of restriction-modification by Ssp antiviral systems is associated with the distribution of prophages in the major clonal group of Acinetobacter baumannii. Moreno-Rodríguez A, Rubio A, Garzón A, Smani Y, Pérez-Pulido AJ. mBio. 2025 Sep 10;16(9):e0213525. doi: 10.1128/mbio.02135-25.

Inhibition of acid sphingomyelinase increases SMN levels and connects sphingolipid metabolism to Spinal Muscular Atrophy. Brokate-Llanos AM, Beltran M, Garzón A, Garcera A, Miralles MP, Celma-Nos F, Campoy-López A, Soler RM, Muñoz MJ, Pérez-Pulido AJ. Biomed Pharmacother. 2025 Nov;192:118610. doi: 10.1016/j.biopha.2025.118610.



L-A/M-mediated killer effect. A) MBA plate killer phenotype assay. Replicate colonies of a killer strain on a sensitive background. The presence of methylene blue, a dye that stains dead cells, helps to confirm the effect of the toxin on the sensitive strain. B) Enlargement of the zone of inhibition where the effect of the toxin can be seen reducing the growth of nearby colonies and producing lethality in colonies further away up to a certain distance from the producer strain.



S. cerevisiae ''flor yeasts'' are naturally able to grow on the sherry wine surface. (A) Oak barrels filled to ¾ with sherry wine spontaneously form self-supporting yeast biofilm on the wine surface, a velum known as ''flor.''(B) This thick biofilm floats and allows flor yeast to gain direct access to oxygen. (C) Cells in this buoyant biofilm are strongly aggregated, showing a flocculation phenotype.

Coenzyme Q Synthesis in *Saccharomyces cerevisae* and its Implication in the Mitochondrial Health. Lifespan and Ageing

Carlos Santos Ocaña

Summary of activities:

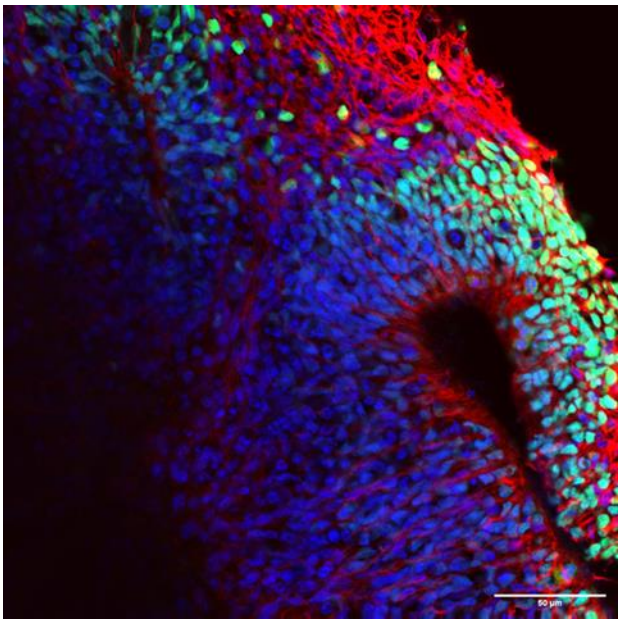
In 2025, the group's researchers continued to teach across various bachelor's and master's degrees at Pablo de Olavide University. At the same time, they have continued their research on the analysis of pathophysiological processes in mitochondrial diseases using two approaches. The first is to collaborate in establishing the diagnosis of new cases using various animal and cell models. This activity has been carried out in collaboration with hospitals, patient associations, and projects such as Impact Genomics, ENoD, from CIBERER, and the Carlos III Health Institute.

The second approach is to generate a model of mitochondrial disease with neurological involvement using brain organoids and their subsequent characterization. In this task, the group is collaborating with other CABD groups, such as those led by María José Sánchez Sanz and Luciano Marcon, as well as with CABD services, such as the Clean Room and the ALMIA microscopy service. By 2025, 60-day brain organoids have been generated, showing the process of neuronal differentiation in patients and controls. This approach is relevant to the overall objectives of the MdM DMC3 as it aims to reveal the relationship between energy availability and the development of the human nervous system.

Two highlights:

Clinical and molecular characterization of SLC31A1-related developmental and epileptic encephalopathy: insights from 13 new cases. Juliá-Palacios N, et al. Brain Commun. 2025 Sep 23;7(5):fcaf348. doi: 10.1093/braincomms/fcaf348.

Modelling the human coenzyme Q deficiency in Drosophila melanogaster. Fernández-Ayala DJM, Jiménez-Gancedo S, Guerra I, Hernández-Camacho JD, Neto M, Scialo F, Astillero-López V, Cortés-Rodríguez AB, Santos-Ocaña C, Rodríguez-Aguilera JC, Casares F, Sanz A, López-Lluch G, Navas P. Free Radic Biol Med. 2025 Mar 16;230:95-111. doi: 10.1016/j.freeradbiomed.2024.12.056. Epub 2025 Jan 27. PMID: 39864756.



Brain organoid of 35 days old of a CoQ_{10} deficient patient stained with DAPI (Blue), Sox2 (Green) and TUJ (Red).

Coordination of Stem Cells, Physiology and Behaviour

Salvador Herrera

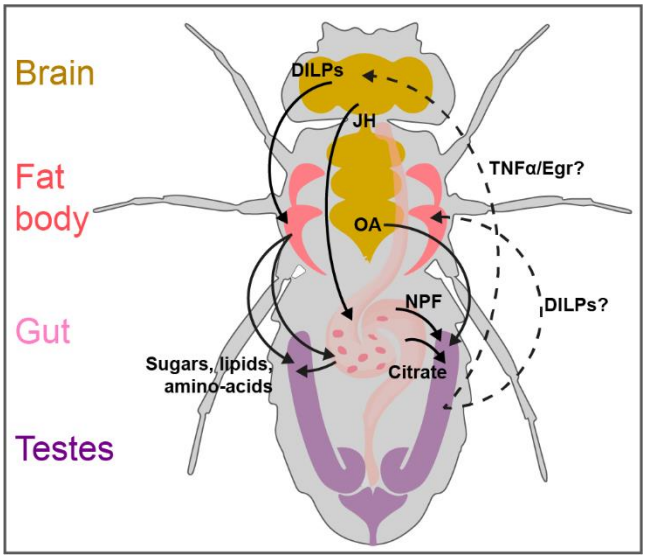
Summary of activities:

During 2025 we made progress in our research about the effects of social interactions on the male gonad and the physiology of the whole organism, using flies as a model. Our data suggests that the presence of females, detected by their pheromones, induces not just the activation of the spermatogenesis at the testis (as we recently published), but also an overall metabolic change aimed to mobilize energy reserves – levels of glycogen and lipids are diminished in the fat body, while increased levels of glucose, trehalose and TAG can be detected in the fly blood. These changes depend on the perception of female sexual pheromones and Octopamine signalling from the brain (homologous to the Noradrenalin of vertebrates). We are also identifying transcriptomic changes in the fat body as a consequence of the interaction with females, related to the secretion of adipokine hormones. Altogether, we are defining these phenomena as a novel “male pre-mating response”, likely aimed to improve the reproductive success of males, that shows some resemblance with the well-studied female post-mating responses.

This research topic, analysing the interorgan communication between brain, gonads and other tissues in response to external cues, is aligned with the MdM DMC3 objective #Q3 about how cells sense and respond to a changing environment. It also pertains the objective #Q5, as we study the relevance of energy constrains in collective cell decisions.

Highlight:

Ana Lazo-Garrido, Javier Martín-Díaz & Salvador C. Herrera "A male pre-mating response”. Oral presentation at the 28th European Drosophila Research Conference.



Summary of the different hypotheses we are studying about the physiologic and metabolic changes that take place during the male pre-mating response.

Development of the Hemato-Vascular System and Stem Cells

María José Sánchez Sanz

Summary of activities:

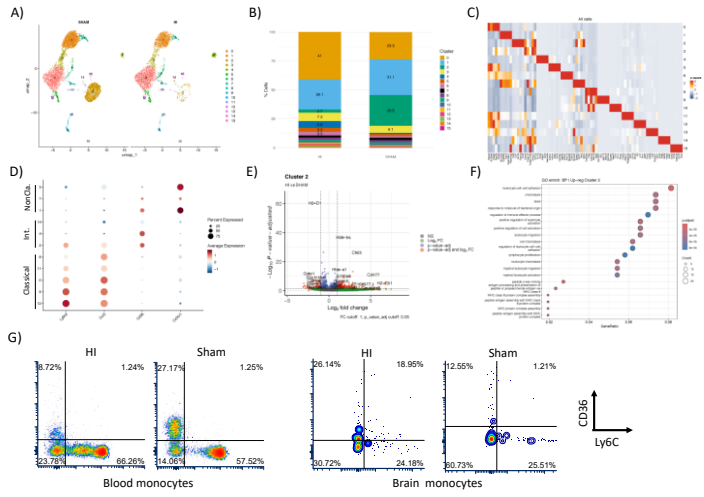
Our laboratory investigates how cells of the hemato-vascular system contribute to disease states through mediating processes such as inflammation and tissue repair. In 2025 the group has continued its work on the single-cell transcriptomic characterization of changes in blood cells and vascular precursors in response to hypoxic–ischemic brain injury in neonates, using the hypoxic–ischemic (HI) mouse model and samples from neonatal patients with suspected hypoxic-ischemic encephalopathy (NHIE). We have identified variations in CD36^{+} monocytes as a potential cellular marker of HI injury and are currently working to define their transcriptional profile and to delineate the mechanisms potentially involved in inflammation and tissue repair. This is an ongoing collaborative research with groups from the Seville Institute of Biomedicine (IBIS) and Hospital Virgen del Rocío.

We have also initiated a collaboration with groups at CABD on a new research line exploring the potential of brain organoids (BOs) as a model for neonatal hypoxic–ischemic brain damage. During 2025, we focused on the characterization of hiPSC-derived BO using immunofluorescence and flow cytometry and evaluated a protocol for organoid vascularization.

This research is relevant to understand how cells sense/respond to their changing environment (Q3-DMC3).

Highlight:

Invited speaker at XVIII CIBER-ER Workshop “Flow Cytometry in enhancing the brain organoid toolbox for screening and analysis pipelines” El Escorial, Madrid, 27-28 March 2025.



Changes in circulating monocytes were assessed after neonatal hypoxic–ischemic brain injury using scRNA-seq (A-F) and flow cytometry (G). HI neonates showed reduced circulating CD36+ monocytes accompanied by increased CD36+ monocyte in the brain.

CRISPR-Cas *in vivo* Optimizations to Understand Early Vertebrate Development and Human Diseases

Miguel Ángel Moreno-Mateos

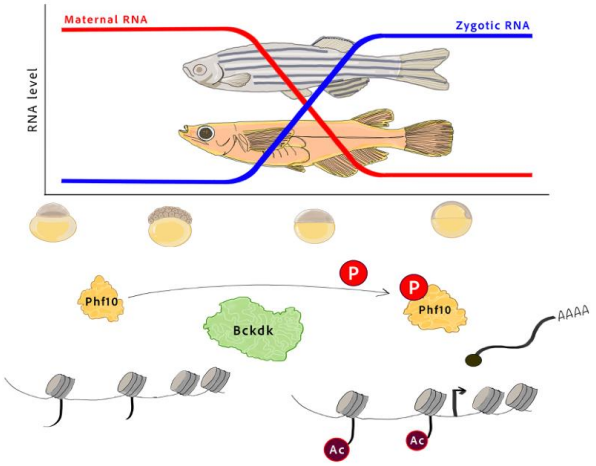
Summary of activities:

This year, we have successfully optimized and published our CRISPR-Cas RNA-targeting platform, culminating in two key publications: Moreno-Sanchez, Hernández-Huertas, Nahón-Cano et al. (2025) and Hernandez-Huertas et al. (2025) that was awarded as the best paper in the CABD in 2025. Building on this technical foundation, our lab continues to utilize RfxCas13d for functional screenings in zebrafish embryos. This work has identified Rfwd3, an E3 ubiquitin ligase, as a critical regulator of the Maternal-to-Zygotic Transition (MZT) as well as novel post-transcriptional MZT regulators. All these new factors controlling early embryogenesis are now being characterized and analysed. Finally, we are investigating the role of Wapl in cohesin regulation, and we have uncovered that knocking down the Wapla paralogue disrupts both zygotic genome activation (ZGA) and epiboly. Altogether, our results are shedding light to a fundamental question in developmental biology: How the maternal contribution in the oocyte drives the first molecular steps during early embryogenesis. In addition, we continue with our mission to enhance the flexibility of CRISPR-Cas systems, and we have been able to optimize ancestral CRISPR-Cas systems that will help to increase the accessibility of the genome to be edited. We are now preparing a manuscript to be submitted along 2026. These and other projects in the lab have been presented as invited talks in different national and international meetings and conferences along 2025 such as 47th SEBBM meeting (Caceres, Spain) , EMBO workshop: CRISPR-Cas: From biology to therapeutic applications (Sorrento, Italy), Encuentros Fundación Medina 2025 (Granada, Spain) or 51st International Embryo Technology Society (Fort Worth, Texas, EEUU). Further we have participated in several dissemination activities and get a CABD award for “Ciencia en los Barrios”.

Two highlights:

CRISPR-RfxCas13d screening uncovers Bckdk as a post-translational regulator of maternal-to-zygotic transition in teleosts. Hernández-Huertas L, Moreno-Sánchez I, Crespo-Cuadrado J, Vargas-Baco A, da Silva Pescador G, Zhang Y, Wen Z, Florens L, Santos-Pereira JM, Bazzini AA, Moreno-Mateos MA. EMBO J. 2025 Dec;44(23):7021-7059. doi: 10.1038/s44318-025-00617-8.

Enhanced RNA-targeting CRISPR-Cas technology in zebrafish. Moreno-Sánchez I, et al. Nat Commun. 2025 Mar 16;16(1):2591. doi: 10.1038/s41467-025-57792-9.



Graphical abstracts from Hernandez-Huertas et al 2025.

Molecular Embryology: Functional Genomics, Mouse Transgenesis and Myogenesis

Jaime J. Carvajal García-Valdecasas and Cristina Vicente García

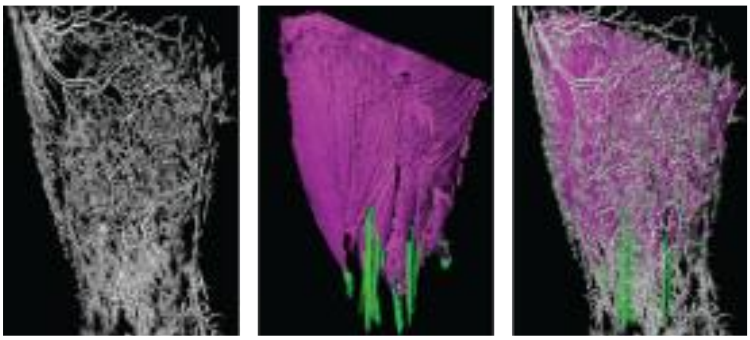
Summary of activities:

How does skeletal muscle develop? More importantly, how is muscle development coordinated with other tissues of the musculoskeletal system? How is muscle mass regulated postnatally and during ageing? How does muscle respond to injury? How is muscle heterogeneity established? What roles do the myogenic regulatory factors Mrf4 and Myf5 play in these processes? In our group, we address these questions using a multidisciplinary approach that combines transgenesis, CRISPR/Cas genome editing, embryology, cell biology, biochemistry, physiology, and omics analyses, alongside advanced imaging techniques like super-resolution and light-sheet microscopy. Last year, we completed a project awarded to Dr. Carvajal by the Agencia Estatal de Investigación that allowed us to deepen our understanding of muscle heterogeneity. Among other findings, we discovered that genes associated with human muscular dystrophies are not necessarily more highly expressed in the muscles more severely affected. However, muscle-type-specific regulatory networks exist and could be leveraged to develop targeted therapeutic strategies. Moreover, we found that some muscles unexpectedly express *Ucp1*, suggesting that skeletal muscle can engage thermoregulatory mechanisms previously thought to be restricted to brown adipose tissue. Finally, we identified sex- and muscle-type specific transcriptomic changes during ageing and in response to injury, and showed that the absence of Mrf4 has a profound impact on these processes. In parallel, we finalized a project awarded to Dr. Vicente by the Junta de Andalucía in which we found that Mrf4, which is exclusively expressed in skeletal muscle, would participate in the coordination of tissues within the musculoskeletal system during development.

Two highlights:

On a personal level, Dr. Carvajal has served as Deputy Vice-President for Scientific Programs (VAPC) at CSIC since 2022. In February 2025, Dr. Vicente secured a permanent M3 position at the CSIC following a merit- and examination-based selection process ("*concurso-oposición*"). In July, she commenced her second maternity leave.

Vicente-García, C (AC); Navarro-Martínez, A; Carvajal, JJ. Light sheet fluorescence microscopy imaging of whole-mount immunostained mouse embryos and limbs. Accepted in *Methods in Molecular Biology* in 2025.



Whole-mount immunostaining of neonatal mouse hindlimbs imaged by light-sheet microscopy, with three-dimensional reconstruction of the muscles (magenta), tendons (green) and nerves (white) using Imaris (Vicente-García, et al., 2026).

Cell Fate Determination in Early Mammalian Development

Bárbara Pernaute and Thomas Spruce

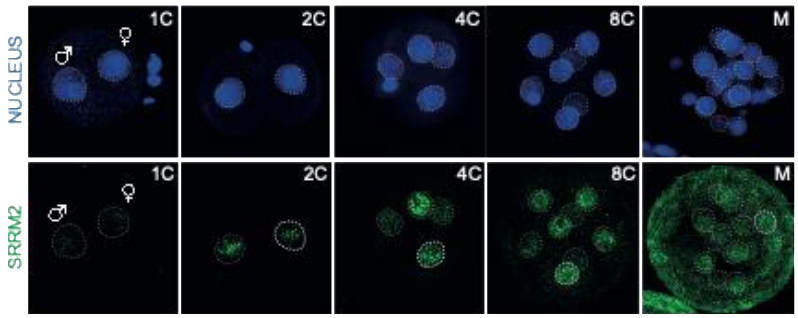
Summary of activities:

Our group studies the mechanisms underlying early development in mammals, focusing on the epigenetic and transcriptomic reprogramming occurring after fertilization which make the embryo totipotent and unique in its cellular and genomic context. 2025 has been a year of expansion for the group with the recruitment of 2 technicians, a postdoctoral researcher and 2 PhD students. Scientifically, we have progressed in the systematic characterization of the DNA damage responses in the early embryo and in the establishment of an efficient system to reprogram embryonic stem cells towards totipotency. We have also started a research line to investigate the impact of nuclear speckle dynamics on early embryo development, splicing regulation and totipotency reprogramming. Thomas Spruce signed a Ramon y Cajal contract with the UPO early in 2025 and was awarded a Proyecto Generación de Conocimiento in the autumn to start and lead an independent research line, exploring the role of novel YAP1 interactions in zygotic genome activation and totipotency acquisition. Our collaboration with the group of Dr. Graf (CRG, Barcelona) resulted in a publication that revealed a role of transcription factor CEBPa in the establishment of the trophectoderm lineage (Wei et al. Sci Adv 2025).

In 2025 I presented our results in national and international talks (Sy-Stem Symposia, Viena; CBMSO Seminar Series, Madrid; Conexión Genoma Meeting, Madrid). I was invited to lecture in a Clinical Embryology course organized by the UIMP (Santander) and to represent the Spanish Society for Developmental Biology in the “Jornada de Sociedades COSCE 2025: Ciencia y Tecnología, Dilemas Éticos”, where I gave a talk on the ethical challenges presented by the recent advances in the generation of human embryo models from embryonic stem cells. Additionally, different members of the group participated in outreach activities during 2025, including “Ciencia en el Barrio”, “European Researchers Night” and science activities at schools.

Highlight:

Role of CEBPa in trophectoderm competence installment. Wei X, Salvador-Martinez I, Meglicki M, Plana-Carmona M, Klonizakis A, Pernaute B, Irimia M, Stik G, Popovic M, Garcia GT, Heyn H, Zernicka-Goetz M, Graf T. Sci Adv. 2025 Nov 28;11(48):eady1693. doi: 10.1126/sciadv.ady1693.



Dynamic changes in nuclear speckles during early mouse embryo development, from 1 cell (1C) to morula (M) stage, as seen by immunofluorescence against the nuclear speckle scaffold protein SRRM2.

Establishment of Cell Polarity and its Relationship to Signalling

Sol Sotillos

Summary of activities:

In 2025, I assumed a Tenured Scientist (Científica Titular) position at the Spanish National Research Council (CSIC). This transition consolidated my independent research program and enabled a structured medium-term agenda.

I co-designed and co-organized the first edition of a Summer Course within the Universidad Pablo de Olavide (UPO) Summer Courses in Carmona, “Genetic Models in Research: From Bacteria to Mouse.” Delivered in a theory-and-practice format, the course provided an integrated overview of diverse model systems and highlighted their experimental advantages and limitations through the application of molecular and cell biology techniques. The program fostered cross-disciplinary dialogue among students, early-career researchers, and senior experts. The course was funded by the MdM DMC3 programme, supporting the dissemination of CABD research.

Bacterial Infections: New Targets and New Prevention and Treatment Strategies

Younes Smani

Summary of activities:

In 2025, our research program advanced the strategic objective of elucidating host-pathogen interactions across multiscale infection models (*in vitro*, *ex vivo*, and *in vivo*), in alignment with the DMC3 Strategic Plan (Q1 & Q3). We consolidated a novel cellular infection model and initiated airway organoid-based studies to define host interactions with *Acinetobacter baumannii*.

At the mechanistic level, we identified key host factors, $iPLA_2$, calcium channels, and TFEB, that regulate *A. baumannii* invasion and intracellular trafficking, providing critical insights into its intracellular lifestyle and immune evasion strategies. These findings strengthen the conceptual framework for targeting intracellular bacterial persistence (PPI A3, UPO & *Convocatoria Proyectos Generación de Conocimientos*, resolution pending).

Addressing adaptive bacterial responses, we launched a strategic research line focused on defining dynamic omics mechanisms and signaling pathways that enable *A. baumannii* to adapt to environmental stressors, including climate change, and to resist host-mediated killing. Preliminary datasets generated in 2025 support the feasibility of this line (DMC3 Strategic Plan Q1 & Q3).

From a translational perspective, we achieved a major milestone with the publication in **EMBO Molecular Medicine** reporting the repurposing of ENOblock as a novel antimicrobial agent synergistic with colistin against *A. baumannii* and *Escherichia coli*. This work elucidated both the mechanism of action and bacterial target of ENOblock. Complementarily, we secured funding from *Instituto de Salud Carlos III* and *Juan de la Cierva* Contract to develop new thiophene-derived antimicrobials, reinforcing our pipeline for therapeutic innovation.

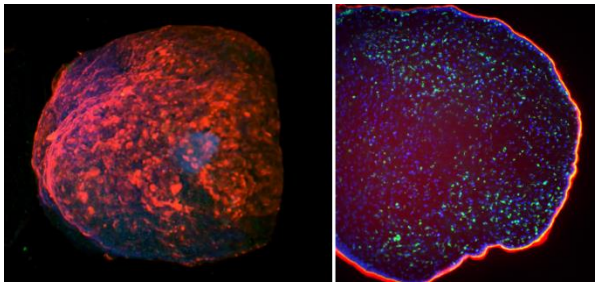
In recognition of our research excellence and technology transfer trajectory, the group received the "***Somos Universidad***" award from UPO.

We further contributed to the scientific community through meetings organization (IIIrd EURESTOP meeting, and 1st *Escuela Sevillana de Microbiología*), peer-review activities for major funding agencies (EUREKA, ESCMID, Poland National Science Centre, University of Naples, ANEP, ISCIII), journals (Nat Com, Cell Biomat, Antimicrob Agents Chemother, JAC-Antimicrob Res), and international conferences (ESCMID Global).

Two highlights:

ENOblock synergizes with colistin to treat Acinetobacter baumannii infections. Molina Panadero I, Moreno Rodríguez A, Rey Hidalgo A, de la Cruz M, Sánchez P, Tomás Gallardo L, Samernate T, Sencanski M, Glisic S, Genilloud O, Nonejuie P, Pérez-Pulido AJ, Hmadcha A, Smani Y. EMBO Mol Med. 2025 Dec;17(12):3496-3524. doi: 10.1038/s44321-025-00331-2.

Repurposing of anticancer drugs to combat MDR pathogens. Molina Panadero I, Smani Y. 2025. In 1st Edition Drug Repurposing. Chemistry, Biochemistry & Red Biotechnology. By Munishwar Nath Gupta. CRC book. ISBN: 9781032712949.



Airway organoid infected with *Acinetobacter baumannii*. Nuclei in blue; cell membranes in red and *A. baumannii* in green.

Obtaining New Antimicrobial Compounds and New Antibiotic Resistance Genes Through a Metagenomic Approach

Eva Camacho and Amando Flores

Summary of activities:

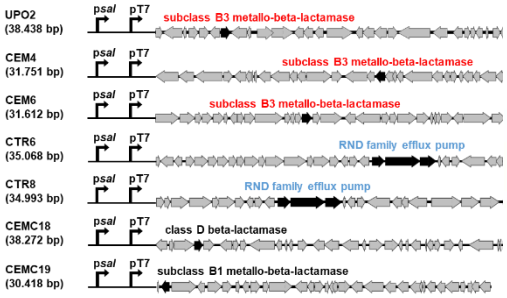
In 2025, we have continued our research using functional metagenomics to explore the vast reservoir of genetic diversity present in environmental microbiomes, with a particular focus on antibiotic resistance and antimicrobial discovery. By constructing and screening diverse metagenomic libraries with optimized vectors and alternative bacterial hosts, we have further identified novel genes involved in antimicrobial biosynthesis and resistance to clinically relevant antibiotics, including last-resort drugs such as carbapenems.

The ongoing characterization of clones producing new antimicrobial compounds active against multidrug-resistant pathogens, as well as the functional validation of previously uncharacterized resistance genes, provides experimental insight into how regulatory and structural genomic changes drive evolutionary innovation and ecological adaptation (Q1). In particular, our work anticipates potential evolutionary trajectories by identifying resistance determinants that are not yet circulating in clinical settings but are present in environmental reservoirs.

By expressing environmental DNA in different bacterial genera such as *Acinetobacter* and *Pseudomonas*, we analyse how horizontally acquired genes integrate into distinct regulatory and metabolic networks. This approach directly addresses how gene regulatory circuits are harmonized across cellular contexts (Q2) and how cells sense and respond to environmental pressures such as antibiotic stress (Q3). Moreover, the link between resistance, antimicrobial production, and metabolic pathways connects our work to the role of energy constraints and metabolic states in shaping collective microbial behaviour and ecological organization (Q5).

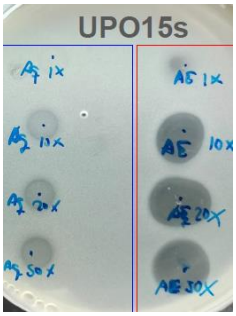
Overall, our research contributes to the MdM DMC3 objective of understanding self-organization across scales, from the integration of new genes into cellular regulatory networks to the emergence of adaptive traits within microbial communities.

In parallel, we have maintained our academic commitments at UPO, teaching over 100 hours in undergraduate and graduate programs. Within this research project, we have supervised two Bachelor's theses (TFG) and one Master's thesis (TFM) in 2025, in addition to participating in university management activities.





MRSA



Developmental Epigenomics

Ozren Bogdanovic

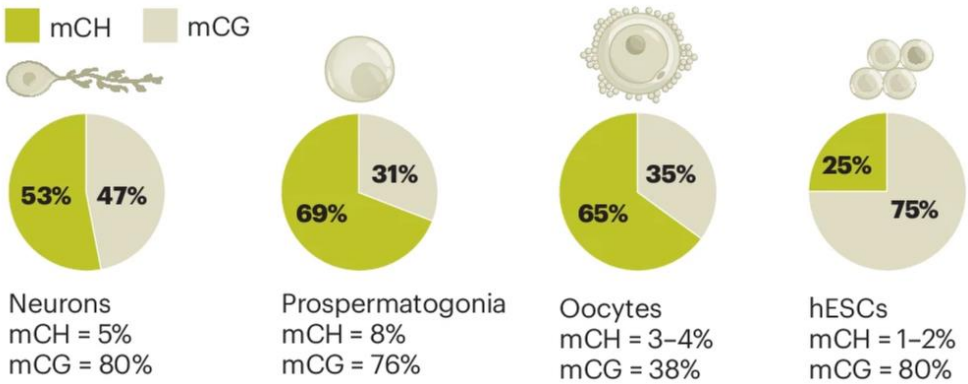
Summary of activities:

In 2025, the work carried out in the Developmental Epigenomics Lab combined conceptual, methodological, and experimental studies aimed at understanding how the epigenome is established and maintained during development. A major output was our *Nature Genetics* review on non-CG DNA methylation - mCH (Brethouwer et al, 2025), which provided a critical synthesis of current evidence on the distribution, mechanisms, and functional relevance of non-canonical methylation (mCH) across animal genomes. By drawing on data from vertebrate neural tissues, oocytes, embryonic stem cells, and teleost models, our review clarified emerging roles for mCH in gene regulation, repeat control, and cellular identity, and highlighted its relevance to early embryogenesis and neurodevelopmental disorders. In parallel, we contributed to a large collaborative study published in *Nature Communications* that introduced Cornetto, a targeted long-read sequencing and iterative assembly strategy designed to improve genome completeness and accuracy, particularly in repetitive and structurally complex regions. This work showed that high-quality diploid genome assemblies can be generated cost-effectively from challenging samples, enabling more reliable analysis of regulatory and disease-relevant genomic variation. Finally, our experimental work on zebrafish germline genomics resulted in the publication of a zebrafish spermatogenesis atlas in *Molecular Systems Biology*. This study, published as an edited and expanded version of a bioRxiv preprint released the previous year, integrated transcriptomic, chromatin accessibility, and DNA methylation data to resolve regulatory dynamics during male germline development.

Two highlights:

Non-CG DNA methylation in animal genomes. Brethouwer T, de Mendoza A, Bogdanovic O. Nat Genet. 2025 Oct;57(10):2395-2407. doi: 10.1038/s41588-025-02303-1.

Targeted sequencing and iterative assembly of near-complete genomes. Gamaarachchi et al. Nat Commun. 2025 Nov 24;16(1):10406. doi: 10.1038/s41467-025-65410-x.



Quantification of non-canonical DNA methylation (mCH) represented either as percentage of total methylated sites in the genome (pie charts), or as percentage of methylated reads supporting either mCH or mCG sequence contexts (Adapted from Brethouwer et al, 2025).

Global Regulation of Gene Expression and Metabolism of Environmental Bacteria: Genetic and Species Rearrangements in Microbial Consortia Impact Biodegradation Potential

Inés Canosa and Amando Flores

Summary of activities:

Our 2025 activities deepen a coherent research program on the adaptation of environmental microbial communities to emerging contaminants, particularly ibuprofen, naproxen, and antibiotics in soil and aquatic ecosystems. We analyse how pre-existing metabolic pathways are rewired through horizontal gene transfer, plasmids, and community restructuring, showing that genetic and species rearrangements within microbial consortia strongly condition biodegradation potential and robustness. This work directly addresses MdM DMC3 Q1 and Q5 by linking genomic and regulatory changes to evolutionary innovation and by quantifying how metabolic states and energy constraints shape collective decisions in space and time.

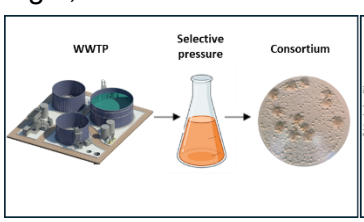
On the applied side, we advance two strategies for water treatment: optimization of natural microbial consortia for pharmaceutical removal and development of microbial support materials that valorise agricultural residues. In 2025, these approaches were combined with advanced catalytic materials to inactivate antibiotic-resistant bacteria and achieve light-assisted disinfection at near-neutral pH, providing scalable routes to irrigation-quality water with low energy and chemical inputs. High-impact publications in ISME Journal, Chemosphere and ChemPlusChem underpin this program, demonstrating how genetic and ecological optimization of consortia, together with MOFs and metal-exchanged zeolites, generate robust self-organizing decontamination systems, especially relevant to Q1, Q3 and Q5 of MdM DMC3**.**

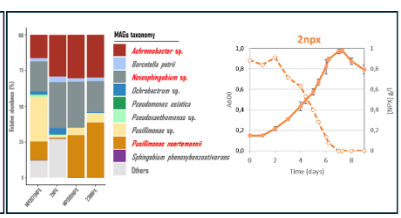
A complementary line on biodiversity and regenerative agriculture examines how management practices in experimental plots in Badajoz, Sevilla and Córdoba affect carbon sequestration and microbial and plant diversity, offering field-scale insight into ecosystem-level self-organization under different resource and disturbance regimes (Q1, Q5). In parallel, we contribute over 120 hours of university teaching in microbiology and environmental biotechnology and assume leadership roles such as CABD *claustro* secretary, UPO department secretary, and area head, while engaging in outreach activities aimed at highlighting for younger generations the societal value of sustained investment in environmental and health-related research.

Two highlights:

Genetic and species rearrangements in microbial consortia impact biodegradation potential. Saati-Santamaría Z, Navarro-Gómez P, Martínez-Mancebo JA, Juárez-Mugarza M, Flores A, Canosa I. ISME J. 2025 Jan 2;19(1):wraf014. doi: 10.1093/ismejo/wraf014.

Mechanochemical synthesis of multivariate UPO-3 (Cu-ZIF-9-ica) MOF for inactivation of antibiotic-resistant bacteria and irrigation-quality water production via heterogeneous photo-Fenton catalysis. Rodríguez-Sánchez N, Domínguez-Santos JE, Bhattacharya B, Prinz C, Canosa I, Flores A, Jiménez-Rodríguez A, Ruiz-Salvador AR, Emmerling F, Ballesteros M. Chemosphere. 2025 386:144610. doi: 10.1016/j.chemosphere.2025.144610.





Developmental Control

Fernando Casares

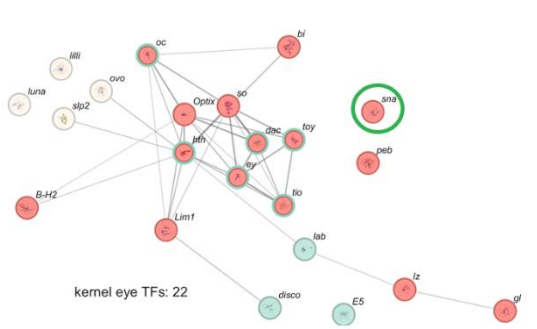
Summary of activities:

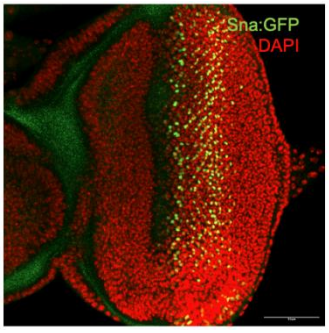
The group has continued to investigate how genome activity is coordinated across cells to drive cell differentiation and organ patterning, and how such coordination ensures **developmental robustness**, using the developing ***Drosophila* eye** as a model system. Although the *Drosophila* eye is among the best-characterized animal organs, it remains unclear whether it is representative of the compound eye more broadly, as *Drosophila* is a derived fly. To address this, we employed a comparative genomics and epigenomics approach to reconstruct a gene regulatory network (GRN) for eye development in a distant relative, the marmalade hoverfly *Episyrphus balteatus*, and compared it with the *Drosophila* eye GRN. This analysis identified a conserved set of transcription factors regulating a core group of eye-specific genes. While both GRNs exhibited dense connectivity, substantial variation was observed in regulatory interactions, as well as in the number and distribution of enhancer elements, supporting the concept that homologous organs can arise through “rewired” GRNs, a phenomenon known as **developmental systems drift**. In a related evolutionary developmental biology collaboration with the McGregor lab (Durham University, UK), we investigated the developmental basis of eye size variation. We found that sequence variation in an enhancer of the *Otd* gene leads to **temporal shifts** in its expression across species, providing a mechanistic explanation for differences in eye size. Because changes in gene expression are coordinated across tissues by morphogens, we also initiated a collaboration with the Iber group (ETH Basel, Switzerland) to examine whether the Hedgehog (Hh) gradient is sufficiently precise to define target gene expression domains. These studies will inform our understanding of the mechanisms underlying robust multicellular patterning. Finally, in 2025 Miguel Brun-Usan joined the group as a Momentum Researcher to develop COSMOS, a computational framework to investigate **the origins of open-ended evolution in multicellular systems** and to extend its application to real biological datasets. All these results address a major question posed by the MdM DMC^3 strategic research plan: Q1: What is the relationship that regulatory and structural changes have with organ evolution?

Two highlights:

Heterochrony in orthodenticle expression is associated with ommatidial size variation between Drosophila species. Torres-Oliva M, Buchberger E, Buffry AD, Kittelmann M, Guerrero G, Sumner-Rooney L, Gaspar P, Bullinger GC, Jimenez JF, Casares F, Arif S, Posnien N, Nunes MDS, McGregor AP, Almudi I. BMC Biol. 2025 Feb 4;23(1):34. doi: 10.1186/s12915-025-02136-8.

Expanding the fly eye gene regulatory network: from *Drosophila* to the hoverfly *Episyrphus balteatus*. Navarro T, Torres J, Sáez-Moreno R, Guerrero G, Almudí I, Iannini A, Figueras J, Wotton K, Aerts S, Casares F. bioRxiv; 2025. doi: 10.1101/2025.09.02.673659.





Left: A STRING representation of the interaction network between transcription factors (“kernel TFs”) expressed in the developing eyes of the flies Drosophila and Episyrphus includes Snail (Sna, circled). Right: Indeed, Sna is expressed in the developing Drosophila eye (right panel, in green), adding a new regulator to the eye gene regulatory network. Further work is needed to connect Sna to the gene network

Regulation of the Bacterial Lifestyle Switch

Fernando Govantes

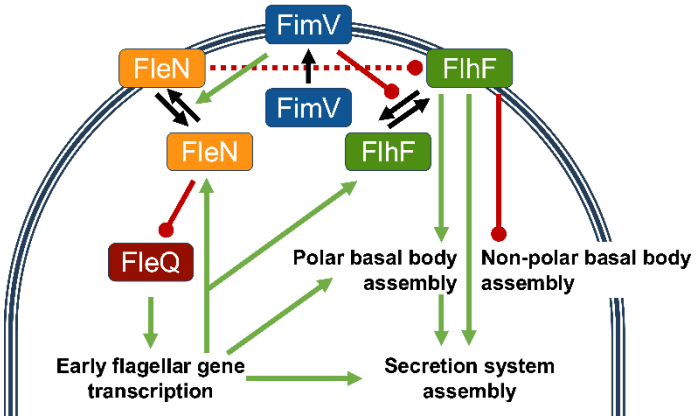
Summary of activities:

During year 2025 the Regulation of the bacterial lifestyle switch group has been active in the characterization of the mechanisms of spatiotemporal regulation of polar flagellar assembly and the regulation of starvation-induced biofilm dispersal in *Pseudomonas putida*. Our findings unveil novel mechanisms by which bacterial cells respond to changes in their environment and incorporate this information to self-organization at the level of individual cells (e.g., flagellar assembly), and cell collectives (e.g., biofilm dispersal) (Q2), and highlight the role of energy constraints and metabolic states in collective cell decisions in time and space (Q5). In addition, we have continued with our ongoing collaboration with Prof. Alejandro Cuetos (Chemical Physics, UPO) in the development of computer models of biofilm development. These studies provide a framework for a better understanding of the role of mechanical stress and metabolic states in the development of biofilm morphology (Q3 and Q5). We have also initiated a new collaboration with Prof. Kai Thormann (Justus-Liebig Universität, Gießen, Germany) on bacterial cell pole determinants, and continued collaboration with Prof. Carmen Beuzón (Universidad de Málaga) on phenotypic heterogeneity during biofilm growth. In this period, our Ph.D student Marta Pulido-Sánchez presented her Ph.D thesis with a *cum laude* grade, and group member Aroa López-Sánchez earned a Profesor Titular (Assistant Professor) position.

Two highlights:

Diffusion of tracer particles in early growing biofilms a computer simulation study. Daza FAG, Rodríguez-Rivas Á, Govantes F, Cuetos A. Colloids Surf B Biointerfaces. 2025 Nov;255:114903. doi: 10.1016/j.colsurfb.2025.114903.

Spatial, temporal and numerical regulation of polar flagella assembly in *Pseudomonas putida*. Pulido-Sánchez M, Leal-Morales A, López-Sánchez A, Cava F, Govantes F. Microbiol Res. 2025 Mar;292:128033. doi: 10.1016/j.micres.2024.128033. Epub 2024 Dec 19. PMID: 39709681.



A recruitment cascade involving polar landmark proteins FimV, FlhF and FleN regulates the timing, location ond number of flagella assembled at the new cell pole.

Molecular and Cellular Mechanisms Regulating Epithelia Morphogenesis and Homeostasis

María Dolores Martín Bermudo

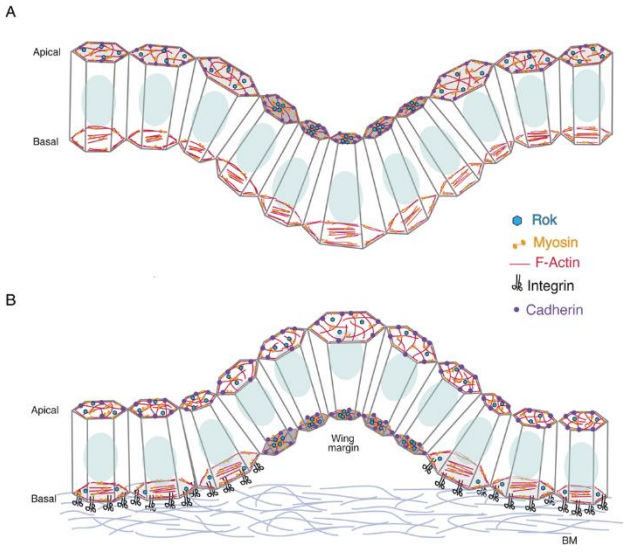
Summary of activities:

Our laboratory primarily focuses on analysing the mechanisms underlying epithelia morphogenesis and homeostasis. We employ a multidisciplinary approach using Drosophila as a model system and integrating genetics, transcriptomics, 4D imaging, biophysics, and computational analysis.

Along this year 2025, our group has identified several novel regulators of Ras-driven cell invasion. These include EGRAP, a new EGFR negative regulator, proteins of the Tensin family, integrins and extracellular matrix (ECM) components, such as laminins. In addition, we have uncovered key regulators of the tumor-promoting crosstalk between epithelial tumor cells and adjacent mesodermal cells, which include regulators of zinc metabolism, the Hh signaling pathway members, and vesicle trafficking. We have also deepened in our understanding of the role of cell–ECM interactions in epithelial morphogenesis and homeostasis, we have shown that a balance between the mechanical forces generated by epithelial cells and those exerted by the ECM is essential for the cell shape changes driving organogenesis. This has been demonstrated in diverse model systems, including the egg chamber, the embryonic tracheal system and the wing imaginal disc, the primordium of the wing. We have also shown that cell–ECM interactions regulate epithelial stem cell proliferation via modulation of Notch signaling, and that the mechanical context determines integrin requirement in maintaining epithelial architecture.

Highlight:

Local weakening of cell-extracellular matrix adhesion triggers basal epithelial tissue folding. Valencia-Expósito A, Khalilgharibi N, Martínez-Abarca Millán A, Mao Y, Martín-Bermudo MD. EMBO J. 2025 Apr;44(7):2002-2024. doi: 10.1038/s44318-025-00384-6.



Model illustrating the mechanisms of basal versus apical folding. (A) During apical folding, apical constriction mediated by forces exerted by the cortical actomyosin network and the transmission of these forces to cadherin-based adherens junctions initiates folding. (B) On the basal side, folding is initiated by a reduction on integrin-mediated adhesion to the BM that triggers a basolateral reorganization of the actin cytoskeleton, the basal localization of cadherins and Rok and basal constriction

Mitochondrial Signalling Control in the Regulation of Ageing

Marta Artal-Sanz and Jesús Fernández Abascal

Summary of activities:

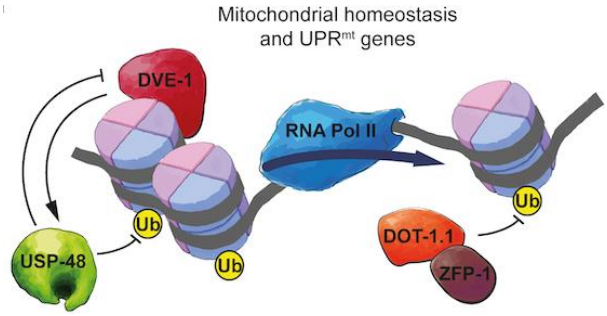
During 2025 the lab continued to develop an additional research line (led by Jesús Fernandez Abascal, Ramón y Cajal Associated Researcher) focused on how mitochondrial stress in neurons is communicated across tissues through neuron–glia–intestine signalling axes. This work aims to elucidate how the systemic propagation of mitochondrial stress influences organismal adaptation, longevity, and vulnerability to neurodegenerative processes. Initial results indicate that neuronal mitochondrial perturbations trigger measurable peripheral responses, supporting a role for intertissue signalling in shaping organismal physiology. This research directly addresses how local mitochondrial perturbations scale into coordinated organismal responses, contributing to a multiscale understanding of self-organization in living systems. The first outcomes of this line are currently being prepared for publication and were presented in the 3rd meeting of the Italian *C. elegans* Research community.

We have followed up on our long-standing interest on how metabolism and mitochondrial function control cell homeostasis through the epigenetic regulation of gene expression. Our current focus is on a novel histone deubiquitinase that modulates stress responses in a metabolic-dependent manner.

The discovery of this mechanism is under review (DOI: https://doi.org/10.21203/rs.3.rs-3337719/v1, Figure 1), and we are now pursuing its function using proteomic and genomic strategies. This work provides fundamental insights into how energetic constraints shape the aging process.

Highlight:

Oral communication. The mitochondrial prohibitin complex PHB regulates neuronal and glial morphology in ageing. 3.0rd Meeting of the Italian *C. elegans* Research Community (M.I.C.e.R.Co.). 2025.



Proposed mechanism. During mitochondrial stress, USP-48 removes ubiquitin from H2B to promote RNA Pol II pausing in transcriptionally active genes related to mitochondrial function and the UPRmt, modulating their expression.

Regulatory Mechanisms of Gene Expression in Pollutant-Degrading Bacteria - Bioremediation

Francisca Reyes-Ramírez and Eva María Camacho Fernández

Summary of activities:

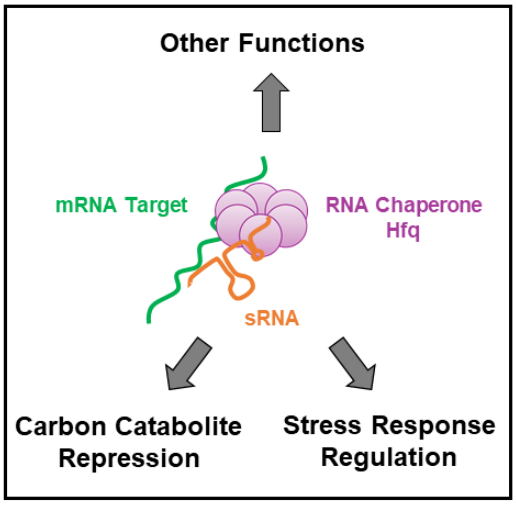
My research group focuses on two main areas: Regulation of gene expression in bacteria and plastic bioremediation.

During 2025, my research focused on dissecting the regulatory mechanisms governing stress responses in the environmental alphaproteobacterium *Sphingopyxis granuli TFA*. A major achievement was the characterization of two histidine kinases with antagonistic activities within the General Stress Response (GSR) signalling pathway. Their coordinated and opposing activities ensure precise control of GSR activation, preventing inappropriate stress responses while maintaining environmental responsiveness. In parallel, we investigated the role of small regulatory RNAs (sRNAs) in stress adaptation. Specifically, we demonstrated that an sRNA previously associated with carbon catabolite repression also contributes to stress-response regulation, revealing a new layer of post-transcriptional control that integrates metabolic and environmental signals. These findings directly address **Q3 of MdM DMC3** by elucidating **how bacterial cells sense environmental changes and incorporate this information into coordinated regulatory responses**.

In collaboration with Dr. Eva María Camacho Fernández (CABD), we advanced functional metagenomics strategies to identify novel enzymes with industrial and environmental applications. We established functional screenings of previously constructed metagenomic libraries derived from pristine and petrochemical-contaminated soils to discover cellulases with improved industrial properties, as well as enzymes capable of hydrolyzing ester bonds in PET and polyurethane. Our results revealed a higher frequency of cellulase-positive clones in pristine soil, consistent with greater lignocellulosic content, whereas contaminated soil showed enrichment in plastic-degrading activities, reflecting microbial ecological adaptation.

Highlight:

Uncovering the regulatory network of the small RNA SuhB and its contribution to stress resistance in Sphingopyxis granuli TFA. García-Romero I, Pires-Acosta A, Floriano B, Reyes-Ramírez F. bioRxiv; 2025. doi: 10.64898/2025.12.09.693200.



The sRNA ShuB functions as a global post-transcriptional hub coordinating metabolic state and environmental stress responses, among other cellular functions. Like many trans-encoded sRNAs shares limited complementarity with its targets mRNA. As a consequence, ShuB require RNA chaperones such as Hfq to facilitate stable base-pairing interactions. This Hfq-dependent mechanism enables ShuB to modulate multiple transcripts, expanding its regulatory scope

Self-Organization of Biological Systems Laboratory

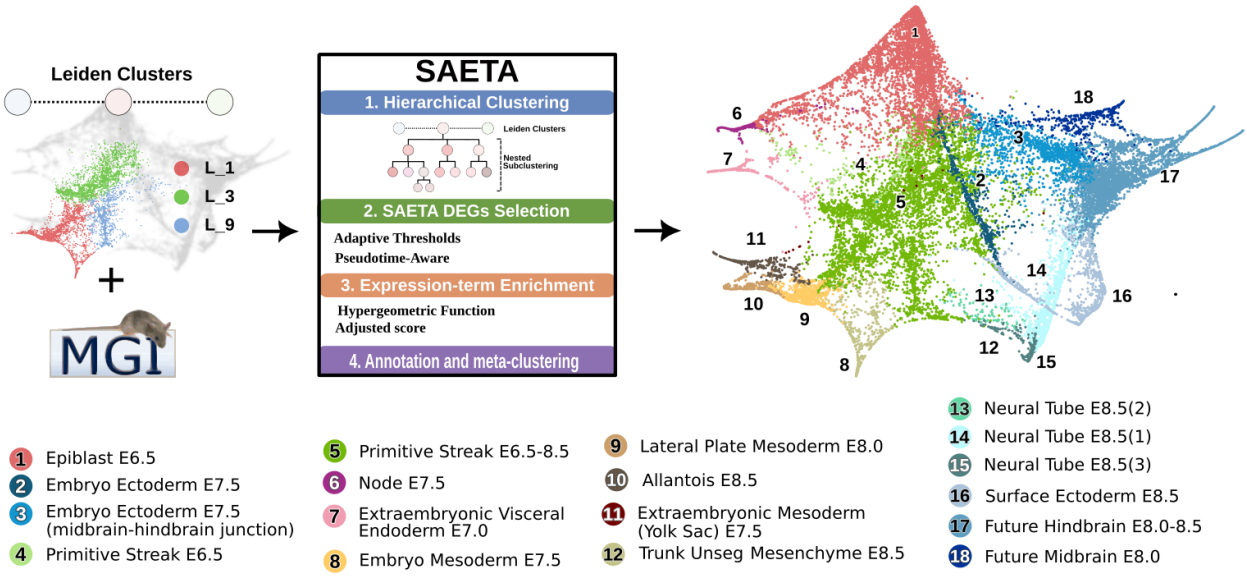
Luciano Marcon

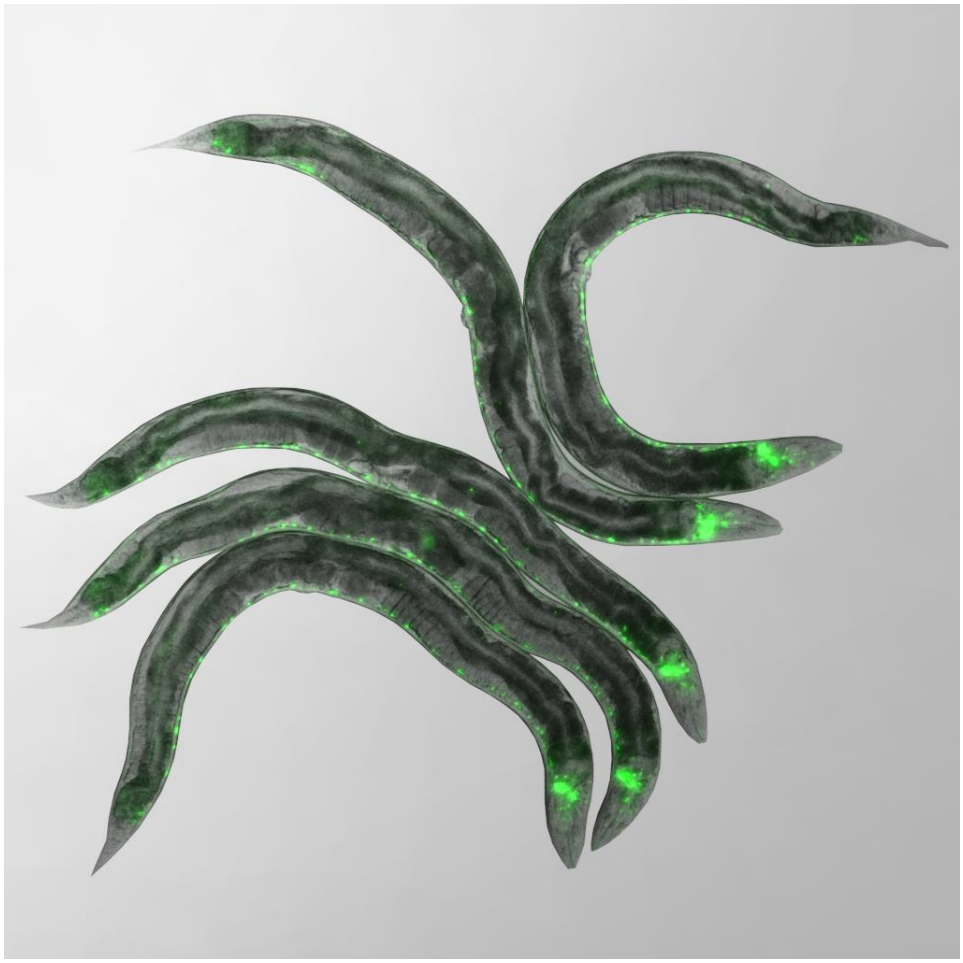
Summary of activities:

The laboratory investigates how initially homogeneous mouse embryoid bodies (EBs) spontaneously break symmetry to generate a body axis. Our goal is to understand how signaling dynamics and gene regulatory networks amplify fluctuations to produce a robust spatial transition from isotropy to polarity. This year, we established a quantitative framework to define the initial symmetry state of EBs. By computationally deriving all possible 3D axes and profiling cell density and Brachyury (T) expression along each axis, we formalized symmetry breaking as a reduction from spherical O(3) symmetry to radial O(2) symmetry. We also addressed a major bottleneck in single-cell RNA sequencing analysis: objective cell type annotation. Standard approaches rely on manual interpretation of Leiden clusters and differential markers over UMAP embeddings. Our predoctoral researcher J.M. Tavira developed **SingleCell Analysis for Enrichment and Transcriptomic Annotation** (**SAETA**), a computational pipeline that integrates curated marker genes from the Mouse Genome Informatics (MGI) database with hierarchical cluster structure and pseudotime scoring to produce automated, reproducible annotations. SAETA now enables systematic comparison of EB datasets and reconstruction of epiblast differentiation trajectories during symmetry breaking. Finally, we advanced a theoretical framework to systematically identify gene regulatory networks capable of generating diffusion-driven instability. In a recent preprint, we constructed a topological atlas of all three-gene networks composed of two diffusible signals and one transcription factor, using automated linear stability analysis to classify pattern-forming behaviors. Networks are organized by single-interaction transitions, enabling exploration of evolutionary rewiring and multifunctional Turing systems.

Highlight:

The Network Basis of Pattern Formation: A Topological Atlas of Multifunctional Turing Networks. Regueira López de Garayo L, Marcon L. bioRxiv; 2025. doi: 10.1101/2025.01.27.634997.





Caenorhabditis elegans nematodes expressing green fluorescent protein in cholinergic neurons under control of the promoter of vesicular acetylcholine transporter *unc-17* (Author: Javier Valle).

Centro Andaluz de Biología del Desarrollo

EXCELENCIA MARÍA DE MAEZTU

AGENCIA ESTATAL DE INVESTIGACIÓN

Junta de Andalucía

UNIVERSIDAD PABLO DE OLAVIDE SEVILLA

CSIC

CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS