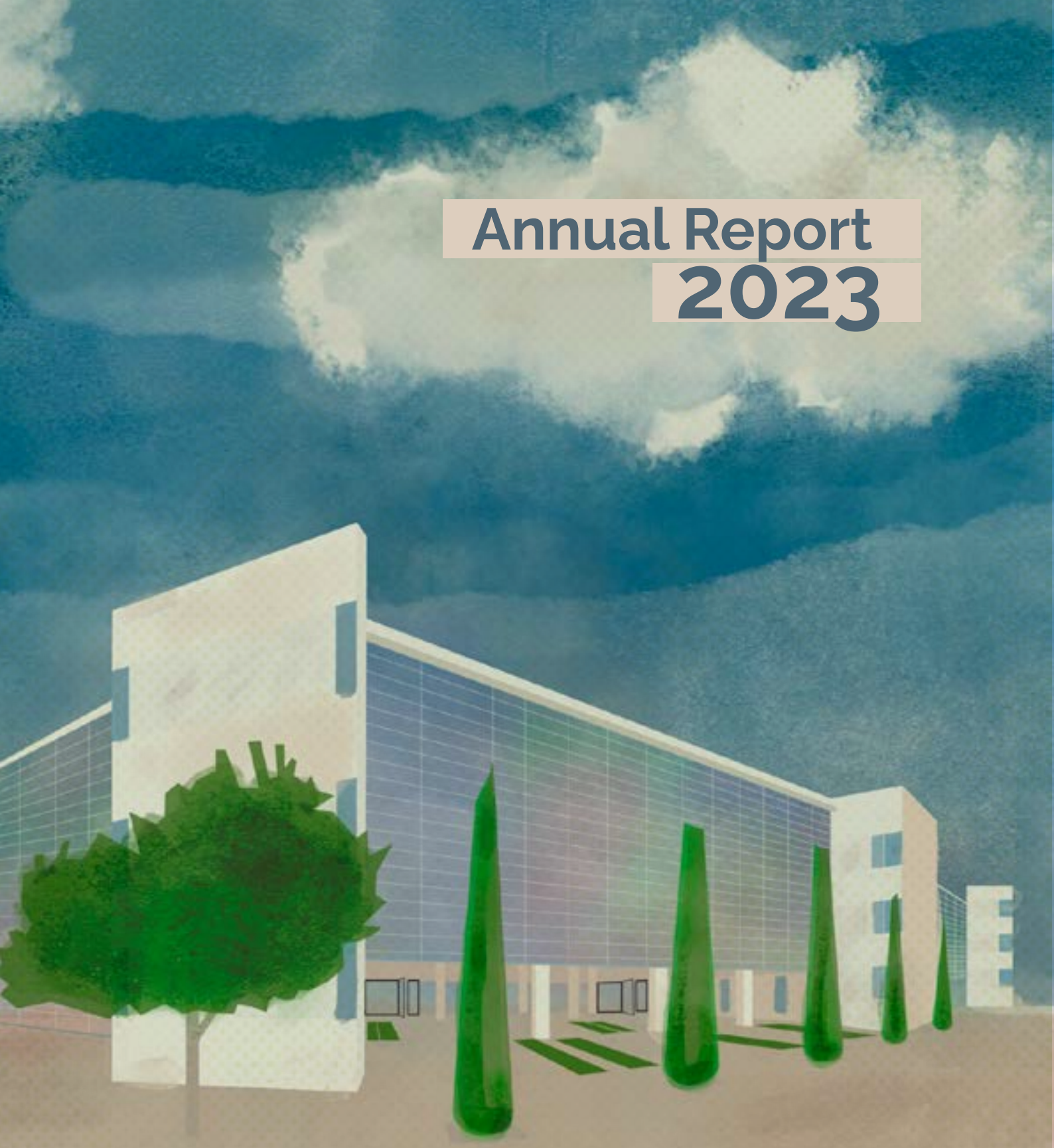
Annual Report 2023



INSTITUTO DE NEUROCIENCIAS

25 1990 - 2024 YEARS Instituto de Neurociencias

EXCELENCIA SEVERO OCHOA 014 - 2027

UNIVERSITAS Miguel Hernández

CSIC Consejo Superior de Investigaciones Científicas

INSTITUTO DE NEUROCIENCIAS
Spanish National Research Council (CSIC)
Miguel Hernández University (UMH) of Elche

https://in.umh-csic.es/en/

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2024

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Saludation

The year 2023 is marked by two significant milestones. On one hand, in January, we launched our third "Severo Ochoa" project, which represents a new boost to the institute's project and specifically to the development of our Strategic Plan for the 2022-2025 period. This plan focuses on the eight Research Programs described in other sections of this report, which define the current strategic lines of the IN. On the other hand, the Miguel Hernández University (UMH) and the Spanish Nationa Research Council (CSIC) have reaffirmed their alliance, notably reflected in the establishment of our institute as a joint center in 1999. With the signing of a new indefinite collaboration agreement in September 2023, a new legal framework for the continuity of the IN is defined. In parallel with this signing, educational agreements for Master's and PhD programs have also been signed, further strengthening the collaboration between our two parent institutions.

An additional outcome of the renewed alliance between CSIC and UMH is the IN expansion project currently underway. During 2023, the construction plans have been drafted, and they will begin to be executed in 2024, with completion expected in 2025. This expansion will provide the IN with more than 2000 m^2 of new work and meeting spaces. The lack of space in recent years has limited our ability to attract talent and implement new technologies. Therefore, this expansion is essential for the IN to maintain the level of research and excellence achieved so far. We hope that with the execution of the project conceived this year, we will have new facilities and laboratories available starting in 2025. It is crucial to highlight that this expansion will be equally funded by UMH and CSIC, with the former covering the construction costs and the latter covering the expenses related to the adaptation and equipping of the new spaces.

Dr. Angel Barco
Instituto de Neurociencias' Director

Another significant achievement to highlight is that 2023 has set a record in terms of competitive funding attracted by our researchers. The funds come from international, regional, and national sources. I am confident that this funding will serve as a basis for important discoveries that will lead to a better understanding of the brain or new therapies to treat its disorders. In the highlighted publications section, the reader will find a selection of the most relevant findings carried out by our researchers during 2023. As every year, the IN has become the new workplace for dozens of young researchers who are either starting their scientific careers with us or coming from important Spanish and foreign research centers to develop a new stage and initiate new lines of research. Our research staff has also increased with the addition of several new CSIC Senior Scientists and university professors. The year 2023 has also been characterized by significant recognitions awarded to IN researchers, a very active agenda of conferences and scientific or outreach meetings in the immediate vicinity of the institute, and some notable visits, such as that of the 2021 Nobel Prize in Medicine, Dr. Ardem Patapoutian.

Finally, I want to highlight the obvious: all these achievements have been made possible thanks to the dedication and effort of all our staff and the constant support of our institutions. Without the commitment of IN employees, including researchers, technicians, administrative and support staff, none of the achievements mentioned above would have been attainable. This exceptional human capital ensures our ability to continue growing as an institution and to face and overcome the new challenges that arise.

University of Alicante

1985

A group of researchers dedicated to studying the structure & function of the nervous system

University Institute

1990

Formally recognized at the University of Alicante

Associated Unit

1995

Associated Unit of The Cajal Institute CSIC

Miguel Hernández University

1996

Transferred to the newly created Miguel Hernández University of Elche

Joint Center

1999

The institute becomes a joint UMH-CSIC center

Own space

2001

Begins the construction of the new building

Move

2004

IN researchers move to the current building

Inauguration

2005

Her Majesty Queen Sofia officially inaugurates the new headquarters of the Institute

Consolider-Ingenio Grant

2007

The Institute receives the prestigious Consolider project for the development of its research

Severo Ochoa Distinction

2014

The Institute achieves the distinction of Severo Ochoa Center of Excellence for its research work

Renewal of SO Distinction

2018

Four years later the distinction of Excellence was renewed

20 years

2019

The Institute celebrates its 20th anniversary since its constitution in 1999 as a joint CSIC-UMH center

Severo Ochoa Distinction

2022

For the third time in a row, the IN center obtains its distinction as a Severo Ochoa Center of Excellence until 2027

Agreement renewal

2023

The CSIC and the UMH renew their collaboration agreement

Who we are

The IN, a joint center of the Spanish National Research Council (CSIC) and the Miguel Hernández University of Elche (UMH), **is today the largest publicly funded center dedicated to brain research in Spain**. More than 360 people dedicate their talent and effort to progress in our understanding of the biological basis of brain function and the mechanisms of brain disease. The IN maintains a balanced ratio between men and women, even in the highest management positions, and a high level of internationality. The accreditation as a “Severo Ochoa Center of Excellence” in 2014 and its renewal in 2018 have allowed us to develop an ambitious and multidisciplinary research program, undertake new methodological initiatives, and recruit talented young researchers.

A bit of History

In 1990, the Valencian Government formally recognized the Instituto de Neurociencias (IN) at the Universidad de Alicante (UA) as a **University Institute, constituted by a group of its researchers that, since 1985, had been dedicated to the study of the structure and function of the nervous system**. The members of the new Institute began to share not only their ideas but also funding and resources in order to improve their research environment. At the same time, a PhD Program was created to train young

scientists in the field of neuroscience. Five years later, the IN became an “Associated Unit” of The Cajal Institute (CSIC), and the first two CSIC research groups moved to the “Associated Unit” in Alicante. In 1996, the Institute along with the School of Medicine was transferred to the newly created University Miguel Hernández of Elche (UMH). During this period the Institute was physically located in the building of the School of Medicine, at the Sant Joan d’ Alacant Campus site.

On the 20th of July 1999, the IN was formally created as a Joint Centre of the UMH and CSIC. Two years later, the UMH initiated the construction of a new building dedicated to housing the IN with the support of the Valencian Government. Furniture and laboratory equipment were provided by the CSIC. Researchers moved into the new premises in 2004, whilst the building was officially inaugurated on the 26th of September 2005 by Her Royal Majesty Queen Sofía of Spain.

The years following the relocation of the IN to its current building coincided with an important period of expansion, resulting in the IN becoming the largest Spanish institute dedicated to the study of the nervous system and its pathologies.

The increase in personnel has been in both young and senior researchers, several of them of recognized international prestige. **The Consolider-Ingenio research grant** received in 2007 provided a solid ground for the growth and consolidation of the IN as a national reference in neuroscience research. Later, the accreditation as a **‘Severo Ochoa Center of Excellence’** in 2014 and its renewal in 2018 enabled the consolidation of our project through the development of an ambitious and multidisciplinary research program.

The IN currently hosts 35 research groups with more than 250 researchers (See graphic IN in Numbers: Personnel). We keep progressing towards our objective of a better understanding of the brain and its disorders and stay as the flagship of neuroscience research in Spain.

Where we are

The IN is located in the town of Sant Joan d’Alacant, 7 Km from the city of Alicante and less than 3 Km away from the Mediterranean Sea, in a region favored by an exceptional climate throughout the year. The IN is situated in the Health Sciences Campus of the UMH, which provides ample opportunity for interaction with the Schools of Medicine and Pharmacy, the University Hospital of San Juan, the Health Sciences Library, and other institutions located on the campus.

The IN houses over fifty **laboratories for independent research groups in a building of approximately 9,000 m²** distributed over four floors. Approximately 30% of the building houses common facilities with state-of-the-art research equipment for leading-edge research in neurosciences.

What we do

The mission of the IN is to generate fundamental knowledge on the development, structure, and function of the nervous system to advance the understanding of the neurobiological roots of human behaviour and diseases of the nervous system. The IN offers its researchers a unique catalogue of technical facilities, services, and a supportive and collaborative environment in which to pursue cutting-edge questions in neuroscience. We have also become a reference center in Europe for training in neuroscience through our international Master's and PhD programs.

IN researchers are not only committed to the challenge of understanding how the brain works. Today's world demands that the knowledge acquired in basic research institutes such as the IN be transferred to society by training highly qualified professionals, applications, products, novel treatments, and practical knowledge. To take on the challenge of increasing the scientific and technical impact of our research and its transfer to society in an integrated way, we have organized our initiatives and projects around five axes of action.

Action Axes

Research Axis

Coordinators E. Herrera & J. Barbas

This axis monitors our scientific production and bibliometric indicators, supervises our scientific seminar programs (external and internal), and coordinates the activity of the Scientific Programs and the implementation of new initiatives related to research at the institutional level. It also acts as an interlocutor with the external Scientific Advisory Board (SAB), which evaluates our scientific production and advises on the research activity and strategies of the Institute.

The 6-member panel is highly international, interdisciplinary, and gender-balanced. Its current composition is:

Prof. Carmen Sandi (Chair)

École Polytechnique Fédérale de Lausanne (EPFL), CH

Prof. María Blasco

Spanish National Cancer Research Centre - CNIO, Madrid, ES

Prof. Alain Chédotal

Institut de la Vision, París, FR

Prof. Cornelius Gross

European Molecular Biology. Laboratory (EMBL) Rome, IT

Prof. Michael Häusser

Wolfson Institute for Biomedical Research. UCL Division of Medicine. London, UK

Prof. Magdalena Götz

Helmholtz Zentrum München. Institute of Stem Cell Research. Neuherberg, DE

Training Axis

Coordinators: E. de la Peña & E. Geijo

This axis supervises our various training programs. These include:

- One-year Master in Neuroscience called "International Master in Neuroscience: From Laboratory to Clinical Practice" (coordinator: E. Geijo) consisting of theoretical lectures and practical exercises to introduce trainees to various methodologies used to study the nervous system.
- PhD Training Program in Neurosciences (coordinator: E. de la Peña and deputy coordinator: Cruz Morenilla) that teaches courses and research training in various areas of basic neurosciences and related disciplines (programming, statistics, etc.).
- Leadership and career opportunities courses for postdocs.
- Career development and specialized courses for technical and administrative personnel.

Both the master's and PhD programs are part of the International Network of Neuroscience Schools (NENS).

Innovation Axis

Coordinators: S. Canals & J. Gallar

This axis seeks opportunities to generate exploitable intellectual property and supervises the activities of the new Scientific Unit for Business Innovation (UCIE, in Spanish). This office is responsible for identifying projects with direct translation potential and supporting them in their transfer process. The axis also promotes innovation activities at the IN by organizing seminars on different aspects (such as the protection of intellectual property, patents, and the creation of spin-offs) and represents IN at innovation fairs. It bridges the gap between neuroscientists and clinicians or pharmaceutical and biotechnology companies, facilitating a two-way exchange that establishes the most appropriate conditions to promote the discovery and development of new diagnostic and therapeutic strategies.

Translation Axis

Coordinators: H. Cabedo & S. De Santis

This axis seeks opportunities for collaboration and translation to the clinic and aims to enhance collaboration between IN researchers and clinicians, hospitals and local health institutions, and patient organizations through meetings and collaboration agreements. Among our partners are the Institute for Clinical and Biomedical Research of Alicante (ISABIAL), the Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (FISABIO), and different CIBERs and RICORs (networks dependent on the ISCIII, aimed at coordinating Spanish research on the most prevalent human diseases).

Outreach Axis

Coordinators: J. A. Moreno Bravo & S. Jurado

This axis coordinates actions aimed at disseminating our scientific discoveries to society, providing advice on scientific and technological matters to public and private entities, as well as promoting scientific culture and rational thinking among the population. It promotes the involvement of citizens with science through communication and educational projects (for example, the defence of animal experimentation or the presence of women in science) and carries out dissemination activities related to neurosciences. In addition, the outreach axis coordinates public awareness activities, such as open house visits, conferences, round tables, etc., and manages the presence of the IN in the media and social media platforms.

The Institute in Numbers

IN scientists have achieved both national and international recognition, as evidenced by their participation in multiple national and international programmes, and their success in obtaining competitive international funding and awards. The number and impact of publications place the IN as one of the highest-ranking research centers in Spain, competitive at the European level.

47
tenure
Full tenure research staff

116
support
Administrative & technical staff

135
predoc
Predoctoral staff

83
postdoc
Postdoctoral staff

83
stays / visitors
During the year

gender

54
female staff

46
male staff

origin

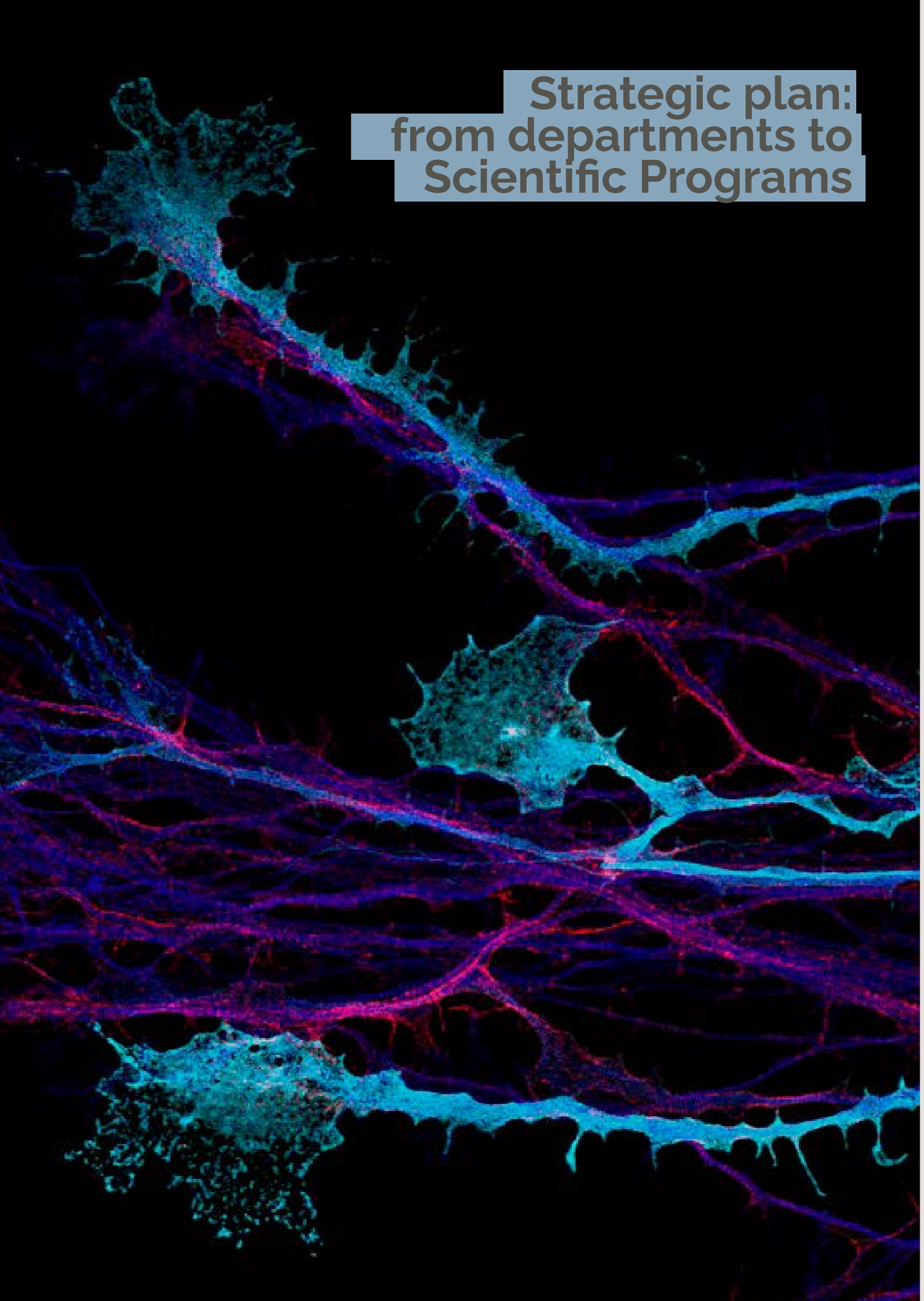
Non-Nationals
11,5%

Spanish national
88,5%

publications
web of Science
83

impact 8,1
impact factor (IF)

145
active projects
in 2023



Strategic plan: from departments to Scientific Programs

Research groups (RG) are the main functional research units at the Institute for Neuroscience. RGs vary in size, from 3 to 25 members, and are composed of both researchers and technical staff, hired through one of our parent institutions, the CSIC and the UMH. Traditionally, RGs have been assigned to one of the three departments that were defined at the creation of the IN more than 20 years ago: **the Department of Developmental Neurobiology, the Department of Cellular and Systems Neurobiology**, and the **Department of Molecular Neurobiology and Neuropathology.**

However, the exponential growth of the IN and changing times have transformed the focus of our research in recent years and brought us closer to a structure more focused on resolving specific scientific questions related to the assembly of brain circuits during development and how these circuits are shaped by experience and altered in disease.

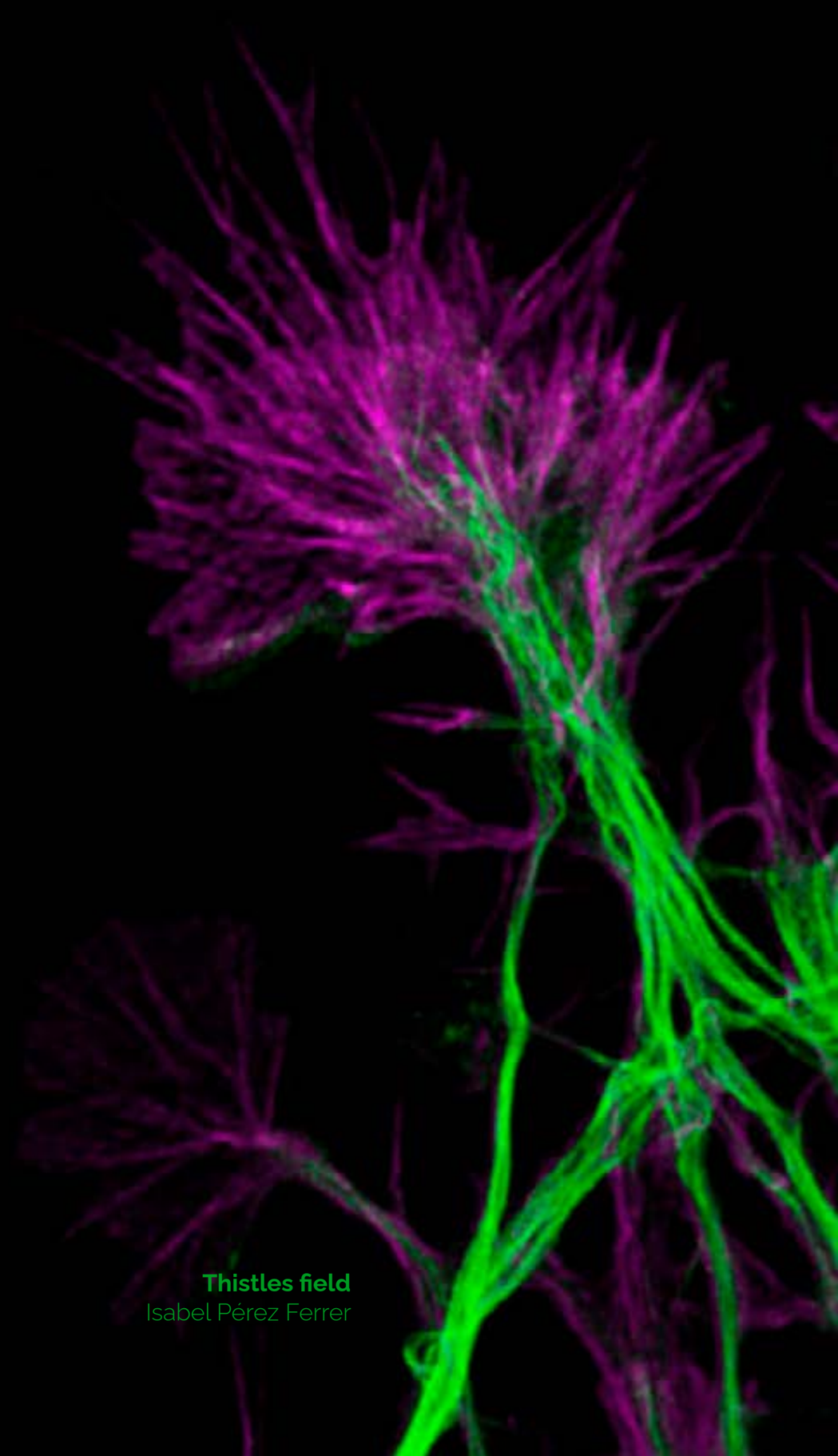
Scientific Programs

In 2022, we defined the research lines we considered strategic, which led to the creation of **eight Scientific Programs** that make up our new Collaborative Research project presented in the 2022-25 Strategic Plan. The scientific objectives of each program were identified using a bottom-up approach in which the principal investigators of the IN, both junior and senior, outlined and discussed our most ambitious scientific goals to seek synergies and collaborations.

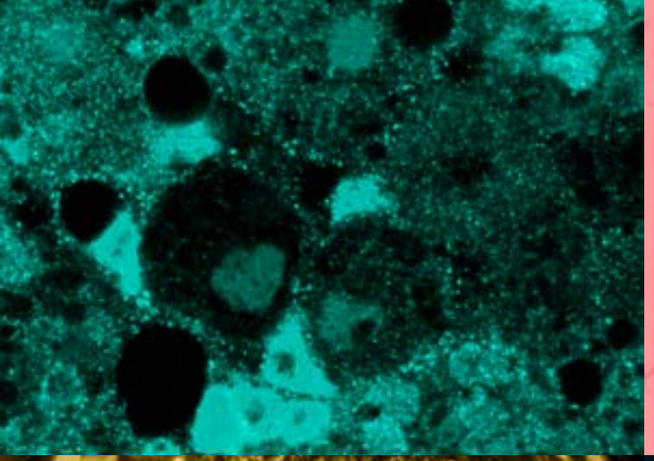
The eight scientific programs cover very diverse aspects and technologies and include a transversal representation of the different groups at the IN. In some of the programs, the main focus of research is on the cells that make up the nervous system. For example, a first program led by Prof. Victor Borrell focuses on the characterization and analysis of neural stem cells, while the second program coordinated by

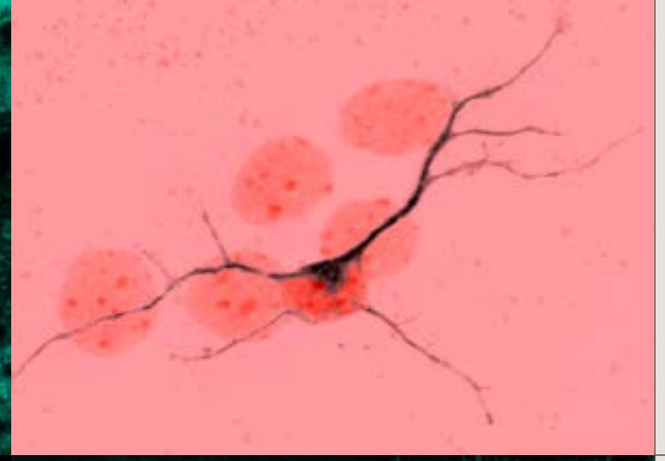
Professor Ángela Nieto analyzes and evaluates cellular changes that occur in tumor processes and degeneration. We also have programs that focus on how neuronal circuits are formed and function and the consequences of their malfunction. This is the case of the program led by Professor Guillermina López-Bendito, which studies how different sensory systems are assembled during embryonic phases and the first postnatal weeks. The program coordinated by Professor Isabel Pérez-Otaño seeks to understand the principles underlying synaptic transmission and cognitive impairment associated with aging once the brain is already formed. Other programs use holistic approaches to investigate interindividual variability and human behavior. Thus, the program coordinated by Professor María Dominguez investigates how environmental factors, pathogens, microorganisms, diet, or stress affect the genome and epigenome of cells that make up the nervous system and their impact on interindividual variation and life trajectories. The program led by Professor Luis Martínez addresses interindividual variability and cognitive abilities in humans, considering socioeconomic status, education, and other cultural aspects. Finally, the last two programs focus on fighting diseases of the nervous system. The program led by Professor Félix Viana is dedicated to unraveling the neurological principles of chronic pain and itching, two very common symptoms in elderly people, while the program led by Professor Jorge Manzanares seeks to identify biomarkers in patients with neurological diseases and psychiatric disorders such as anxiety, depression, or addictions.

Our goal with this new structuring in research programs is to strengthen the links between research groups, improve the scientific development of each individual group, and promote new joint projects among the center's researchers. In this way, we hope to contribute to advancing knowledge about the nervous system and in the fight against neurological diseases and psychiatric disorders.



Thistles field
Isabel Pérez Ferrer



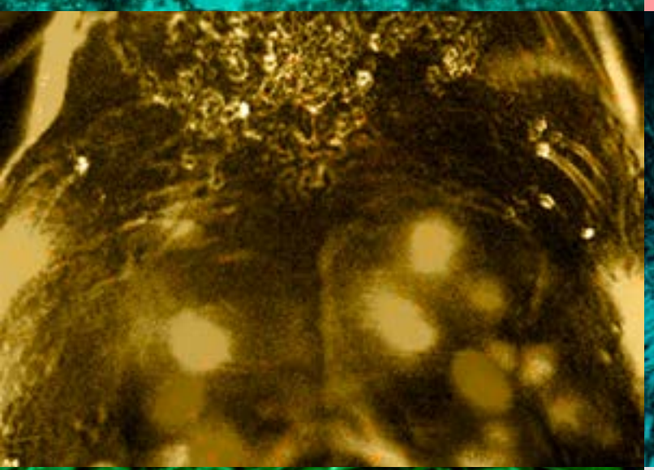


Sp1_ Neural stem cell regulation and differentiation

Director: Víctor Borrell Franco

Sp2_Cell plasticity in brain disease and repair

Director: Ángela Nieto



Sp3_Building & adapting circuits into functional networks

Director: Guillermina López-Bendito

Sp4_Synaptic modulation of neural circuits and behaviour

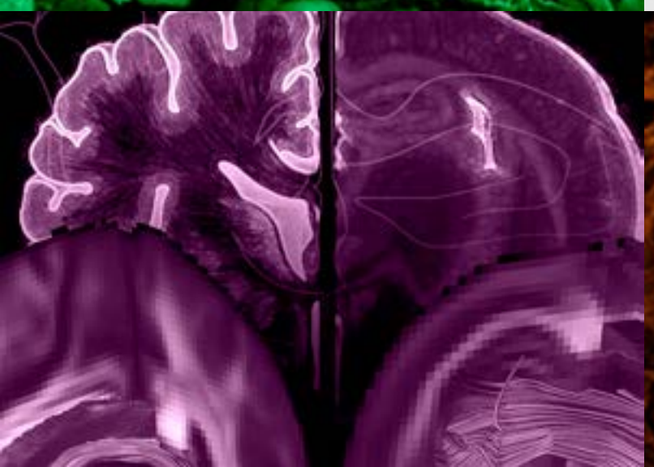
Director: Isabel Pérez Otaño

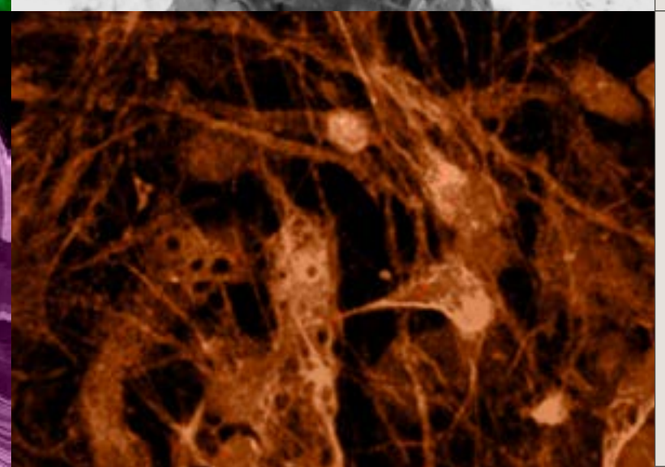
Sp5_Neurobiology of pain & inflammation

Director: Félix Viana de la Iglesia

Sp6_Genetic & epigenetic basis of Individuality & Aging

Director: María Domínguez Castellano





Sp7_Human cognition & behaviour

Director: Luis Martínez Otero

Sp8_ Translational research of neurological and psychiatric disorders

Director: Jorge Manzanares Robles

Research Groups

Transcriptional and Epigenetic Mechanisms of Neuronal Plasticity
Angel Barco

Neurogenesis & Cortical Expansión
Víctor Borrell

Molecular Control of Axonal Myelination
Hugo Cabedo

Plasticity of Brain Networks
Santiago Canals

Asymmetric Division of Neural Stem Cells in Development and Tumorigenesis
Ana Carmena

Sensory Transduction and Nociception
Elvira de la Peña / Ana Gomis / Félix Viana

Translational Imaging Biomarkers
Silvia De Santis

Developmental and Cognitive Disorders
Isabel del Pino

Mechanisms of Growth Control & Cancer
María Domínguez

Neuropharmacology, Molecular Immunobiology and Behavior
Teresa Femenía

Ocular Neurobiology
Juana Gallar / María del Carmen Acosta / Víctor Meseguer

Physiology of the Cerebral Cortex
Emilio Geijo

Behavior of Organisms
Alex Gómez- Marín

Molecular Mechanisms of Neurosecretion
Luis M. Gutiérrez / Manuel Criado

Generation and Regeneration of Bilateral Neural Circuits
Eloisa Herrera

Synaptic Neuromodulation
Sandra Jurado

Neural Circuits in Vision for Action
Andreas Kardamakis

Synaptic Physiology
Juan Lerma

Cognition and Social Interactions
Felix Leroy

Cellular Plasticity and Neuropathology
José P. López-Atalaya

Development, Plasticity and Reprogramming of Sensory Circuits
Guillermina López-Bendito

Translational Neuropsychopharmacology of Neurological and Psychiatric Diseases
Jorge Manzanares

Neurobiology of Mental, Neurodegenerative and Neuro-oncological Diseases
Salvador Martínez / Diego Echevarría / Eduardo de Puelles

Visual Analogy Laboratory
Luis M. Martínez Otero

Neuroendocrine Control of Organ Growth and Sexual Maturation
Javier Morante

Development, Wiring and Function of Cerebellar Circuits
Juan Antonio Moreno Bravo

Cell Plasticity in Development & Disease
Ángela Nieto / Berta L. Sánchez-Laorden

Cell-to-tissue Architecture in the Nervous System
José Carlos Pastor Pareja

Development, Refinement, and Consolidation of Neural Circuits
Isabel Pérez Otaño

Sensory-motor Processing by Subcortical Areas
Ramón Reig

Altered Molecular Mechanism in Alzheimer's Disease and Dementia
Javier Sáez Valero/ Salud García Ayllón

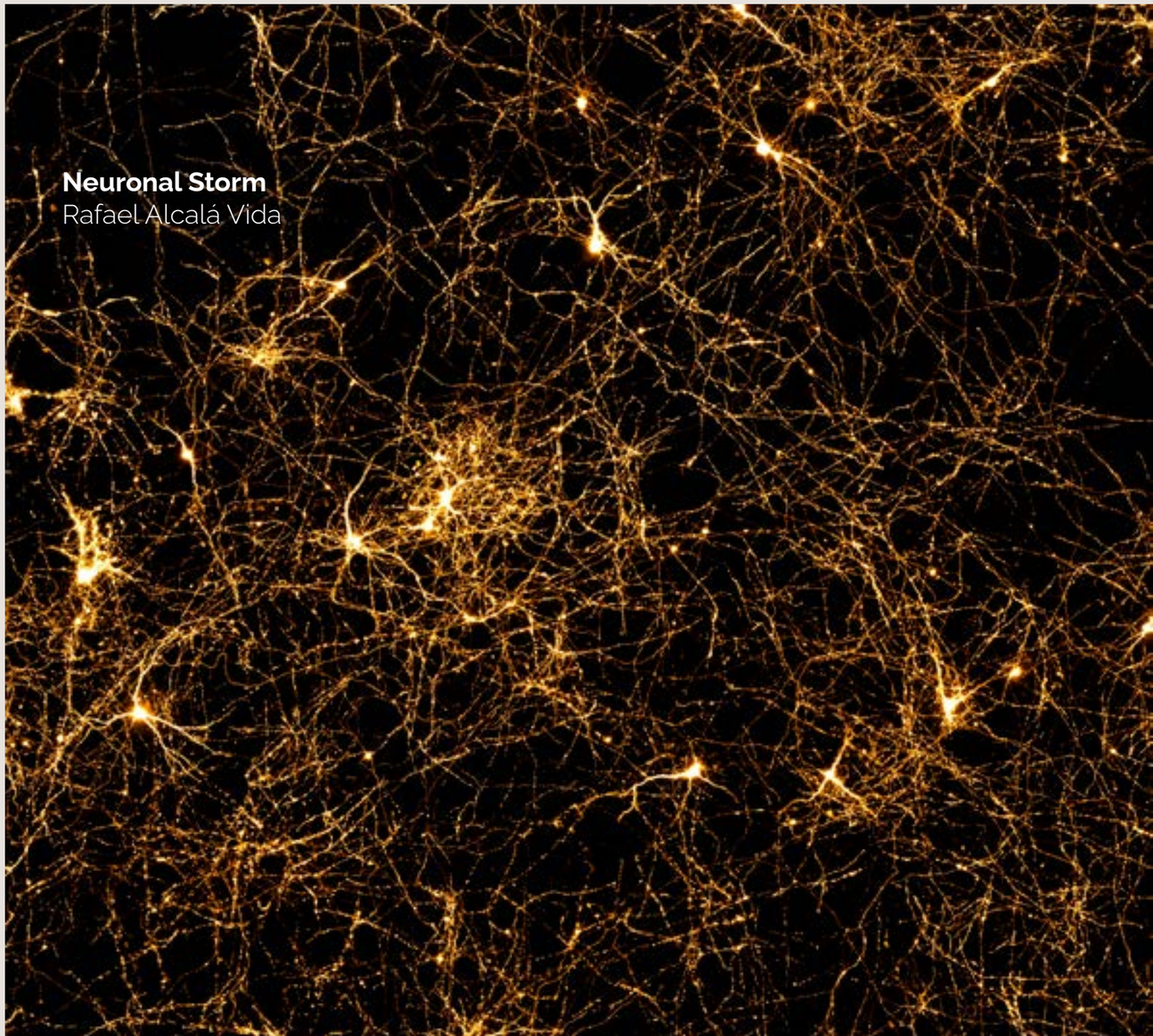
Functional Epi-Genomics of Aging and Alzheimer's Disease
José Vicente Sánchez Mut

Neurogenetic basis of Behavior
Juan A. Sánchez Alcañiz

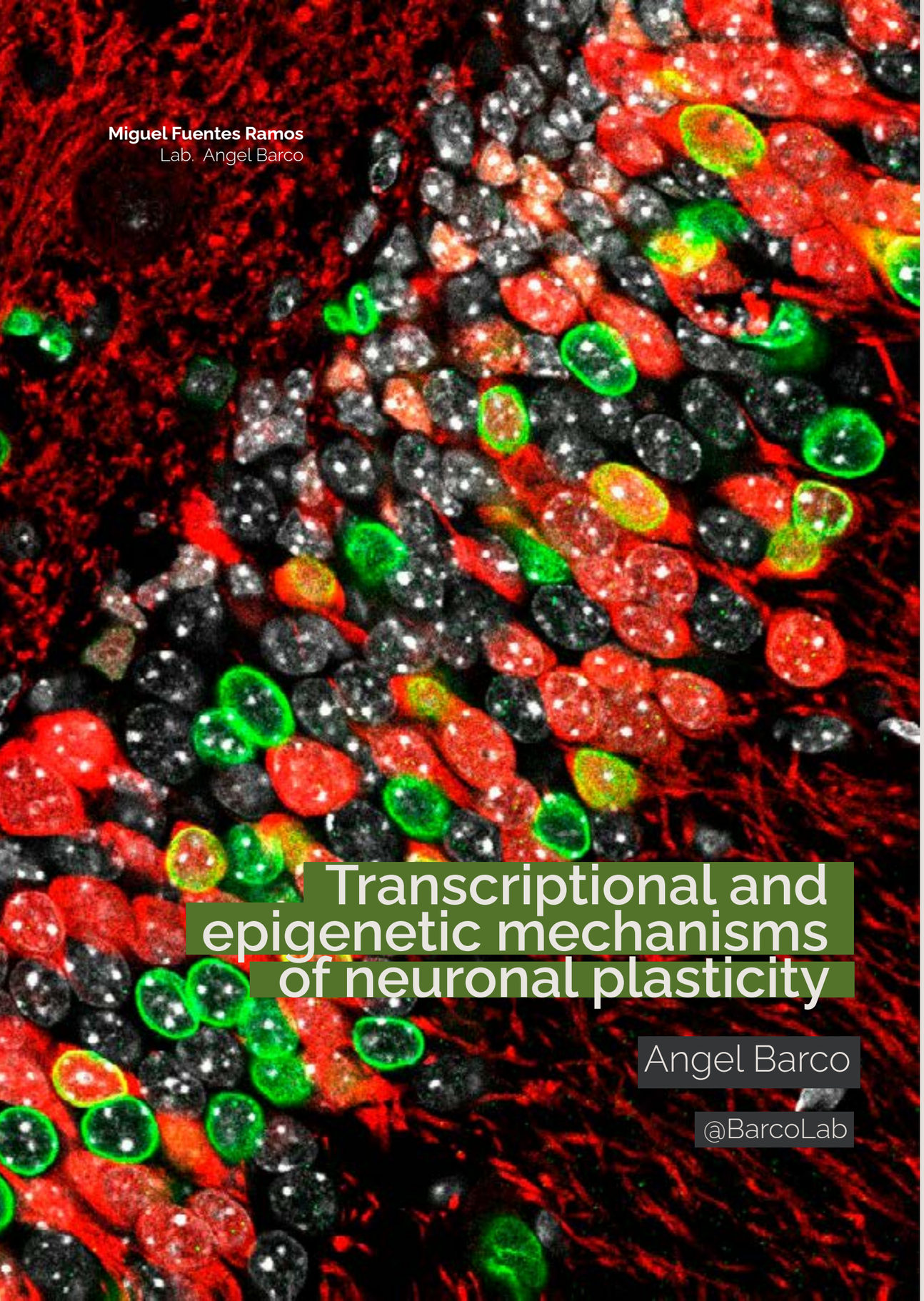
Wiring and Function of Somatosensory Circuits
Francisco J. Taberner Sanchis

Molecular Neurogenetics
Francisco J. Tejedor

Molecular and Cellular Physiology of Synaptic Transmission
John Wesseling



Neuronal Storm
Rafael Alcalá Vida



Transcriptional and epigenetic mechanisms of neuronal plasticity

Angel Barco

@BarcoLab

Our research focuses on **molecular mechanisms that regulate experience and activity-dependent neuronal gene expression in brain cells**. We also aim to determine how the malfunction of epigenetic mechanisms leads to different pathological situations in the nervous system. To tackle these questions, we use a **multidisciplinary approach that combines mouse genetics, genomics, bioinformatics, behavioral and electrophysiological analyses, and molecular and cellular biology techniques. We are particularly interested in the application of next-generation** sequencing (NGS) techniques and epigenetic editing approaches in the nervous system.

We currently work on two main lines of research:

- **The interplay of transcriptional and epigenetic mechanisms in activity-dependent transcription**. Activity-driven transcription and epigenetic remodeling represent an essential part of the neuronal response to stimulation. Both types of mechanisms have been postulated as appropriate molecular substrates for enduring changes in animal behavior, including learning and memory. In particular, we are investigating the participation of specific activity-regulated transcription factors, such as CREB and AP1, and epigenetic enzymes, such as CBP and p300, in these processes. Our experiments aim to clarify long-standing questions concerning the role of epigenetic mechanisms in gene expression and determine the necessity and/or sufficiency of specific experience-generated modifications of the neuronal epigenome in memory maintenance and expression.

- **Contribution of epigenetic mechanisms to intellectual disability (ID) disorders**. We investigate the contribution of epigenetic mechanisms, such as histone acetylation and methylation, to the pathoetiology of different neurological conditions associated with cognitive impairments and autism, and originated by mutations into genes encoding epigenetic regulators. This is the case of Rubinstein-Taybi syndrome caused by mutations in the genes encoding the lysine acetyltransferases CBP and p300, Claes-Jensen X-linked intellectual disability caused by mutations in the gene encoding the lysine demethylases KDM5C, and others. Towards this end, we generate and characterize cellular and mouse models for these conditions, explore the molecular causes of the disease using novel epigenome analysis techniques, and tackle new therapies.

Relevant publications

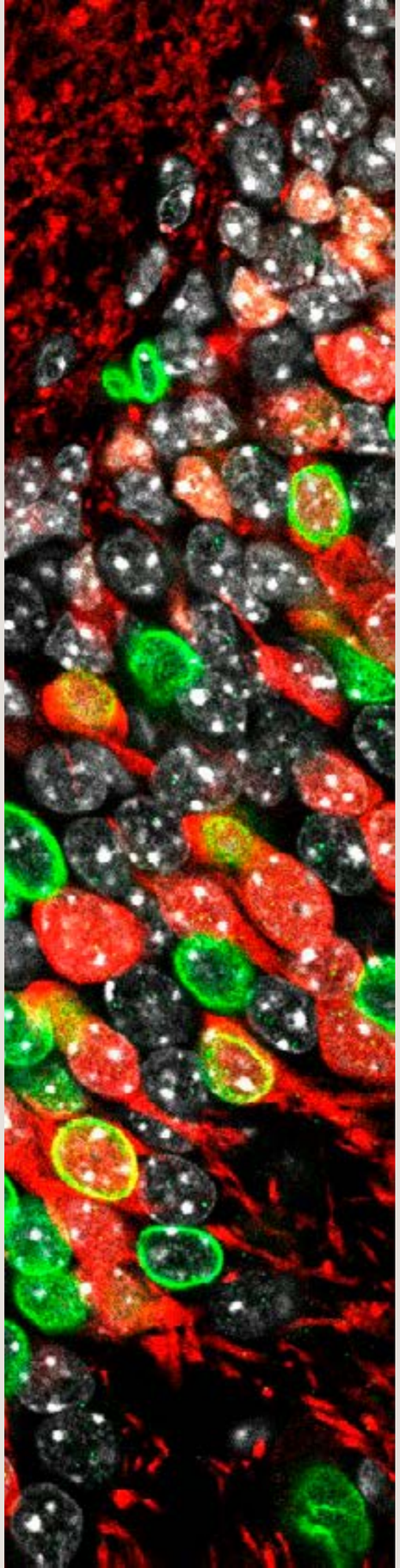
Lipinski, M., Niñerola, S., Fuentes-Ramos, M., Valor, L.M., del Blanco, B., López-Atalaya, J.P. and Barco, A. (2022). **CBP is required for establishing adaptive gene programs in the adult mouse brain.** *Journal of Neuroscience*, 42(42), 7984-8001. https://doi.org/10.1523/JNEUROSCI.0970-22.2022

Fernández-Nogales, M., López-Cascales, M.T., Murcia-Belmonte, V., Escalante, A., Fernández-Albert, J., Muñoz-Viana, R., Barco, A. and Herrera, E. (2022). **Multiomic Analysis of Neurons with Divergent Projection Patterns Identifies Novel Regulators of Axon Pathfinding.** *Advanced Science*, 9(29), 2200615. https://doi.org/10.1002/advs.202200615

Fuentes-Ramos, M., Alaiz-Noya, M. and Barco, A. (2021). **Transcriptome and epigenome analysis of engram cells: Next-generation sequencing technologies in memory research.** *Neuroscience and Biobehavioral Reviews*, 127, 865-875. https://doi.org/10.1016/j.neubiorev.2021.06.010

Lipinski, M., Muñoz-Viana, R., del Blanco, B., Marquez-Galera, A., Medrano-Relinque, J., Caramés, J.M., Szczepankiewicz, A., Fernandez-Albert, J., Navarrón, C.M., Olivares, R., Wilczynski, G.M., Canals, S., Lopez-Atalaya, J.P. and Barco, A. (2020). **KAT3-dependent acetylation of cell type-specific genes maintains neuronal identity in the adult mouse brain.** *Nature Communications*, 11, 2588. https://doi.org/10.1038/s41467-020-16246-0

Fernandez-Albert, J., Lipinski, M., Lopez-Cascales, M.T., Rowley, M.J., Martin-Gonzalez, A.M., del Blanco, B., Corces, V.G. and Barco, A. (2019). **Immediate and deferred epigenomic signatures of** *in vivo* **neuronal activation in mouse hippocampus.** *Nature Neuroscience*, 22, 1718-1730. https://doi.org/10.1038/s41593-019-0476-2



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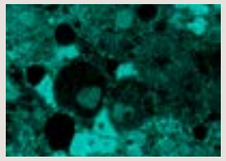
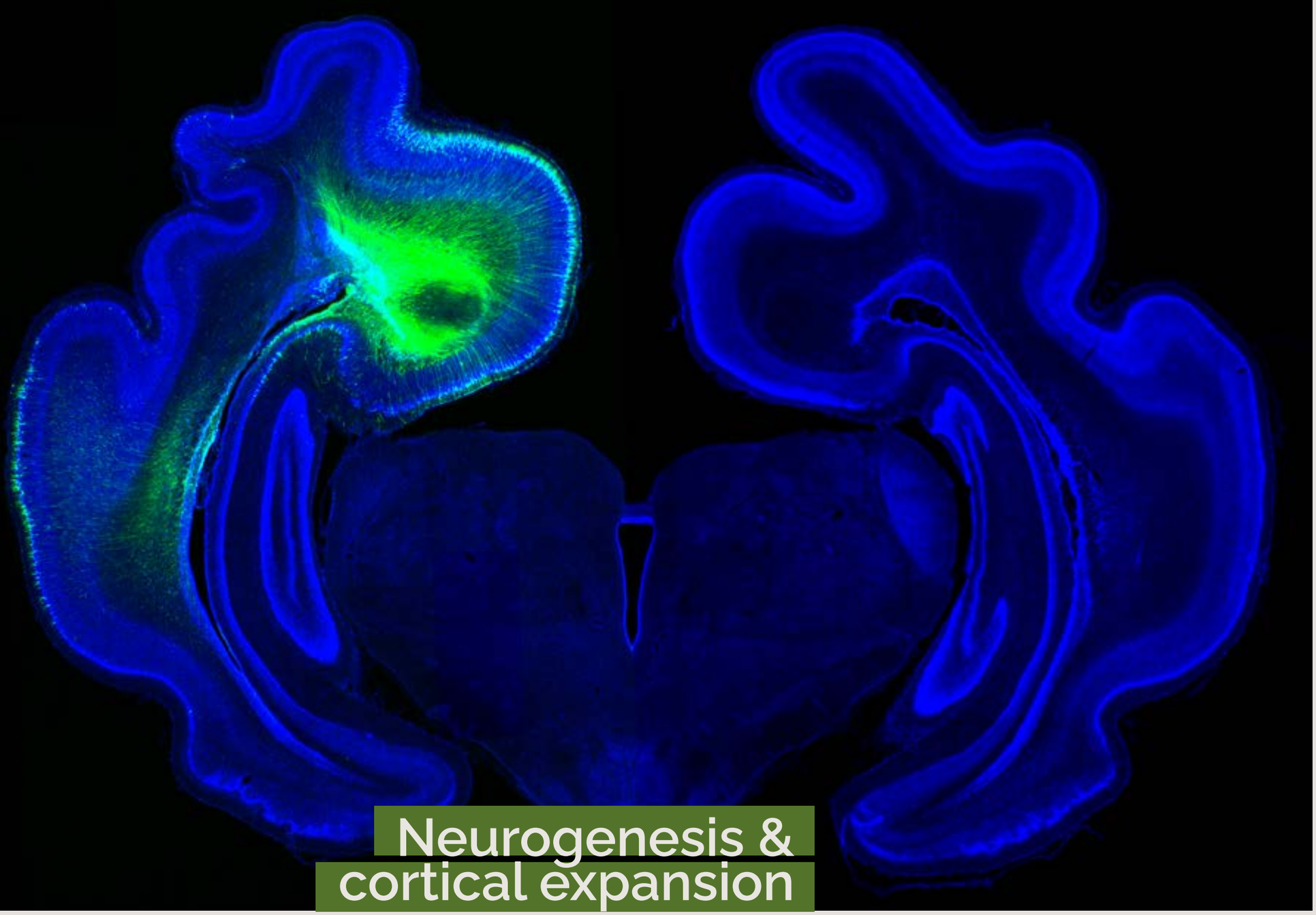
Department:

Molecular Neurobiology and Neuropathology



Sp1_ Neural stem cell regulation and differentiation

Sp6_Genetic & epigenetic basis of Individuality & aging



Neurogenesis & cortical expansion

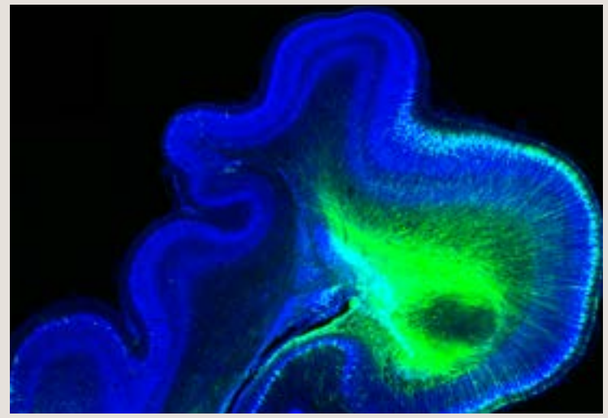
Víctor Borrell

@BorrellLab

Our laboratory is interested in understanding the cellular and molecular mechanisms governing the expansion and folding of the cerebral cortex observed across mammalian evolution. The cerebral cortex is the largest structure in the brain and is responsible, among others, for the higher cognitive functions that distinguish humans from other mammals. The expansion of the cerebral cortex observed along evolution underlies the growth in intellectual capacity. This evolutionary expansion is recapitulated during embryonic development in higher mammals, when the cerebral cortex undergoes massive growth in surface area and folds onto itself.

Multiple genetic mutations are known to cause intellectual disability and epilepsy. These mutations are consistently linked to defects of cortical development, and functional studies in rodents have shown that these genes play essential roles in distinct aspects of cortical neurogenesis, neuron migration, or cortical folding.

We want to identify and understand the cellular, molecular, and genetic mechanisms involved in the expansion and folding of the mammalian cerebral cortex, and its consequences on the function of cortical circuits. To this end, we combine transcriptomic and epigenomic analyses at the tissue and single-cell level (scRNA-seq, ATAC-seq), with a wide variety of experimental animal models (snake, chick, mouse, ferret, human cerebral organoids) and strategies for the genetic manipulation of the developing brain (including *in vitro*, in ovo and *in vivo* electroporation, viral vectors, transgenic and knock-out animals). We employ a range of state-of-the-art imaging techniques on live and fixed tissue (superresolution, spinning-disk), histological, cellular, and molecular biology methods, structural magnetic resonance imaging and tractography, and optical imaging of intrinsic signals for unveiling the functional architecture of the cerebral cortex.



We are currently studying the evolution of genetic mechanisms that regulate cerebral cortex expansion across amniotes and the mechanisms of cerebral cortex folding in mammals. With an ERC-Synergy grant we are studying how genetics, molecular biology, and mechanics interact to give rise to this folding, and what is the impact of these mechanisms on cortical function. Finally, we are also studying the consequences of the dysregulation of all these mechanisms, including the development of pediatric brain cancer.

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Relevant publications

Del-Valle-Anton, L. and Borrell, V. (2022). **Folding brains: from development to disease modeling.** *Physiological Reviews,* 102(2), 511-550. https://doi.org/10.1152/physrev.00016.2021

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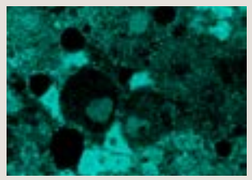
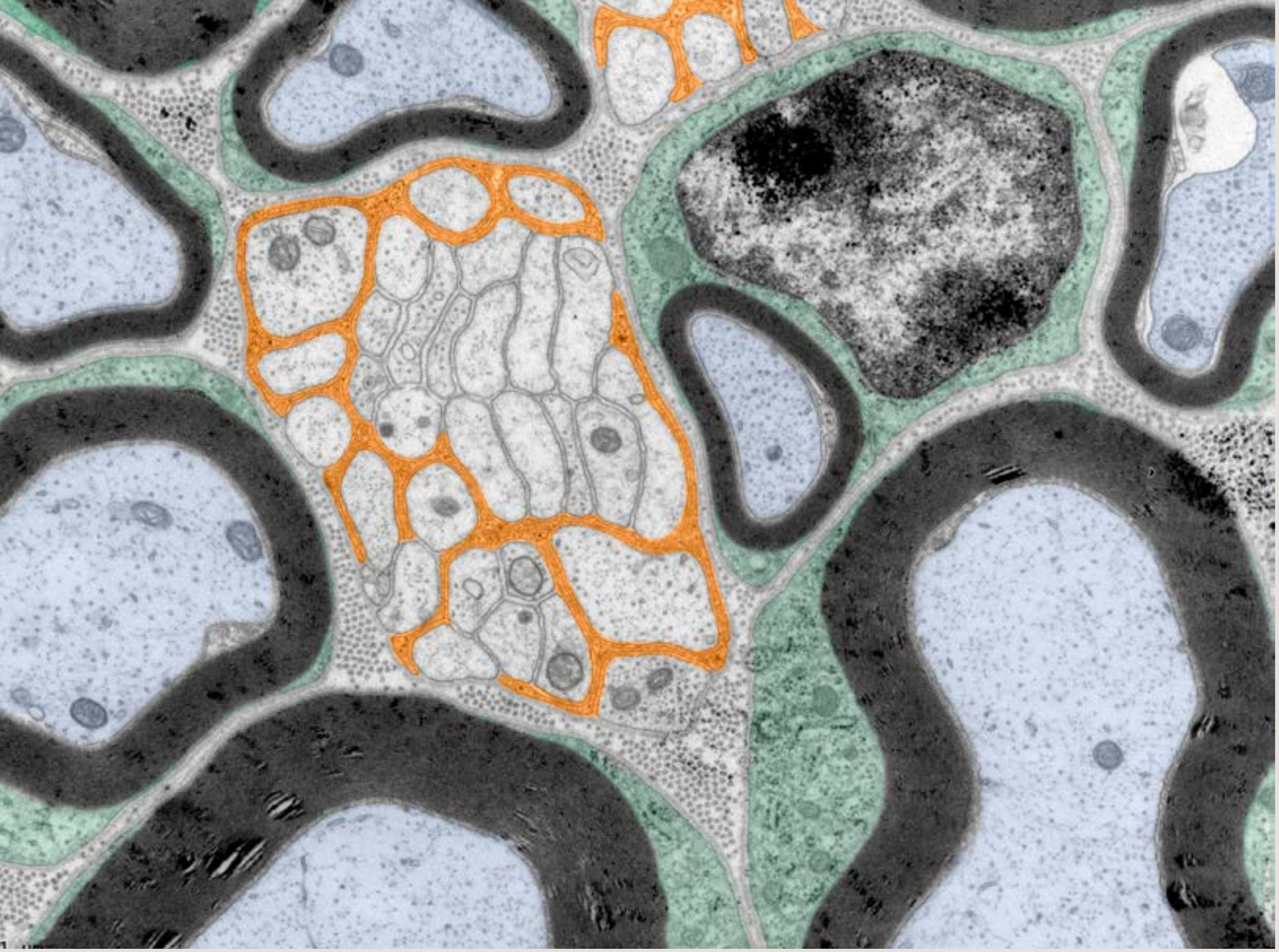
Department:

Developmental Neurobiology



Sp1_ Neural stem cell regulation and differentiation



Molecular control of axonal myelination

Hugo Cabedo

@MyelinAlicante

Nerve conduction velocity is inversely proportional to the electrical resistance of the axon and the capacitance of the plasma membrane that surrounds it. To increase nerve impulse velocity some invertebrates (such as squids) decrease resistance of the axon by greatly increasing its diameter. In more complex nervous systems, like higher vertebrates, this would increase by more than a hundred times the volume of the nervous system. To increase nerve conduction velocity without changing the axonal diameter (and nervous system volume) it is necessary to reduce the capacitance by increasing the thickness of the lipid membrane surrounding the axon. This has been achieved in vertebrates by depositing large amounts of the plasma membrane of specialized hypertrophied neighboring cells (oligodendrocytes or Schwann cells). Rudolf Virchow first described this membrane, known as “myelin”, in 1854.

In our group, we try to elucidate the molecular mechanisms controlling axonal myelination. Our goal is to use this information to develop new strategies in the treatment of demyelinating diseases such as multiple sclerosis in the central nervous system, and Charcot-Marie-Tooth in the peripheral nervous system. We also use this information to try to improve nerve regeneration after traumatic injuries. In order to achieve our goals we use state-of-the-art technologies such as Next-Generation Sequencing of patient’s DNA and genetic modification of mice to generate animal models of disease.

Relevant publications

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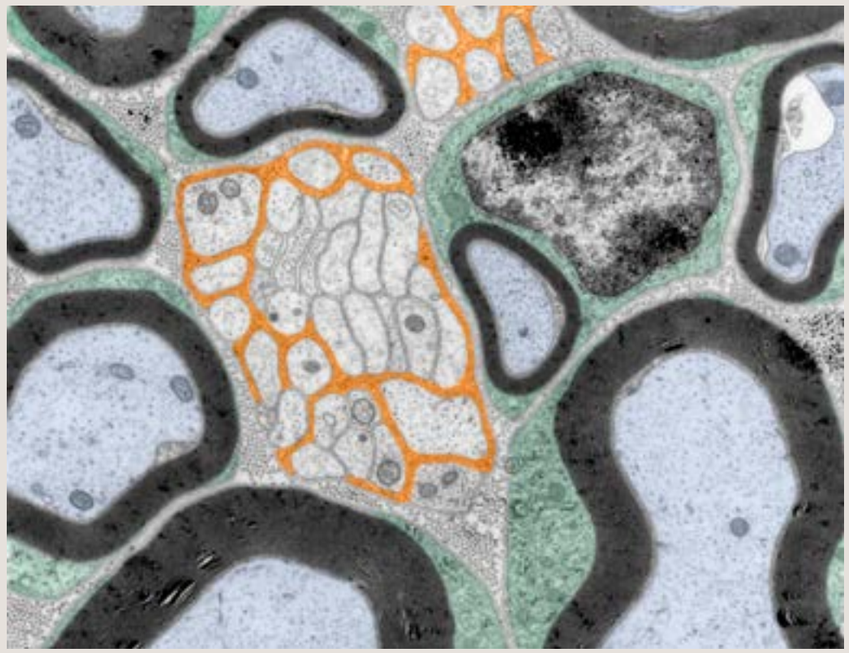

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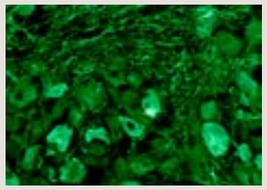
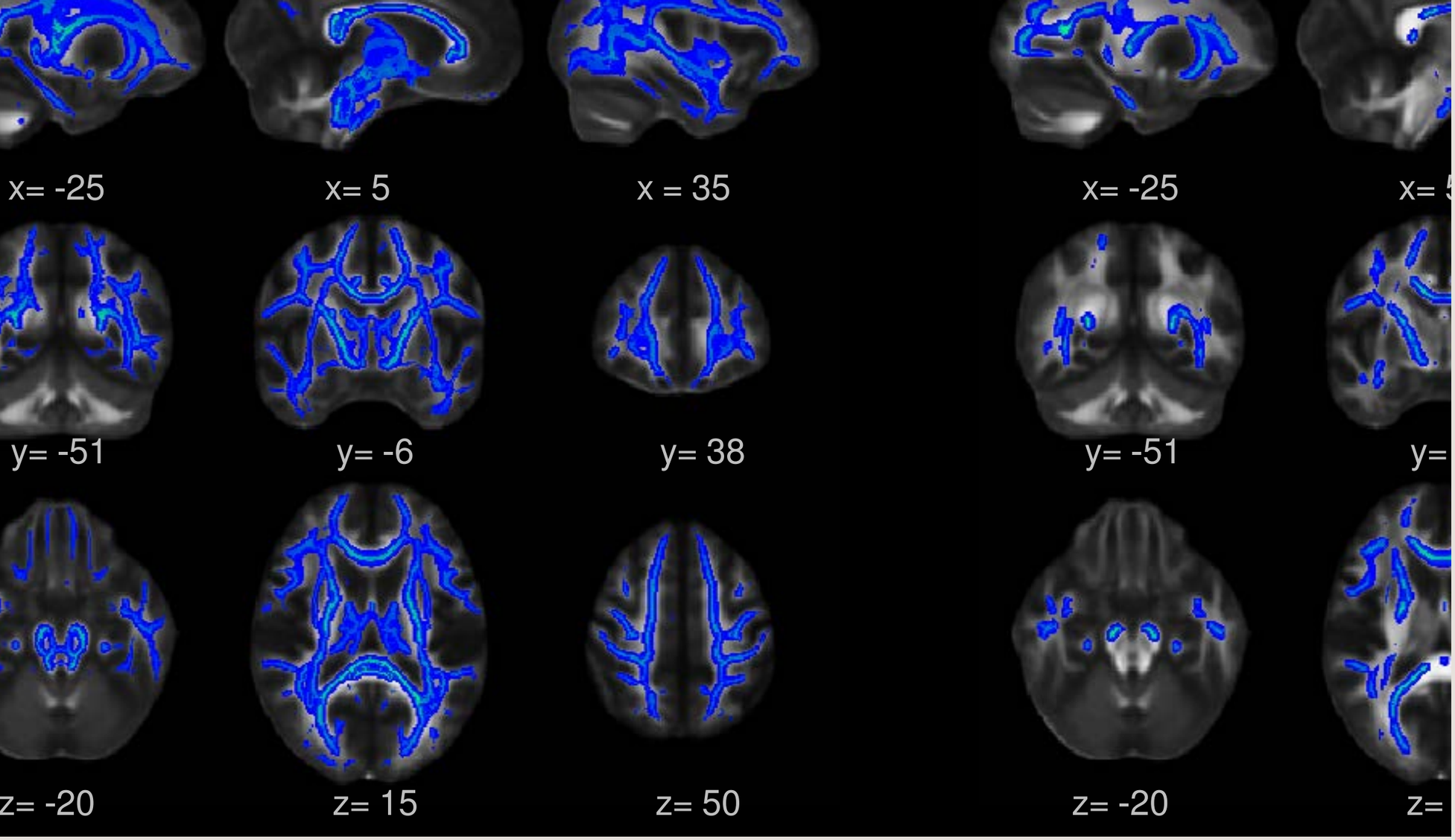


Sp5_Neurobiology of pain & inflammation



Plasticity of brain networks

Santiago Canals / Encarni Marcos @CanalsLab

How are memories encoded, stored, and retrieved in our brains?

Experience-dependent modulations of synaptic strength shape the functional structure of the brain, recruiting relevant networks in a particular context and supporting behavioral adaptation. Little is known, however, about how synapse dynamics are transformed into network dynamics. We have demonstrated that brain circuits involved in learning and memory are functionally reorganized after local potentiation of synaptic transmission in the hippocampus. We are currently investigating the mechanisms underlying this network reorganization, focusing on short- and long-term synaptic plasticity and the balance between excitation and inhibition. To this end, we combine functional magnetic resonance imaging with recordings of neuronal activity (electrophysiology, calcium recordings) and techniques that allow us to perturb it (Deep Brain Stimulation, optogenetics, pharmacogenetics), in murine models of learning and memory.

The same cellular mechanisms that mediate experience-dependent neuroplasticity and allow learning from, and react to, changes in the environment can also be activated by drugs of abuse. Human and animal studies indicate that the refractory nature of addiction results from drug-induced stimulation of reward-related learning networks. As a consequence, drug-seeking behavior becomes hard-wired in the brains of drug consumers. By applying the same multidisciplinary approach, and parallel studies in human subjects, we investigate the functional and structural reorganization of brain networks supporting addiction and relapse.

We use and develop state-of-the-art MRI tools to investigate the transformations that occur from the microscopic to the macroscopic organizational levels when a new memory is formed, or a pathological process develops.

Relevant publications

Selim, M.K., Harel, M., De Santis, S., Perini, I., Sommer, W.H., Heilig, M., Zangen, A. and Canals, S. (2023). **Repetitive deep TMS in alcohol dependent patients halts progression of white matter changes in early abstinence.** *Psychiatry and Clinical Neuroscience.* https://doi.org/10.1111/pcn.13624

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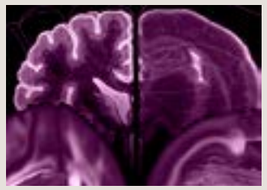
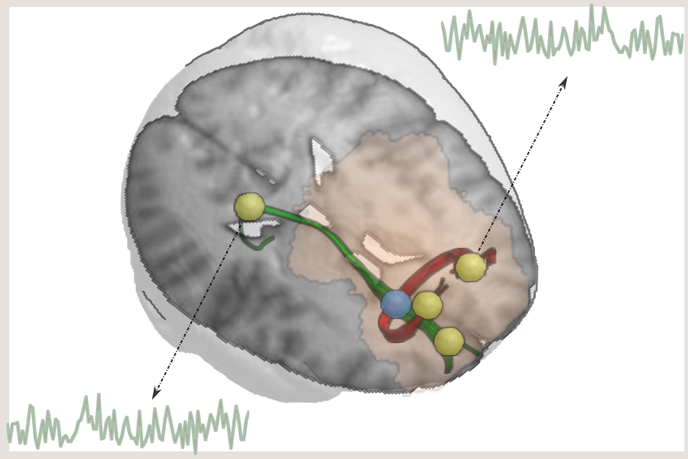
Department:

Department: Cellular and Systems Neurobiology



Sp7_Human cognition & behaviour



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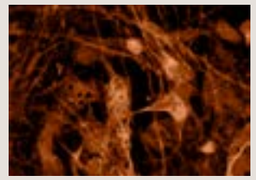

Sp8_ Translational research of neurological and psychiatric disorders

Asymmetric division of neural stem cells in development and tumorigenesis

Ana Carmena

Our lab is currently focused on analyzing in depth the process of Asymmetric Stem Cell Division (ASCD), a universal mechanism to generate cellular diversity during Development and an important process in the context of Cancer and Stem Cell Biology. Specifically, we are interested in investigating and contributing to answering two fundamental questions in the field:

1.- **Which are the mechanisms that regulate the asymmetry of the division to finally render two different daughter cells?** Our model system for answering this question is the embryonic and larval neuroblasts, the neural stem cells of the *Drosophila* central nervous system.

2.- **Which are the connections between failures in the process of ASCD and tumorigenesis?** Our model systems to investigate this are the neural stem cells of the *Drosophila* larval brain and human glioblastoma neurosphere cultures.

Relevant publications

De Torres-Jurado, A., Manzanero-Ortiz, S., and Carmena, A. (2022). **Glial-secreted Netrins regulate Robo1/ Rac1-Cdc42 signaling threshold levels during** *Drosophila* **asymmetric neural stem and progenitor cell division.** *Current Biology*, 32 (10), 2174–2188. https://doi.org/10.1016/j.cub.2022.04.001

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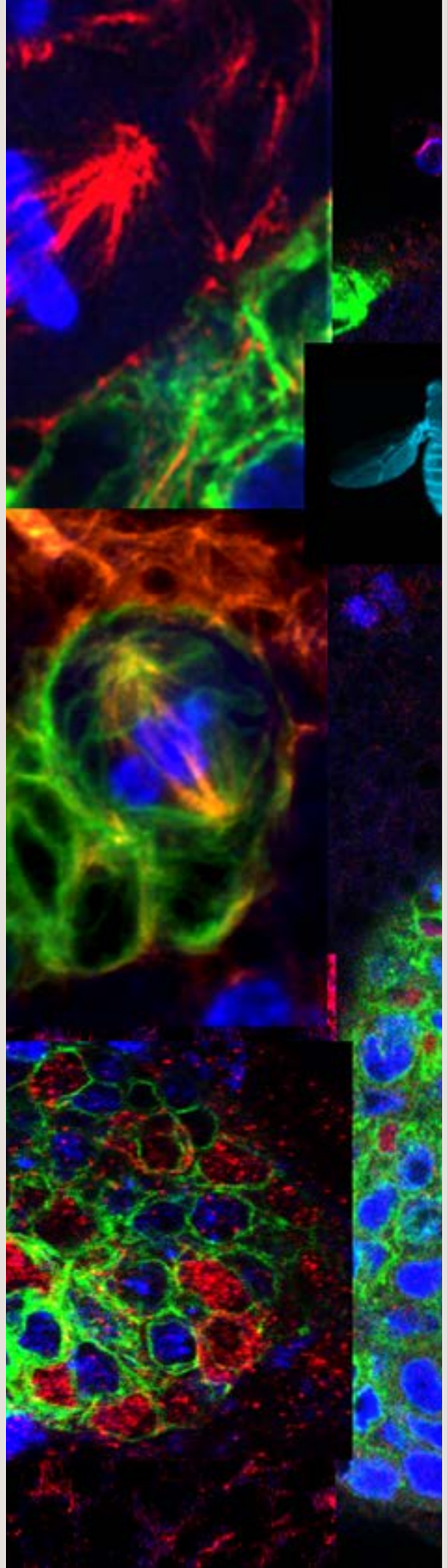

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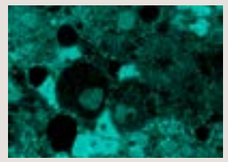
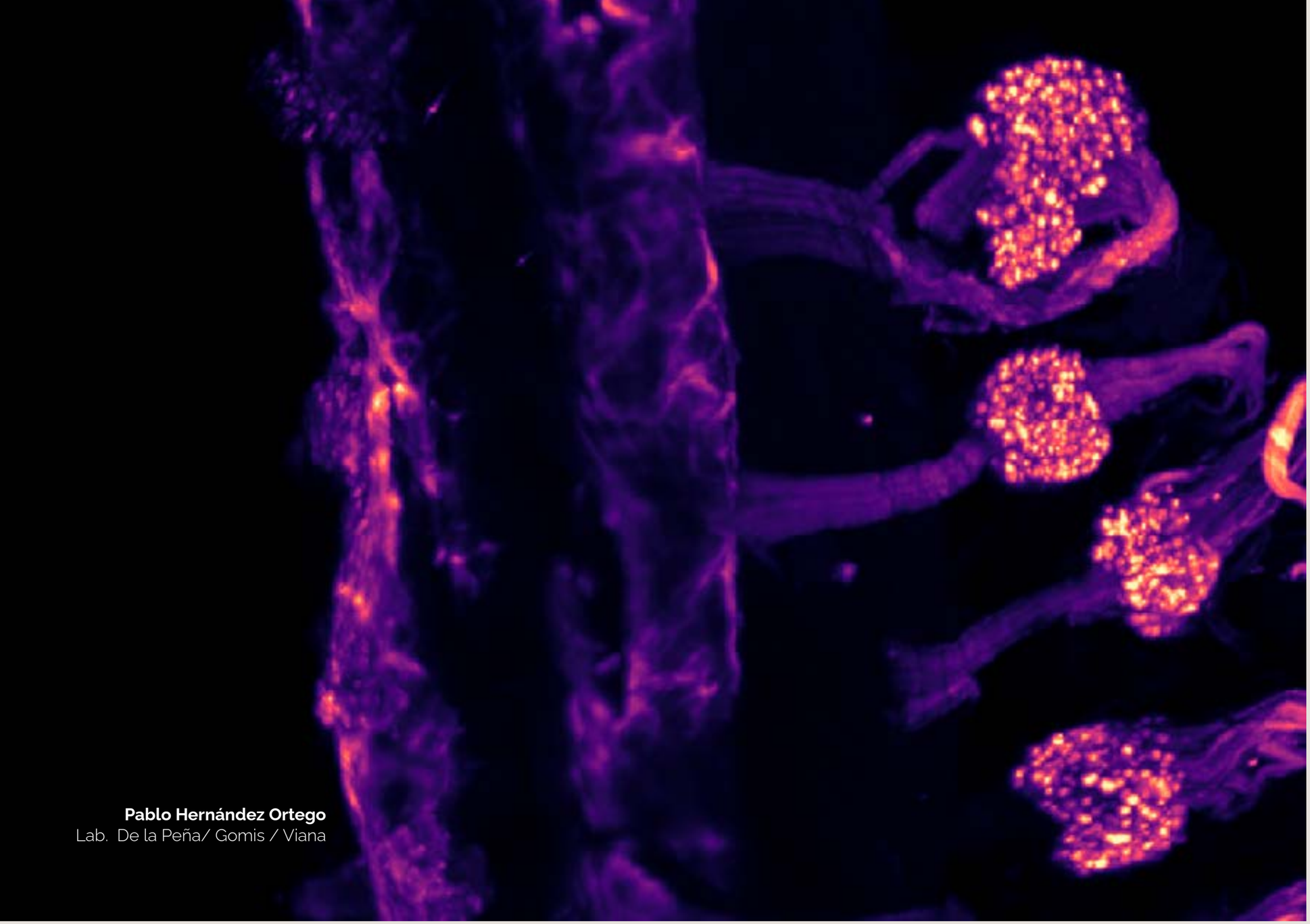


Sp1_ Neural stem cell regulation and differentiation



Pablo Hernández Ortego
Lab. De la Peña/ Gomis / Viana

Sensory transduction and nociception

Elvira de la Peña / Ana Gomis / Félix Viana

@painchannels

Our research aims to understand the cellular and molecular mechanisms involved in detecting and transducing physical and chemical stimuli by mammalian sensory nerve endings, emphasizing nociceptive terminals.

More specifically, a major goal of our current projects is to study changes in the expression and function of TRPs and Piezo2 channels in different pathological conditions that lead to abnormal pain sensations. This knowledge is fundamental to use these molecular receptors as analgesic targets eventually. We are studying the role of TRPs, potassium channels, and Piezo2 ion channels in pain conditions, including tissue inflammation and neuropathy induced by chemotherapeutic agents, the transcriptional profiling and functional studies to elucidate the molecular diversity of cold thermoreceptor neurons and its relevance to chronic pain mechanism, the molecular and functional characterization of thermosensory and mechanosensory circuits in the spinal cord and understanding the cellular and molecular bases of low and high threshold mechanotransduction *in vivo*.

We are also investigating nociceptive changes in patients with chemotherapy-induced peripheral neuropathy, trying to identify potential targets for interventions, with the ultimate aim of developing treatments that are more effective and have fewer side effects.

We use a broad range of techniques in our studies that include calcium imaging, transcriptional profiling of neurons, *in vivo* and *in vitro* electrophysiology, and behavioral assays.

Relevant publications

Marcotti, A., Fernández-Trillo, J., González, A., Vizcaíno-Escoto, M., Ros-Arlanzón, P., Romero, L., Vela, J.M., Gomis, A., Viana, F. and de la Peña, E. (2023). **TRPA1 modulation by Sigma 1 receptor prevents oxaliplatin-induced painful peripheral neuropathy.** *Brain*, 146 (2), 475-491. https://doi.org/10.1093/brain/awac273

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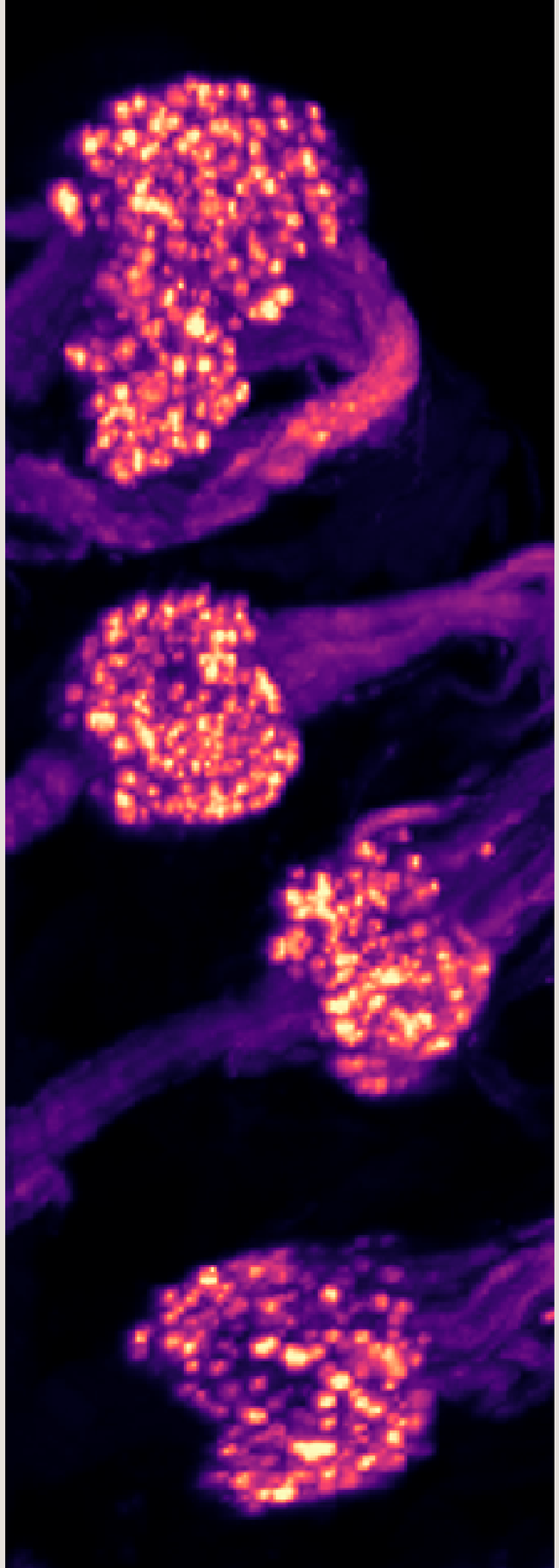

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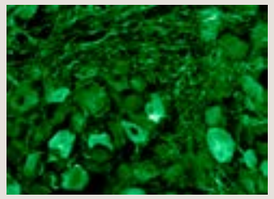
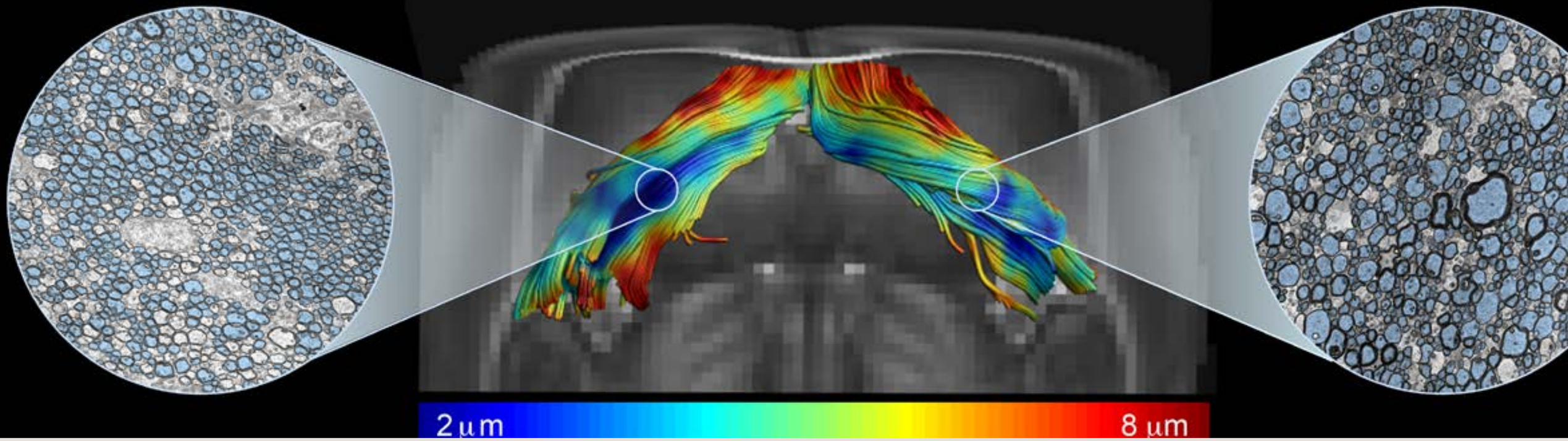


Sp5_Neurobiology of pain & inflammation



Translational Imaging Biomarkers

Silvia De Santis

@LabMri

Neuroinflammation and neurodegeneration are hot topics in brain research, and they have become very promising targets for developing novel disease-modifying treatments in pathological conditions. In order to characterize the aspects of brain tissue in both preclinical and human models, non-invasive tools are needed to measure biomarkers of the inflammatory state and salient microstructural characteristics, such as the level of myelination, axonal diameter, and density.

Our research focuses on the development, optimization, and application of innovative, non-invasive, and translational resonance imaging tools, relevant to both basic and clinical research. The objective is to characterize such biomarkers throughout life, with special attention to healthy aging, as well as identify early biomarkers, which can precede and predict diseases such as multiple sclerosis and Alzheimer's, all taking into account the gender dimension.

To achieve this goal, we are planning to: 1) transfer the developed framework from the preclinical to the clinical setting by incorporating artificial intelligence tools; 2) investigate the evolution of inflammatory markers throughout life, in rodents and humans and considering the gender dimension; 3) characterize the role of inflammation in animal models and in patients and Alzheimer's disease; and 4) disentangling inflammation and degeneration in early stages of patients with multiple sclerosis. Overall, thanks to a unique combination of technical and applied skills at the intersection between physics, biology, and medicine, our research is expected to bring basic neuroscience closer to the clinic and ultimately improve the way brain disorders are diagnosed and treated.

Relevant publications

Cerdán Cerdá, A., Toschi, N., Treaba. C. A., Barletta, V., Herranz, E., Mehndiratta, A., Gomez-Sanchez, J. A., Mainero, C., De Santis, S. (2024). **A translational MRI approach to validate acute axonal damage detection as an early event in multiple sclerosis.** *eLife* 13:e79169. https://doi.org/10.7554/eLife.79169

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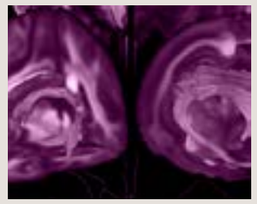
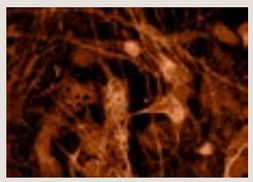
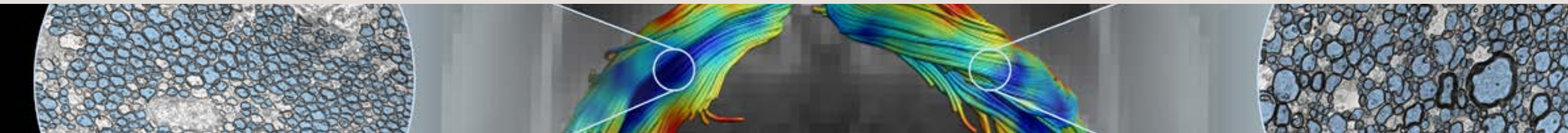
Molecular Neurobiology and Neuropathology



Sp7_Human cognition & behaviour



Sp8_ Translational research of neurological and psychiatric disorders



Developmental and cognitive disorders

Isabel del Pino Pariente

@DelPino_lab

Brain function emerges from a precisely timed sequence of developmental milestones. These milestones constitute a developmental trajectory, shaped by the interaction between genetic mechanisms and electrical activity of excitable neural cell types. Importantly, Disruptions to this developmental trajectory can result in neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia, ultimately leading to brain dysfunction. Our laboratory focuses on understanding how genetic predisposition and activity-dependent mechanisms influence the brain developmental trajectory leading to impaired cognitive function. Our long-term goal is to generate fundamental insights that inform the rational design of therapeutic strategies aimed at redirecting aberrant developmental trajectories toward normal outcomes.

During our first year at the Institute of Neuroscience CSIC-UMH, our laboratory has achieved significant advances in fundamental and translational research, each contributing to our overarching goal of understanding and addressing the neurodevelopmental mechanisms underlying different neurodevelopmental disorders.

Precision Medicine in epilepsy-related malformations: Through a pioneering pilot trial, we investigated the potential of a new therapeutic approach as a targeted treatment for MOGHE , one form of epilepsy-related Malformations. By identifying and targeting the underlying genetic variant associated with MOGHE, we provide evidence for improvement of seizure control and cognitive function post-epilepsy surgery, laying the groundwork for precision medicine approaches in epilepsy care.

Identification of developmental deficits in Austism-spectrum disease models: Investigating the brain developmental trajectory in a mouse model of ASD, we uncovered a specific alteration in the maturation of striatal neurons. This finding shed light on the contribution of striatal interneuron developmental deficits to ASD pathogenesis thereby advancing our understanding of neurodevelopmental disorders.

Together, these advances underscore the critical importance of elucidating the biological mechanisms underlying brain development and dysfunction. By leveraging interdisciplinary and translational research, as well as global collaborations, we aim to bridge the gap between basic science and clinical applications, ultimately driving innovations in neurological care and therapeutic interventions.

Relevant publications

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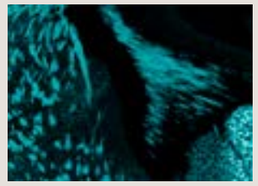
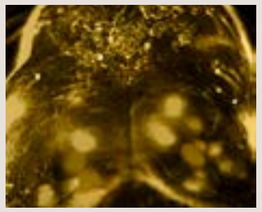
Developmental Neurobiology



Sp4_Synaptic modulation of neural circuits and behaviour



Sp3_Building & adapting circuits into functional networks

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Alexandra Typou

Mechanisms of growth control & cancer

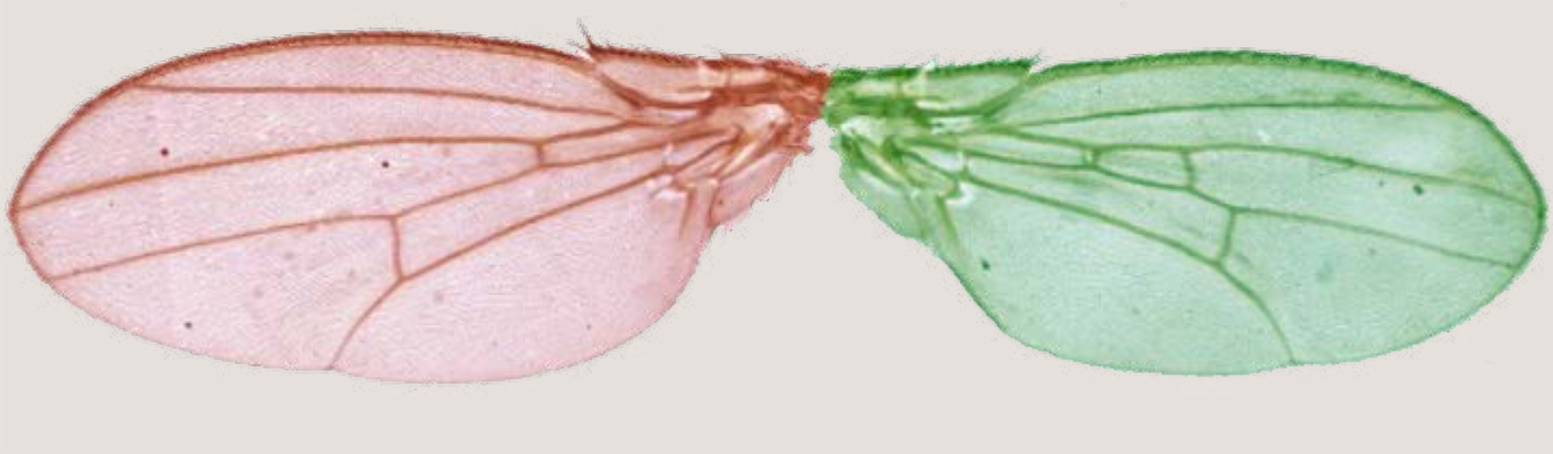
María Domínguez

We focus our research on unraveling the factors and mechanisms that orchestrate the precise growth of organs and organisms, as well as understanding how these delicate controls can become unbalanced, leading to tumor formation in certain individuals and moments of life. Our work focuses on two key areas to decipher the genetic, molecular, and neural aspects involved in these processes.

Firstly, using bilateral symmetry as a model of rigorous growth control, we explore the factors that impact organisms' ability to maintain this symmetry. Through techniques such as geometric morphometrics and "fluctuating asymmetry," we analyze humoral, neural, mechanical, and bioelectric factors contributing to synchronization between the left and right sides of the body. We highlight the brain's relevance, emphasizing the influence of the relaxin system ILP8-Lgr3 and inhibitory commissural interneurons in interhemispheric communication and between body parts. Additionally, we elucidate a compensatory mechanism during starvation ("*catch-up growth*") involving another relaxin system, ILP7-Lgr4, linked to physical fitness and resilience.

In our second line of research, we focus on cancer and therapeutics. Through genetic screenings, we explore factors contributing to cancer initiation and oncogenic cooperation mechanisms. Recently, we have dedicated efforts to deciphering the initial steps of the "black box" of cancer and leveraging the innate immune response for innovative treatments. Using automated platforms and molecular analysis, we identify systemic signals for more effective interventions with fewer side effects. Some factors, such as FDA-approved asthma drugs, could be repurposed to treat T-ALL childhood leukemia, providing a safe and effective option. Our pharmacogenetic studies point to the nitric oxide-dependent inflammatory pathway, with potential local and systemic impact on cancer-related to the PI3K/AKT/PTEN oncogenic pathway.

In summary, our research aims to advance understanding of growth, bilateral symmetry, and tumorigenesis, exploring innovative therapeutic strategies to address the challenges of biological growth.



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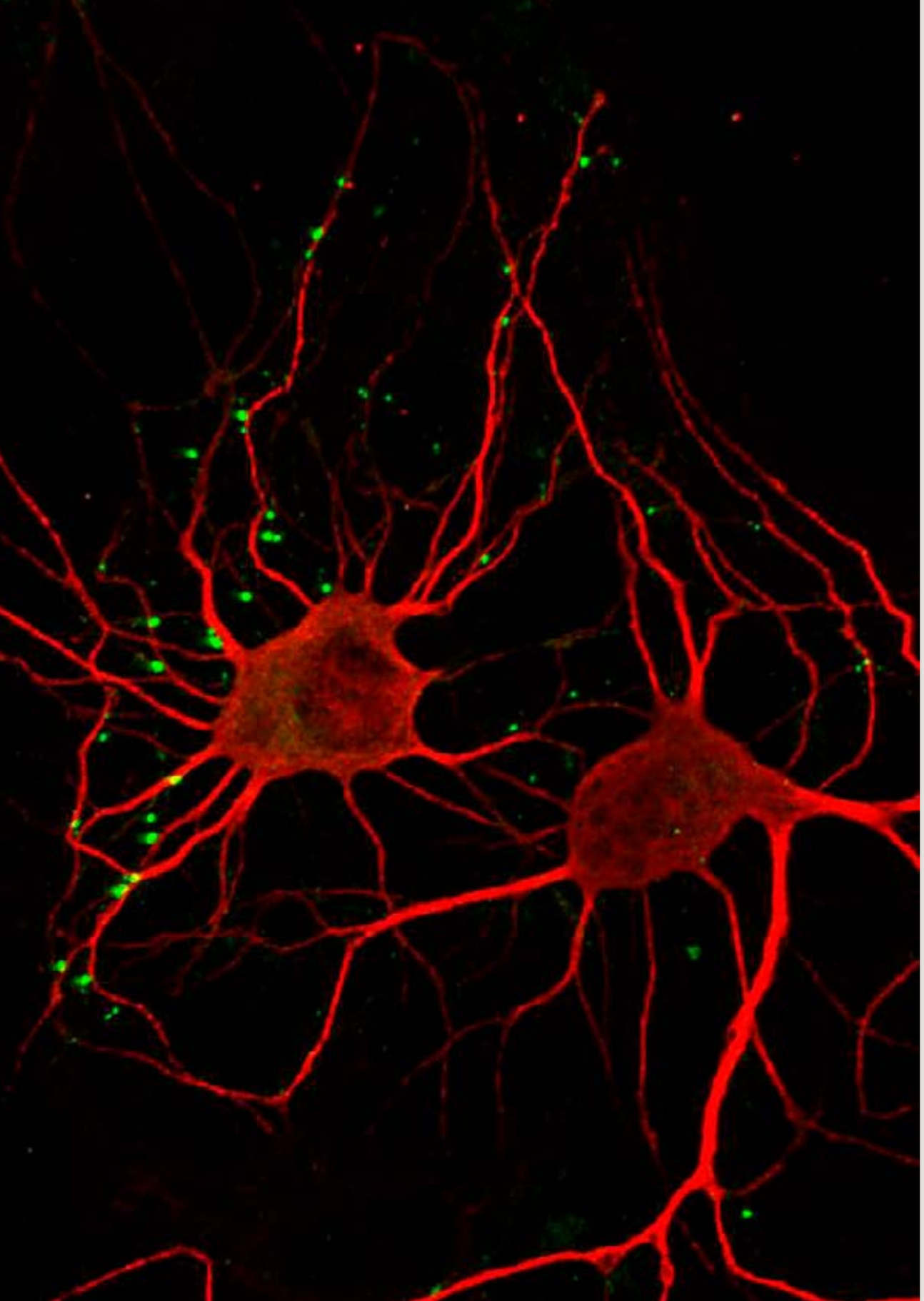
Sp6_Genetic & epigenetic basis of Individuality & aging



Institute for Neuroscience UMH-CSIC

Neuropharmacology, Molecular Immunobiology and Behavior

Teresa Femenía

Our research group aims to understand how pathophysiological brain circuit function, with emphasis on psychiatric and neurological disorders, is mediated by mechanisms related to the immune system. We aim to determine:

1) How innate immune system receptors, such as the Pattern Recognition Receptors (PRRs; e.g. Toll-like receptors) operate during molecular signaling to regulate emotional and cognitive functions.

2) How crosstalk with the periphery affects these functions by evaluating the functional impact of immune alterations linked to stress or diseases accompanied by low-grade inflammation such as metabolic disorders, which are commonly associated with mood and anxiety disorders.

Although there has been a long-standing relationship between the immune system and psychiatry, the role of immune receptors in non-immune function, such as in synaptic plasticity or molecular mechanisms regulating emotion and cognition, remains largely unknown. From an immunomodulatory perspective, identifying the diverse functions of the innate immune receptors in a non-traditional context of immunity and deciphering their molecular signaling pathways in the brain with cell-type-specificity will allow us to gain insight into novel and more specific therapeutic strategies for improving mental health.

Our laboratory uses a multi-disciplinary approach by employing state-of-the-art techniques, including mouse genetic strategies, molecular, *in vitro*, and *in vivo* pharmacology, local brain drug delivery techniques, stereotaxic surgery, imaging, and behavior.

Relevant publications

Yáñez-Gómez, F., Ramos-Miguel, A., García-Sevilla, J., Manzanares, J. and Femenía, T. (2023). **Regulation of Cortico-Thalamic JNK1/2 and ERK1/2 MAPKs and Apoptosis-Related Signaling Pathways in PDYN Gene-Deficient Mice Following Acute and Chronic Mild Stress.** *International Journal of Molecular Science,* 24(3):2303. https://doi.org/10.3390/ijms24032303

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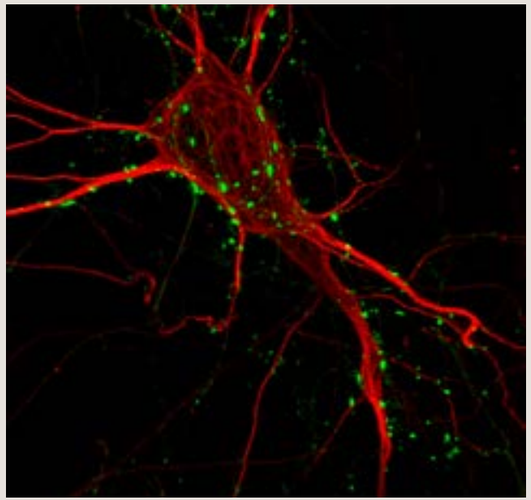

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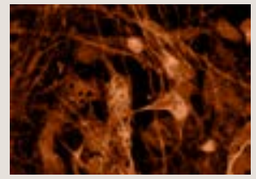
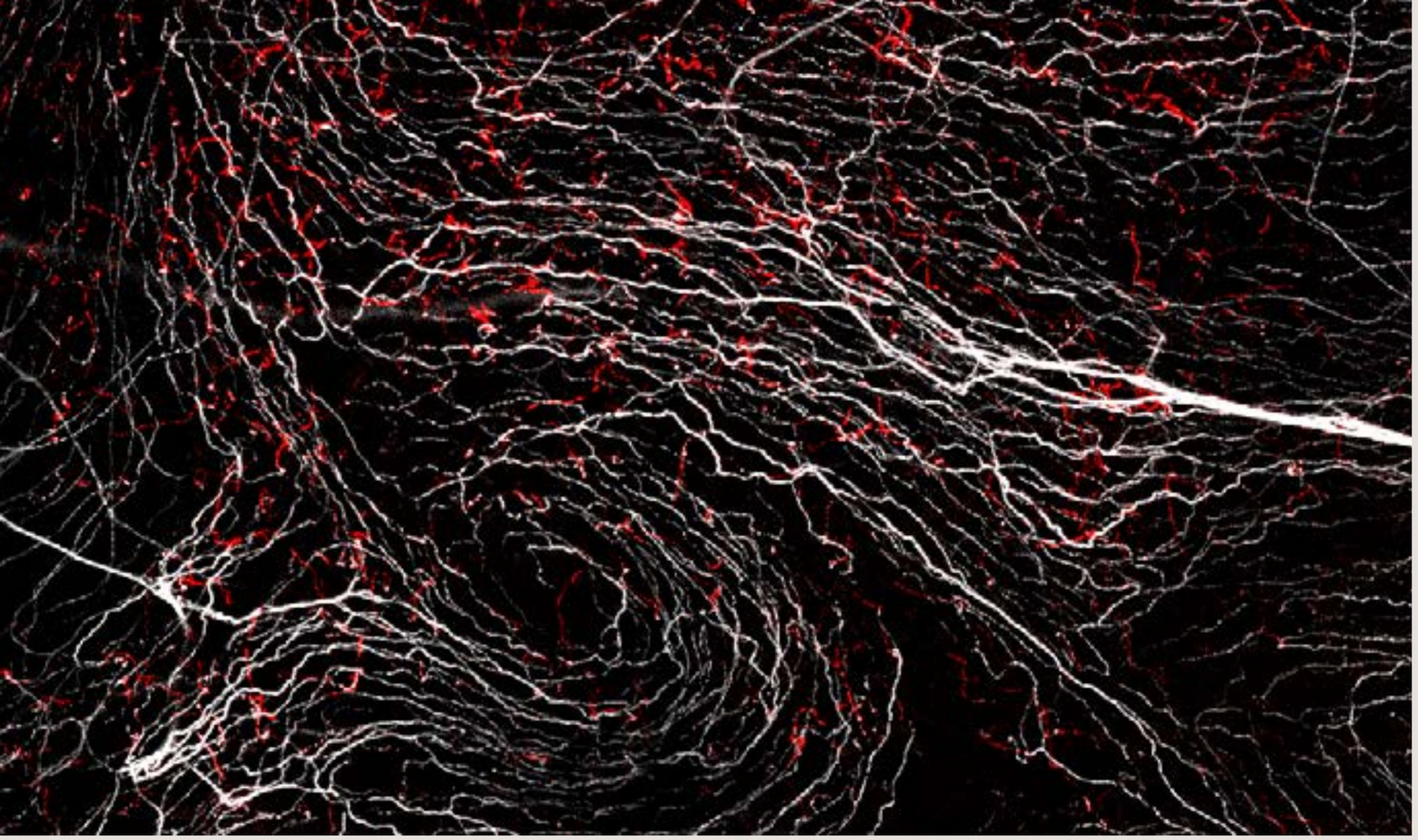


Sp8_Translational research of neurological and psychiatric disorders



Ocular Neurobiology

Juana Gallar / María del Carmen Acosta / Víctor Meseguer

The main interest of the Ocular Neurobiology Group (ONG) is to study the functional activity of sensory nerves from the ocular surface, responsible for the genesis of the different sensations evoked by stimulation of the eye surface and for the trophic maintenance of ocular tissues. The CNS also uses this sensory input to drive several protective reflexes, ensuring the correct moisturizing of the ocular surface.

Using morphological techniques (studying corneal nerve morphology in fixed and living tissue), electrophysiological techniques (recording nerve activity of sensory receptors in both nerve endings and axons, as well as the extracellular recording of ocular trigeminal, thalamic, and brain cortex neurons along the somatosensory pathway), pharmacological and opto-pharmacological tools to modulate the neurons' activity, and psychophysical studies (analyzing the characteristics of the sensations evoked by selective stimulation of the ocular surface), the ONG investigates the functional characteristics of the primary sensory neurons, and thalamic and cortical neurons innervating the anterior surface of the eye with particular attention to those neurons participating in evoking ocular sensations of eye dryness, discomfort and pain.

The ONG has described:

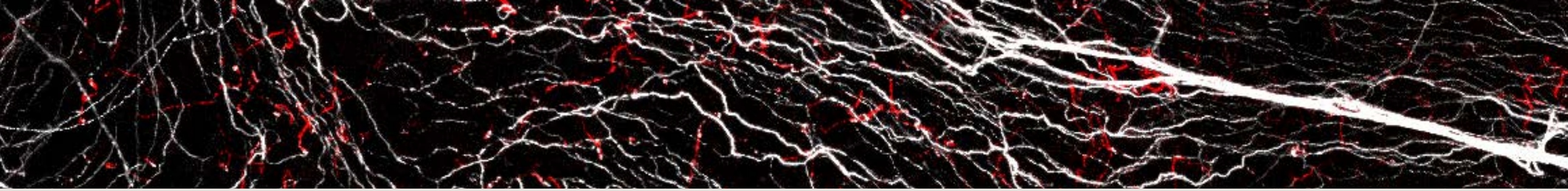
1) The sensitivity of the ocular surface to selective stimulation in healthy subjects and its changes with aging.

2) The correlation between the electrical activity of specific types of ocular sensory nerves and the different sensations evoked in humans.

3) The changes in ocular sensitivity under different conditions such as dry eye disease, ocular inflammation, after ocular refractive surgery, or using several ophthalmic drugs.

4) The role of the ocular surface nerve activity in regulation by the CNS of basal and reflex tearing and blinking.

Currently, the ONG studies the molecular and cellular mechanisms underlying spontaneous and stimulus-evoked corneal sensory nerve activity, trigeminal sensory input's role in the reflex regulation of tear production and blinking, and their changes with inflammation, aging, dry eye, and contact lens wearing. The ONG is also interested in describing the mechanisms responsible for the altered sensations experienced in corneal nerve neuropathies and developing new treatments to promote nerve regeneration to combat corneal blindness.



Relevant publications

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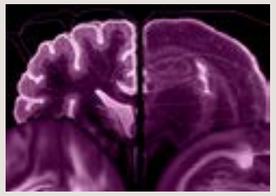
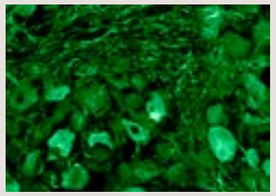
Department:

Cellular and Systems Neurobiology



Sp7_Human cognition & behaviour



Sp5_Neurobiology of pain & inflammation

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Susana Quirce Vázquez (Ayuda Margarita Salas, Grupo Oftalmología Experimental, IMIB, Murcia)

Behavior of Organisms

Alex Gómez-Marín

After more than two decades studying inanimate matter (stochastic thermodynamics), invertebrate behavior (fly and worm motor-sensory neuro-ethology), and subsequently vertebrate cognition (rodent behavioral individuality and learning), we currently concentrate on the study of human consciousness. Such a research trajectory seeks to fulfill, or at least address, the original promise of neuroscience, namely, to understand "the mind". We are therefore more interested in humans in the real world than in "animal models" in laboratory conditions. To that end we weave together different levels and disciplines: computationally, we harness the power of *big data* and AI; theoretically, we delve into mathematical approaches such as "integrated information theory" and complexity science; philosophically, we engage with the current revival of panpsychism as a way out of the two-alternative forced choice between dualism and materialism (and mechanistic reductionism); empirically, we investigate death-related phenomena and extended perception. Our efforts are directed to rehabilitate the scientific study of what we call "the edges" of consciousness, phenomena that are "marginalized" but also "frontier" in the scientific study of who we are as human beings. Back to the future, our conceptual umbrella and mission consists of exploring the forgotten grand hypothesis of the brain as "permissive" (rather than "productive") of thought, memory, perception, and consciousness.

Relevant publications

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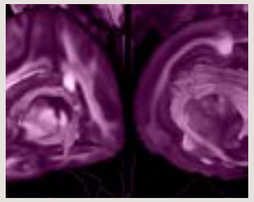

Sp7_Human cognition & behaviour

Independent Investigator

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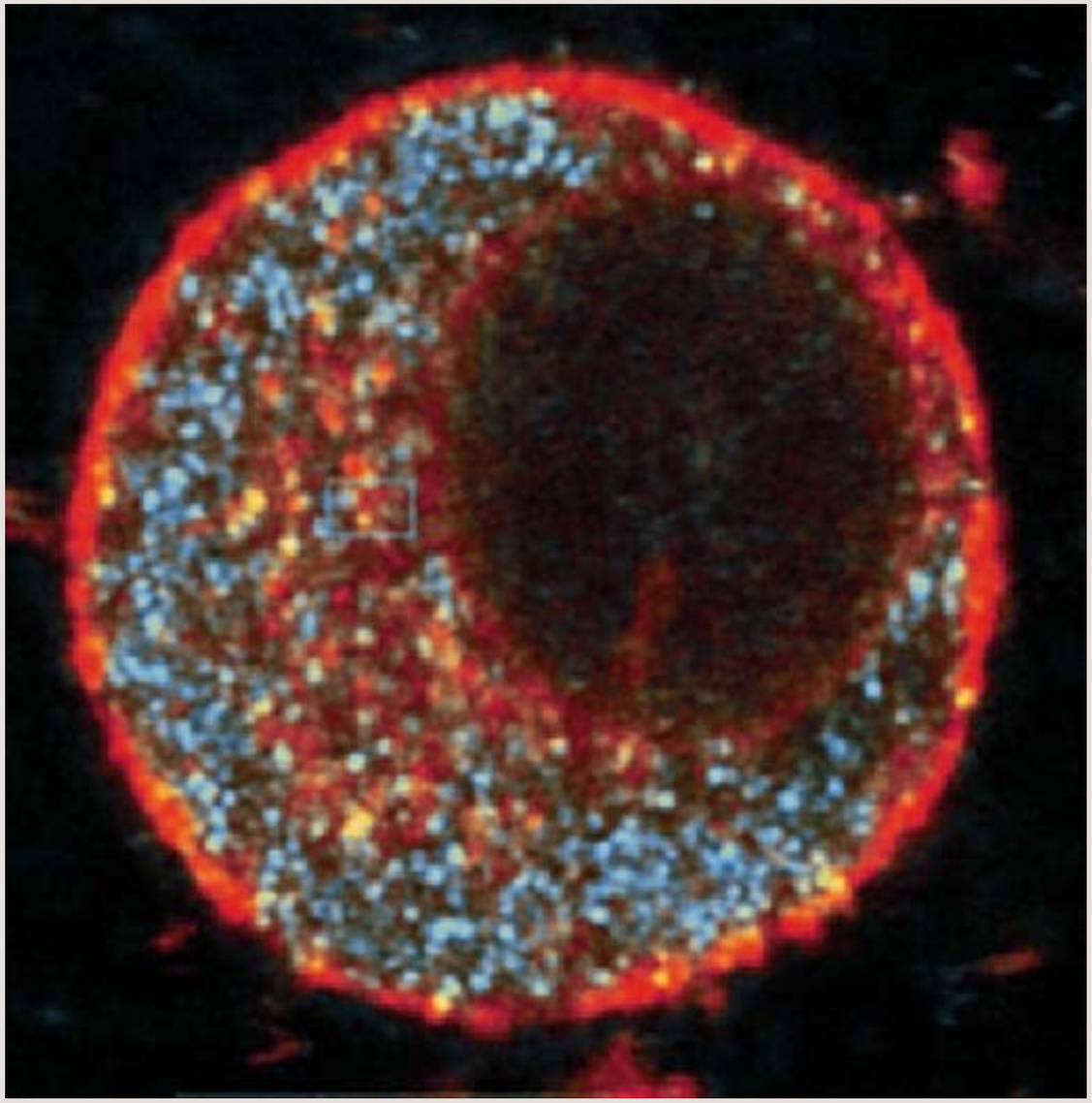

Molecular mechanisms of neurosecretion

Luis M. Gutiérrez / Manuel Criado

Adrenomedullary chromaffin cells have been used as an excellent experimental model to study exocytosis and therefore the molecular mechanisms of neurotransmission. It is now clear that the proteins involved in the processes of vesicle docking, membrane fusion, and neurotransmitter release are common to many cellular systems (SNARE hypothesis).

Our research interest is focused on two different aspects of the molecular mechanisms of neurotransmission:

The implication of the cytoskeleton in different aspects of neurosecretion and the determination of the role and regulation of SNARE proteins in the process of membrane fusion.

Experimental approaches involve strategies using antibodies, sequence peptide design, and protein overexpression that demonstrate the participation of specific protein domains in exocytosis.

In addition, the role of these proteins in the secretory stages has been studied using amperometry and TIRFM, techniques that resolve single fusion events. In addition, the group incorporated the line of research on the role of nicotinic receptors in the neurosecretory systems coordinated by Dr. Criado.

Recently, we have studied the role of signaling lipids in exocytosis, and especially the function of FTY-720, an analog of sphingosine, on exocytosis and cancer.

Relevant publications

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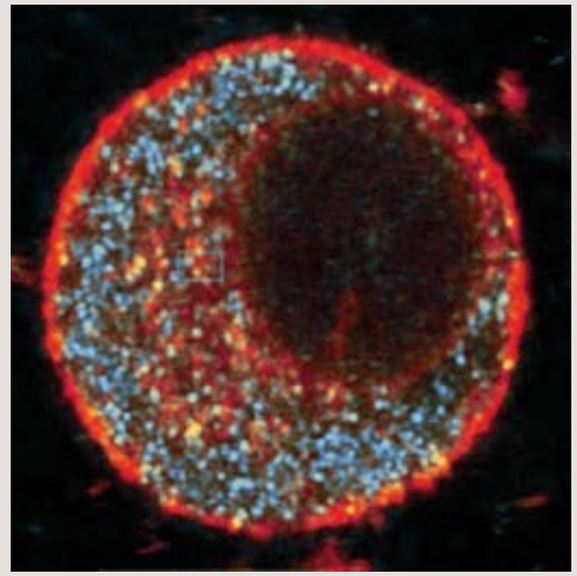

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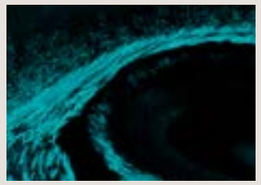
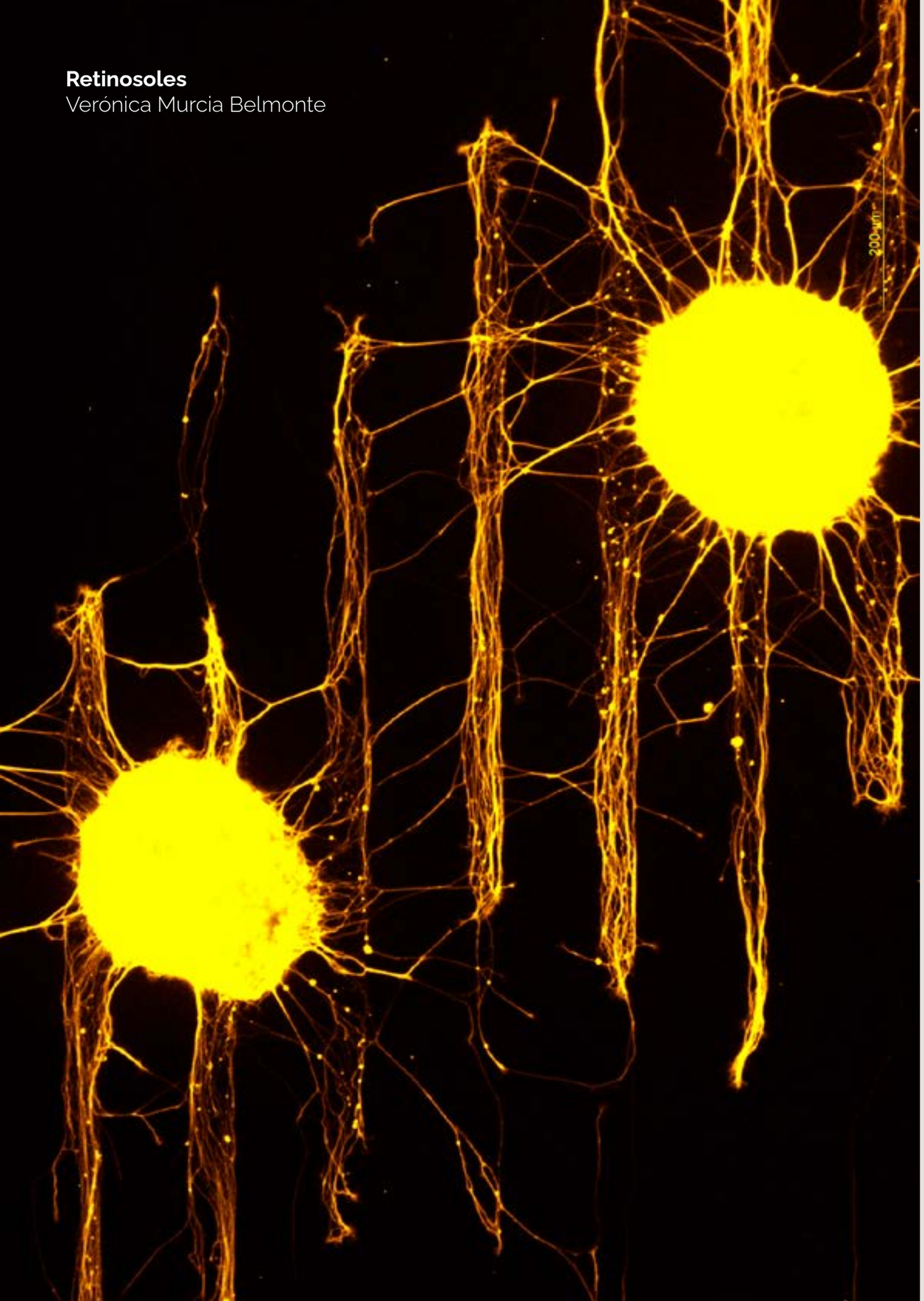


Sp4_Synaptic modulation of neural circuits and behavior



Retinosoles
Verónica Murcia Belmonte

Institute for Neuroscience UMH-CSIC

Generation and Regeneration of Bilateral Neural Circuits

Eloísa Herrera

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For proper development and connectivity of the brain, it is crucial that the axons of the various neuronal types grow and direct themselves toward the locations where they will establish synapses with other neurons. In our laboratory, we work to identify the molecular bases that determine axonal trajectories during nervous system development, focusing on the decision of crossing or avoiding the midline that retinal axons take when they reach the optic chiasm. We also analyze how visual axons reach their final targets in both hemispheres of the brain and how sensory information coming from both sides of the body is integrated and processed.

Axonal divergence at the midline is critical for defining numerous functions of the mature brain, including sensory interpretation and coordination of locomotion, as many of these functions depend on the communication between both brain hemispheres. To investigate the mechanisms that control the development of bilateral circuits, we use the mouse as a model and employ a multidisciplinary approach that includes mouse genetics and *in utero* electroporation combined with anatomical, genomic, cellular, molecular, and biochemical studies both *in vitro* and *in vivo*.

Relevant publications

Fernández-Nogales, M., López-Cascales, M.T., MurciaBelmonte, V., Escalante, A., Fernández-Albert, J., Muñoz-Viana, R., Barco, A. and Herrera, E. (2022). **Multiomic Analysis of Neurons with Divergent Projection Patterns Identifies Novel Regulators of Axon Pathfinding**. *Advanced Science*, 9(29). https://doi.org/10.1002/advs.202200615

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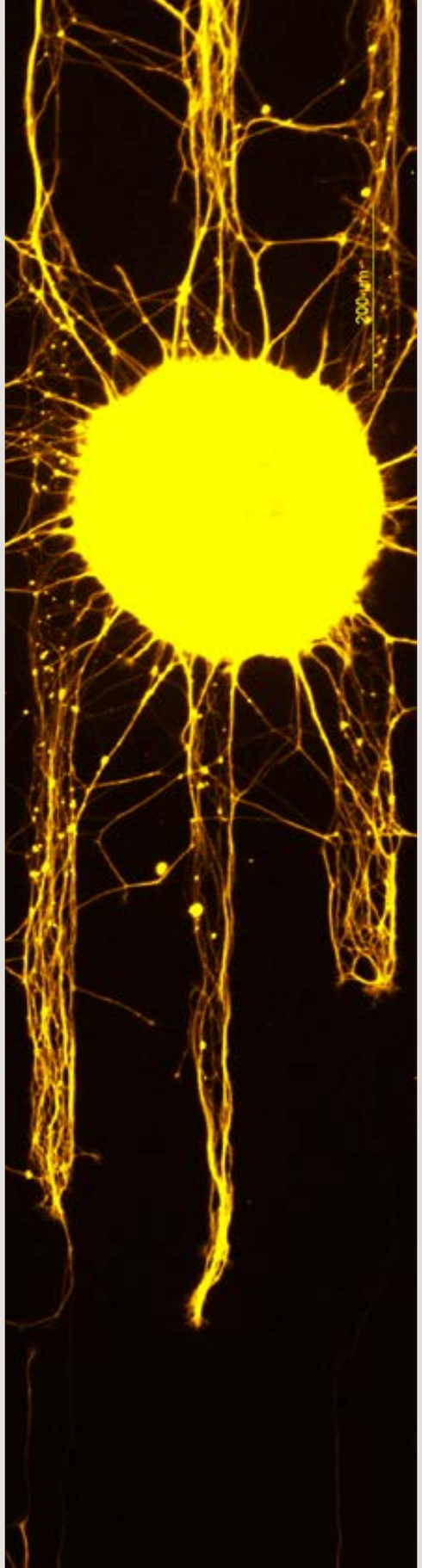

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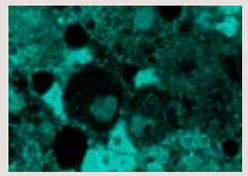
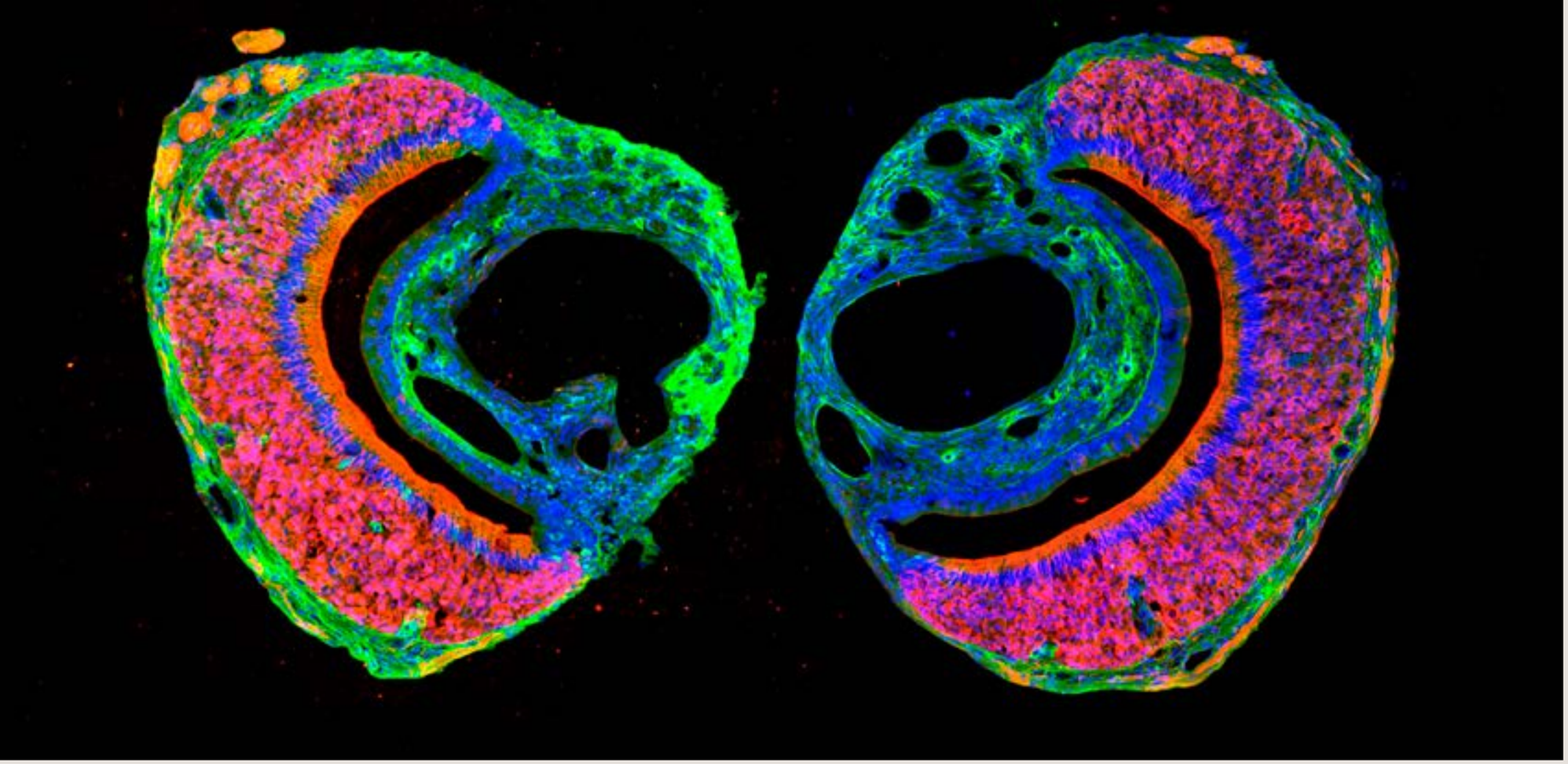


Sp1_ Neural stem cell regulation and differentiation

Sp3_ Building & adapting circuits into functional networks



Synaptic Neuromodulation

Sandra Jurado

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Neuromodulators expand the abilities of neuronal networks to process information and to perform fine-tuning computations that impact cognition, emotion, and behavior. Despite their key role, the molecular mechanisms orchestrating neuromodulatory function in the central nervous system (CNS) are much more unknown than those of inhibitory or excitatory transmission.

Our laboratory is interested in understanding the function of hypothalamic circuits, as major regulators of neuromodulation in the CNS. In particular, we are focused on the oxytocin (OXT) and vasopressin (VSP) systems, two neuropeptides involved in a myriad of homeostatic functions like stress regulation and energy balance as well as complex behaviors such as social interaction. We have

implemented novel state-of-the-art imaging techniques (Light Sheet Microscopy) in combination with behavioral assays and electrophysiological methods to explore the functional properties of these circuits, from their development to their decline during natural and pathological conditions like neurodegenerative disorders.

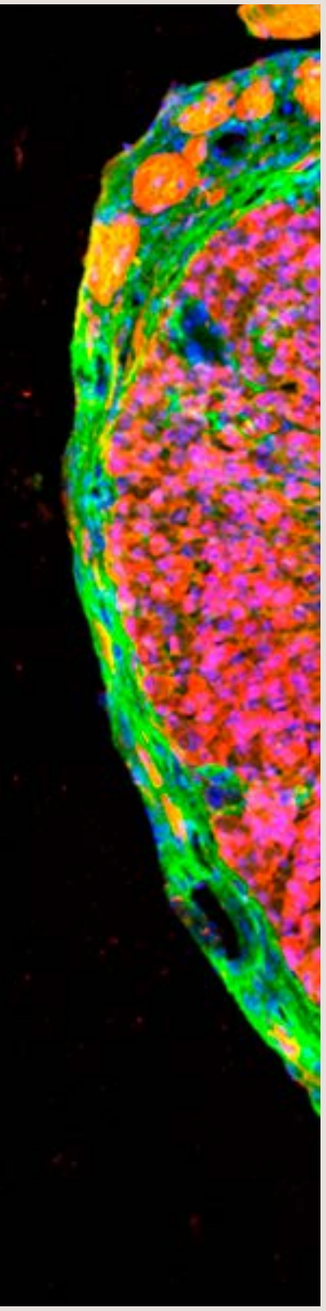
We currently work on three research lines:

1. Release of hypothalamic neuropeptides. We employ live cell imaging technologies to investigate the mechanisms underlying neuropeptide-containing vesicle dynamics and release. Our results indicate OXT exocytosis is regulated by specific SNARE molecules, which provide new targets to modulate OXT levels *in vitro* and *in vivo.*

2. Development, specification, and plasticity of hypothalamic circuits. Our group employs novel brain clarification techniques such as iDISCO+ and electrophysiology to examine the specification of neuromodulatory circuits and their plastic adaptations during adulthood and aging.

3. Impact of natural aging and neurodegeneration on social behavior. Agitation and social anxiety are common Alzheimer´s disease symptoms even in the early stages of the disease, indicating a malfunction of hypothalamic circuits involved in stress and social responses. Thus, a major focus of our group is to understand how hypothalamic circuits (OXT-VSP systems) are affected by both natural and pathological aging, and how these alterations may impact the social behavior of aged subjects.

Following our recent work (Portalés et al., 2023), we are currently studying the potential causal relationship between age-related social deficits such as social anxiety and the dysfunction of the oxytocinergic system, with the overarching goal of providing molecular targets to ameliorate the consequences of this understudied aspect of both natural and pathological aging.



Relevant publications

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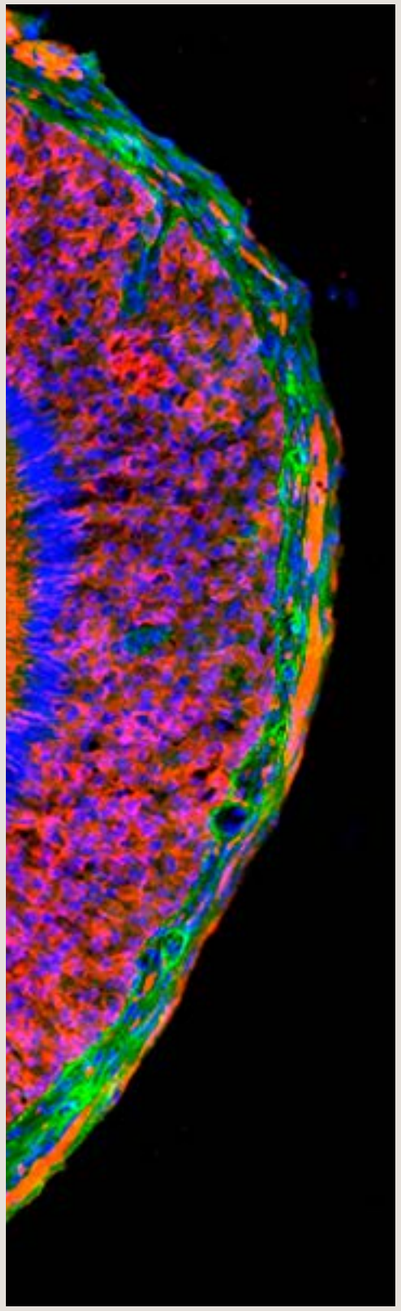

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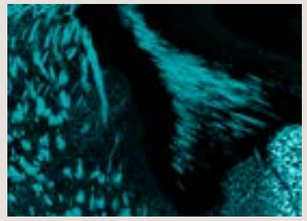
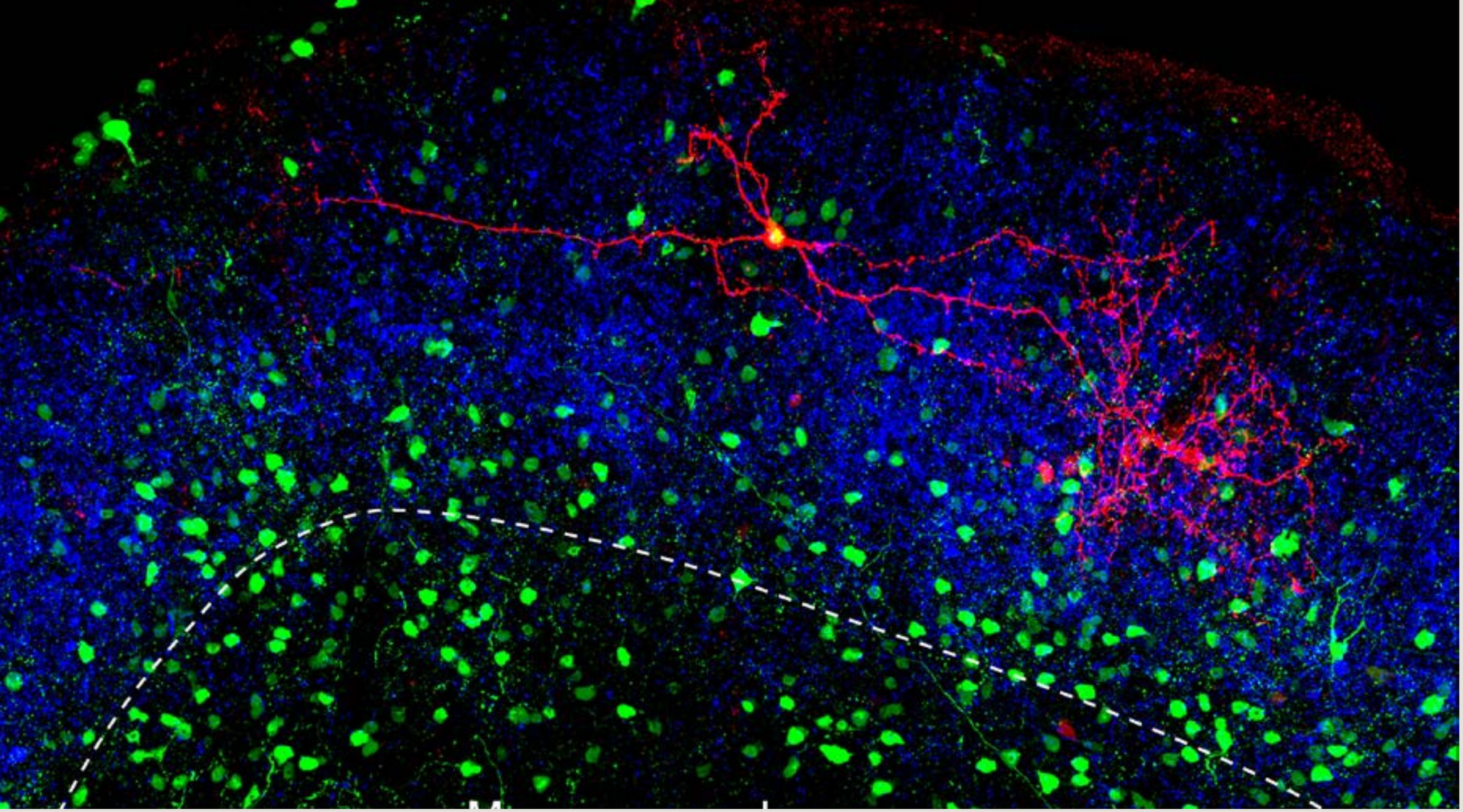


Sp4_Synaptic modulation of neural circuits and behavior



Neural circuits in vision for action

Andreas Kardamakis

What we see usually determines how we act. Yet, orienting to visual events of interest while ignoring distractions, in spite of its seemingly effortless execution, belies a complex and multi-level behaviour that can be shaped suitably during tasks. How the nervous system achieves this versatility in visual-based behaviour is a fundamental, yet unresolved, question in neuroscience.

Our goal is to understand how vision is adapted into search behavior. We have developed paradigms to investigate transitions between visual attention and distraction interactions in freely-moving mice, as well as in head-restrained configurations. Our expertise lies in microcircuit and systems approaches that involve a combination of viral-based approaches, whole-cell & in vivo electrophysiology using high-density Neuropixels probes, optogenetics, calcium and voltage imaging (ex vivo) and computation.

Our current research objectives aim to provide a comprehensive investigation of the visual and frontocortical neural circuits that regulate local cell populations in the mouse superior colliculus. These populations serve as a shared platform for selectively initiating goal-dependent orienting movements, while also routing salient visual distractions into behavior. Both modes of visual search behaviour rely on a weighted computation between visual stimulus salience and task-dependent valence, the neural implementation of which involves synaptic interactions arising from the retina, frontal cortex including the motor cortex and substantia nigra with midbrain orienting and inhibitory neurons in the superior colliculus.

manipulations of collicular activity in the control of attention-distraction state transitions in freely moving mice, 2) Combinatorial interrogation of long-range connections between visual and frontal inputs to cell-type-specific neurons in the superior colliculus using voltage imaging and whole-cell electrophysiology in midbrain slices and 3) High-density recordings of frontal and collicular circuits during guided visuospatial navigation with distractions.

From a neurobiological perspective, we anticipate our projects will yield results that will update our current views on the processes involved in the versatile control of visuospatial behaviour by unravelling key principles linking vision to action. Understanding the mode of communication between cortical and subcortical areas may also lead to the development of brain-machine interfaces for the manipulation of midbrain activity for restoring visuomotor function in affected individuals.

From a algorithmic perspective, our experiments are designed to test several hypotheses that will also advance our knowledge on the neurocomputational logic of attention-distraction networks, ergo visual search behaviour , thereby inspiring the creation of brain-like heuristic and learning approaches to real-world applications, such as machine vision and robotics.

Relevant publications

Cui, P., Song, K., Mariatos-Metaxas, D., Isla, A.G., Femenia, T., Lazaridis, I., Meletis, K., Kumar, A. and Kardamakis, A.A. (2023). **Recurrent circuits encode visual center-surround computations in the superior colliculus.** *Biorxiv*. DOI: https://doi.org/10.1101/2023.09.03.556096

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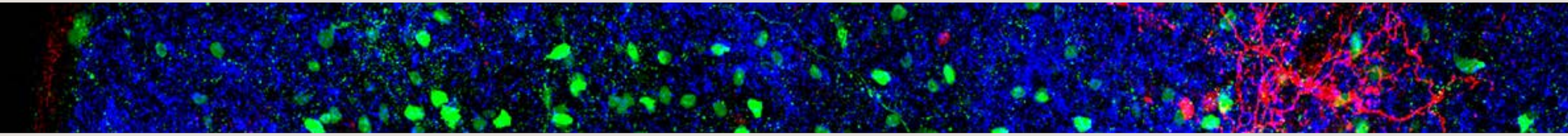

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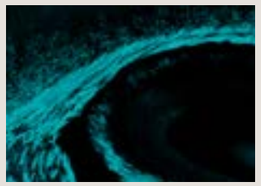

Sp4_Synaptic modulation of neural circuits and behavior

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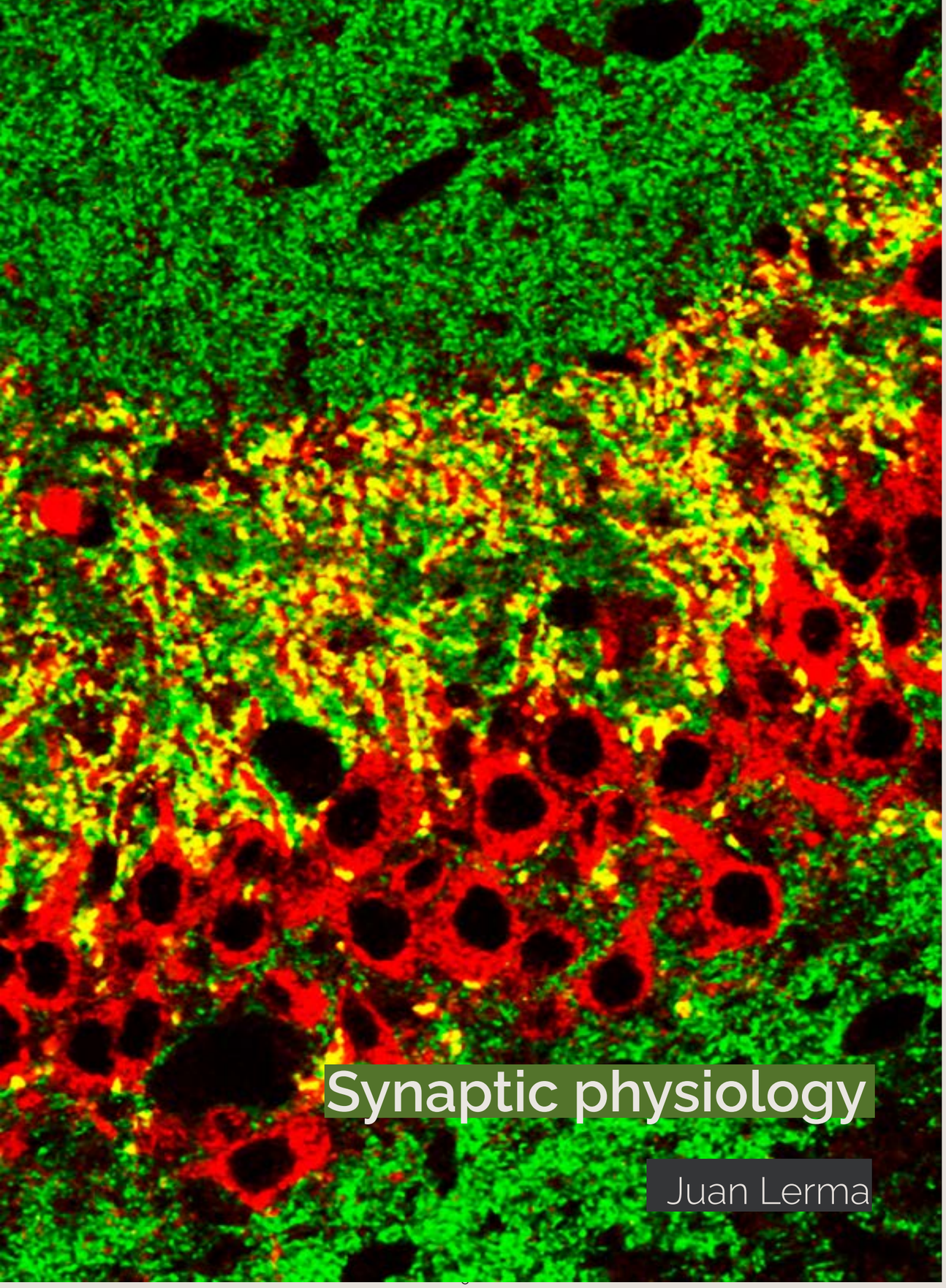

Neurons communicate with each other by releasing neuroactive substances that activate specific proteins situated at the postsynaptic membrane. This is a finely regulated process on which the correct performance of our brain depends, which is to say ourselves. Our group works on the structure and function of glutamate receptors, the most important signaling system in the brain since it mediates more than 90% of the excitatory neurotransmission. We described for the first time the existence in central neurons of a type of functional glutamate receptor, the kainate receptor (KAR), and demonstrated that KAR proteins form functional channels. Since then, we and other groups have addressed specific questions on the physiological role of KARs. But their role in both physiology and particularly pathology is still elusive.

New data, however, indicate their involvement in mood disorders. *De novo* copy number variation (deletion or duplication of a chromosomal region) of synaptic genes has been recently implicated as risk factors for mental retardation or autism. Amongst them is GRIK4, a gene coding for a glutamate receptor subunit of the kainate type. We generated transgenic mice overexpressing Grik4 in the forebrain. These mice displayed social impairment, enhanced anxiety, and depressive states, accompanied by altered synaptic transmission in the hippocampus and the amygdala. Normalizing gene and protein levels results in total rescue of both functional and behavioral abnormalities.

Following a similar strategy, we identified that triplication of the KAR encoding gene GRIK1 is the cause of spatial memory impairment observed in Down syndrome. Normalization of Grik1 dosage in Ts2Cje mice specifically restored spatial memory and reversed bidirectional alterations to CA1 inhibition, but not the changes in synaptic plasticity or the other behavioral modifications observed. We have proposed that modified information gating caused by disturbed inhibitory tone rather than generalized over-inhibition underlies some of the characteristic cognitive deficits in Down syndrome.

Taken together, our data indicate that a single gene variation in the glutamatergic system results in behavioral symptomatology consistent with autism spectrum disorders and Down syndrome, resulting from alterations in synaptic function in regions involved in social activity and spatial memory.

Relevant publications

Xu, X., Beleza, R.O., Gonçalves, F.Q., Valbuena, S., Alçada-Morais, S., Gonçalves, N., Magalhães, J., Rocha, J.M.M., Ferreira, S., Figueira, A.S.G., Lerma, J., Cunha, R.A., Rodrigues, R.J., Marques and J.M. (2022). **Adenosine A2A receptors control synaptic remodeling in the adult brain.** *Scientific Reports*, 12, 14690. https://doi.org/10.1038/s41598-022-18884-4

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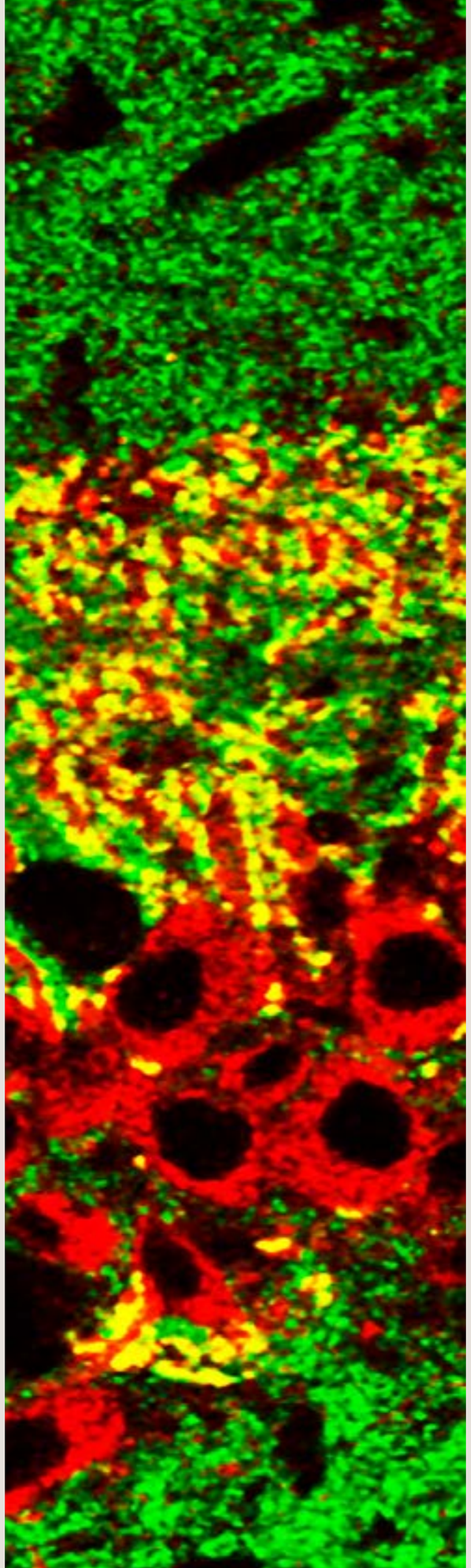

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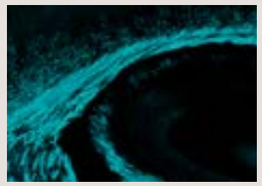

Sp4_Synaptic modulation of neural circuits and behavior

Cognition and social interaction

Félix Leroy

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The cognition and social interactions laboratory investigates how cognitive information (past experiences and decisions) prioritizes, determines, and calibrates innate behaviors. Indeed, while the cognitive functions of the cortex (neocortex and hippocampus) have been extensively studied, we know much less about its ability to regulate motivated behaviors fulfilling physiological, safety, and social needs. The lateral septum (LS) is ideally positioned to integrate cortical signals in order to regulate the activity of hypothalamic and midbrain nuclei controlling motivated behaviors. LS also receives numerous modulatory inputs from subcortical brain regions.

Based on recent cortical-LS-subcortical circuit studies, we study how LS integration of cognitive inputs regulates motivated behaviors. This is all the more important since malfunctions occurring within cortical-LS circuits may lead to altered social behaviors, a hallmark of many psychiatric disorders.

Our research is supported by the European Research Council, the Generalitat Valenciana, the Brain and Behavior Foundation, and the Agencia Estatal de Investigación.

Relevant publications

De León Reyes, N., Sierra Díaz, P., Nogueira, R., Ruiz-Pino, A., Nomura, Y., de Solis, C., Schulkin, J., Asok, A. and Leroy, F. (2023). **Corticotropin-releasing hormone signaling from prefrontal cortex to lateral septum suppresses interaction with familiar mice**. *Cell*, 186(19), 4152-4171.e31. https://doi.org/10.1016/j.cell.2023.08.010

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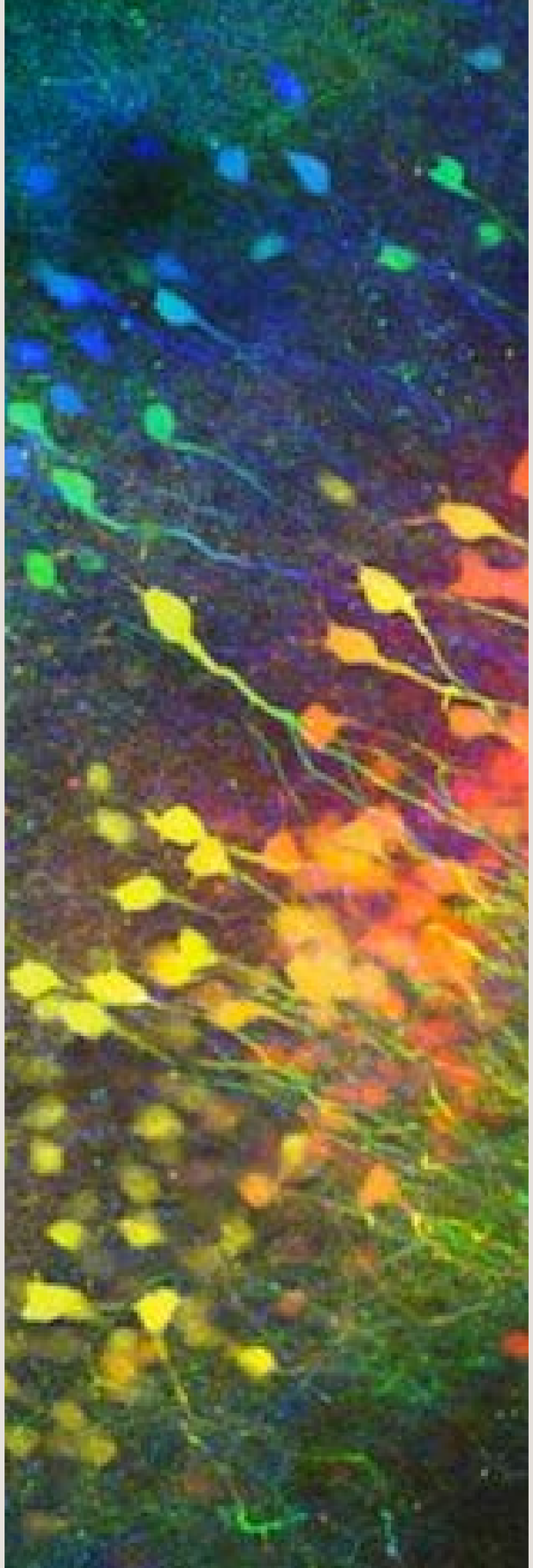

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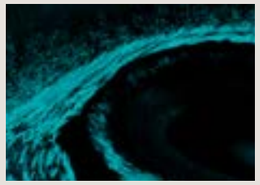
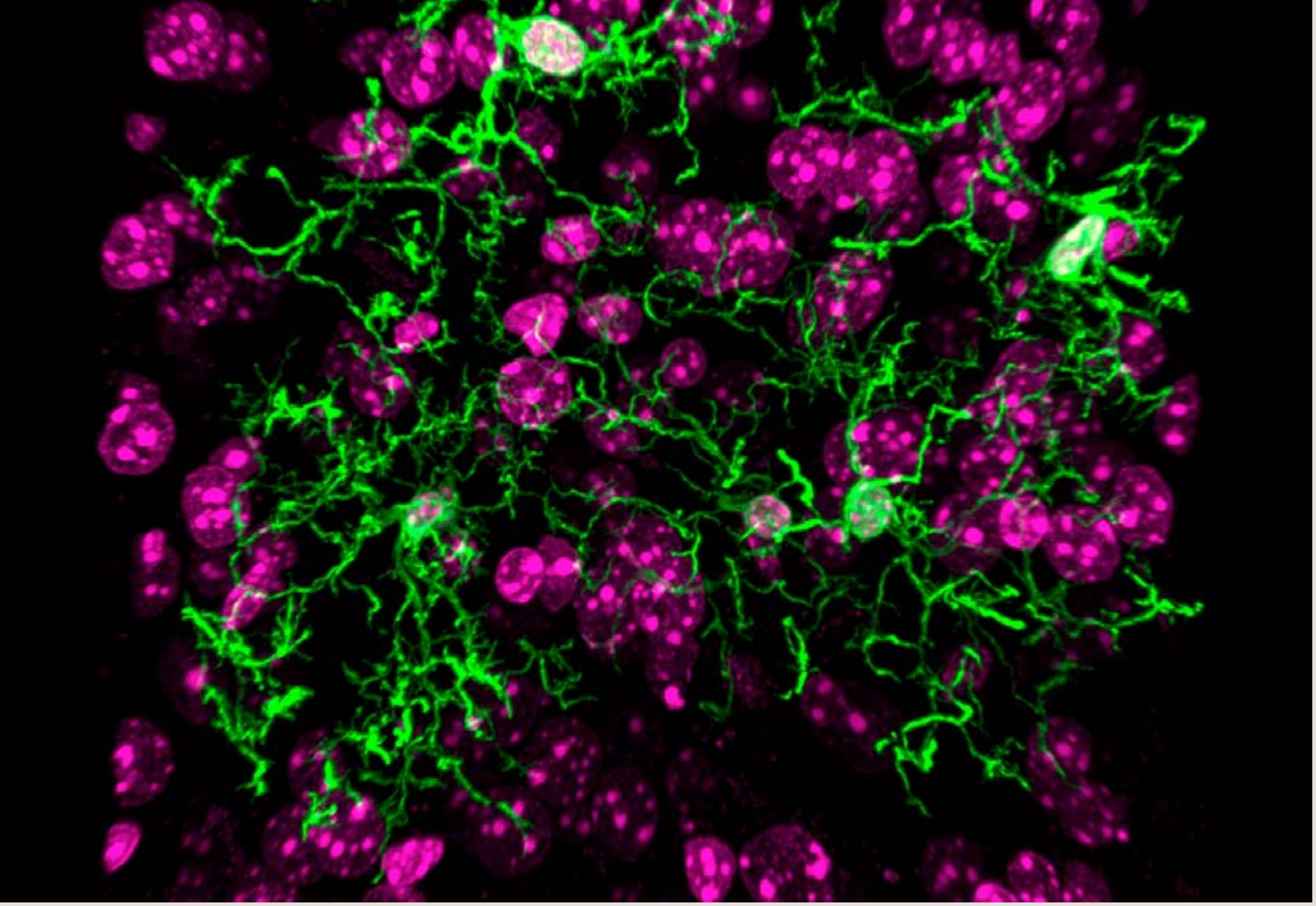
Departamento:
Cellular and Systems Neurobiology



Sp4_Synaptic modulation of neural circuits and behavior



Cellular Plasticity and Neuropathology

José P. López-Atalaya

Aging constitutes a major risk factor for most common neurodegenerative disorders, including Alzheimer's disease. Neuroinflammation is a prominent feature of aging and is central to neurodegenerative diseases. However, the role of neuroinflammation in age-related cognitive decline, as well as its contribution to the onset and progression of neurodegenerative dementias is not well understood. We investigate the mechanistic links between neuroinflammatory processes in brain aging and neurodegenerative diseases.

We seek to understand how the brain's innate immune cells integrate within neural circuits to influence brain function in health and disease. Our research focuses on elucidating how microglia cells interpret cues from their tissue microenvironment to adopt specialized roles. We are particularly interested in unveiling the core gene regulatory networks regulating the transitions and maintenance of distinct phenotypic and functional states of the brain's innate immune cells.

To this aim, we combine genetic mouse models of Alzheimer's disease and *postmortem* brain samples from patients, genomewide transcriptomics and epigenomic profiling at population and single-cell level, and state-of-the-art histological, cellular, and molecular biology methods. Our ultimate goal is to develop novel effective approaches to help older adults ward off age-related cognitive impairment and to open new avenues for therapeutic intervention to delay or prevent the progression of the most prevalent neurodegenerative conditions.

Relevant publications

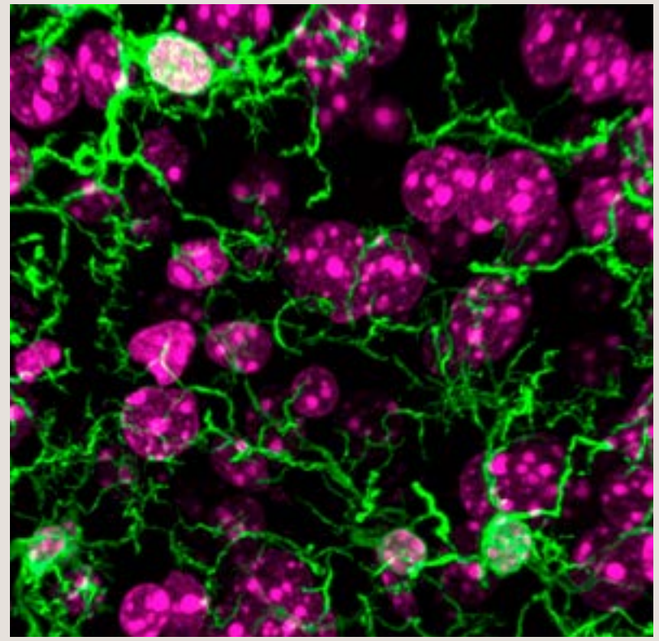
Ghirardini, E., Sagona, G., Marquez-Galera, A., Calugi, F., Navarron, C.M., Cacciante, F., Chen, S., Di Vetta, F., Dadà, L., Mazziotti, R., Lupori, L., Putignano, E., Baldi, P., López-Atalaya, J.P., Pizzorusso, T. and Baroncelli, L. (2023). **Cell-specific vulnerability to metabolic failure: the crucial role of parvalbumin expressing neurons in creatine transporter deficiency**. *Acta Neuropathologica Communications*, 11(1):34. https://doi.org/10.1186/s40478-023-01533-w

Lipinski, M., Niñerola, S., Fuentes-Ramos, M., Valor, L.M., del Blanco, B., López-Atalaya, J.P. and Barco, A. (2022). **CBP is required for establishing adaptive gene programs in the adult mouse brain.** *The Journal of Neuroscience*, 42(42), 7984-8001. https://doi.org/10.1523/JNEUROSCI.0970-22.2022

Chinnappa, K., Cárdenas, A., Prieto-Colomina, A., Villalba, A., Márquez-Galera, Á., Soler, R., Nomura, Y., Llorens, E., Tomasello, U., López-Atalaya, J.P. and Borrell, V. (2022). **Secondary loss of miR-3607 reduced cortical progenitor amplification during rodent evolution**. *Science Advances*, 8(2), eabj4010. https://doi.org/10.1126/sciadv.abj4010

Cid, E., Marquez-Galera, A., Valero, M., Gal, B., Medeiros, D.C., Navarron, C.M., Ballesteros-Esteban, L., Reig-Viader, R., Morales, A.V., Fernandez-Lamo, I., Gomez-Dominguez, D., Sato, M., Hayashi, Y., Bayés, À., Barco, A., López-Atalaya, J.P. and de la Prida, L.M. (2022). **Sublayer- and cell-type-specific neurodegenerative transcriptional trajectories in hippocampal sclerosis**. *Cell Reports*, 35(10), 109229. https://doi.org/10.1016/j.celrep.2021.109229

Herrero-Navarro, Á., Puche-Aroca, L., Moreno-Juan, V., Sempere-Ferràndez, A., Espinosa, A., Susín, R., Torres-Masjoan, L., Leyva-Díaz, E., Karow, M., Figueres-Oñate, M., López-Mascaraque, L., López-Atalaya, J.P., Berninger, B. and López-Bendito, G. (2021). **Astrocytes and neurons share region-specific transcriptional signatures that confer regional identity to neuronal reprogramming**. *Science Advances*, 7(15), eabe8978. https://doi.org/10.1126/sciadv.abe8978



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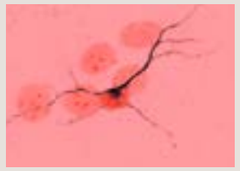
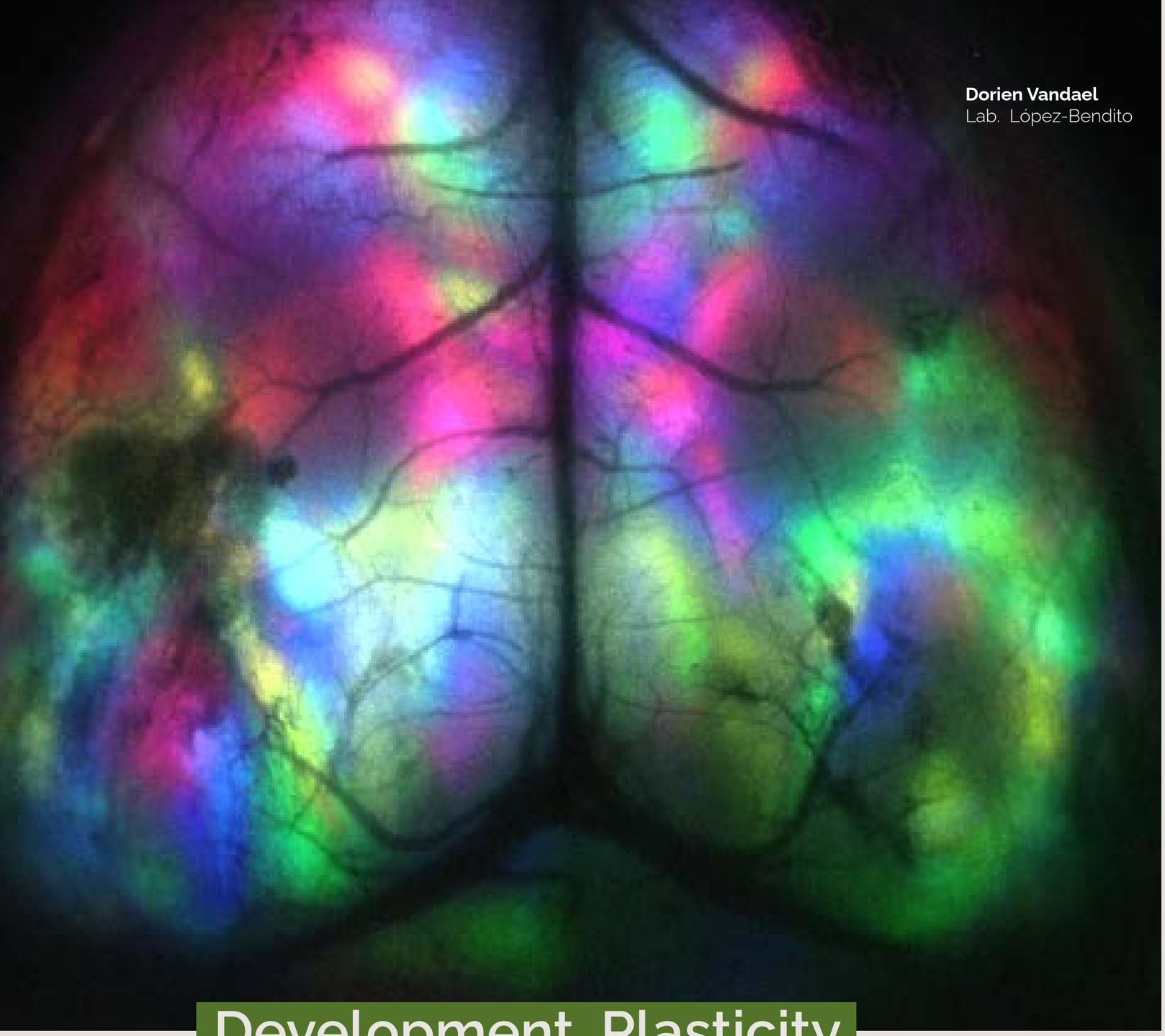
Department:

Molecular Neurobiology and Neuropathology



Sp2_Cell plasticity in brain disease and repair



Development, Plasticity and Reprogramming of Sensory Circuits

Guillermina López-Bendito

@GLB_Lab

Dr. López-Bendito´s lab studies the development and plasticity of brain circuits during embryonic and postnatal development. To this end, the team combines experimental embryology techniques with the generation of new transgenic mouse lines, cellular reprogramming *in vivo*, sensory deprivation paradigms and cutting-edge real-time imaging and *in vivo* electrophysiology techniques. This sophisticated and multidisciplinary approach has unveiled that sensory representations emerge while circuits are being assembled in embryonic life and that spontaneous activity helps to construct these early circuits.

Briefly, their research has pioneered three essential aspects of neurodevelopment. First, they contributed to determining the molecular mechanisms involved in the construction of sensory circuits in the brain. Second, her lab revealed the involvement of spontaneous brain activity in the formation of these circuits during fetal development. Finally, their research program on plasticity and cell reprogramming in the developing brain is aimed at the recovery of brain circuits after the early loss of a sensory organ. The long-term aspiration of this lab is to design tools to restore defective neuronal connections in patients with sensory deficits, such as blindness or deafness.

Relevant publications

Guillamón-Vivancos, T., Aníbal-Martínez, M., Puche-Aroca, L., Moreno-Bravo, J.A., Valdeolmillos, M., Martini, F.J. and López-Bendito, G. (2022). **Input-dependent segregation of visual and somatosensory circuits in the mouse superior colliculus.** *Science*, 377(6608), 845-850. https://doi.org/10.1126/science.abq2960

Herrero-Navarro Á., Puche-Aroca, L., Moreno-Juan, V., Sempere-Ferràndez, A., Espinosa, A., Susín, R., Torres-Masjoan, L., Leyva-Díaz, E., Karow, M., Figueres-Oñate, M., López-Mascaraque, L., López-Atalaya, J.P., Berninger, B. and López-Bendito, G. (2021). **Astrocytes and neurons share region-specific transcriptional signatures that confer regional identity to neuronal reprogramming**. *Science Advances*, 7(15), eabe8978. https://doi.org/10.1126/sciadv.abe8978

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Antón-Bolaños, N., Sempere-Ferràndez, A., Guillamón-Vivancos, T., Martini, F.J., Pérez-Saiz, L., Gezelius, H., Filipchuk, A., Valdeolmillos, M. and López-Bendito, G. (2019). **Prenatal activity from thalamic neurons governs the emergence of functional cortical maps in mice.** *Science*, 364(6444), 987-990. https://doi.org/10.1126/science.aav7617

Mire, E., Mezzera, C., Leyva-Díaz, E., Paternain, A.V., Squarzoni, P., Bluy, L., Castillo-Paterna, M., López, M.J., Peregrín, S., Tessier-Lavigne, M., Garel, S., Galcerán, J., Lerma, J. and López-Bendito, G. (2012). **Spontaneous activity regulates Robo1 transcription to mediate a switch in thalamocortical axon growth.** *Nature Neuroscience*, 15, 1134-1143. https://doi.org/10.1038/nn.3160

Department:

Developmental Neurobiology

Sp3_ Building & adapting circuits into functional networks

Relevant information for the year 2023

During 2023, Dr. López-Bendito has been named Research Professor of the CSIC, Corresponding Academic of the ***Real Academia de Ciencias Exactas, Físicas y Naturales de España*** and has received the Rei Jaume I Award for Medical Research. She has also begun her role as president of the EMBO Young Investigator Program Committee. The group has published a scientific article and two reviews:

Moreno-Juan V, Aníbal-Martínez M, Herrero-Navarro Á, Valdeolmillos M, Martini FJ, López-Bendito G (2023) **Spontaneous Thalamic Activity Modulates the Cortical Innervation of the Primary Visual Nucleus of the Thalamus**. Neuroscience 508:87-97. https://doi.org/10.1016/j.neuroscience.2022.07.022

Guillamón-Vivancos T, Vandael D, Torres D, López-Bendito G, Martini FJ, (2023) **Mesoscale calcium imaging *in vivo*: evolution and contribution to developmental neuroscience.** Front Neurosci 17:1210199. https://doi.org/10.3389/fnins.2023.1210199

Huerga-Gómez I, Martini FJ, López-Bendito G (2023) **Building thalamic neuronal networks during mouse development**. Front Neural Circuits 17:1098913. https://doi.org/10.3389/fncir.2023.1098913

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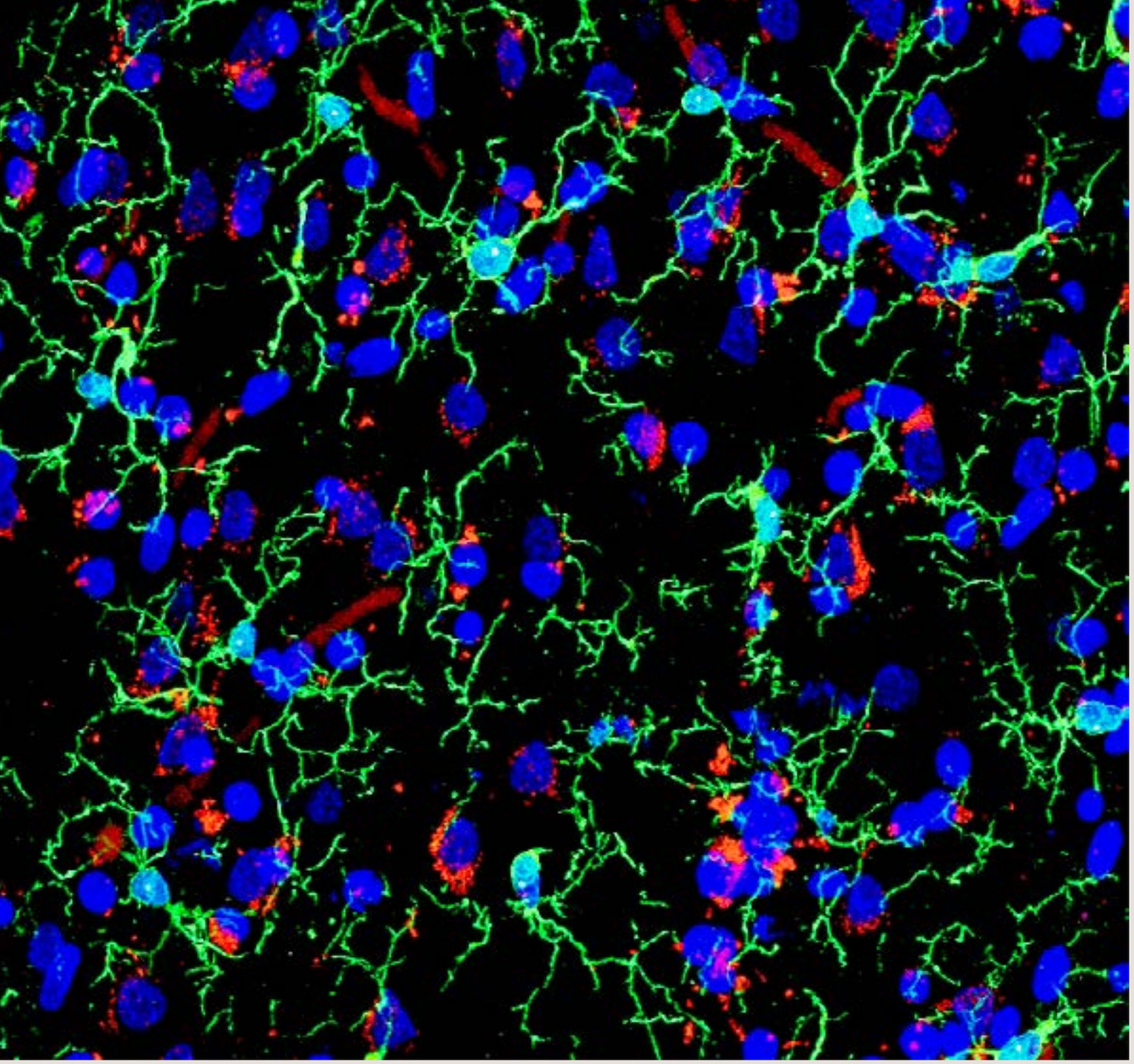
Lorenzo Puche Aroca
Pablo Castellano Ruiz
Francesco Dori
Elena Pérez Montoyo
Eleni Giannopoulou
Técnicos
Luis Miguel Rodríguez Malmierca
Belén Andrés Bayón
María Aurelia Torregrosa Mira
Administración
Helena Campos Martín
Gestión científica
Verónica Miguela Fernández



Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares

The research lines of our laboratory focus on the identification of biomarkers that may be involved in the onset and development of psychiatric disorders (anxiety, depression, post-traumatic stress, etc.), addictive disorders and neurological disorders (Parkinson's, Alzheimer's, etc.), which are essential for the discovery of new therapeutic targets to improve the pharmacological approach to these diseases.

Improving knowledge of the changes involved in the aetiology and/or development of various neuropsychiatric or neurological disorders is one of the major challenges of the laboratory, and is closely linked to the discovery of new drugs with greater efficacy and safety. We are particularly interested in the role of the endocannabinoid system in the regulation of various functional aspects and the potential therapeutic usefulness of its pharmacological manipulation. In this sense, the administration of cannabinoid compounds and the evaluation of their behavioural and neurochemical effects is a fundamental pillar of the laboratory's research.

We use a variety of methods to evaluate the behavioural properties of animal models with emotional traits (anxiety, depression, stress), cognitive alterations (memory consolidation processes, prepulse inhibition), reinforcing and motivational effects of various substances of abuse (alcohol, cocaine, nicotine, cannabis, heroin) and, more recently, the consequences of perinatal exposure (pregnancy and lactation) to drugs such as alcohol or cannabis. Similarly, to study functional changes at the level of the brain, we mainly use tools that allow us to analyse changes in gene expression employing real-time PCR techniques, as well as procedures for analysing protein expression using immunohistochemical techniques.

The constant relationship of the members of the laboratory with psychiatrists and neurologists has allowed us to establish a mutual bridge of information between preclinical and clinical research, combining animal models with the study of biomarkers in clinical biological samples (post-mortem brain tissue, cerebrospinal fluid, blood) that may have diagnostic, prognostic or therapeutic utility. One of the main objectives is to maintain and strengthen this type of synergistic strategy to promote translational research, with the ultimate aim of providing therapeutic benefits to patients.

Relevant publications

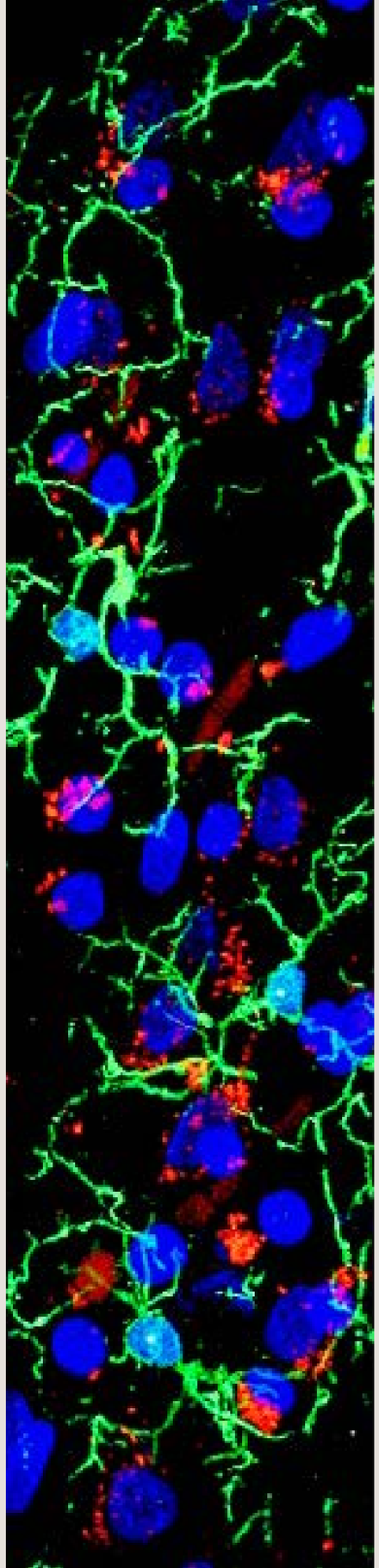
Rubio, G., Gasparyan, A., Duque, A., García-Gutierrez, M.S., Navarrete, F., Navarro, D. and Manzanares, J. (2023). **Emotional Processing and Maltreatment During Childhood as Factors of Vulnerability to Alcohol Abuse in Young Adults.** *International Journal of Mental Health and Addiction*. https://doi.org/10.1007/s11469-023-01097-9

García Gutiérrez, M.S., Navarro, D., Austrich Olivares, A. and Manzanares, J. (2023). **Unveiling behavioral and molecular neuroadaptations related to the antidepressant action of cannabidiol in the unpredictable chronic mild stress model.** *Frontiers in Pharmacology*, 14:1171646. https://doi.org/10.3389/fphar.2023.1171646

Gasparyan, A., Navarro, D., Navarrete, F., Austrich Olivares, A., Scoma, E.R., Hambardikar, V.D., Acosta, G.B., Solesio, M.E. and Manzanares, J. (2023). **Cannabidiol repairs behavioral and brain disturbances in a model of fetal alcohol spectrum disorder.** *Pharmacological Research*, 188:106655. https://doi.org/10.1016/j.phrs.2023.106655

Fernandez-Miranda, J.J., Pascual-Pastor, F., Díaz-Fernandez, S., Navarro, D. and Manzanares, J. (2022). **Differences in Substance Use Disorders and Other Mental Disorders in Mental Health and Addiction Settings: Sociodemographic, Clinical, Drug Treatment, and Gender Differences.** *International Journal of Mental Health and Addiction.* https://doi.org/10.1007/s11469-022-00989-6

Gasparyan, A., Navarrete, F., Rodriguez-Arias,M., Miñarro, J. and Manzanares, J. (2021). **Cannabidiol Modulates Behavioural and Gene Expression Alterations Induced by Spontaneous Cocaine Withdrawal**. *Neurotherapeutics*, 18(1), 615-623. https://doi.org/10.1007/s13311-020-00976-6



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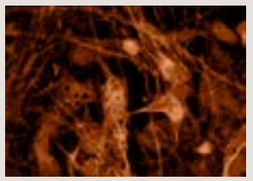
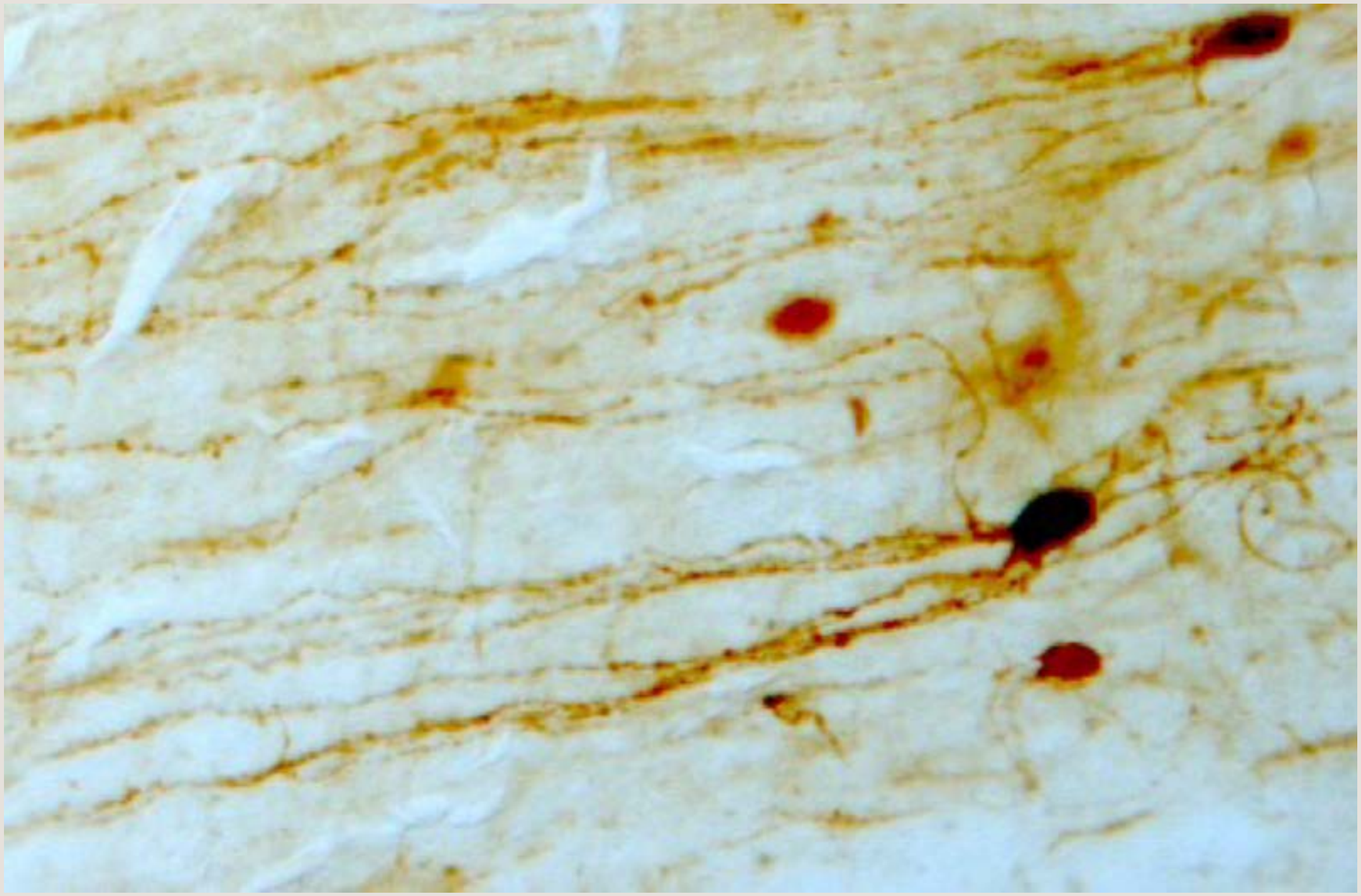
Departamento:

Molecular Neurobiology and Neuropathology



Sp8_Translational research of neurological and psychiatric disorders



Neurobiology of mental, neurodegenerative and neuro-oncological diseases

Salvador Martínez / Emilio Geijo / Diego Echevarría / Eduardo de Puelles

We have ascribed the expression of the ACE2 receptor in the progenitors of the dentate gyrus during their migration in human brain development, highlighting the possibility of an alteration of this migration in congenital COVID-19 cases (*Cellular and Molecular Life Sciences* 2023 and *Medicina (Buenos Aires)* 2023).

Deletion of selective medial neuronal types (PV, SOM, and pyramidal neurons), using the cre-lox model to delete the Lis1 gene, provides structural and functional changes in the cortical circuitry. Studies of the structure of the cerebral cortex (anterior cingulate, retrosplenial, and hippocampus) are producing results that confirm our hypothesis of using Lis1 expression as an experimental approach to develop models of mental illness.

Work on the neurobiological mechanisms of immune tolerance and tumor infiltration of glioblastoma multiforme cells in the cerebral cortex has focused on studying cellular processes of vascular coaptation and chaperone-mediated autophagy activation in pericytes (*Cells* 2023).

Concerning our activity in the clinical trial and study of new therapeutic targets for ALS, we have studied cellular and molecular mechanisms that may operate exclusively in motor neurons, as candidates for the selective vulnerability of these neurons in ALS (Brain Structure & Function, Epub 2023). In collaboration with David del Pozo's group (CABIMER, Seville) we have demonstrated the role of MAPK/MAK/MRK kinase (MOK) in the pathogenesis of ALS (*PNAS* 2023).

In collaboration with Carlos Bueno (IMIB, Murcia), we have described nuclear movement during neuronal differentiation of mesenchymal cells and the existence of internuclear communication of the cells in the process of differentiation to neurons.

Relevant publications

Hernandez-Lopez, J.M., Hernandez-Medina, C., Medina-Corvalan, C., Rodenas, M., Francisca, A., Pérez-García, C., Echevarria, D., Carratala. F., Geijo-Barrientos, E. and Martinez, S. (2023). **Neuronal progenitors of the dentate gyrus express the SARS-CoV-2 cell receptor during migration in the developing human hippocampus.** *Cellular and Molecular Life Sciences*, 80(6):140. https://doi.org/10.1007/s00018-023-04787-8

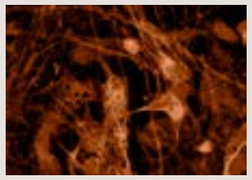
Martínez-Morga, M., Hernandez-Lopez, J.M., Hernandez-Medina, C., Martínez-Morga, S. and Martínez, S. (2023). **Expresión de ACE2 en cerebro durante el desarrollo y susceptibilidad de infección cerebral por SARS-CoV-2 [ACE2 expression in the brain during development and susceptibility to brain infection by SARS-CoV-2**]. *Medicina (Buenos Aires)*, 83(II): 2-5. http://hdl.handle.net/10261/309649

Pombero, A., García-Lopez, R. and Martínez, S. (2023). **Pericyte-Glioblastoma Cell Interaction: A Key Target to Prevent Glioblastoma Progression**. *Cells*, 12(9):1324. https://doi.org/10.3390/cells12091324

Ovsepian, S.V., O'Leary, V.B. and Martinez, S. (Epub 2023). **Selective vulnerability of motor neuron types and functional groups to degeneration in amyotrophic lateral sclerosis: review of the neurobiological mechanisms and functional correlates.** *Brain Structure & Function*, 229(1):1-14. https://doi.org/10.1007/s00429-023-02728-6

Pérez-Cabello, J.A., Silvera-Carrasco, L., Franco, J.M., Capilla-Gonzalez, V., Armaos, A., Gómez-Lima, M. García-García, R., Yap, X.W., Leal-Lasarte, M., Lall, D., Baloh, R.H., Martinez, S., Miyata, Y., Tartaglia, G.G., Sawarkar, R. García-Dominguez, M., Pozo, D. and Roodveldt, C. (2023). **MAPK/MAK/MRK overlapping kinase (MOK) controls microglial inflammatory/type-I IFN responses via Brd4 and is involved in ALS**. *PNAS*, 120 (28) e2302143120. https://doi.org/10.1073/pnas.2302143120

Sp3_ Building & adapting circuits into functional networks



Sp8_ Translational research of neurological and psychiatric disorders

Presentation of the following posters 2023:

Jornada del Día Mundial de las Enfermedades Raras (Alicante 2/03/23)
Oral communication: 'Efecto de las células mesenquimales de médula ósea (HBMSCS) en la adrenoleucodistrofia (X-ALD)'
Authors: Pérez García, C. & Martínez, S.

VII Congreso Internacional de Terapia Ocupacional de la UMH (Alicante, 05/10-12/23)
Poster: 'Proyecto PA-TO: Posters Anatómicos aplicados a la Terapia Ocupacional'
Authors: Verónica Company Devesa, Puelles, E., Morales-Delgado, N., Madrigal Verdu, P., Pombero, A., García-López, R., Pérez, C., Echevarría, D., Martínez, S. & Andreu-Cervera, A.

XXX Congreso de la Sociedad Anatómica Española (Girona 9/09/23)
Póster: 'LIS1 regulates development of somatostatin-positive interneurons in the cingulate cortex'.
Autores: Pombero, A., García-Lopez, R., Geijo, E & Martínez, S.

Póster: 'MEDIPILLS 2.0: Creation of anatomical micropills combining real and virtual dissection in medicine grade'.
Autores: García-López, R. , Morales-Delgado, N, Andreu-Cervera, A., Madrigal, M.P., Martínez, S., Echevarria, D., Puelles, E., Pérez, C. & Pombero, A.

Póster: 'Anatomical posters applied to occupational therapy: The PA-TO Project'
Autores: Andreu-Cervera, A., Company, V., Puelles, E., Madrigal, M.P., Pombero, A., García-López, R., Pérez, C., Echevarría, D., Martínez, S. & Morales-Delgado, N.

IBRO 2023 (Granada, 9-13/19/2023)
Póster: 'Effect of LIS1 mutation on the development of somatostatin-positive interneurons of the cingulate cortex'
Autores: Pombero, A., García-Lopez, R., Geijo,E. & Martínez, S.

Póster: 'Conditional mutation of LIS1 gene in mouse cerebellar cortex'
Autores: Echevarria, D., Almagro-García, F., Palomera Beneito, C., Geijo-Barrientos, E. & Martínez, S.

43 Reunión del Grupo Español de Neurotransmisión y Neuroprotección (GENN) (Alcalá de Henares,13-16/12/23)
Póster: 'Efectos de la mutación LIS1 sobre el desarrollo de interneuronas parvalbúmina positivas de la corteza cingular'
Autores: Madrigal, M. P., Geijo, E. & Martínez, S.

VII Congreso Internacional de Terapia Ocupacional de la UMH (Alicante, 10-12/05/23)
Poster: 'Proyecto PA-TO: Posters Anatómicos aplicados a la Terapia Ocupacional'
Autores: Verónica Company Devesa, Puelles, E., Morales-Delgado, N., Madrigal Verdu, P., Pombero, A., García-López, R., Pérez, C., Echevarría, D., Martínez, S. & Andreu-Cervera, A.

Department:

Neurobiology of mental, neurodegenerative and neurooncological diseases.

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Lorena Martínez Hostyn
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Lorena Rodríguez Serrano
(TFM Occupational Therapy in Neurology)
Administration
María Jesús Arencibia Rojas

Visual Analogy Laboratory

Luis M. Martínez Otero

@MartinezLab

The work we do in the laboratory could be framed within the broad field of “Systems and computational neuroscience”. Our interests lie in the neural mechanisms that underlie some cognitive abilities. For many years we have studied the visual system, the way in which circuits within the brain represent and process information that they receive through the retina and how their processing could condition our behavior and understanding of the world.

In the last few years our interests have moved towards human cognition in two directions. First, how cognitive processes in general are inherently contextual, and how they adapt instantaneously to the different circumstances and situations in which we find ourselves or process any type of information. And second, how our minds are not constrained within the skull but extend outside the brain itself into the body and the world around us.

The relevance of this new perspective of an extended mind is profound. If our minds themselves can include aspects of our social and physical environments, then the kinds of social and physical environments we create can reconfigure our minds and our capacity for thought and reason.

Relevant publications

Constant, A., Tschantz, B., Millidge, F., Criado-Boado, L.M., Martinez, Müller, J. and Clark, A. (2021). **The Acquisition of Culturally Patterned Attention Styles under Active Inference.** *Frontiers in Neurorobotics,* 15, 729665. https://doi.org/10.3389/fnbot.2021.729665

Reiff, T., Antonello, Z.A., Ballesta-Illán, E., Mira, L., Sala, S., Navarro, M., Martinez, L.M. and Domínguez, M. (2019). **Notch and EGFR regulate apoptosis in progenitor cells to ensure gut homeostasis in** *Drosophila***.** *The EMBO Journal*, 38(21), e101346. https://doi.org/10.15252/embj.2018101346

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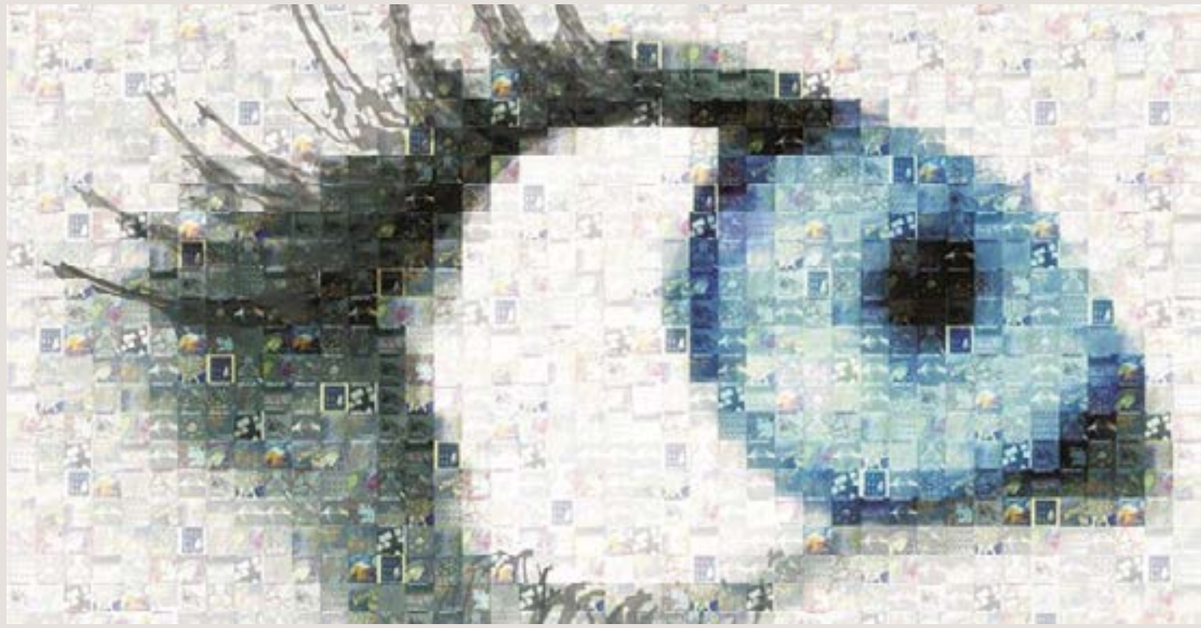
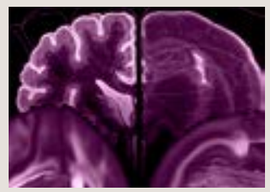


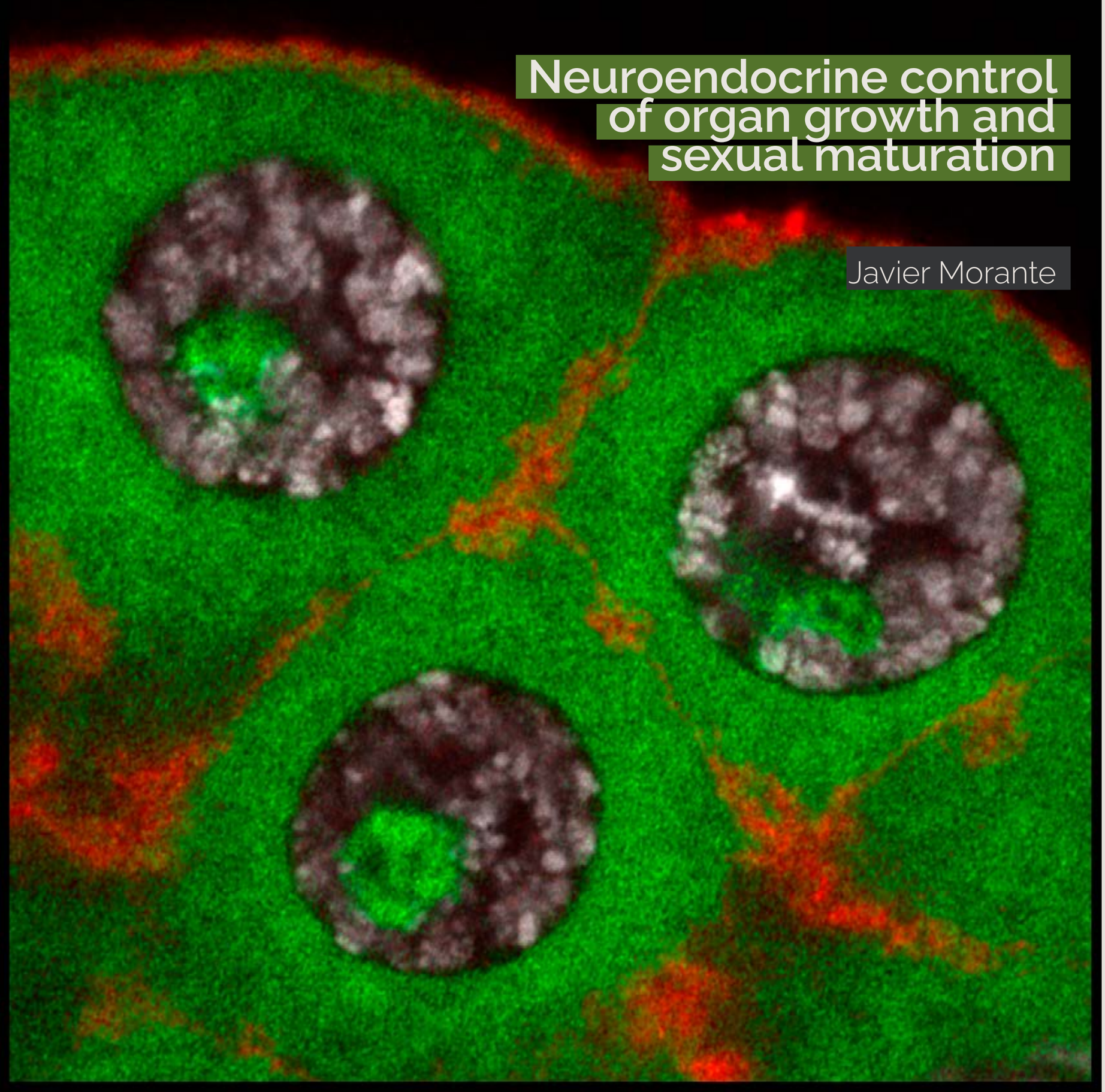
Department:
Cellular and Systems Neurobiology



Sp7_Human cognition & behaviour

Neuroendocrine control of organ growth and sexual maturation

Javier Morante



During development, the release of circulating steroid hormones from neuroendocrine circuits induces a shift from juvenile growth to sexual maturation in humans and insects alike. The initiation of this change is a strictly controlled process, requiring the evaluation of checkpoints based on nutrient levels and growth status to decide whether to activate these neuroendocrine circuits and release steroids that trigger maturation or continue juvenile development.

How exactly these external and internal cues are integrated to dictate when an animal can reach sexual maturity, as well as what molecular and cellular mechanisms acting at the level of neuroendocrine cells trigger this critical decision, remain fascinating unknowns. Childhood obesity, the prevalence of which is increasing to pandemic proportions, has been associated with precocious puberty in girls. On the other hand, malnutrition and intensive physical training can delay puberty.

Previous work in mice and humans has also shown that a deficiency of leptin, a hormone secreted by fat cells, or its receptors, which signal the amount of energy stored in the body in neuroendocrine circuits, leads to hyperphagia, early-onset obesity and delayed or complete inability to initiate the pubertal transition. By using *Drosophila*, we aim to uncover the molecular and cellular mechanisms and neuroendocrine circuits required for the regulation of sexual maturation and body weight control.

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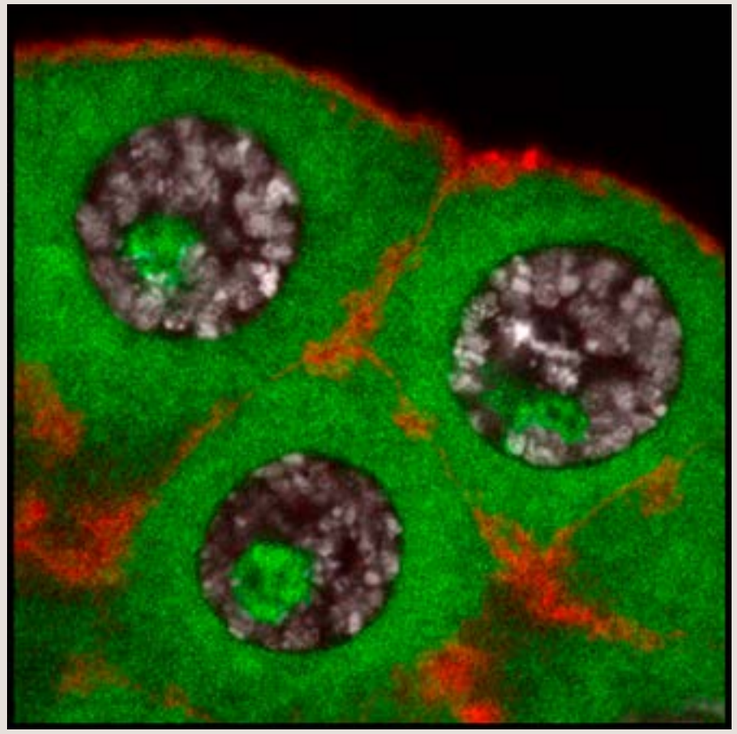

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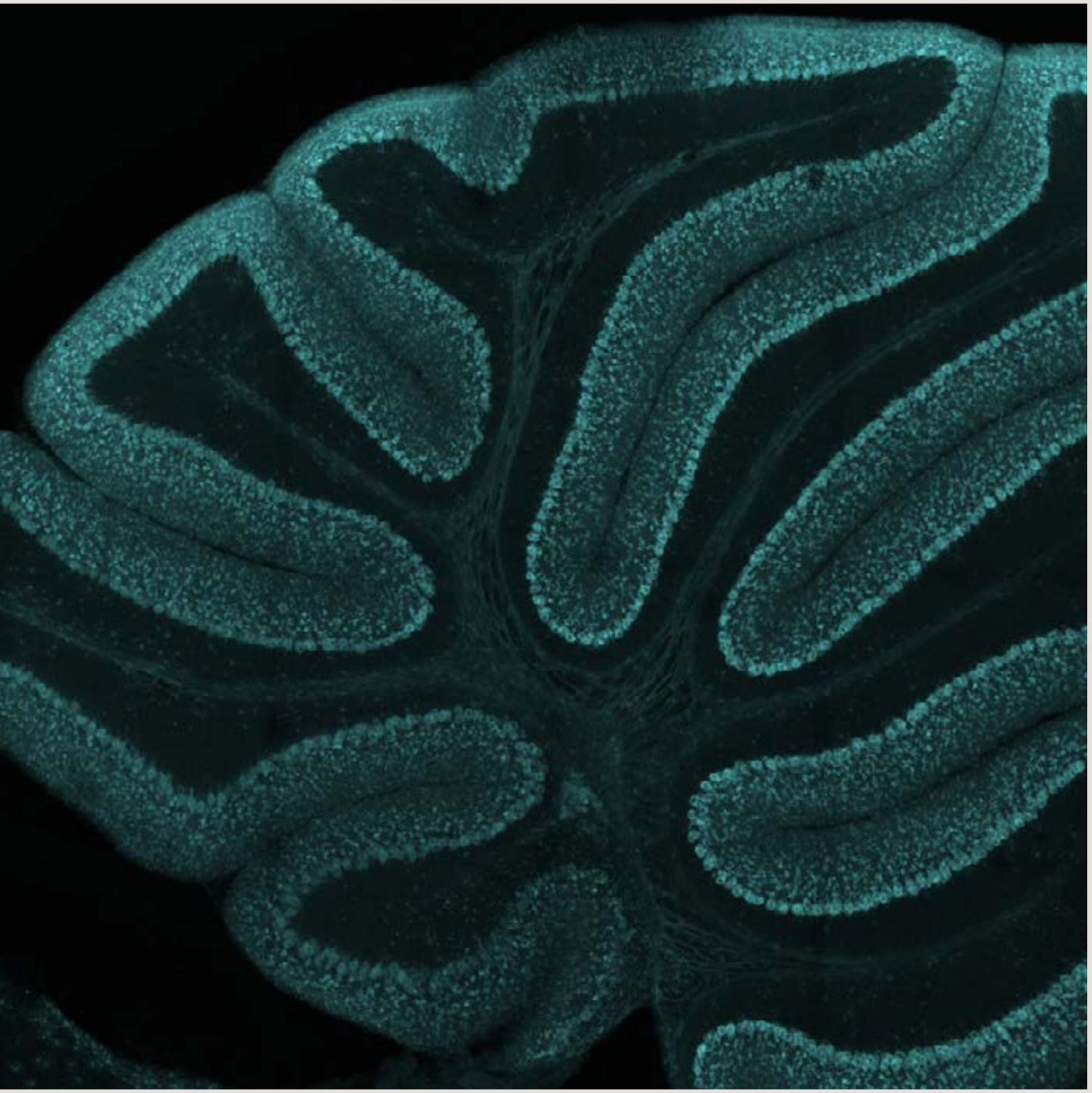
Developmental Neurobiology

Sp6_Genetic & epigenetic basis of Individuality & aging



Development, wiring and function of cerebellar circuits

Juan Antonio Moreno Bravo

The goal of the lab is to understand how early alterations of the cerebellum are related to diverse neurodevelopmental disorders. The questions we pursue are grounded in determining, from a developmental perspective, how cerebellar abnormalities impact brain function.

We combine mouse genetics to develop animal models with cerebellar alterations, state-of-the-art histological, cellular, and molecular biology methods and techniques, transcriptomics, and functional analyses.

Our ultimate goal is to understand the contribution of the cerebellum to cognition in both typical development and developmental disorders and to translate this knowledge into clinical applications.

Our research is focused on two main research lines:

- Understanding cerebellar long-range connectivity that relays cerebellar output to diverse brain areas. We aim to elucidate how the cerebellum influences the development and function of remote brain circuits, with particular interest in the cerebellar modulation of the developing cortical circuits.
- Investigating the development and assembly of local cerebellar circuits. We seek to determine basic molecular and activity-dependent mechanisms underlying the formation and function of these circuits and how alterations in these processes lead to abnormal function of the cerebellum.

Relevant publications

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Sp3_ Building & adapting circuits into functional networks

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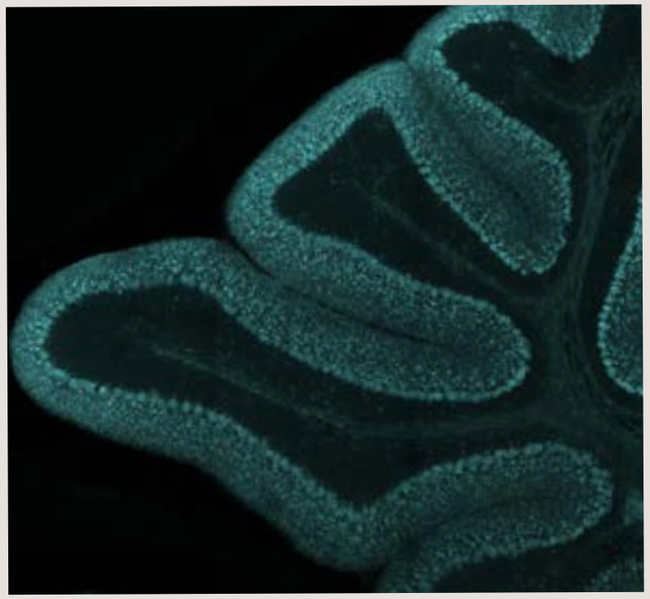

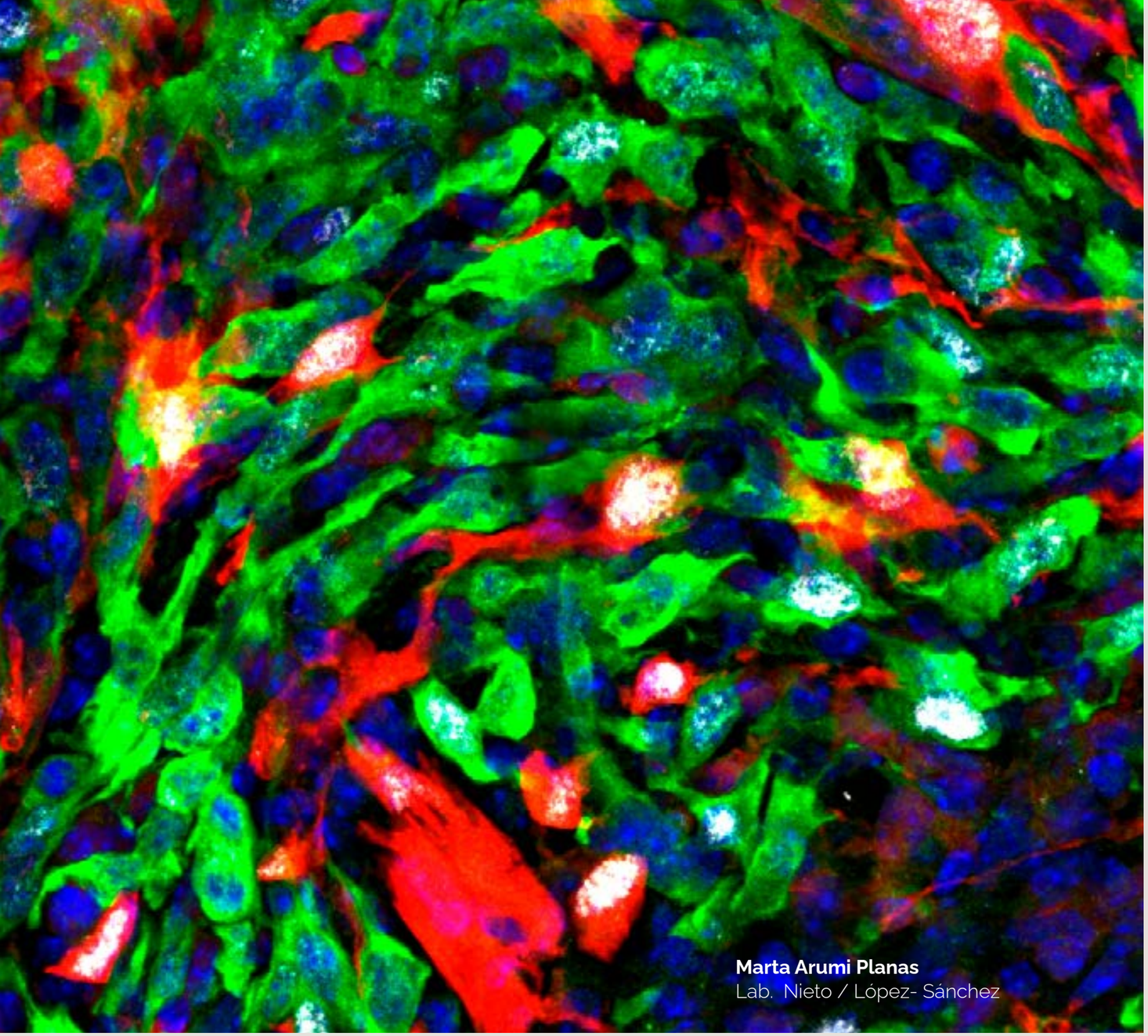

Marta Arumi Planas
Lab. Nieto / López- Sánchez

Cell Plasticity in Development & Disease

Ángela Nieto / Berta L. Sánchez-Laorden

For the last 30 years, the group has been studying cell movements and plasticity in health and disease. We study the epithelial-to-mesenchymal transition (EMT), a fundamental process during embryonic development that allows cells to delaminate and migrate toward their final destinations.

We described how different transcription factors, the so-called EMT-TFs, are activated in different vertebrates to regulate massive cell movements during gastrulation, neural crest migration, or organ positioning. We have extended our studies to biomedical research, as we found that pathological activation of these factors in adults leads to several prominent pathologies, including cancer and fibrosis. As such, aberrant activation of the EMT program in tumors leads to the acquisition of invasive and migratory properties, required for cancer dissemination and progression to the metastatic disease.

The EMT is a very complex process in which different EMT transcription factors (EMT-TFs) promote different plasticity programs in embryonic and cancer cells. How the EMT-TFs orchestrate these programs and, especially, how the highly plastic partial EMT states can trigger the development of fibrosis or influence metastatic potential and therapy resistance is not well understood. We are characterizing the programs induced by different EMT-TFs. We have developed new models to investigate EMT-TF expression codes and signaling pathways that can discriminate EMT states to predict cell behavior and prognosis in pathological contexts, including organ fibrosis, breast cancer, and melanoma.

We are also characterizing novel functions of these EMT-TFs during neural crest development, neuronal differentiation, vascular integrity, and brain metastasis. In summary, our main contribution has been showing how the reactivation of developmental programs in adults leads to the progression of devastating pathologies. This aberrant reactivation can be considered a sign of defective homeostasis, leading to diseases whose prevalence increases with aging, such as cancer and organ degeneration by fibrosis.

Our ultimate goal is to gain insight into the mechanisms that drive cellular plasticity in these devastating diseases. We are actively working in newly generated animal models to try to prevent or attenuate the loss of tissue homeostasis, in order to propose better anti-metastatic therapies and to promote tissue regeneration.

Relevant publications

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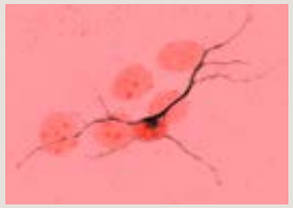
Department:

Developmental Neurobiology



Sp2_ Cell plasticity in brain disease and repair

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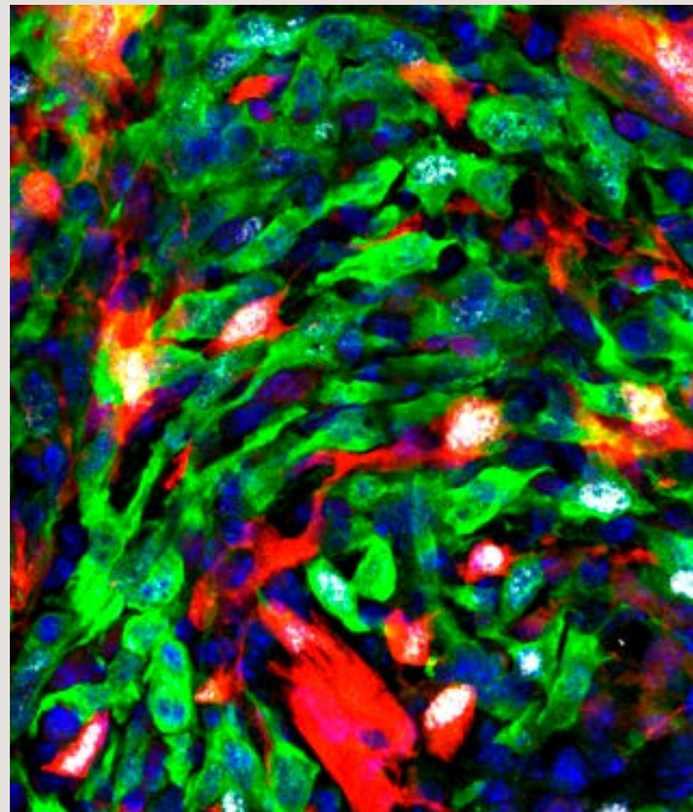

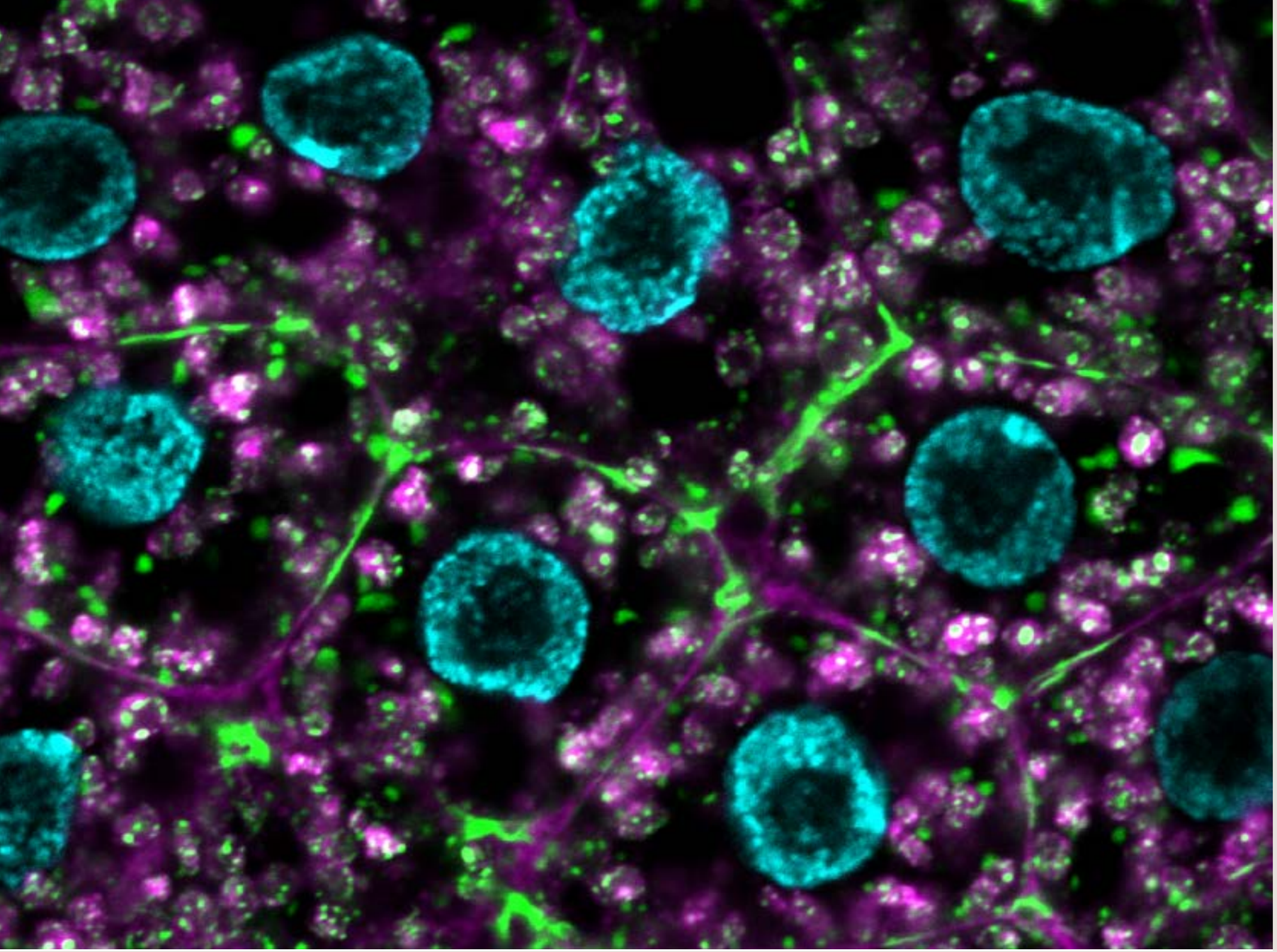

Cell-to-tissue architecture in the nervous system

José Carlos Pastor Pareja

Tissue-level organization of cells in animals is supported by the basement membrane (BM), a planar polymer of extracellular matrix proteins that underlies epithelia and surrounds organs and nervous tissue. Understanding tissue architecture and its underlying cellular and molecular determinants is essential for deciphering the mechanisms of normal nervous system morphogenesis and altered physiology in disease and aging. In our laboratory, we use the fruit fly (*Drosophila melanogaster*) to study the secretion and assembly of the BM. Taking advantage of the sophisticated genetic tools available in *Drosophila*, and in combination with advanced imaging, we are investigating the biogenesis of BM components, their assembly into normal and fibrotic polymers, and their roles in the morphogenesis of the nervous system, intercellular signaling, immune responses, regeneration, and tumor progression.

A particularly interesting aspect of the biogenesis of the extracellular matrix is its trafficking through the secretory pathway. The huge dimensions of collagen and other matrix proteins make them prone to aged-dependent aggregation and challenge our current models of how secretion works. In this regard, we are examining the highly specialized organization of the secretory pathway in neurons and their so-called “Golgi outposts”: Golgi fragments lacking the polarized organization typical of this organelle. Understanding outpost formation may shed light on the causes and consequences of Golgi fragmentation, notably increased in neurodegenerative diseases.

Relevant publications

Lei, Y., Huang, Y., Yang, K., Cao, X., Song, Y., Martín-Blanco, E. and Pastor-Pareja, J.C. (2023). **FGF signaling promotes spreading of fat body precursors necessary for adult adipogenesis in *Drosophila***. *PLoS Biology*, 21, e3002050 https://doi.org/10.1371/journal.pbio.3002050

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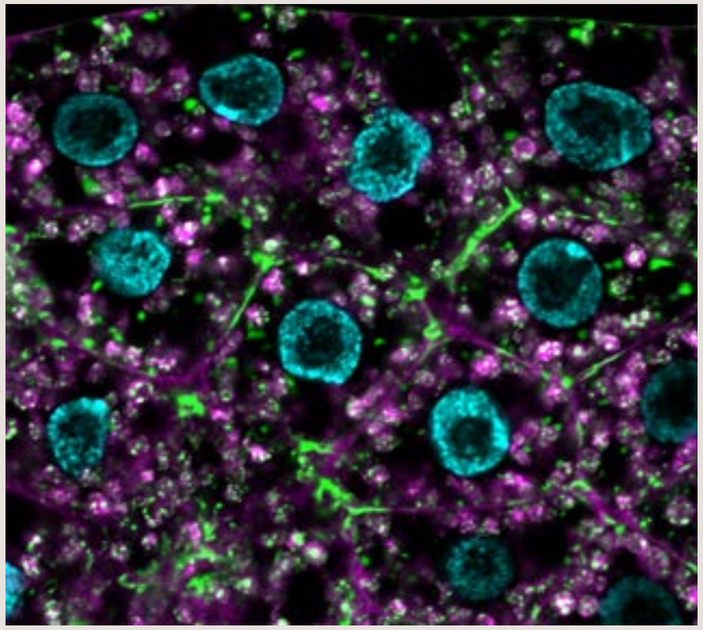
Department:

Developmental Neurobiology

Sp6_Genetic & epigenetic basis of Individuality & aging



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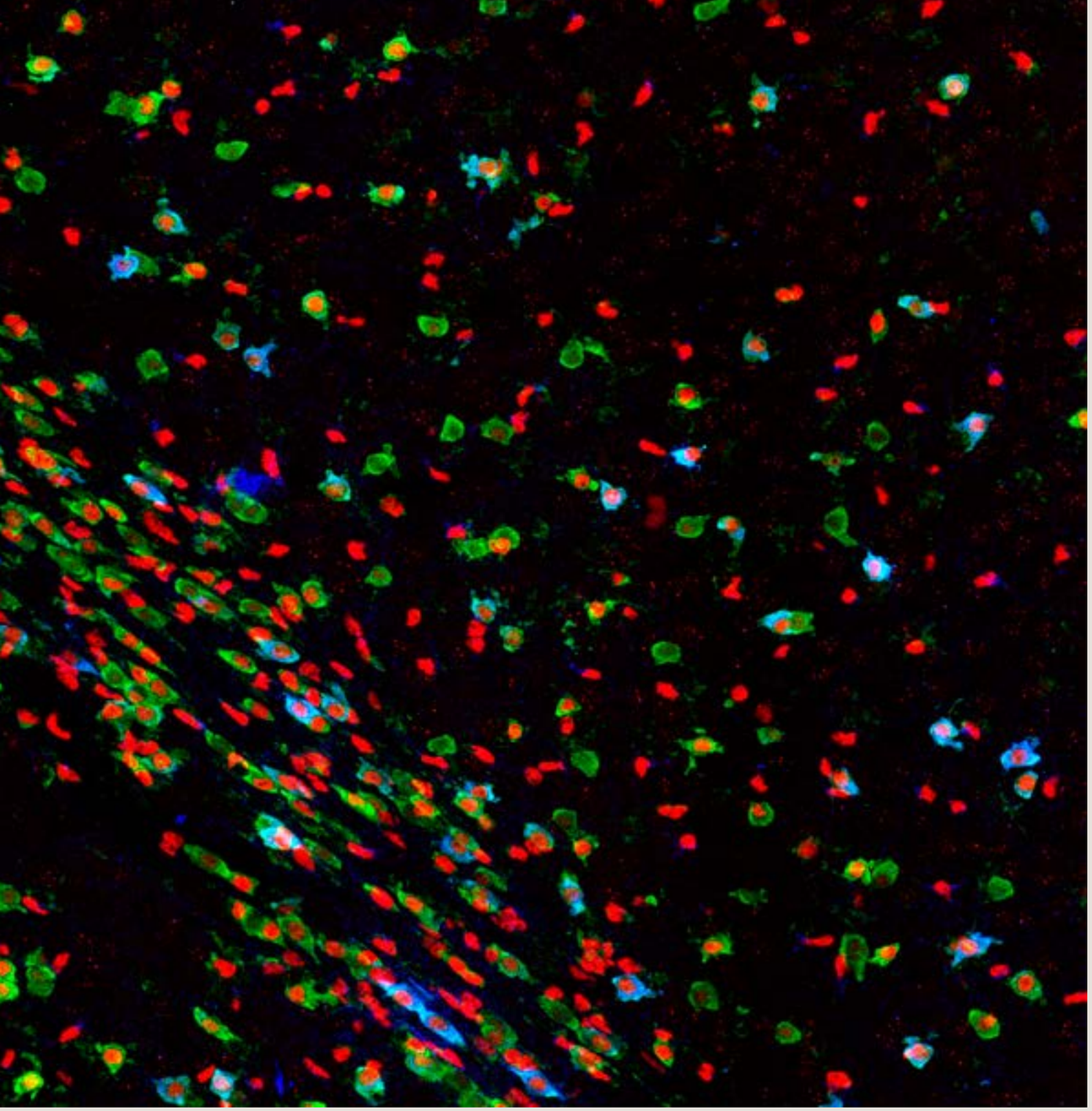


Development, refinement, and consolidation of neural circuits

Isabel Pérez Otaño

@IPO_lab

Brains generate cognition, thought, emotion, and adaptive behaviors through coordinated actions of circuits that are hard-wired during development with others that retain remarkable plasticity into adulthood. A fundamental question is how experiences shape these neural circuits so the individual learns and interacts adequately with their environment.

Much of the remodeling involves changes at synapses, the microscopic structures that connect neurons with each other into functional circuits. Synapse changes occur throughout life but are maximal during 'so-called' critical periods of postnatal development–when synapses have a high potential for plasticity and massive formation and elimination of synapses refines initially redundant circuitry. Yet this plasticity potential needs to be 'tamed' so the correct synaptic partners are specified to support precise learning and cognitive-guided behaviors. Understanding how this is achieved is one major goal of our lab.

A central theme stems from our discovery of a unique class of NMDA receptors, defined by the presence of non-conventional GluN3A subunits, that work as gate-keepers of experience-dependent plasticity and synaptic refinements (*Nature Reviews Neuroscience* 2016). Transient waves of GluN3A expression are typical of primary or sensory cortical areas and guide the hard-wiring of sensory circuits. By contrast, adult expression is retained into adulthood in less-differentiated association and trans-modal cortical areas, high-order thalamic nucleus, and regions engaged in emotional control (*Cerebral Cortex* 2021). Expression is most prominent in specific brain populations. In the last years, we have generated a collection of mouse genetic tools to map cellular populations, circuits, and behaviors that rely on GluN3A plasticity and understand roles in juvenile and adult plasticity and in the control of functional integration.

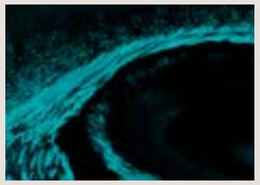
Other areas of investigation include:

1) Targeting circuit plasticity and cognition: Neurons rely on translational control to modify selected synapses and program circuits. We have discovered a novel signaling complex formed by the postsynaptic scaffold GIT1 and the mammalian target of rapamycin complex 1 (mTORC1) that nucleates protein synthesis at synapses and whose assembly is negatively regulated by GluN3A expression, imposing limits on memory capacity. Regulated interactions between GluN3A and GIT1 determine the capacity for storing persistent or remote memories, opening an entry point for modulating cognition (*eLife* 2021).

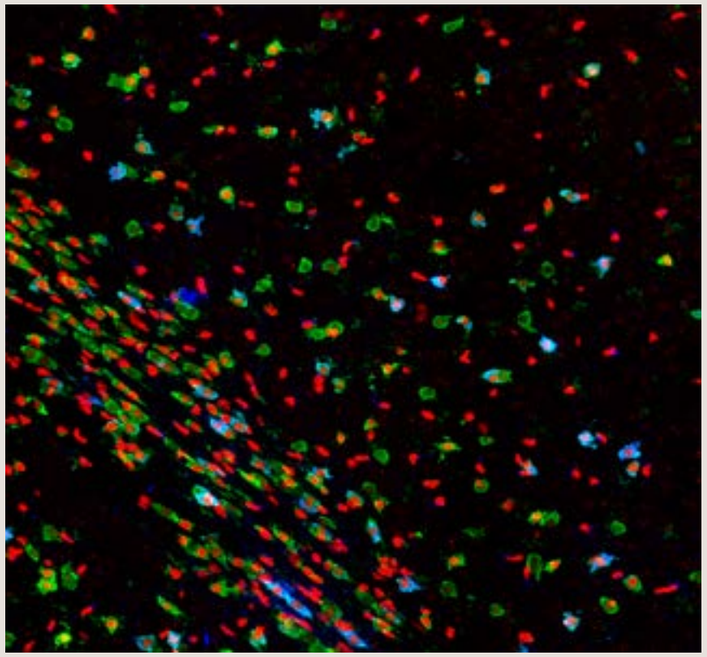
2) Identifying plasticity niches in non-neuronal cells, with a focus on the ability of GluN3A to control adaptive myelination and target functional restoration.

Department:

Cellular and Systems Neurobiology



Sp4_Synaptic modulation of neural circuits and behavior



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Master students
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Relevant publications

Verhaeghe, R., Elia-Zudaire, O., Escamilla, S., Saez-Valero, J. and Pérez-Otaño I. **No evidence for age-dependent cognitive decline or neurodegeneration in strain-matched Grin3a knockout mice**. *Alzheimer's & Dementia: the journal of the Alzheimer's disease association*, 10.1002/alz.13375 (2023).https://doi.org/10.1002/alz.13375

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Conde-Dusman, M.J., Dey, P.N., Elía-Zudaire, O., Rabaneda, L.G., García-Lira, C., Grand, T., Briz, V., Velasco, E.R., Andero, R., Niñerola, S., Barco, A., Paoletti, P., Wesseling, J.F., Gardoni, F., Tavalin, S.J. and Pérez-Otaño, I. (2021). **Control of protein synthesis and memory by GluN3A-NMDA receptors through inhibition of GIT1/mTORC1 assembly**. *eLife*. 10, e71575. https://doi.org/10.7554/eLife.71575

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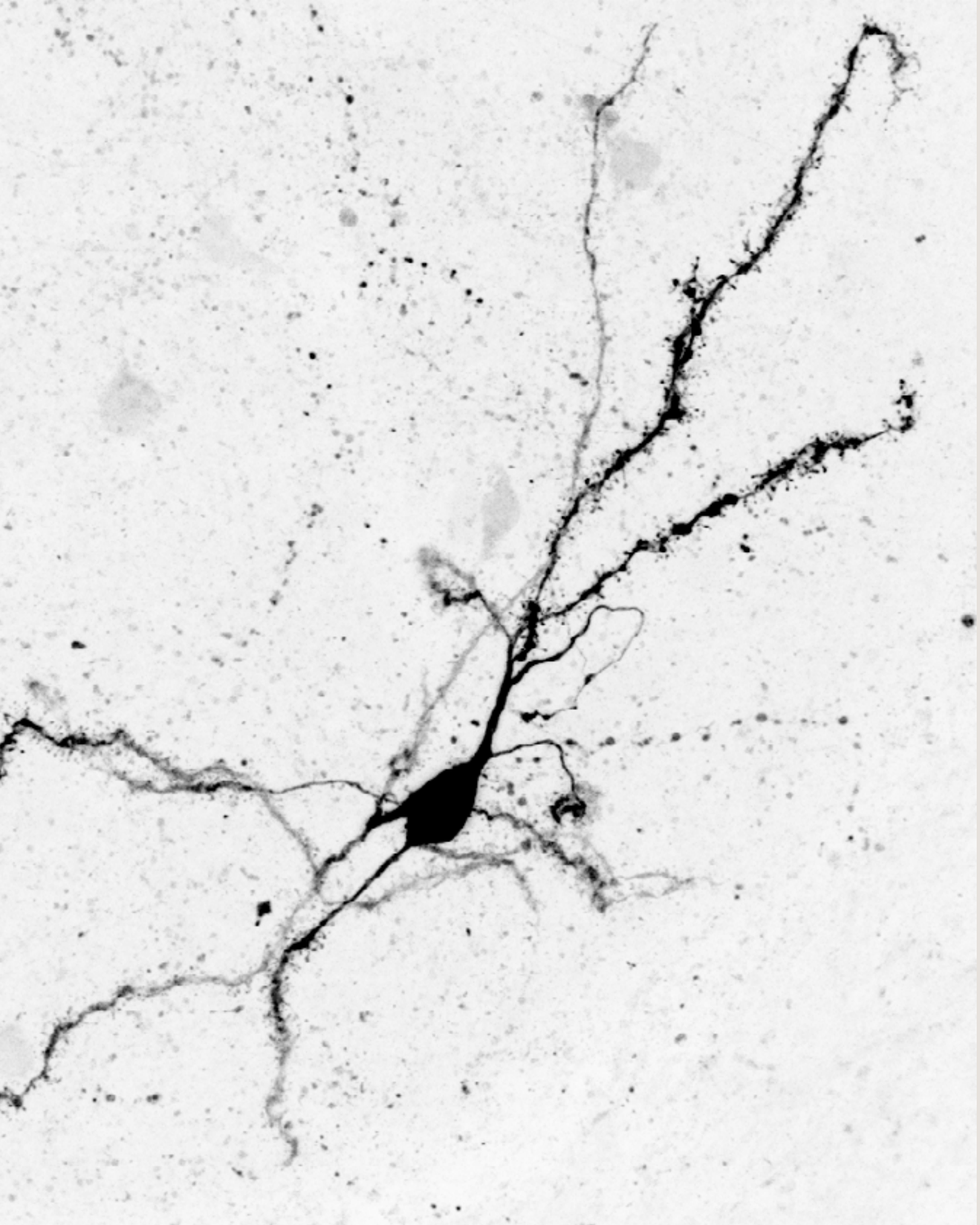

Sensory-motor processing by subcortical areas

Ramón Reig

The basal ganglia (BG) are involved in a wide range of functions such as decision-making, reward motor learning, selection motor sequences, as well as cognitive and emotional functions, most of them require the integration of sensory information. Problems in the basal ganglia function can generate numerous and diverse neurological disorders as Parkinson's and Huntington's diseases, Tourette syndrome, obsessive-compulsive disorder (OCD), dystonia, attention-deficit hyperactivity disorder (ADHD), and different types of addictions.

The basal ganglia are composed of several subcortical nuclei (striatum, globus pallidus, substantia nigra, and subthalamic nucleus) interconnected with the cerebral cortex, thalamus, and other brain areas. The striatum (caudate nucleus & putamen) is the "door" or input layer of the basal ganglia that receives inputs from multiple cortical areas such as prefrontal, motor or sensory, and thalamus. The striatum also receives massive dopaminergic innervation from the substantia nigra pars compacta.

The striatum is best known for its role in planning and selecting motor sequences. However, the selection of proper motor sequences also requires the prioritizing of sensory information. Sensory information from different modalities such as tactile, visual, auditory, and olfactory converges in the striatum. All of these simultaneous inputs have to be processed, filtered, and integrated in order to select the appropriate ones. How striatal neurons process the information is largely unknown.

We aim to study the role of the striatum in sensory processing and its interplay with motor functions. At the same time, we aim to understand different neurological diseases or disorders such as Parkinson's or ADHD, related to the striatal function. To answer this question we use complementary electrophysiological, behavioral, optical, and anatomical methods.

Relevant publications

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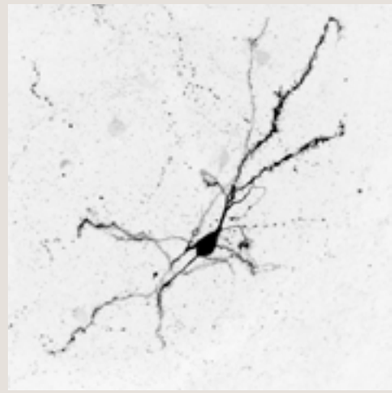

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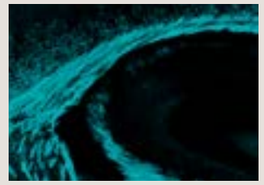
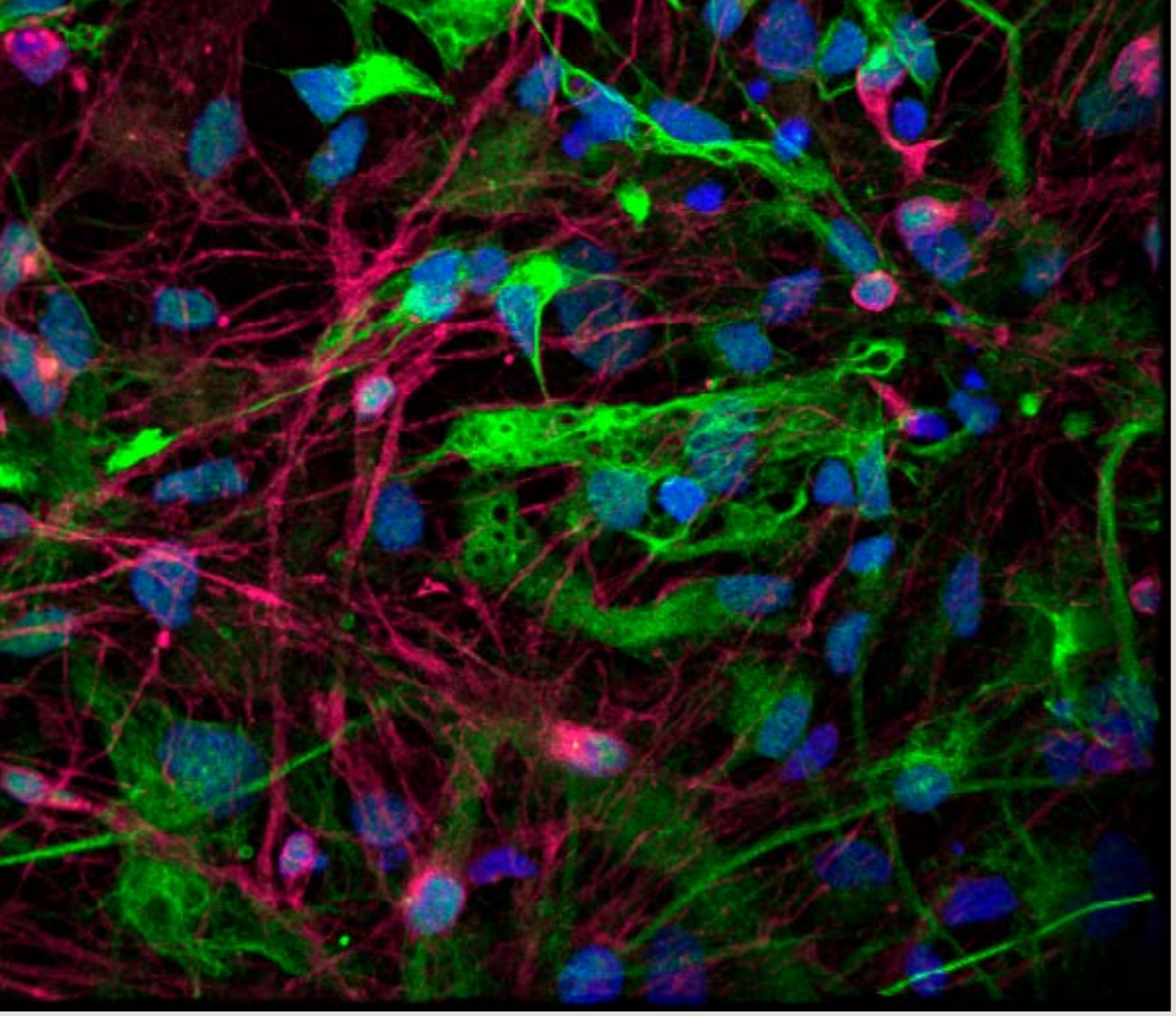
Sp3_ Building & adapting circuits into functional networks



Sp4_Synaptic modulation of neural circuits and behavior



Altered molecular mechanism in Alzheimer's disease and dementia

Javier Sáez Valero / Salud García Ayllón

Our research line is focused on molecular mechanisms in Alzheimer's disease (AD), defining a potential diagnostic use and implication in therapy. We also study human proteins related to the COVID-19.

Our group is part of CIBERNED (Center for Networked Biomedical Research in Neurodegenerative Diseases) with members from the Institute of Health and Biomedical Research ISABIAL and FISABIO. Our expertise comprises:

- Biochemical characterization of post-translational modifications of proteins in brain / cerebrospinal fluid (CSF) / plasma and other fluids; including glycosylation and phosphorylation, characterization of proteolytic fragments and aggregates, and localization in extracellular vesicles.
- Characterization of ligand-receptor interactions associated with signaling pathways.
- Evaluation of therapeutic inhibition of key enzymes such as cholinesterases and secretases.
- Validation of our findings in human cellular models, including human pluripotent stem cells (iPSc).

Among the recent studies, there are:

We have shown that glycosylation of acetylcholinesterase, the main therapeutic target of AD treatments, is altered in the brains of Alzheimer's patients. This altered glycosylation seems to compromise the functionality of the enzyme. We have reported that presenilin1, an enzyme involved in the production of β-amyloid peptide, influences acetylcholinesterase glycosylation and may determine the localization of functional acetylcholinesterase in the membrane.

We have also shown that in COVID-19 patients the plasma levels of GFAP proteins, markers of astrocyte damage, NfL and T-tau, markers of neuronal degeneration, were increased in the acute phase of the pathology, indicating vulnerability in the nervous system. These levels were altered in subjects with and without neurological affectation, with a higher increase in the latter, and returned to normal values with the patient's recovery.

In collaboration with clinical groups, we also report i) that altered levels of α-synuclein protein in CSF could be a potential diagnostic marker of psychotic syndrome in the prodromal phase of AD; ii) that levels of ADAM10, an α-secretase enzyme, which are lower in the CSF of AD patients, are not altered in patients with mutations that determine the early onset of the disease.

Finally, we collaborated with Isabel Pérez Otaño's group in describing the NMDA receptor subunit, GluN3A, in the brain of AD subjects.

Relevant publications

Cortés-Gómez, M.Á., Barberá, V.M., Alom, J., Sáez-Valero, J. and García-Ayllón, M.S. (2023). **Presenilin 1 Modulates Acetylcholinesterase Trafficking and Maturation.** *International Journal of Molecular Science,* 24(2):1437. https://doi.org/10.3390/ijms24021437

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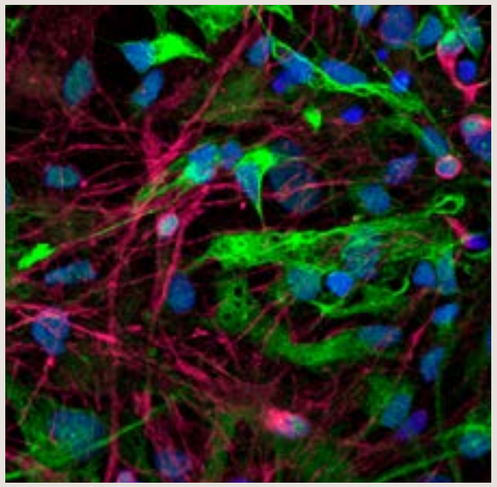

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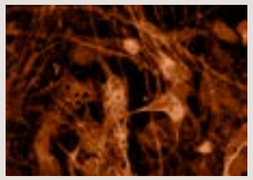
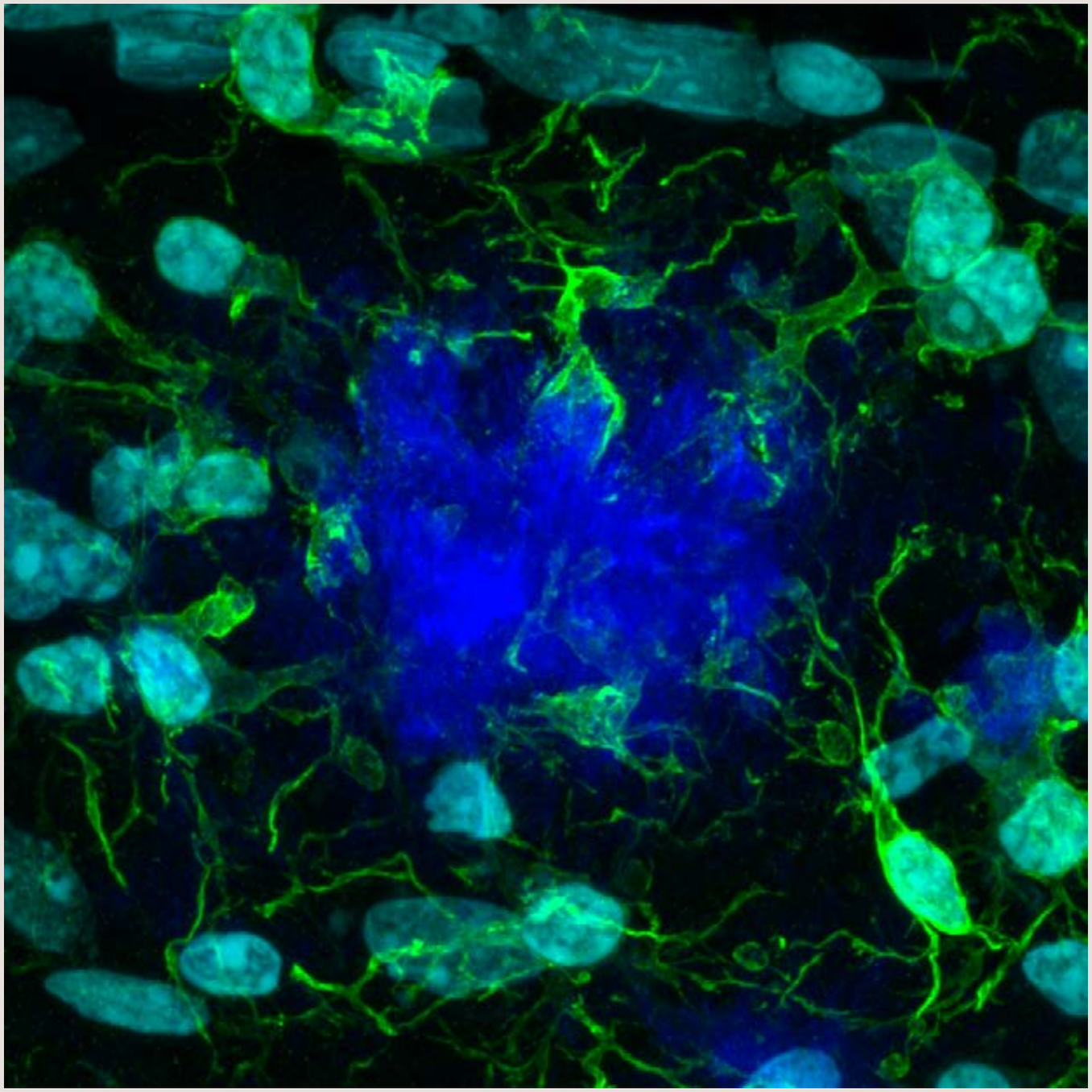


Sp8_ Translational research of neurological and psychiatric disorders



Functional Epi-Genomics of Aging and Alzheimer's Disease

José Vicente Sánchez Mut

Our laboratory investigates the molecular underpinnings of age-related cognitive decline and neurodegeneration, with a particular interest in Alzheimer's disease (AD). We hypothesize that genetics, epigenetics, and the interaction of both ('neural-epi-genetics') have long-lasting effects on brain function.

To tackle this hypothesis, we use mouse models and human samples and combine molecular and behavioral neuroscience with state-of-the-art single-cell, next generation sequencing (NGS), bioinformatic tools, and epi-genetic editing.

Our ultimate goal is to better understand age-related brain malfunctioning and to identify new biomarkers and targets to further develop current dementia-related therapies.

Relevant publications

Burns, A.M., Farinelli-Scharly, M., Hugues-Ascery, S., Sanchez-Mut, J.V., Santoni, G. and Gräff, J. (2022). **The HDAC inhibitor CI-994 acts as a molecular memory aid by facilitating synaptic and intracellular communication after learning**. *PNAS. Proceedings of the National Academy of Sciences*, 119(22), e211679711. https://doi.org/10.1073/pnas.2116797119

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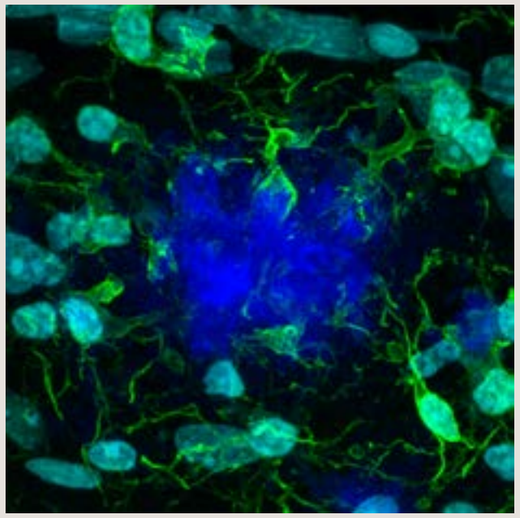

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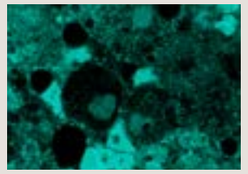
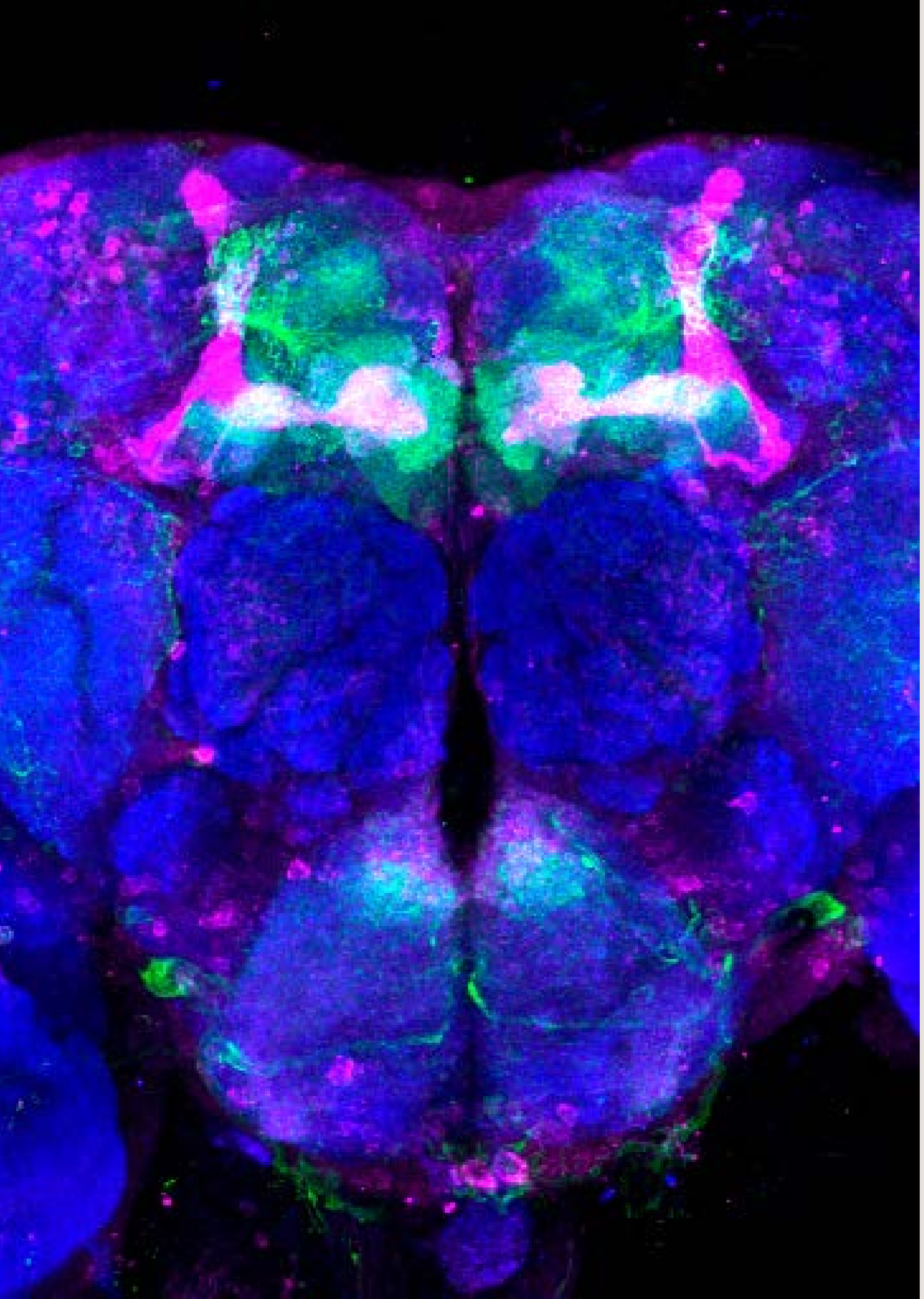


Sp1_ Neural stem cell regulation and differentiation

Sp6_Genetic & epigenetic basis of Individuality & aging



Neurogenetic basis of behavior

Juan A. Sánchez Alcañiz

Animal survival depends on the proper interpretation of environmental information. Through evolution, animals have developed an exquisite array of sensory organs that can collect large amounts of different environmental cues. This information is sent to the central brain where it is processed and integrated with previous experiences and internal states to produce the proper behavior. In order to understand how his information is processed and integrated we must understand both the neural circuitry involved in such processing and the genes responsible for the neuronal functioning.

Our group focuses its research on the study of feeding as a proxy to understand how sensory information is collected and integrated and the genetic and neural network underlying its processing. We use the gustatory system of *Drosophila melanogaster* as a model, as gustatory cues produce clear and opposing behaviors that can be analyzed in great detail. In addition, *Drosophila melanogaster* is a great biological system where we study those processes due to its image accessibility and manipulation of neural circuits, modification genetically, and ease of studying its behavioral output. We combine immunohistochemistry, confocal microscopy, molecular biology, and state-of-the-art high-throughput behavioral analysis and bioinformatics to decipher the neural circuitry underlying feeding behavior.

Relevant publications

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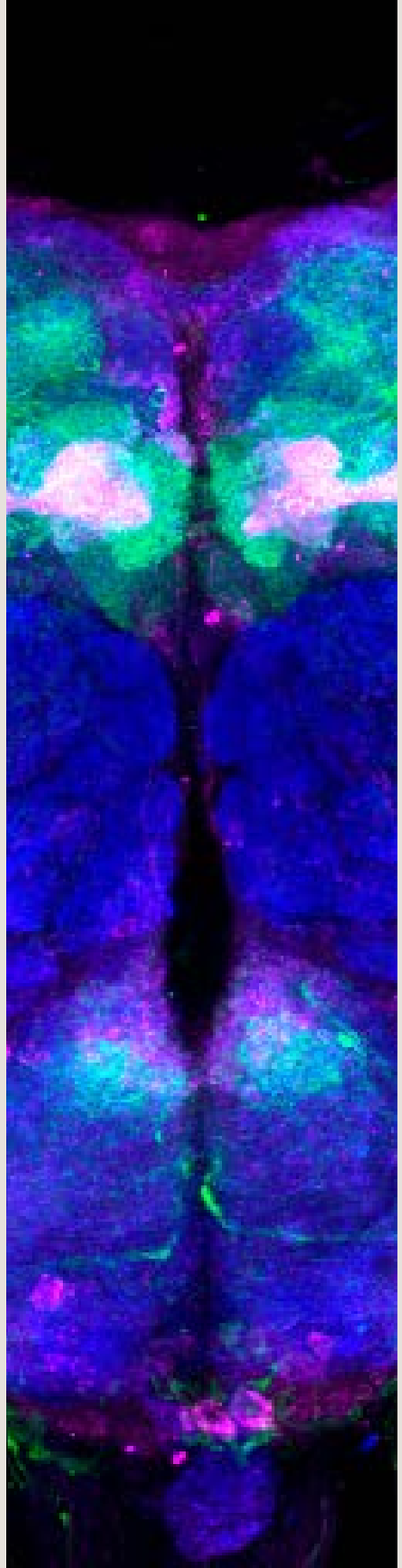

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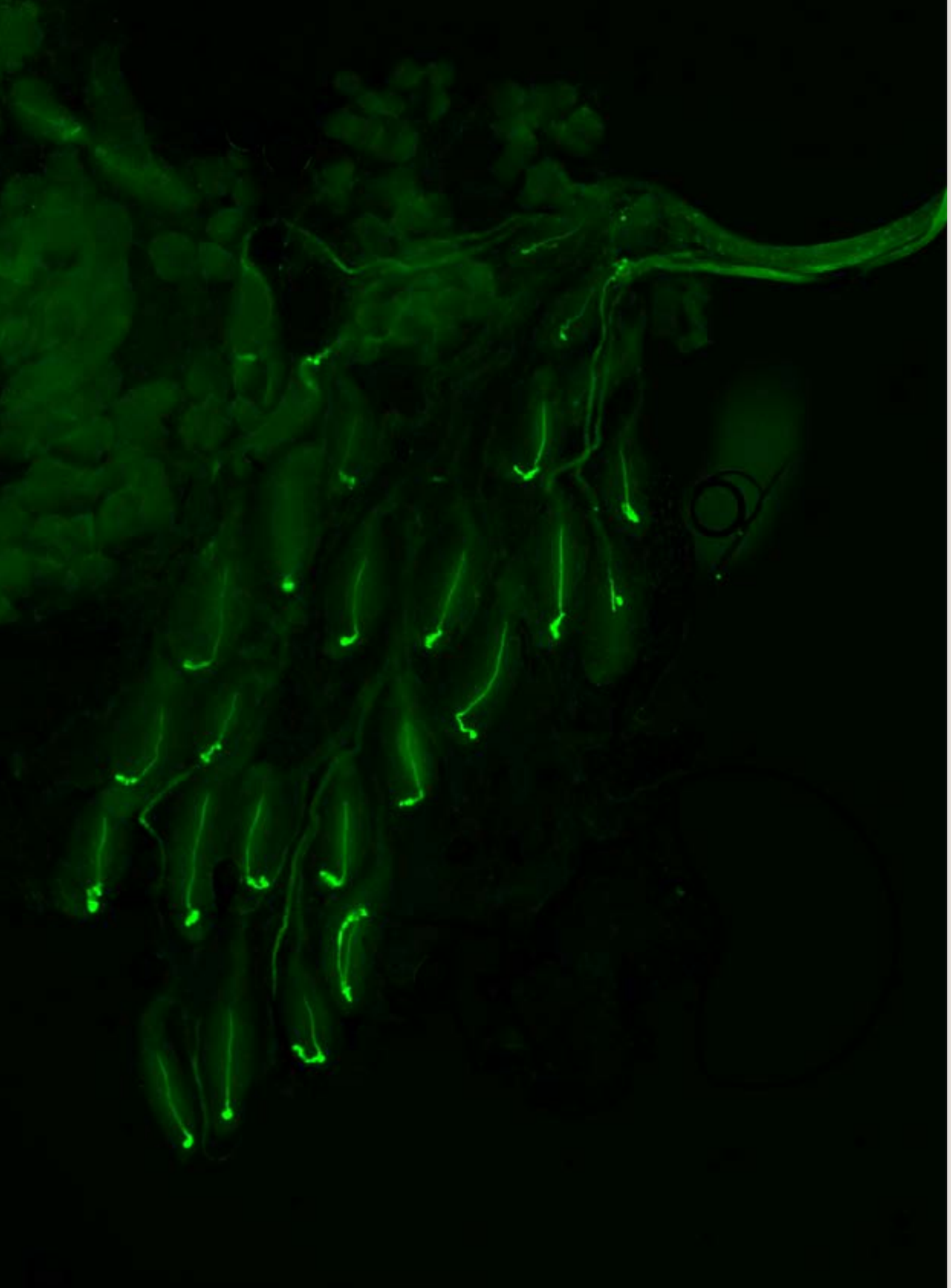
Sp6_Bases genéticas y epigenéticas de la individualidad y el envejecimiento



Wiring and Function of Somatosensory Circuits

Francisco J. Taberner Sanchis

Specialized subsets of primary sensory neurons innervating different body tissues detect and transduce different environmental cues into an itch, touch, temperature, or pain information. When these signals eventually reach the brain, they generate the sensory percept and evoke convenient physiological and behavioral responses for the survival of the animal. On its way to the brain, this sensory information undergoes an initial processing in the spinal cord. In healthy individuals, local excitatory and inhibitory spinal cord interneurons form modality-specific processing microcircuits.

These circuits dynamically tune down or amplify the sensory signals in response to other sensory modalities or brain descending signals. However, in certain pathologies like nerve injury or in different inflammatory conditions, the normal processing at the spinal cord is altered and unconventional maladaptive circuits are wired up, resulting in chronic pain and itch. Due to the intrinsic complexity of the spinal cord circuitry, and the lack of an appropriate tool set for capturing and interrogating the spinal cord neuronal ensembles in behaving animals, our knowledge of the cellular and molecular substrates that constitute the sensory microcircuits and facilitate maladaptive changes are still largely unknown.

The overarching goal of the group is to define the spinal circuits associated with pain signals, to better understand processing alterations associated with chronicity, age, and gender. In addition, we are trying to understand how different sensory modalities influence each other, as in the case of cold alleviating pain or itch, with the final aim of exploring and developing therapeutic strategies to improve the quality of life in patients suffering from chronic itch and pain.

To achieve this objective, we seek to characterize the molecular identity and intrinsic electrophysiological properties of the interneurons that constitute these sensory microcircuits, as well as define the changes they undergo in pathological states. We combine the development of minimally-invasive circuit marking and manipulation technologies with other state-of-the-art techniques, including different viral tracing approaches, optogenetics, whole spinal cord imaging, and single-nucleus sequencing with well-established electrophysiological techniques.

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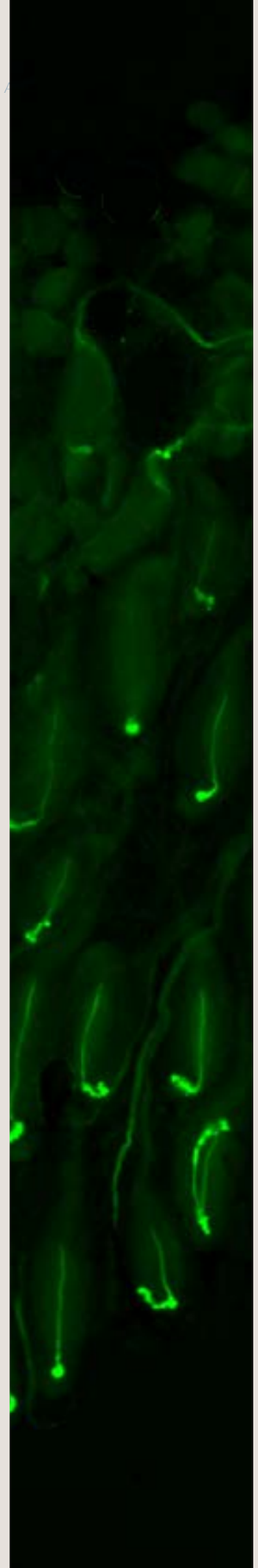

Relevant publications

Nees, T.A., Wang, N., Adamek, P., Zeitzschel, N., Verkest, C., La Porta, C., Schaefer, I., Virnich, J., Balkaya, S., Prato, V., Morelli, C., Begay, V., Lee, Y.J., Tappe-Theodor, A., Lewin, G.R., Heppenstall, P.A., Taberner, F.J. and Lechner, S.G. (2023). **Role of TMEM100 in mechanically insensitive nociceptor un-silencing**. *Nature Communications*,14(1):1899. https://doi.org/10.1038/s41467-023-37602-w

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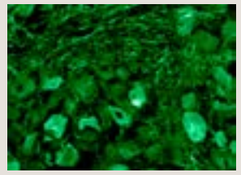

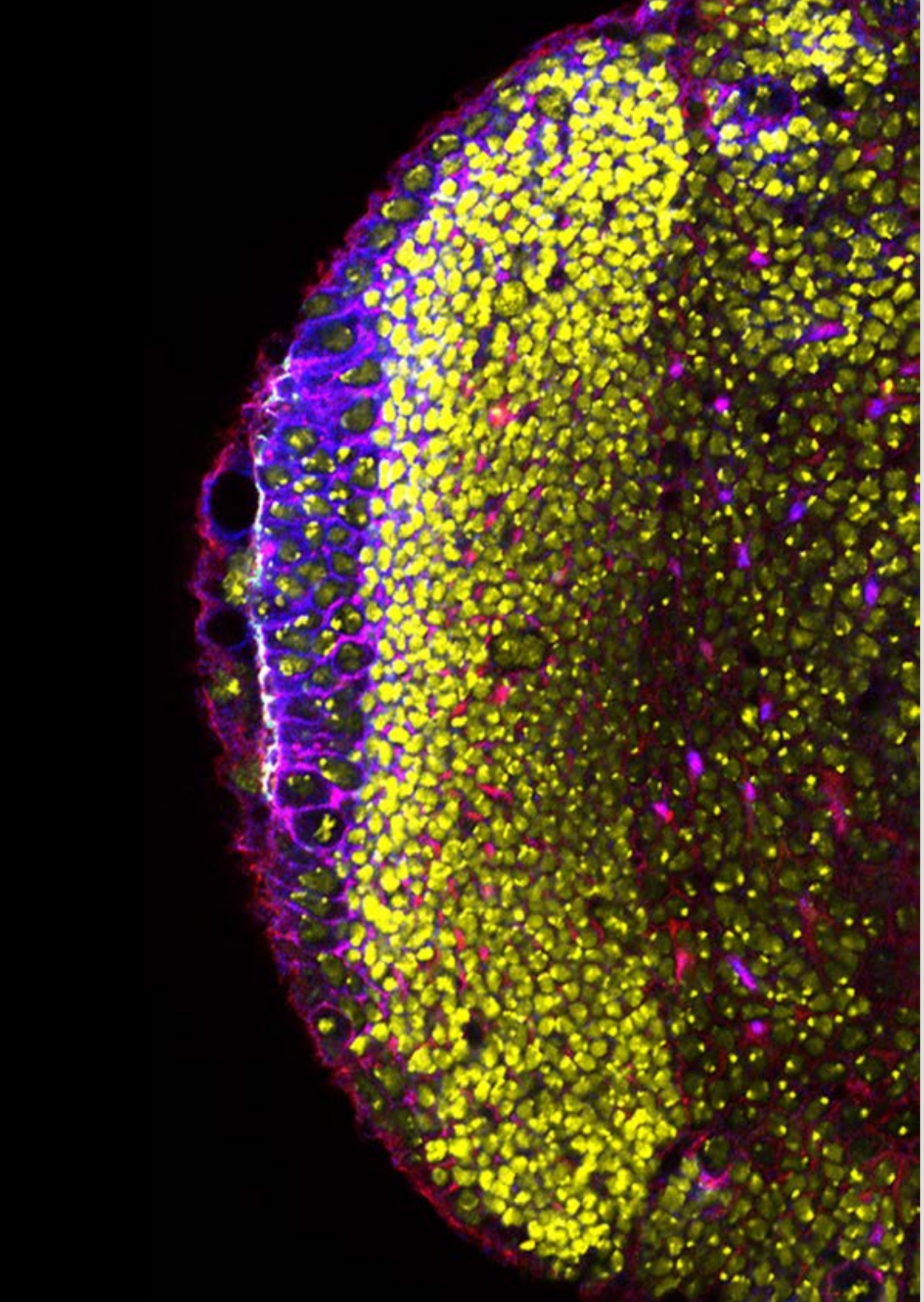

Molecular neurogenetics

Francisco J. Tejedor

One of the most important issues in Developmental Neurobiology is to elucidate how the large number and rich cellular diversity of the brain is generated in such a precise spatio-temporal manner. Our work focuses on the regulation of neural progenitor cell proliferation and neurogenesis. We are particularly interested in the regulation of the balance between neural proliferation and neuronal differentiation during the development of the nervous system since this is essential for its proper growth, structure, and function. Our goal is to identify genes and unravel molecular mechanisms underlying these cellular processes. At this end, we are using the proliferation centers of the larval optic lobe (OL) of *Drosophila melanogaster* as an experimental model system. At the same time, we are interested in how genetic alterations of these genes may contribute to developmental neuropathologies.

Following this approach, we identified the gene minibrain (mnb, also called Dyrk1A in vertebrates) as a major regulator of neural progenitor cell proliferation and neurogenesis in *Drosophila* melanogaster. Mnb/Dyrk1A encodes a very well evolutionary conserved protein-kinase, which plays several functions through brain development. We are focusing on its roles in the regulation of neural proliferation, cell cycle, neurogenesis, and neuronal differentiation, unraveling the underlying molecular mechanisms. Remarkably, haploinsufficiency of DYRK1A causes an intellectual disability syndrome characterized by microcephaly. Mnb/Dyrk1A has also raised great interest because it is one of the most interesting candidate genes for the neuropathologies of Down Syndrome (DS).

As a matter of fact, the MNB/DYRK1A kinase is presently considered a suitable drug target for the therapy of DS neuropathologies. We are using experimental models to determine what cellular functions and molecular mechanisms are altered by an excess and a loss of Mnb/Dyrk1 function to generate neurobiological alterations reminiscent of DS and

microcephaly neuropathologies. We are also testing the suitability of MNB/DYRK1A kinase inhibitors to interfere with neuronal functions as a prospect to apply pharmacological therapeutic approaches to DS neuropathologies.

Finally, we are studying the integration of Mnb/Dyrk1A, proneural genes, and Notch signaling pathways in the regulation of the neuroepithelial-neuroblast transition at the larval OL.

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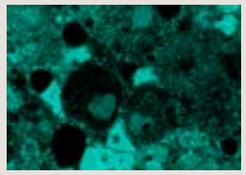
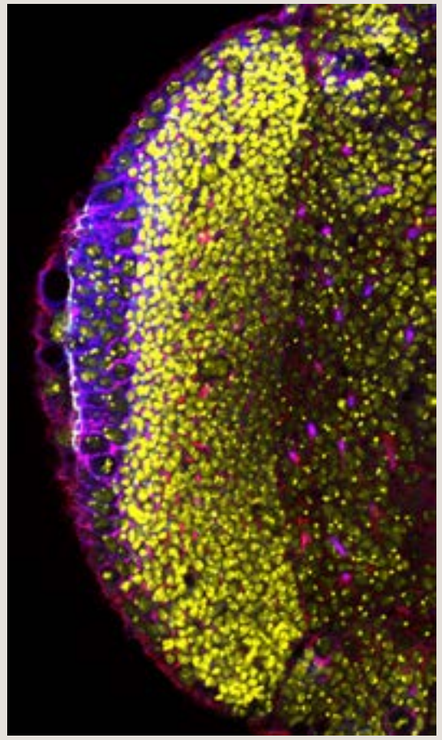
Developmental Neurobiology



Sp1_ Neural stem cell regulation and differentiation



Publicaciones destacadas

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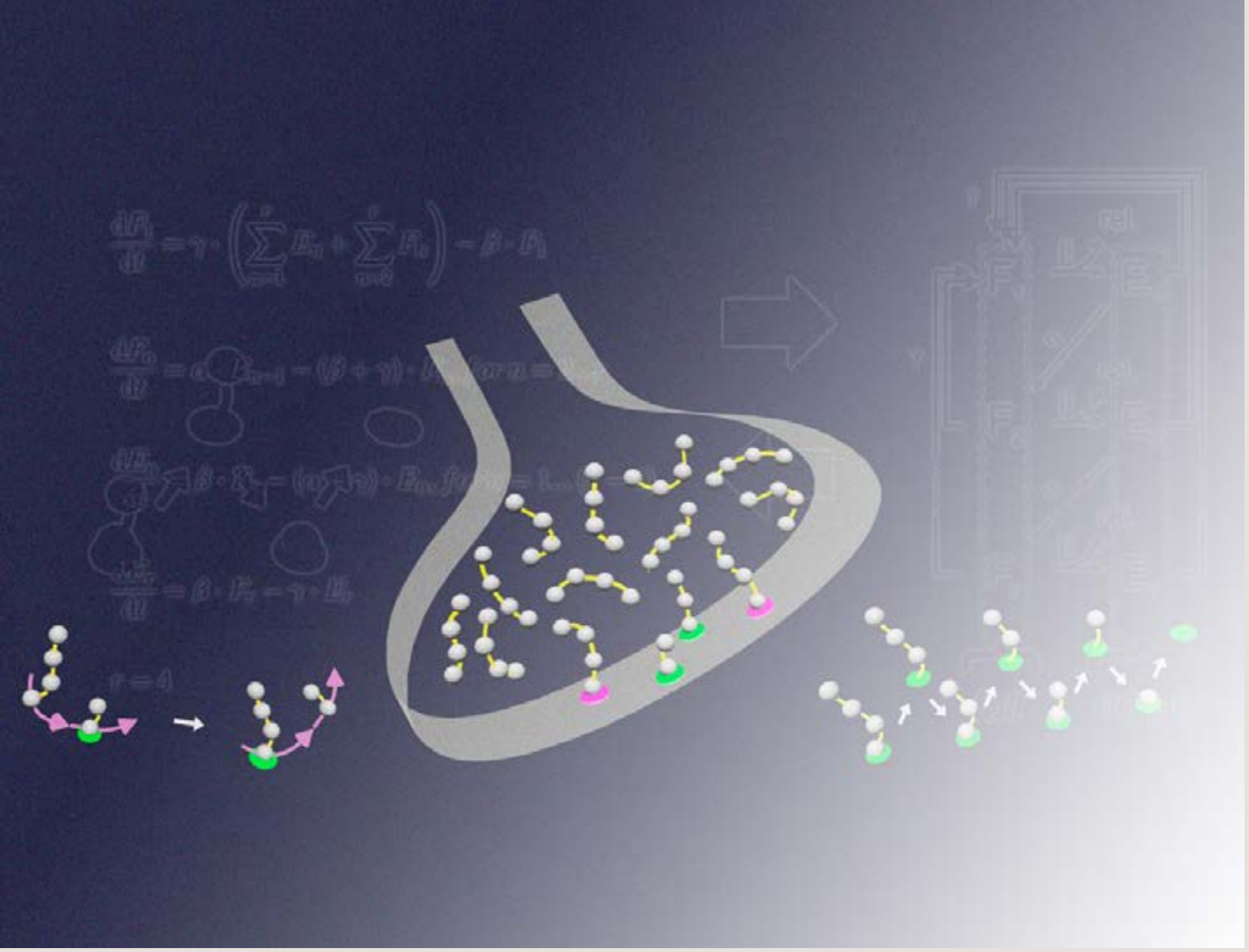
Principal Investigator
Francisco J. Tejedor
PhD Investigator
Francisco Gutierrez Aviño



Molecular and cellular physiology of synaptic transmission

John Wesseling

We are developing and testing a new framework for understanding the dynamic changes in connection strength that occur at essentially every type of chemical synapse during normal use on time scales from milliseconds to minutes. The dynamic changes are known as short-term plasticity and have a presynaptic origin. Parameters such as directionality, timing, and range all vary greatly between individual synapses, suggesting that the underlying mechanisms can be modulated over development and/or as a result of learning. We believe that the new framework is needed for understanding how information is encoded, processed, stored, and decoded in neural circuits, and may also help elucidate what goes wrong in some diseases.

We began by developing assays for each of the rate-limiting steps in synaptic vesicle trafficking at a variety of central synapses using electrophysiological and optical imaging techniques. The assays allowed us to ask how the underlying mechanisms interact with each other. The framework that emerged is mathematically simpler than predicted, but in a way that requires reevaluating conventional views about the underlying cell biology.

Specifically, the conventional view has been that recycling vesicles accumulate in so-called pools that can be recruited for release sequentially during heavy use. The new framework suggests that the various pools are instead arranged in parallel and each serves as an autonomous supply that feeds a single site in the plasma membrane where transmitter release occurs via exocytosis; individual presynaptic terminals typically have around 10 release sites. Follow-up cell biology experiments have now confirmed that individual synaptic terminals do indeed contain multiple reserve pools that are processed in parallel. Intriguingly, it seems that the efficiency of the release machinery can be tuned separately for each release site, endowing each with the capacity to function as a computationally simple frequency filter tuned to transmit the information encoded within a preferred band of spike frequencies.

Relevant publications

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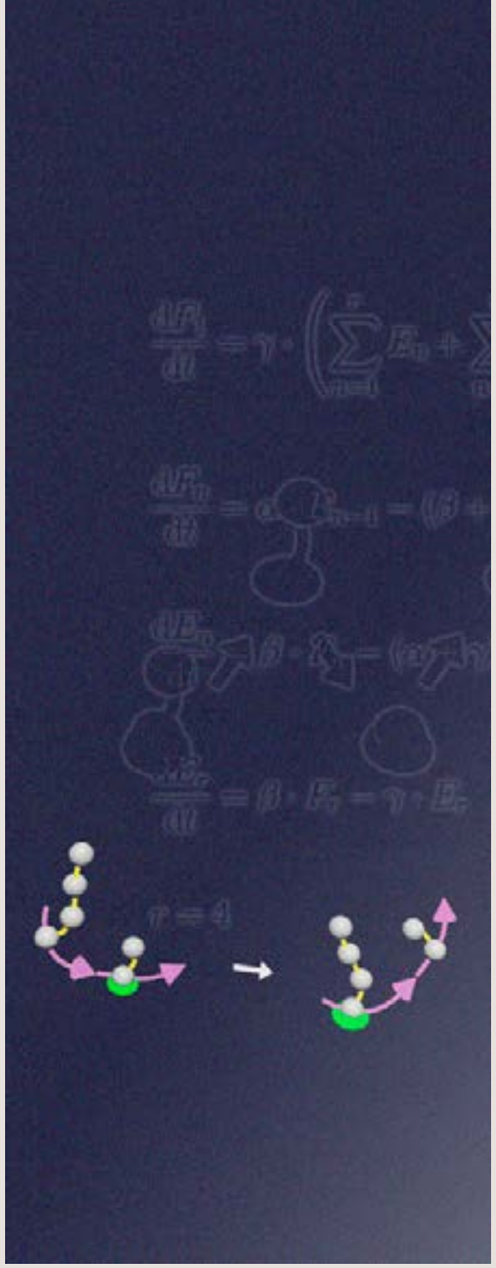
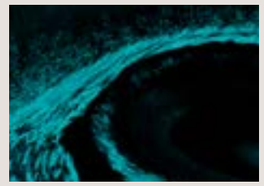


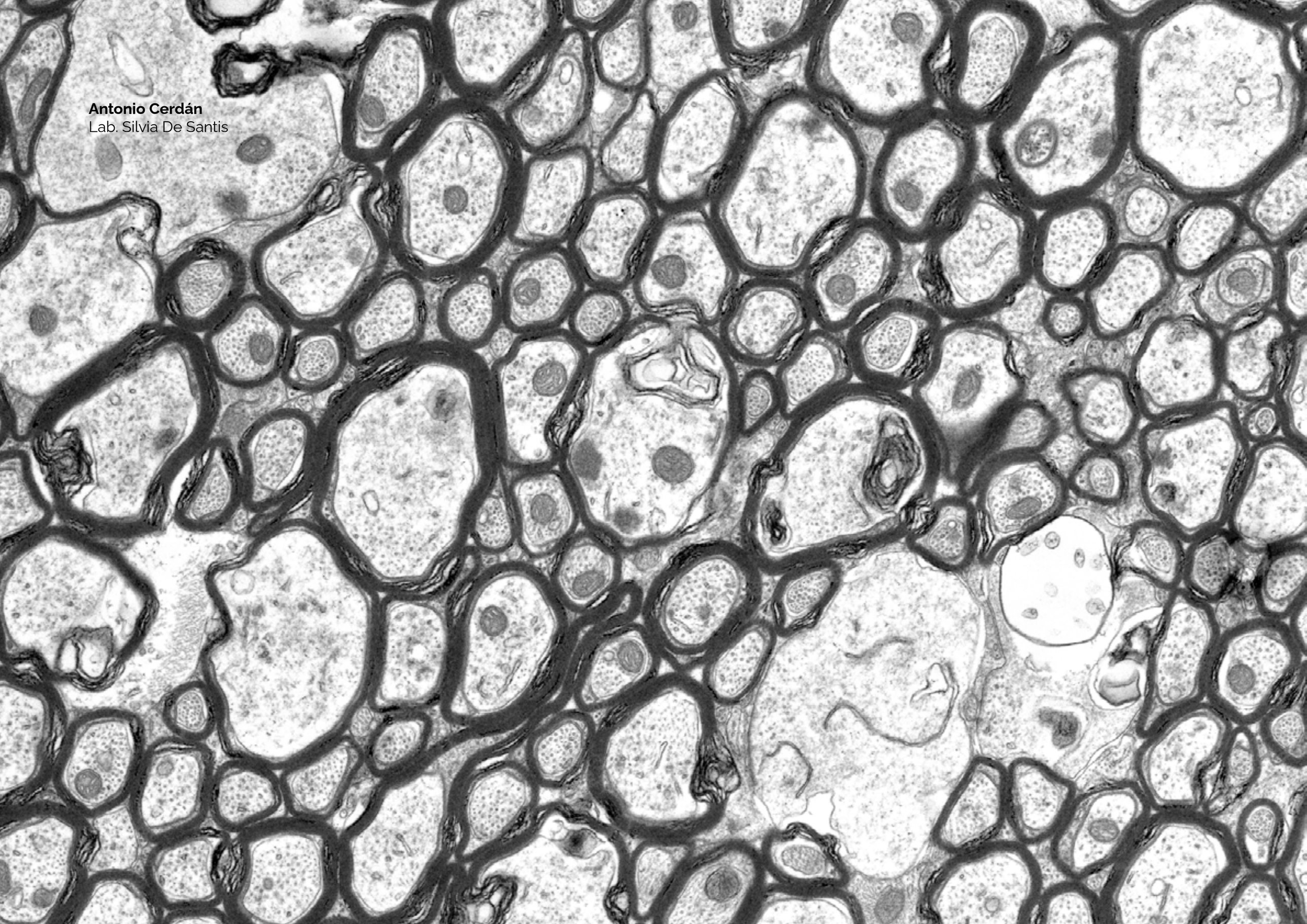
Principal Investigator
John F. Wesseling
PhD Student
Sergio Del Olmo Cabrera
Juan José Rodríguez Gotor
Doris Santiago
Technical Staff
Diana Baeza Soler

Department:

Cellular and Systems Neurobiology



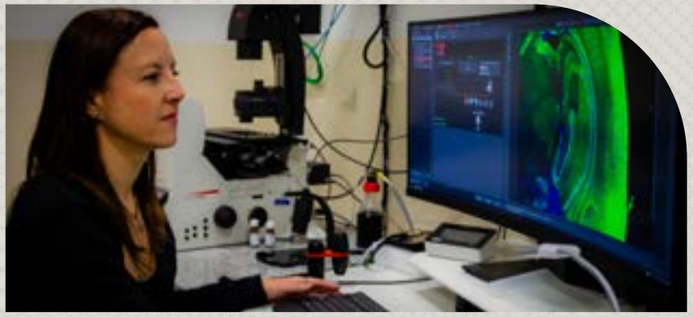
Sp4_Synaptic modulation of neural circuits and behavior



Antonio Cerdán
Lab. Silvia De Santis

Servicies and Facilities

Microscopy



The Institute for Neurosciences (IN) Microscopy facility is a microscopy and image analysis platform that provides services and training to both the IN and external users.

This commonly used service is equipped with state-of-the-art equipment that allows for a wide variety of techniques such as confocal, multiphoton, light sheet microscopy (in vivo and clarified), or super-resolution microscopy (Airyscan, SR-SIM, PALMA / dSTORM). Images and videos from still samples, live tissues, cell cultures, sections, or intact animals can be acquired.

The facility also features high-performance workstations and software packages for image processing and analysis.

Technician staff
Giovanna Expósito Romero
Almudena Iñigo Portugués

Scientific Responsible
Eloisa Herrera

Molecular Imaging

The Functional Magnetic Resonance Unit provides state-of-the-art Magnetic Resonance (MRI) equipment and scientific advice on MRI to public and private research institutions.

This facility was created in 2011 as a central service at the Institute for Neurosciences CSIC-UMH. The service has a fully equipped Bruker BioSpec 7Tesla (30 cm internal diameter) equipment to perform *in vivo* and *ex vivo* MR imaging and spectroscopy. The service is equipped with various volume and surface coils for rodent brain and whole body imaging.

The unit provides the instrumentation necessary to anesthetize animals using inhalation or injectable anesthesia. In addition, it has equipment for non-invasive and fully MRI-compatible physiological monitoring during image acquisition, including monitoring of body temperature, blood pressure, heart and respiratory rate, and oxygen saturation. There is a 4-channel electrical stimulation device, as well as optical fibers and LED light sources, for electrical or optogenetic brain stimulation experiments, respectively, combined with functional mapping with fMRI. Additional equipment to perform surgeries and artificial ventilation can be provided upon request.

Technician staff
Luis Tuset Sanchís

Scientific Responsible
Santiago Canals

Animal Housing

SPF *Animal House*

The Genetically Modified Mice Unit is one of the 3 animal facilities of the UMH Animal Experimentation Service. This is a specific pathogen-free facility with a capacity for around 15,000 mice. The IN has full control of this facility and established a service for in-house cryopreservation of gametes and embryos, mouse genotyping, and generation of transgenic mice.

Zebrafish Facility

The Zebrafish Facility has two different locations and is able to grow and maintain zebrafish under controlled conditions. The facility´s two installations have room for 150 tanks for adults and 100 for breeding purposes. Transgenic and wild-type lines are maintained and embryos can be produced from them for development and genetic studies.s.

Drosophila Unit

The IN *Drosophila* Unit has specialized staff and equipment to provide full support to genetic research and experimentation with the model organism *Drosophila melanogaster* (common fruit fly). Our staff prepares fruit fly culture medium (fly food) and supplies it in vials to the six laboratories currently using *Drosophila* at the IN. In addition, this unit stores more than 10,000 wild, mutant, and transgenic strains in two accessible climate chambers (18ºC) with controlled temperature and humidity for optimal and pathogen-free growth of the different fly lines and offers space to store experimental crosses (25ºC) in two large incubators.

Animal Research

Platform to study rodent behavior

The SPF animal house also houses an area for the study of mouse behavior. Specifically, 8 fully equipped rooms allow everything from the basic behavioral characterization of mutant lines and wild types to the evaluation of specific aspects of social behavior, anxiety and depression, sleep, learning and memory, and simple or complex motor skills. To this end, the platform for the study of behavior (PEC) makes numerous labyrinths available to IN researchers, including a "Morris" water maze; boxes to study operant conditioning, both fear conditioning and the startle reflex; 24-hour monitoring equipment and the Erasmus ladder, among others.

Veterinary
Gonzalo Moreno del Val

Biologist specialized in animal welfare
Patricia Muñoz Robledano

Veterinary Staff
Antonio Murcia Belmonte

Behavior study platform
Ariadna Díaz Tahoces

Zebrafish Facility

Technician
Teresa María Gómez Martínez

Drosophila

Technician
Irene Beatriz Oliveira Avalos
Sergio Ucendo Navarro

Estabulación
Mª Carmen Checa Lara
Jénifer Gómez Gabaldón
Verónica Jiménez Villar
Ana Lorena Marín Sánchez
Erika Moyano Soler
Mª Carmen Navarro García
Rebeca Ortiz Méndez
Sandra Gonzalez Mosteiro
Lucía Yuste Jimenez
Marta Blanco Berrocal
Begoña Moreno Arias
Amaya Velasco Herrero
Julia Rodríguez Esteban
Adrian Pascual Úbeda
Yomar Valderrama Cabrera
Raúl Pardo Mérida
Mª Ángeles Soler Ripoll
Darío Carratalá Sánchez

Omics and gene analysis

The Omics and Genetic Analysis Service of the Institute for Neurosciences (IN) is a genomic and transcriptomic analysis platform that provides services and training to both IN staff and external users. This central facility includes a suite of state-of-the-art equipment that enables a wide variety of techniques to be performed including spatial transcriptomics, single cell level genomics, cell isolation and sorting (FACS), QPCR, DNA and RNA quality control, construction of libraries, DNA sonication, bioinformatics platform for data analysis and storage. Genomic and transcriptomic problems of fixed cells, disaggregated living tissues, cultures, and cellular organelles can be analyzed.

The service also features high-performance workstations and software packages for data analysis

Technician staff
Antonio Javier Caler Escribano
José Mulet Soler

Scientific Responsible
Jose P. López-Atalaya

Cell Culture & Sterilization

The Cell Culture Unit is a service provided by the Institute for Neurosciences that offers researchers the optimal environment for maintaining viable and healthy cell cultures. This unit consists of three distinct, spatially separated areas designed to support different types of cell cultures: Cell Lines, Primary Cultures, and Organotypic Cultures.

Each facility is well-equipped with class I and/or class II laminar flow cabinets, incubators, inverted phase-contrast and fluorescence microscopes, and all the necessary materials for performing specialized cell culture techniques. Biosafety level 2 areas are also included for working with high-risk materials, such as human samples and viruses. Additionally, the unit features a next-generation system for the quantitative, real-time analysis of live cells.

Technician Responsible

Sonia Vega de los Reyes

Technician staff

Sara Carratalá Gosálbez
Mar Francés Pérez
Trinidad Gil García
Trinidad Guillén Carrillo

Neurotropic Vectors

The Neurotropic Vectors Unit is dedicated to producing viral-origin vectors for studying the nervous system under both normal and pathological conditions. In recent years, the use of advanced molecular tools in neurons has become essential for understanding the mechanisms underlying brain function and disorders.

Genetically modified viruses have emerged as the ideal vectors for delivering these tools into brain cells, providing neuroscientists with unprecedented control over cells and circuits. To support our neuroscientists in utilizing these cutting-edge methodologies, the Vector Unit centralizes the production and distribution of neurotropic vectors.

Technician staff

María de los Ángeles Hernández Vellisca

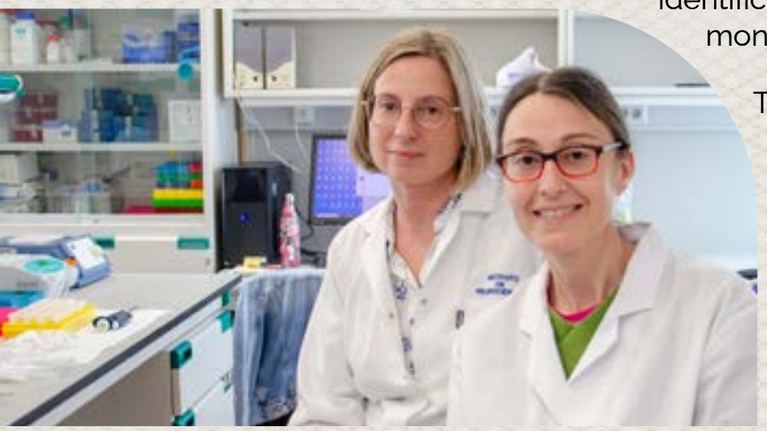
Scientific Responsible

Cristina García Frigola

Genotyping

The Genotyping Service of Transgenic Animals (UGAT) is an associated service to the Animal Research Facilities of the RMG Animal House and has as a mission to collaborate in the genotyping of the animals born at the RMG in the most efficient and consistent way.

The goal of the UGAT is to accelerate the genotyping process so the animals remain the shortest possible time without a genetic identification, and always in the one-month time period.



The UGAT picks up the samples generated by the Animal House technicians when they wean and label the animals. The obtained DNA is analysed by PCR and the users perform the final assignment of the genotypes and enter the results in the RMG management program (AniBio).

Users provide the UGAT with the needed primers as wells as a PCR program that produces accurate and reproducible results. Should the users need help with the design of primers or the PCR program, the UGAT provides technical support whenever is needed.

Technician staff
Mª Trinidad Gil García
Eva Mª Sabater Sánchez

Scientific Responsible
Juan Galcerán

SHARE. Electronic workshop

The Scientific Hardware and Electronics (SHARE) service offers support for adapting and creating experimental instruments and devices tailored to the specific needs of IN research groups. Equipped with state-of-the-art precision machinery, SHARE specializes in the prototyping and manufacturing of new scientific devices, as well as performing local repairs on scientific and technical equipment. The service is closely connected with the Innovation Unit (UCIE).

SHARE provides both knowledge and tools to drive technological innovation and fosters a 'Do it yourself' culture.

Technician staff
Victor Javier Rodríguez Milán
David Cerverón Morales

Scientific Responsible
Ana Gomis

Scientific equipment

The Institute for Neurosciences has state-of-the-art scientific equipment in techniques for histology, molecular biology, and microbiology. It also has ultra-freezers, microelectrodes, cold rooms, and centrifuge machines. In addition, the IN has a maintenance service that continually guarantees the correct functioning of this equipment.

Administration & management

Manager
Mª Teresa García Hedo

Director's assistant
Javier Rodolfo Cantón Menor

Economic management & Accounting
Bibian García García
Eva García Raigal
Ana María López Martínez
Rosana Martínez Fitor,
Isabel Ortega Castillo,
David Rodríguez Dueñas,
Raúl Romero Garrido,
José Sánchez Ardila
Antonio Valero Villar
María del Mar Sanmamed Aramburu
Palmira Bagán Ortuño
Basilisa Ojeda Soria

Staff management CSIC
Mª José Soria Pedrera

Internationalization
Julio Barbas González

Warehouse
Mª Teresa García Hedo

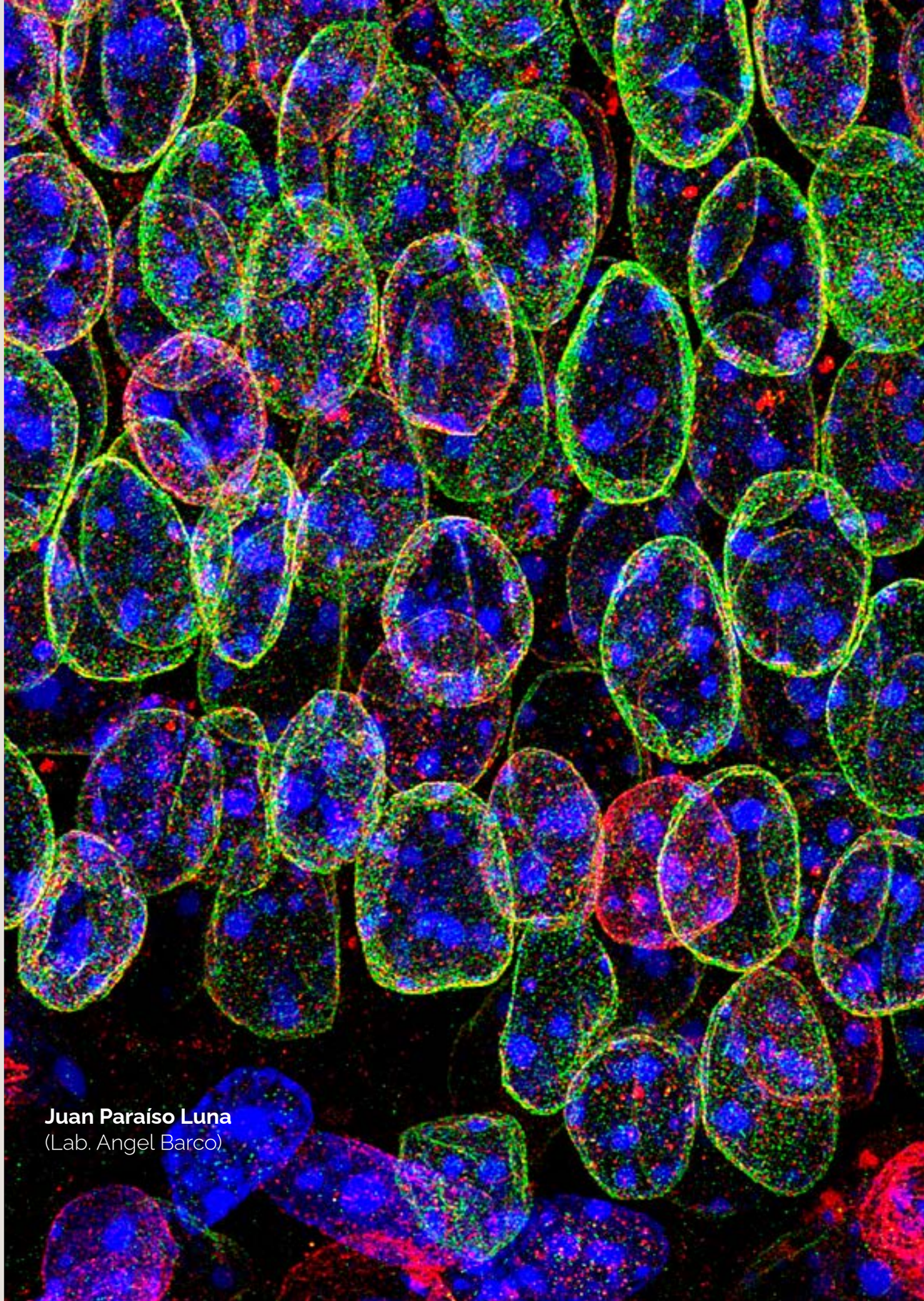
Support Services

IT / Webmaster
Mª Isabel Sánchez Febrero

Audiovisual Service / Graphic Design
Rebeca de las Heras Ponce

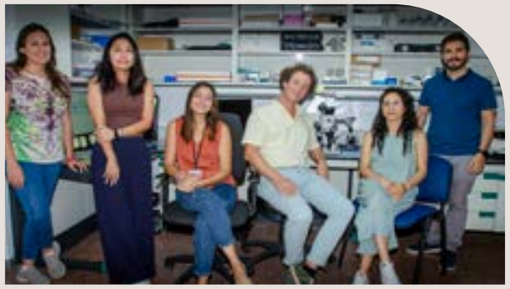
Press Officer
Elena Garrido Huarte

Maintenance
Jesús Campos Roldán
Álvaro Daniel Fenoll Esclapez
Hassan El Ghamrasni Abderrahim



Juan Paraíso Luna
(Lab. Angel Barco)

Research Highlights



A study led by the laboratory directed by **Félix Leroy** discovered a neural circuit that suppresses social interaction with familiar individuals and promotes interactions with novel ones. The research, published in the journal *Cell*, described, for the first time, a group of neurons located in the prefrontal cortex, which are characterized by producing the corticotropin-releasing hormone (CRH) and emitting their axons to the region of the lateral septum. These results could lead to the development of medications to treat disorders such as separation anxiety or avoidant personality.

A multicenter investigation, developed by **Berta Sánchez-Laorden**'s laboratory together with the Navarrabiomed and IRB Barcelona biomedical research centers, determined that the drug ranolazine, used to treat heart conditions, manages to delay the appearance of tumors resistant to melanoma treatment, blocking the metabolism of fatty acids. This work, published in the journal *Nature Metabolism*, revealed, for the first time functionally in mice, that fatty acid metabolism plays an important role in developing resistance to melanoma treatment.

A study published in the journal *Science Advances* describes how information from the sense of touch is transmitted between brain hemispheres. Researchers from the laboratory led by **Ramón Reig** conducted a pioneering study in mice, confirming that a dual representation occurs between hemispheres. This dual representation allows for the perception of continuous, uninterrupted sensations across both sides of the body.

A study led by the **Santiago Canals** laboratory found a way to stop the progression of white matter deterioration in the brain of patients with Alcohol Use Disorder. This work, in which researcher **Silvia De Santis** also participated, was published in the journal *Psychiatry and Clinical Neurosciences* and demonstrated that alteration of the white matter is a central characteristic of the pathology. Furthermore, it opens a new therapeutic avenue to prevent relapse.

The research group led by **José Carlos Pastor-Pareja** published a study in the journal *PLoS Biology* that showed that fibroblast growth factor signaling plays a determining role in the process of adipocyte formation in the vinegar fly (*Drosophila melanogaster*) during the adult stage.

The journal *Pharmacological Research* published a study led by the **Jorge Manzanares** laboratory that demonstrated that cannabidiol repairs brain damage and behavioral alterations in mice with fetal alcohol spectrum. The results of this work indicated that the administration of cannabidiol during the postnatal period improves the processes of neuron creation and increases cell survival by increasing plasticity in the hippocampus.

The laboratory led by **Isabel Pérez Otaño** published a study in the journal *Cell Reports* that revealed that the GluN3A subunit tunes the trafficking and synaptic content of these receptors during postnatal development in rodents, controlling the timing of maturation of NMDA signaling and the refinement of the neural network.

The *International Journal of Mental Health and Addiction* published another study led by **Jorge Manzanares** that revealed that child abuse modulates emotional processing when faced with alcohol-related stimuli during adolescence. The results of this work, which was carried out on more than 600 teenagers with different patterns of alcohol consumption and family history of alcoholism, indicated that the startle response could be considered a biomarker to establish personalized preventive strategies during adolescence.

Another investigation led by **Berta L. Sánchez-Laorden** demonstrated the immunosuppressive function of Snail1, a key gene in embryonic development, in the tumor microenvironment of melanoma. Experiments carried out in rodents during this study, published in the journal *Oncogene*, confirmed that blocking Snail1 in fibroblasts slows the ability of melanoma to grow and metastasize.

The research group led by **Salvador Martínez** published a study in the journal Cellular and Molecular Life Sciences revealing that COVID-19 transmission to the fetus could affect brain development and memory. The researchers focused on identifying the expression of the ACE2 enzyme, which serves as the entry point for SARS-CoV-2 into the body, during fetal development. They determined that this protein is expressed during the development of the cerebral cortex, the region responsible for memory formation and learning processes.

Scientific Events

Researchers at the Instituto de Neurociencias are very active in organizing scientific meetings. Thanks to this kind of initiative, Alicante has established itself as a key point in the field of Neuroscience. Dozens of doctoral students, postdoctoral researchers, and group leaders from all over the world visit the city of Alicante every year to participate in the events organized at our facilities.

Many of these events can be viewed on our YouTube channel. Among the most outstanding activities, this year include the following:

IN Seminar Program #SeminarIN

Every Friday, the IN Assembly Hall hosts a session of the successful international seminar program, in which dozens of leading scientists from around the world interact with our researchers. The list of international researchers who have visited our center throughout this year can be consulted in the annexes to this report.

Healthy Longevity Symposium

The researcher Salvador Martínez Pérez organized three editions of this symposium, which took place on February 28, May 31, and July 27 in the IN assembly hall. This event is part of the activities of the UMH Research Chair in Medicine and Neurosciences.

1st NALCN Workshop: "The Sodium Leak Channel in Health and Disease"

The Instituto de Neurociencias CSIC-UMH was the venue for the first edition of this meeting, held from August 31 to September 3 which main objective was to cover all aspects of NALCN research, including involvement of patient families & physicians, and research highlighting in vivo studies, along with NALCN molecular structure and function. This event was co-organized by IN researcher Isabel del Pino Pariente and is part of the ERA-NET NEURON RestoreLeak project.

EMBO Workshop "Gene regulatory mechanisms in neural fate decisions"

More than 200 neuroscientists met in Sant Joan d'Alacant to celebrate this meeting of the European Molecular Biology Organization (EMBO). The event, which took place from September 7 to 10 at the Complejo San Juan in Alicante, was a meeting point between young researchers and world leaders in the fields of neuroscience and biomedicine. IN researcher Víctor Borrell was part of the organizing committee of the workshop.

4th AXON Conference "Development Plasticity & Regeneration of Neural Circuits"

From September 27 to 29, the Villa Gadea Hotel in Altea hosted the fourth edition of the AXON conference: Development Plasticity & Regeneration of Neural Circuits. The event, organized by IN researchers Guillermina López-Bendito and Eloísa Herrera, brought together more than 120 researchers, from various parts of the world, to explore the most cutting-edge advances in the field of generation and regeneration of neuronal circuits.

II Congress of Neurobiology of Pain and Inflammation

On September 28 and 29, a scientific conference organized by Elvira de la Peña, José A. Gómez Sánchez, Alerie Guzmán de la Fuente, Francisco Taberner, and Félix Viana was held, which brought together more than 70 researchers from the national and international panorama, leaders in the study of pain and inflammation.

XVI IN Progress Report

This annual event in which half of the IN research group leaders presented the work that their laboratories have carried out in the last two years to all the center's researchers took place on October 10 and 17. Researchers Jose López-Atalaya, Ángela Nieto, Luis Martínez, Alex Gómez-Marín, Silvia De Santis, Luis Miguel Gutiérrez, Sandra Jurado, Andreas Kardamakis, María del Carmen Acosta, Hugo Cabedo, Félix Viana, Francisco Tejedor, Jorge Manzanares, Emilio Geijo, Santiago Canals, Teresa Femenía, Francisco Taberner, Juan Antonio Moreno-Bravo, Isabel del Pino, Guillermina López Bendito, Ramón Reig, José Carlos Pastor-Pareja, and María Domínguez participated in this 16th edition.

XX Christmas Meeting

Every year, on the days preceding Christmas, the IN holds a meeting that brings together young researchers working abroad who are interested in discovering the IN as a possible destination in their scientific careers. During those days, they could present their main scientific achievements, meet our staff and visit our facilities. This year it took place on December 20 and 21 and was coordinated by Teresa Femenía, Andreas Kardamakis, and Félix Leroy.

Training & Formation

PhD Program

The Institute is responsible for the official PhD Program in Neurosciences at the Miguel Hernández University (UMH) of Elche, which has obtained the highest official quality qualifications.

During the 2021-22 academic year, the coordination of the UMH PhD Programs has been carried out by the Deputy Vice Chancellor for Research, Miguel Ángel Sogorb. The Coordination of the PhD Program in Neurosciences has been in charge of Elvira de la Peña, the deputy coordinator, Cruz Morenilla, and the members of the Academic Committee of the PhD Program (CAPD).

The CAPD is made up of the director of the Instituto de Neurociencias, Ángel Barco, the deputy director, Emilio Geijo, and the directors of the Research Departments, Sandra Jurado, Guillermina López-Bendito and José López-Atalaya.

The PhD Program has had the administrative support of the UMH Studies Management Service, particularly Virtudes García.

The student representatives of this course were Manuela de las Casas and Eduardo Fernández.

There have been **102 students enrolled in the PhD Program in Neurosciences** (46 women and 52 men), 25% of whom are foreigners. A significant percentage of these students completed the Master's in Neurosciences at the UMH, for which the Instituto de Neurociencias is also responsible. There were 18 new students.

During the 2022-2023 academic year, the Extraordinary Doctorate Award for the 2021-2022 academic year was awarded to doctors: Verónica Company Devesa, Mª José Conde Dusman, Kaviya Chinnapa and Roberto Montanari.

During this course, **56 IN researchers have been directing Doctoral Theses** (34 male directors and 22 female directors). Likewise, 36 researchers have tutored doctoral theses (13 female tutors and 23 male tutors).

In total, **14 doctoral theses have been defended by 6 male PhD students and 8 female PhD students.** Nine of them with an international mention (5 female PhD students and 4 male PhD students). All doctoral theses presented at least one quality indicator recognized by CENAI/ANECA in the field of evaluation to which the

thesis belongs. The list of theses read in 2023 can be consulted in the annexes to this report.

The students have carried out different training activities that have been reflected in their activity plan. Among them, attendance at the Research Seminars of the Instituto de Neurociencias, an activity of

the program supervised by Javier Morante. Around this activity, the student representatives organized the **Meet the Speaker** activity, in which they held informal talks with the guest speaker. They also participate in the preparation of the **IN Seminar Program** by inviting two speakers per course.

During this academic year, the doctoral program organized the I Course "Introduction to Scientific Coding and Data Analysis", which was taught by IN researcher Javier Alegre Cortés; the I Image Analysis Course, organized by Javier Morante and Giovanna Expósito Romero, which included the professor of the University of Barcelona Manuel Bosch Miramón, the professor of the University of Valencia José Manuel Morante Redolat and Delisa García Ibáñez, from the company Zeiss; and the Applied Statistics Course "Continuous support for statistical problems in the laboratory", taught by Victoria Fornés, statistician of the UMH Office of Responsible Research.

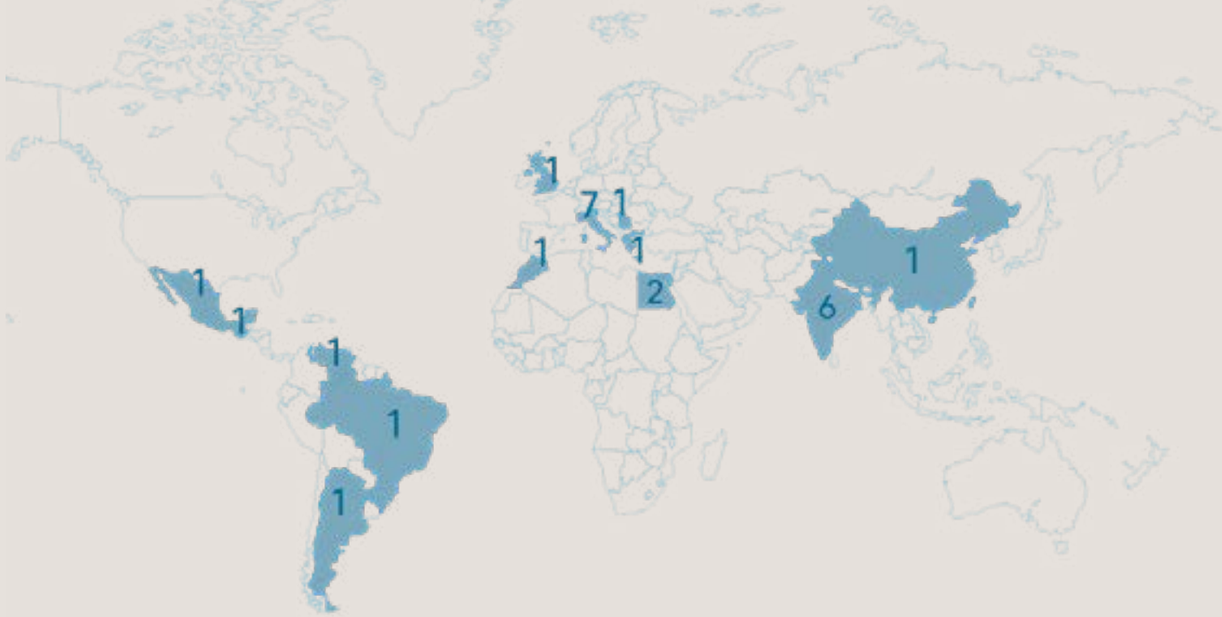
In addition, this year the **Third Annual Congress of PhD Students** organized by the UMH was held, in which the students Marta Arumi Planas and Francisco Manuel Cabello Torres were part of the organizing committee together with the Vice-Rector for Research. The coordinator, Cruz Morenilla, and Francisco Navarrete (CAPD-Neurosciences) were part of the Scientific Committee.

Regarding scientific dissemination, doctoral students are very involved in Brain Awareness Week, an activity organized by the Instituto de Neurociencias, coordinated by the professor of the PhD Program Juan Antonio Moreno, that is held every year in March at the Sant

Joan d'Alacant Campus of the UMH. During this academic year, 61 students have held demonstration workshops, serving students from different schools and the general public.

The PhD Program is part of **The Network of European Neuroscience Schools** (NENS) belonging to the **Federation of European Neuroscience Societies** (FENS). Through this federation, our students can access workshops, courses, and exchange scholarships between collaborating universities.

Distribution of international students of the PhD Program



Master's Training

An Official UMH Master's Degree is taught in its entirety at the Instituto de Neurociencias: **Master in Neurosciences: from the bench to the bedside.** This master's degree is officially taught in English and is international, since the 2016-17 academic year a student exchange program has been maintained with the Developmental Neurobiology course of the Institut Pasteur - Université Pierre et Marie Curie (Paris). In addition, there are also scholarship programs available for foreign students: annually there are two scholarships from the Carolina Foundation for Ibero-American students, and the Severo Ochoa Program funds a program of five Master's scholarships for foreign students.

The students Jocelyn Ángel Gutiérrez (Mexico) and Luisa Gutiérrez Esteve (Mexico) enjoyed a scholarship from the Carolina Foundation, and the students Mark Garnitskii (Russia), Caroline Hamal (Belgium), Beate Jost (Belgium), Alberth Patricio Muñoz Gualán (Ecuador) and Claudia María Pérez Archila (Guatemala) obtained one of the Severo Ochoa - CSIC Program scholarships.

In the 2022-23 academic year, **the master's degree had 15 students enrolled** (10 women and 5 men). Two students (both with scholarships funded by the Severo Ochoa Program) did not complete their Master Research Project (MRP) in the 2022-23 academic year and postponed it to the following academic year. Furthermore, this year a student who had pending it from the previous year, defended her MRP.

Twelve of the enrolled students took the **training course for the use of laboratory animals**, organized by the Office of Responsible Research of the UMH which finances the master's degree to help students obtain accreditation for the handling and use of laboratory animals, a very important requirement to continue research work in the field of Neurosciences.

In addition to participating in the Master in Neurosciences, several members of the IN have taught 3 other master's degrees at the UMH and 7 at other universities. In addition, members of the IN have been tutors or co-tutors of 20 Master Research Projects.

Undergraduate training

During the 2022-2023 academic year, several IN members contributed to undergraduate education, delivering courses across six-degree programs at UMH and three-degree programs at other universities. Additionally, 26 Final Degree Projects were completed under their supervision.

Participation in the "NeurotechEU" network

Several IN members are part of NeurotechEU (European University of Brain and Technology;). During the 2021-22 academic year, there have been several activities that have had the organization or participation of IN members:

VII Conference “Sciences has a Woman´s name”

Date: 27-02-2023 / Virtual

NeurotechEU First Hackathon

Date: 30-05-2023 - 01-06-2023 / Location: Stockholm (Sweden)

Stratneuro Retreat

Date: 28-05-2023 - 29-05-2023 / Location: Stockholm (Sweden)

NeurotechEU Course on “ A reviewer: artificial intelligence applied to the massive analysis of scientific information”

Date:: 27-06-2023 - 28-06-2023 / virtual

Summer School of Quantitative EEG

Date: 17-07-2023 – 21-07-2022 / Location: Cluj-Napona (Romania)

NeurotechEU Summer School on “Preclinical Magnetic Resonance Imaging and Spectroscopy”

Coordinated by IN researchers Santiago Canals and Silvia De Santis

Date: 24-07-2023 – 26-07-2022 / Location: Instituto de Neurociencias UMH-CSIC, Sant Joan d’Alacant (Spain)

Bonn Brain III Conference

Date: 23-08-2023 / Location: Bonn (Germany)

Donders Brain, Cognition, and Technology Summer School

Date: 04-09-2023 – 15-09-2022 / Location: Nijmegen (Netherlands)

Donders (f)MRI Toolkit

Date: 18-09-2023 - 22-09-2023 / Location: Nijmegen (Netherlands)

Neurodegenerative Disorders I: Genes, Mechanisms and Clinical Aspects

Date: 25-09-2023 – 29-09-2022 / Location: Nijmegen (Netherlands)

Eureka. Birras y Ciencia: “Red Hot Chili Peppers: la historia del picante y su premio Nobel”

Talk by IN researcher Juana Gallar

Date: 29-09-2003 / Location: Elche (Spain)

Brain Circuits

Date: 02-10-2023 - 06-10-2023 / Location: Stockholm (Sweden)

Functional Cognitive Neuroanatomy

Date: 09-10-2023 - 13-10-2023 / Location: Stockholm (Sweden)

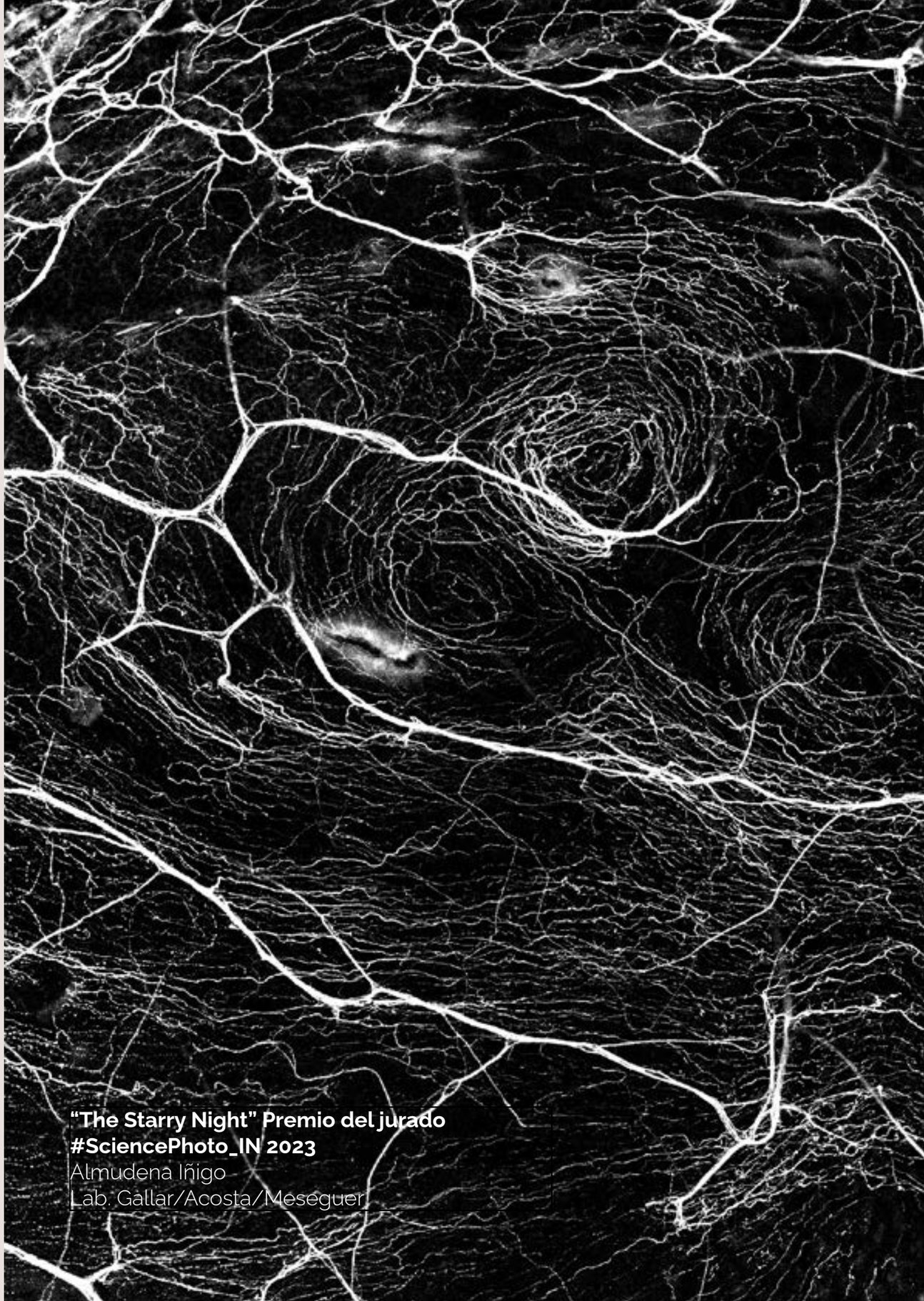
NeurotechEU Technological and Societal Innovation Summit 2023

Date: 02-10-2023 - 05-10-2023 / Location: Bodrum (Türkiye)

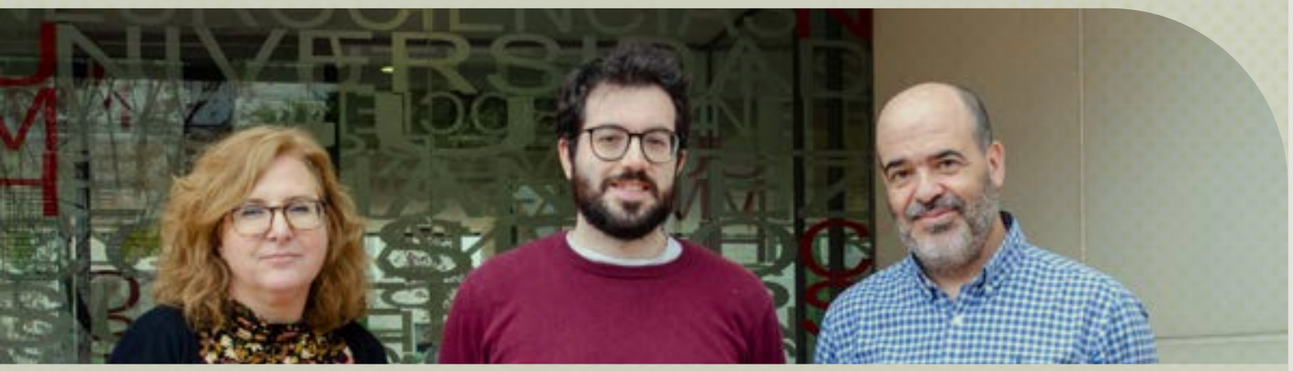
NeurotechEU Hands-on Workshop on Science Communication

Organized by UMH Synapses Club

Date: 19-12-2023 / Location: Instituto de Neurociencias UMH-CSIC, Sant Joan d’Alacant (Spain)



“The Starry Night” Premio del jurado #SciencePhoto_IN 2023
Almudena Iñigo
Lab. Gallar/Acosta/Meseguer



Innovation UCIE

In order to encourage research applied to productive activity, the Agencia Valenciana de Innovación (AVI) supported the creation of an Innovation and Technology Transfer Office (UCIE) at the IN with the specific aim of identifying and nurturing knowledge transfer. This unit, called IN.pulse, has become the link between what the IN investigates and the potential transfer of research results into innovative products.

Although the main activity of the IN is the generation of new knowledge through basic research on the development and function of neuronal circuits, their genetic programmes, and cognitive capacities, many of these research programmes have produced important results that can be transferred to society, both through the health system and to the productive sector. The innovation axis of the IN, supported by IN.pulse, is responsible for identifying and accompanying these projects in their transfer process, as well as promoting innovation activities at the IN.

In 2023, the IN obtained funding of €500,000 from the AVI to launch the FrAIlty project, led by researchers María Domínguez and Roberto Santoro, which focuses specifically on the use of artificial intelligence and robotics to create a platform for the detection of biomarkers, drugs and genes related to ageing.

Staff

José Manuel del RíoVerona
Andrés Giner Antó
Visi Navarro Robledillo

IN.pulse
UNIDAD CIENTÍFICA DE INNOVACIÓN EMPRESARIAL

GENERALITAT VALENCIANA | AVI

Translation

Translational research at the Instituto de Neurociencias UMH-CSIC

One of our main objectives is to turn the research carried out at the IN into novel therapies for diseases of the nervous system. To do this, we conduct research on nerve regeneration, demyelinating diseases, Parkinson's disease, Alzheimer's, ALS, and chronic pain, among others. IN researchers have developed lines of translational research in close collaboration with doctors from local and national hospitals and other health institutions.

The axis aims to promote these collaborations through the organization of meetings and the establishment of collaboration agreements between the IN and organizations of professionals and patients, and institutes dedicated to clinical research such as the Institute of Health and Biomedical Research of Alicante (**ISABIAL**), the Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (**FISABIO**) and different networks dependent on the ISCIII (**CIBER** and **RICOR**) aimed at coordinating Spanish research on the most prevalent human diseases.

Outreach activities

Our staff is constantly involved in participating and implementing outreach activities that make it possible to bring the basic research carried out at the IN closer to the entire society. During 2023 we have carried out the following activities:

Cycle of school visits 'Con Ciencia Sé'

One Tuesday of every month, high school and vocational training students from our region take a guided tour to see the main technological facilities of the IN, and also enjoy informative conferences given by our researchers. We have received more than 160 students during the 7 visits of school centers that took place throughout 2023. This is an activity promoted by the CSIC with the support of the Ministry of Science and Innovation.

International Day of Women and Girls in Science #11F

To commemorate the International Day of Women and Girls in Science, celebrated annually on February 11, the IN organized several activities to highlight the roles of women in scientific and technical professions. Several IN researchers participated in informational talks at educational centers and exchange spaces in the Alicante region, such as the Sala Euterpe. Additionally, on February 10, a special seminar was held by Mónica di Luca, former president of the European Brain Council and Professor of Pharmacology at the University of Milan, in which she shared her experiences and personal insights on the challenges women face in pursuing research careers.

Brain Awareness Week

We organize Brain Awareness Week (BAW) annually in collaboration with the European DANA Brain Alliance. The main event is an open house and science fair, which in 2023 took place from March 13 to 17. All institute staff participated, from principal investigators and PhD students to technicians and administrative personnel. During the morning sessions, school groups from the province visited and enjoyed various exhibitions and informative mini-talks. In the afternoons, sessions were open to the general public, and as in previous years, numerous families chose BAW as a leisure activity to enjoy science in Alicante. This year, approximately 4.000 people visited us.

Cycle 'Brain and Society'

Within the framework of the BAW, on March 14, a new edition of the Brain and Society Cycle took place at the Espacio Séneca in Alicante with the round table 'Cajal's legacy in the 21st century' led by Fernando de Castro Soubriet, head of the Developmental Neurobiology Group at the Cajal Institute (CSIC), Elena Giné Domínguez, professor at the Department of Cell Biology at the Complutense University of Madrid, and the IN researchers Alerie Guzmán and Alicia Alonso. This is an activity supported by the Remedios Caro Almela Chair of Neurobiology.

#SciencePhoto_IN Photography Contest

In June we launched the third edition of the #SciencePhoto_IN scientific photography contest, launched by the postdoctoral organization of the Institute of Neurpromoted by the postdoctoral organization of the Institute of Neurosciences (OPINA) in collaboration with the IN social media team, to create among the entire community IN a joint catalog of scientific photography. The winners of this edition were Almudena Íñigo (jury prize) and Álvaro Morcuende (public prize).

Global Day Against Pain

The scientific program Neurobiology of Pain and Inflammation of the Institute for Neurosciences organized the round table 'Sport and Pain', which took place on October 17 at the Espacio Séneca in Alicante on the occasion of World Day Against Pain. Renowned specialists participated in the event, organized by researchers Félix Viana, Elvira de la Peña, Ana Gomis, Hugo Cabedo, and Francisco J. Taberner, to address the topic from perspectives as diverse as clinical research, medical surgery, rehabilitation, physiotherapy, or the training and recovery of elite athletes.

Mediterranean Researchers Night

The IN participated in the celebration of the European Night of Women Researchers through the Mednight project. A series of informative talks was held at Fnac Alicante on September 29. The event, presented by Sergio Escamilla, featured the following talks: "Why is the Brain White?" by researcher Alerie Guzmán de la Fuente; "Pain in Women" by researcher Miguel Delicado; and "Mothers Never Forget: Stem Cells and Alzheimer's" by researcher María Ángeles Cortés Gómez.

CSIC Science and Technology Week

During November, researchers José Vicente Sánchez Mut, Rafael Soler, Paula Sierra, Jorge Maldonado, and Sergio Escamilla traveled to different educational centers in the province of Alicante to give informative talks on various topics related to the research they carry out every day at the Institute for Neurosciences.

Communication

In 2023 we launched our communications office which, in addition to providing support in outreach activities, is responsible for communicating our results and managing relations with the media. This is a common service that provides support to all researchers who request it.

Press officer: Elena Garrido

Presence in the media

The Institute for Neurosciences has maintained a strong presence in traditional media (print and digital press, television, and radio) through the participation of its researchers in numerous interviews and appearances, both in local and national outlets. The work carried out at the IN has been mentioned 557 times in the media during 2023. These appearances are the result of the impact of the 26 press releases shared with the media during this period and the proactive attitude of our researchers, who are frequently consulted as experts on various current scientific topics.

Website

We continue improving our web page, increasing its attractiveness and accessibility by adding multimedia material and new content both publicly accessible and on our intranet. During 2023 we published 50 news items on the web (including the 26 press releases sent to the media). Thus our website is conceived as the gateway to all the news that happens at the IN.

Social media

Our social networks continue to see excellent growth in followers, and we strive to create engaging content regularly. A strong social media presence is crucial for staying connected with our community and keeping them informed about the latest advances in neuroscience research. Additionally, we have launched a new and revamped YouTube channel where the events that have been celebrated can be viewed, along with informative content about the progress we have made.

@NeuroAlc
8.027 followers

@instituto_neurociencias
983 followers

Instituto de Neurociencias CSIC - UMH
2.230 followers

Instituto de Neurociencias de Alicante
2.011 followers

@institutoneurocienciasumhcsic1
124 followers

Awards & distinctions 2023

Guillermina López Bendito

Rei Jaume I Award in Medical Research.

Full member of the Royal Academy of Exact, Physical and Natural Sciences of Spain.

Outstanding Collaborator Award from Cruz Roja Elche.

Member of the Scientific Committee of the Fondation pour l'Audition (FPA).

Ángela Nieto

Top 100 Women Leaders of Spain by magasIN (El Español & Atresmedia).

Honorary Doctor from the Universitat Jaume I de Castelló.

ELLE *Hope Award* (ELLE Cancer Ball).

MUY Biomedicina Award from MUY INTERESANTE magazine.

Víctor Borrell

Synergy Grant from the European Research Council to coordinate the UNFOLD project.

Eloísa Herrera

President of the Spanish Society of Developmental Biology (SEBD).

Gonzalo Moreno del Val

Vice President of the General Council of Veterinary Colleges of Spain.

Carlos Sánchez Huertas (Lab. Eloísa Herrera)

Award for the best poster at the EMBO Meeting

Gene Regulatory Mechanism in Neural Fate Decisions.

Rafael Soler Ortuño (Lab. Víctor Borrell)

EMBO Scientific Exchange Grant to spend a stay abroad.

Patricia Torres Raves (Lab. Ángel Barco)

Sant Lluc Award for the best TFM of the URV School of Medicine.

Collaborations & Alliances

There are regular collaborations between IN's researchers and scientists from the most prestigious biomedical research institutions. IN's researchers are encouraged to participate in European Networks of Excellence, integrated projects, and international training networks (MTI), as well as in high-performance technology platforms, to facilitate mobility with partner laboratories. The IN has established collaborations with public and private institutions such as:

- Valencian Innovation Agency of the Generalitat Valenciana (AVI-GVA).
- Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (FISABIO)
- Institute for Health and Biomedical Research of Alicante (ISABIAL)
- Women for Africa Foundation (FMxA). In particular, the NI regularly participates in the "Science by Women" programme, so that female doctors from different African countries can carry out research projects at the Institute during 6-month stays.
- Alliance of "Severo Ochoa" Centres of Excellence and "María de Maeztu" Units of Excellence (SOMMa).

The international character of our Master's and Doctoral teaching programmes is essential to expand our presence in the early stages of research training and to compete for the best students.

Visits 2023

Spanish Association Against Cancer

The project director of the Spanish Association against Cancer (AECC), Gloria Vizan, the president of the AECC in Alicante, Fermín Crespo, and its manager, Juan Lledó, visited the Institute of Neurosciences on May 11, 2023. During their visit, the AECC representatives were informed about the development of two of the projects being investigated at the Severo Ochoa Center of Excellence financed by the AECC in the last two years.

Nobel Prize 2021

El Dr. Ardem Patapoutian, galardonado en el año 2021 con el Premio Nobel de Fisiología y Medicina por su descubrimiento de los sensores moleculares del tacto, visitó el Instituto de Neurociencias el 5 de junio de 2023, con motivo de su participación en el jurado de los Premios Rei Jaume I de Investigación.

“Dendritic Spines” Premio del público #SciencePhoto_IN 2023
Álvaro Morcuende (Lab. Femenía)

Remedios Caro Almela Chair of Neurobiology

The Remedios Caro Almela Chair in Neurobiology was established in the year 2000 through the philanthropic efforts of Fernando Martínez Ramos and his family, in honor of his late wife, Remedios Caro Almela. This initiative reflects the family's dedication to commemorating her memory and supporting advancements in neurobiology. The chair has been periodically renewed, ensuring the continuity of its mission: to foster research on the nervous system, with a particular emphasis on understanding its development under both normal and pathological conditions. Through this endowment, the Martínez-Caro family contributes to the ongoing exploration of neuroscience, preserving the legacy of Remedios Caro Almela.[GHE1]

Since its creation and until his retirement in 2012, Professor Constantino Sotelo has been the Chairman, doing an excellent job for more than ten years. In 2013, Professor Richard Morris was appointed as the new Chairman.

Richard Morris
& Constantino Sotelo

Professor Constantino Sotelo (2000-2012)

Professor at the CNRS in France and Director of Unit 106 INSERM, Hospital de la Salpetriere, Paris.

Professor Sotelo has contributed extensively to our knowledge about the anatomy and function of the cerebellum and conducted pioneering studies on neuronal plasticity and axonal regeneration. Currently, he is emeritus Professor at the Institute de la Vision in Paris.

Professor Richard Morris (2013-presente)

Professor of Neuroscience at the University of Edinburgh and Member of the Royal Society.

Professor Morris has made countless contributions to the neurobiology of learning and memory, applying concepts and work techniques that enable the development of new therapies for Alzheimer's disease, among others.

XI "Remedios Caro Almela" Prize for Research in Developmental Neurobiology

The Remedios Caro Almela Prize jury awarded the **XI Prize to Professor Frank Bradke,** who leads the 'Axonal Growth and Regeneration' group at the German Center for Neurodegenerative Diseases (DZNE). The jury highlighted that Professor Bradke's work is widely recognized for defining a new conceptual framework for axonogenesis during nervous system development. Furthermore, the researcher was the first to demonstrate that microtubules perform instructive functions during axon formation in a decentralized manner relative to the cell body.

His fundamental discoveries in the developing nervous system allowed the researcher to carry out pioneering work in axonal regeneration in pathological states. Bradke has been able to span distant fields of cell biology, developmental neurobiology, and regeneration, and has continued to innovate the field by answering some of the fundamental questions about how neurons polarize, connect, and build circuits in the mammal's nervous system.

The Ceremony of the XI Remedios Caro Almela Award took place on November 24 in the Assembly Hall of the Institute of Neurosciences. The rector of the UMH, Juan José Ruiz, and the director of the Institute of Neurosciences, Ángel Barco, presented the award to the German researcher.

Annexes

Publications 2023

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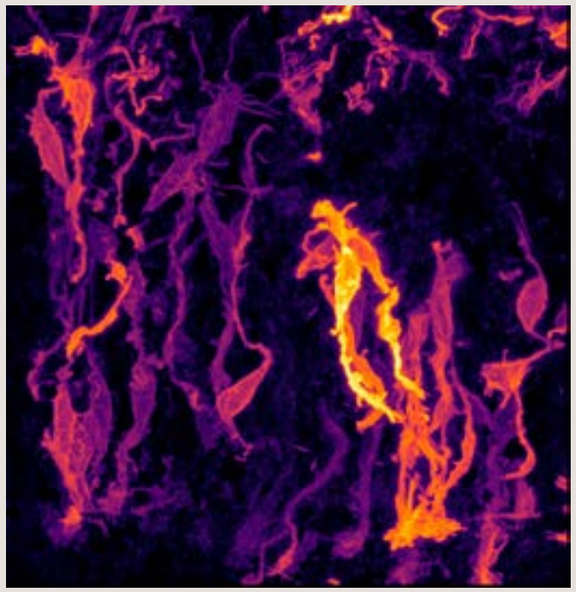

Radial glia dance
Enrico Negri

Seminars 2023

13/01 Anna Planas
IIBB-CSIC, IDIBAPS, Barcelona
Microglia as a target to improve brain function in aging and cerebrovascular diseases

27/01 Hanns Ulrich Zeilhofer
University of Zurich, Switzerland
A spinal cord circuit processing environmental cold sensations

03/02 Lisa Sevenich
Georg-Speyer-Haus, Frankfurt, Germany
Defining and defeating brain metastasis: Perspectives for immune-targeted therapy

10/02 Monica di Luca
Università degli Studi di Milano, Milan, Italy
Synapse dynamic in health and diseases

17/02 Denis Duboule
Department of Genetics and Evolution, University of Geneva, Switzerland
Understanding the Hox clock by using pseudo-embryos

24/02 Vivek Malhotra
CRG, Barcelona
A Tango1 for protein secretion and tissue fibrosis

03/03 Giovanna Mallucci
Altos lab, Cambridge, UK
Mechanisms to Medicines in Neurodegeneration

10/03 David Bennett

Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital. Oxford, UK

Human pain channelopathies

24/03 Johannes Gräff

Brain Mind Institute, EPFL, Lausanne, Switzerland

Memory aids on the chromatin – Epigenetic mechanisms before and after memory

31/03 Nils Brose

Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany

Dynamic Control and Plasticity of Presynaptic Function in Health and Disease

14/04 Bryan Strange

Centre for Biomedical Technology, Universidad Politécnica de Madrid

Memory for the exceptional and exceptional human memory

21/04 Manuel Valiente

CNIO, Madrid

Strategies to target brain metastasis in mice and human

05/05 Emilie Pacary

Neurocentre Magendie. Bordeaux, France

Developmentally-born and adult-born neurons in the dentate gyrus: new evidence of significant differences

12/05 Manel Esteller

Instituto de Investigación contra la Leucemia Josep Carreras, Barcelona

Neuro-epigenetics and beyond

19/05 Susumu Hirabayashi

London Institute of Medical Sciences, London, UK

Exploring host-tumour metabolic interactions using *Drosophila*

26/05 Gabriel Corfas

Kresge Hearing Research Institute, Michigan Medicine, Ann Arbor, USA

Mechanisms of experience-dependent myelin plasticity and its impact on cortical circuits

02/06 Paolo Giacobini

Centre de Recherche Jean-Pierre Aubert. Lille, France

Anti-Müllerian Hormone and the pathophysiology of Polycystic Ovary Syndrome: insights from mice and humans

05/06 Ardem Patapoutian

Department of Neuroscience, Dorris Neuroscience Center - The Scripps Research Institute, La Jolla, USA

How Do You Feel? The Molecules That Sense Touch

09/06 Wieland B. Huttner

Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

Development of the neocortex and human evolution–neural stem cells, human-specific genes, and human-specific protein variants

16/06 Nuria Flames

Instituto de Biomedicina de Valencia-CSIC

Mechanisms of neuronal diversification and evolution

29/06 Tom Baden

University of Sussex, Brighton, UK

The Evolution of Computation in the Brain: Insights from studying the Retina

30/06 Lucia Prieto-Godino

The Francis Crick Institute, London, UK

Evolution of central neural circuits in Drosophilids

07/07 Enrique Martín-Blanco

Instituto de Biología Molecular de Barcelona-CSIC

How and why the embryonic ventral nerve cord of *Drosophila* condenses

14/07 Gorka Orive

UPV/EHU, Vitoria

A Scientific Journey to Entrepreneurship

06/09 Nathalie Dehorter

Queensland Brain Institute, Brisbane, Australia

Monitoring the Monitors: Molecular Control of the Developing Interneurons in Health and Disease

22/09

Giles Yeo

University of Cambridge, UK

Is obesity a choice?

29/09

Michael Coleman

University of Cambridge, UK

Programmed axon death in animal models and in human disease

06/10

Peter Brophy

The University of Edinburgh, Scotland

Assembly of axonal domains that promote nerve conduction: the axon initial segment and the node of Ranvier

20/10

Evgeny Pavlov

Molecular Pathobiology Department, New York University, USA

Multiple mechanisms of mitochondrial inner membrane permeabilization during stress

27/10

Marija Kundakovic

Fordham University, New York, USA

Epigenomic programming of brain plasticity and disease risk by ovarian hormones

03/11

Alberto Pascual

Hospital Universitario Virgen del Rocío/ CSIC/ Universidad de Sevilla

Metabolic requirements of microglia in health and disease

17/11

Alfonso Martínez-Arias

Universitat Pompeu Fabra, Barcelona

What gastruloids (embryonic stem cell models of early embryonic development) tell us about development and evolution

01/12

Roberto Toro

Institut Pasteur, Paris, France

Role of mechanical morphogenesis on the development and evolution of the brain

PhD Thesis 2023

Universidad Miguel Hernandez de Elche (UMH)

Iris Juárez Leal

Contribution of the stria medullaris to the habenular complex: from the prethalamic eminence to the habenula

Eduardo de Puelles Martínez de la Torre y Diego Echevarría Aza

Leticia Pérez Saiz

Developmental progression of thalamic and cortical sensory networks in mice

Guillermina López Bendito y Francisco José Martini

Matthew Paul Lennol

Deciphering apolipoprotein E-associated alterations in Alzheimer's disease

Javier Sáez Valero e Inmaculada Cuchillo Ibáñez

Roberto Santoro

The neural control of body symmetry, and an automated high-resolution pupae counting device

María Domínguez Castellano

Michael Joe Munyua Gachomba

Multimodal cues displayed by submissive rats promote prosocial choices by dominants

Cristina Márquez Vega

Irene Huerga Gómez

Activity-dependent regulation of thalamic interneuron and microglia in the visual thalamus

Guillermina López Bendito

Salma Moustafa Mahmoud Amin

Characterizing of Robo downstream signalling to promote direct neurogenesis

Víctor Borrell Franco

Sergio Molina Rodríguez
Design and validation of an fNIRS system to assess functional activity of the prefrontal cortex

Luis Miguel Martínez Otero y Joaquín Ibáñez Ballesteros

Óscar Elía Zudaire
Non-conventional GluN3A signaling modulates memory ontogeny, formation and consolidation

Isabel Pérez Otaño

Lucía Jimena del Valle Antón
Characterization of progenitor cell types and lineages in ferret cerebral cortex and its conservation in mammalian phylogeny

Víctor Borrell Franco

Sandra Manzanero Ortiz
Functional analysis of tumor suppressor gene p53 in the process of asymmetric cell division

Ana Carmena

Final Master's Projects 2023

Caroline Hamal
Analysis of the oxytocinergic circuit during natural aging

S. Jurado / P. Madrigal

Paula Pérez Archila
Neuromodulation in tumor progression upon disruption of the brain reward system

M. Domínguez / M. Aguilar

Jocelyn Ángel Gutiérrez
Identification of a novel role of TLR9 in the mechanisms regulating neuroplasticity

T. Femenía

Luisa Gutiérrez Esteve
Characterization of a progressive murine model of Parkinson's disease

A. Gasparyan / D. Navarro

Alejandro Sospedra Orellano
Where decision-making, memory and personality meet: a cognitive-behavioral neuroscience study

S. Canals / E. Marcos

Anna Ollé Lladóz
Characterization of the effects of anesthetics in spinal cord microcircuits processing noxious stimuli

F. Taberner

Beate Jost
Understanding melanoma adaptive reprogramming in brain metastasis

B. Sánchez-Laorden / F.J. Rodríguez

Carlos Avilés Granados
Altered levels of ACE2 and TMPRSS2 in Alzheimer's disease and Down syndrome patients: concerns regarding susceptibility to COVID-19

J. Sáez / M.S. García Ayllón

Erika María Torres San Narciso
Estudio de familia con mutación genética ALS-2 y fenotipo de Charcot-Marie Tooth tipo 2, De la clínica a la investigación básica

H. Cabedo / C. Díaz

Esther Guarch de Jesús
Validating *Drosophila* RNAi lines as potential novel asymmetric cell division regulators: the spen gene

A. Carmena

Jorge Maldonado Torres
Unravelling the map of corticostriatal inhibitory projections

R. Reig

Julia Montserrat Castro Marsal
Evolutionary mechanisms of thermal sensitivity of the TRPM8 ion channel

F. Viana / J. Fernández Trillo

Neus Alcañiz Igual
Identification of Differential Expressed Genes in Alzheimer´s Disease and Potential Implications

J.V. Sánchez Mut

Raquel Peña Romero
Validation and optimization of a calcium fiber photometry protocol to study Parvalbumin interneurons' role in memory formation

S. Canals / A. Pérez Segura

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