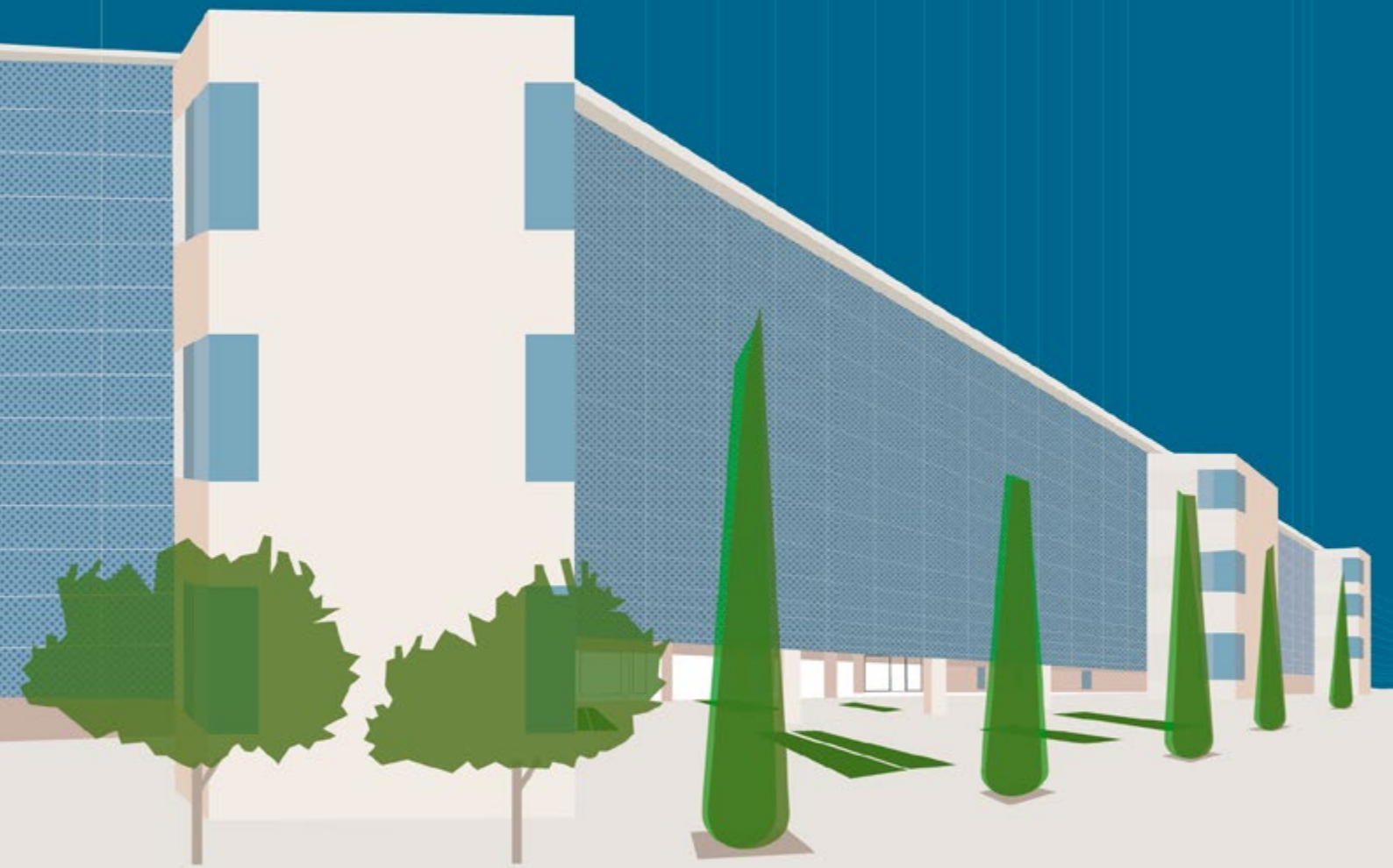
INSTITUTO DE NEUROCIENCIAS

Annual Report
2022



INSTITUTO DE NEUROCIENCIAS

EXCELENCIA SEVERO OCHOA 2014 - 2027

UNIVERSITAS Miguel Hernández

CSIC

INSTITUTO DE NEUROCIENCIAS
Consejo Superior de Investigaciones Científicas
(CSIC)
Universidad Miguel Hernández (UMH)

http://in.umh-csic.es/

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2023

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Saludation

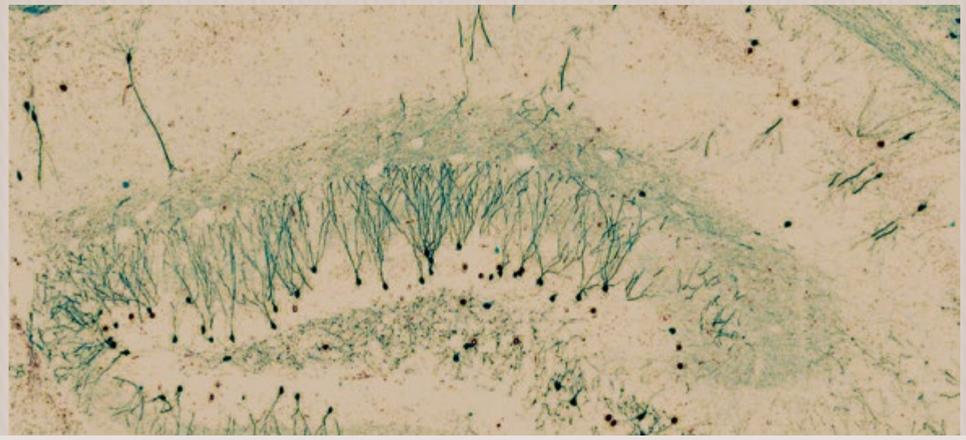
The year 2022 has been a year of renewal for our institute. **We launched our new Strategic Plan for the period 2022-2025.** To kick off this plan, we launched eight Research Programs in January, that will guide our efforts and shape our research agenda in the years to come. Also, in the first few months of the year, we gave our website a complete makeover to create a more modern and engaging platform that better showcases the diverse range of activities and objectives of our institute. Our new website goes beyond our research tasks to highlight the full scope of our mission, including our commitment to training the next generation of researchers, communicating our discoveries to society, and translating our research to the clinic and industry. The website is a user-friendly and informative space that demonstrates the breadth of our work and reinforces our position as a leading research institute.

In addition, we have achieved several important milestones this year, including: i/ receiving the prestigious equality badge awarded by the CSIC in recognition of our efforts to promote gender equality and diversity in the workplace; ii/ secured funding from the Valencian Innovation Agency to renovate our UCIE office, providing an innovative and collaborative workspace for our researchers and, iii/ renewed the continuation agreement for the "Remedios Caro Almela" Neurobiology Chair. Through a new agreement with the Martínez Caro family, we will be proud to sponsor two new editions of the highly acclaimed International Developmental Neurobiology Award. This award is a testament to our commitment to fostering cutting-edge research and advancing scientific discovery in this important area of study.

Dr. Ángel Barco
Instituto de Neurocienciass' Director

In addition to the aforementioned milestones, we are thrilled to announce that we have been awarded the "Severo Ochoa" Center of Excellence accreditation for the third consecutive time, reaffirming our position as one of Spain's leading research centers. This distinction, granted by the Ministry of Science and Innovation, recognizes our ongoing efforts to push the boundaries of scientific discovery and innovation. We owe this success to the unwavering dedication and hard work of our staff, as well as the continued support of our parent institutions, the CSIC and UMH.

As we reflect on **another year of progress and achievement, I would like to express my sincere gratitude to all members of the IN community, including our researchers, technicians, and administrative and support personnel.** Your passion and commitment have been instrumental in driving our success, and I am confident that together, we will continue to overcome challenges and push the boundaries of knowledge and innovation.



University of Alicante

1985

Group of researchers dedicated to studing the structure & function of the nervous system

University Insitute

1990

Formally recognised at the University of Alicante

Asociated Unit

1995

Asociated Unit of the Instituto Cajal CSIC

University Miguel Hernández

1996

Transferred to the newly created University Miguel Hernández of Elche

Joint Centre

1999

The institute becomes a mixed UMH-CSIC center

Own space

2001

Begins the construction of the new building

Move

2004

IN researchers move to the current building

Who we are

The IN, a joint center of the Spanish Research Council (CSIC) and the Universidad Miguel Hernández de Elche (UMH), **is today the largest publicly funded center dedicated to brain research in Spain.** More than 300 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 at 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 Ph.D. Program was created to train young scientists in the

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 Ocho Center of Excellence for its research work

Renewal of SO Distinction

2018

Four years later the distinction of Excellence was renewed

20 años

2019

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

Severo Ochoa Distinction

2022

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

field of neuroscience. Five years later, the IN became an “Associated Unit” of the Instituto Cajal del Consejo Superior de Investigaciones Científicas (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 San Juan 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 house 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 solid ground for the growth and consolidation of the IN as a national reference in neuroscience research.** Later, the accreditation as a “Center of Excelence Severo Ochoa” in 2014 and its renewal in 2018 enabled the consolidation of our project through the development of an ambitious and multidisciplinar y research program.

The IN currently host 35 research groups with more than 230 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 favoured 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 in 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 behavior and diseases of the nervous system. The IN offers its researchers a unique catalog 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 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:

Axis of Action

Research Axis

Coordinators E. Herrera y 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)
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Prof. María Blasco
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Prof. Cornelius Gross
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Prof. Michael Häusser
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Prof. Magdalena Götz
Helmholtz Zentrum München. Institute of Stem Cell Research. Neuherberg, DE
magdalena.goetz@helmoltz-muenchen.de

Training Axis

Coordinators: E. de la Peña y 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” (Director: 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 (Director: E. de la Peña) 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 and PhD programs are part of the international network of neuroscience schools (NENS).

Innovation Axis

Coordinators: S. Canals y 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). The 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 closes the gap with doctors, 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 y 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 new 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: S. Jurado y J.A. Moreno

This axis coordinates actions aimed at disseminating our scientific discoveries to society, informing and advising public and private entities on scientific and technological matters, and promoting scientific culture and rational thought in our society. It is committed to promoting the involvement of society with science through communication and educational projects (for example, defense of animal experimentation, and promotion of women in science), and by carrying out dissemination activities related to neuroscience. The outreach axis also coordinates public awareness activities, such as open doors visits, conferences, and round tables on the social implications of brain science, and oversees the IN’s presence in the media and on social media.

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 (See graphics Impact Factor and Budget).

tenure

46 **Full tenure research staff**

+ 2 % > 2021

106 support

Administrative & technical staff

+ 6 % > 2021

112 predoc

Predoctoral staff

- 4% > 2021

non-tenure

13 **Non- tenure research staff**

+ 18 % > 2021

62 postdoc

Postdoctoral staff

+ 5 % > 2021

Personnel

gender

60 female staff

40 male staff

origen

Non-Nationals 12%

Spanish national 88%

publications

web of Science

103

+ 9,7% > 2021

impact 8,1

factor de impacto (FI)

15+ % > 2021

89 active research projects in 2022

+ 20% > 2021

Strategic plan: from departments to scientific programs

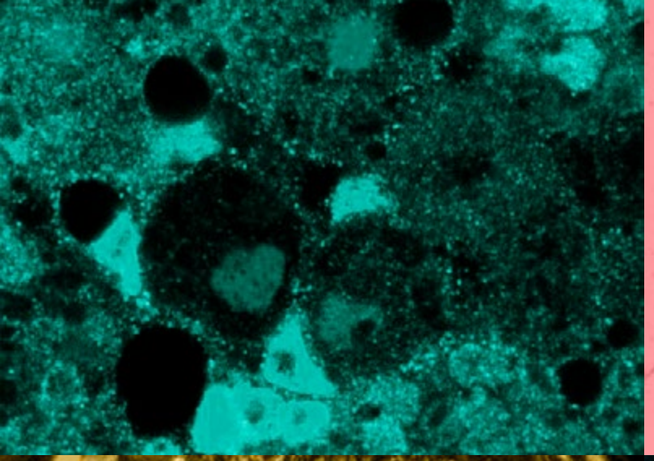
The main functional research unit at the *Instituto de Neurociencias* are the research groups (RG). RGs vary in size, from 3 to 25 members, and are composed of both researchers and technical staff, hired through one of our parent institutions, the CSIC and the UMH. Traditionally, RGs have been assigned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

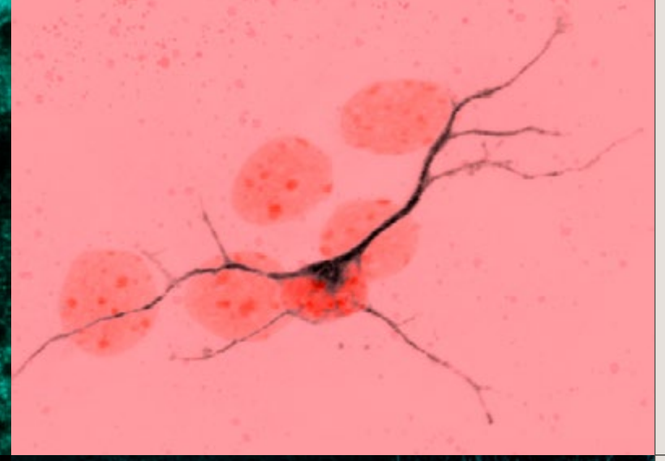
However, the exponential growth of the IN and changing times have transformed the focus of our research in recent years, and brought us closer to a structure more focused on resolving specific scientific questions related to the assembly of brain circuits during development and how these circuits are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

Scientific Programs

In 2022, we defined the research lines we consider strategic and 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



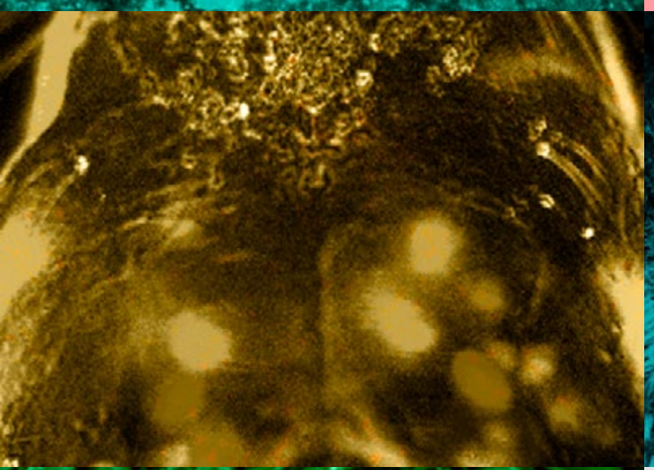


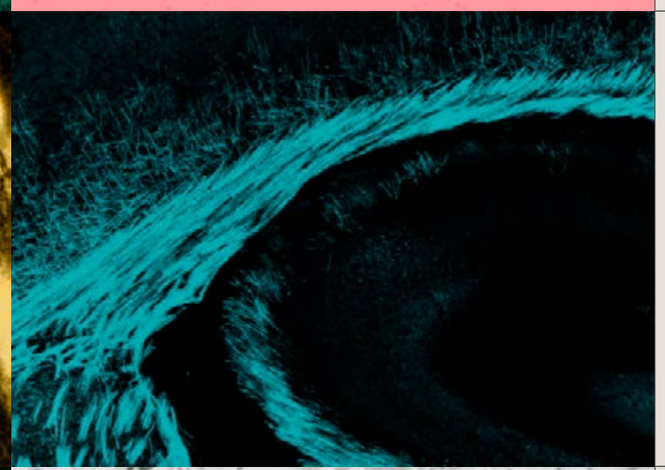
Sp1_ Neural stem cell regulation and differentiation

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 behavior

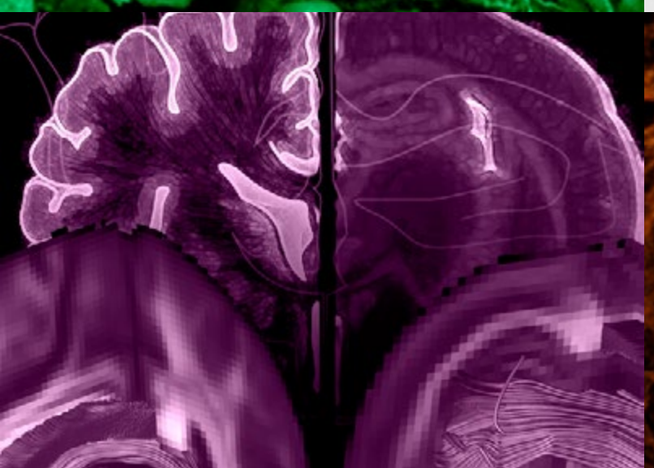
Director: Isabel Pérez Otaño

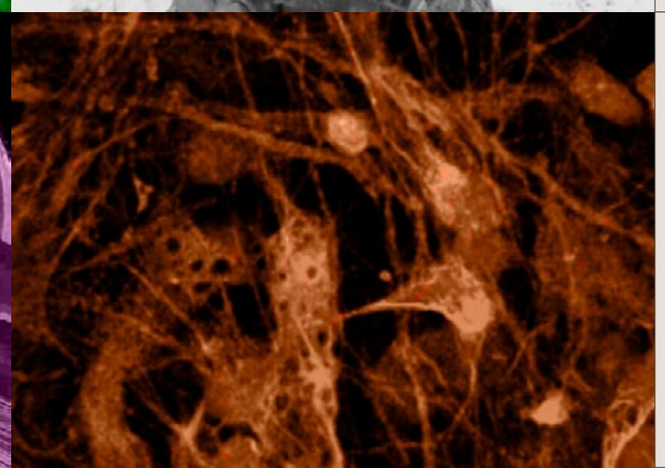
Sp5_Neurobiology of pain & inflammation

Director: Félix Viana de la Iglesia

Sp6_Genetic & epigenetic basis of Individuality & aging

Director: María Domínguez Castellano





Sp7_Human cognition & behaviour

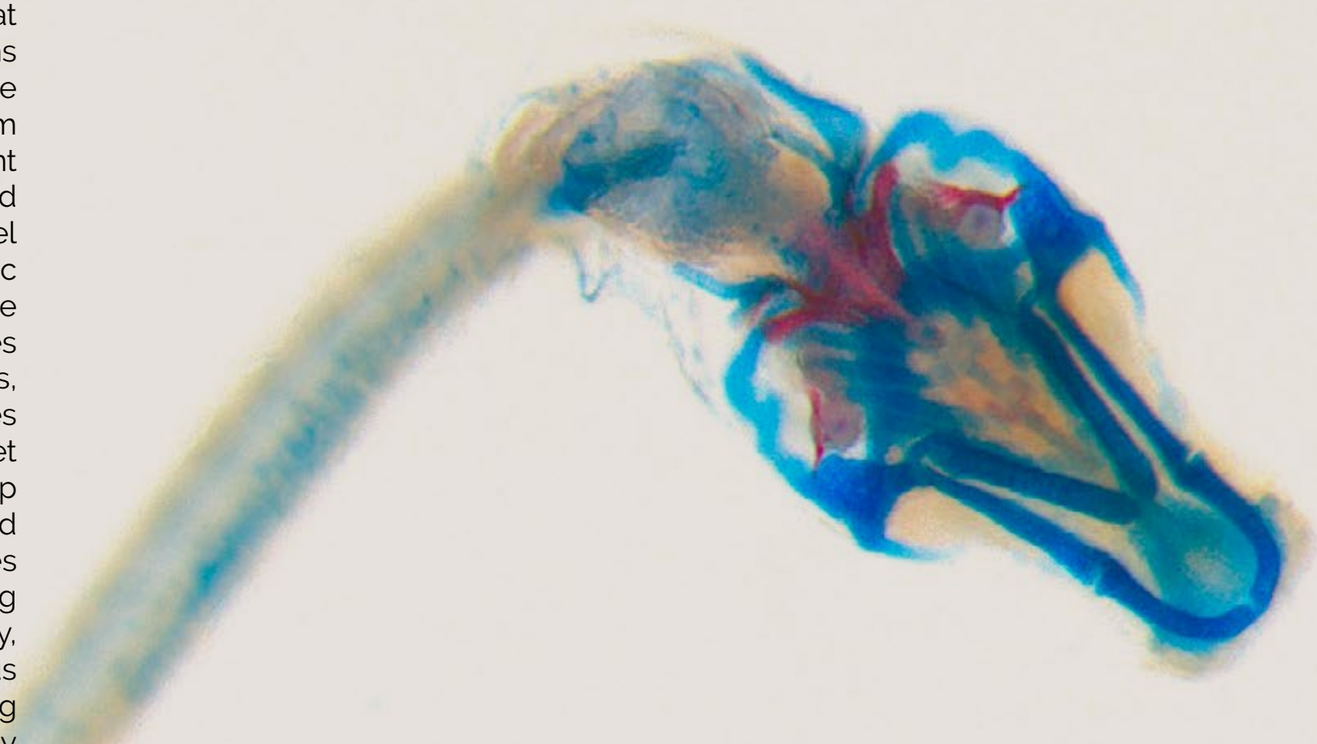
Director: Luis Martínez Otero

Sp8_ Translational research of neurological and psychiatric disorders

Director: Jorge Manzanares Robles

by Prof. Angela 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 Prof. Guillermina López-Bendito, which studies how different sensory systems are assembled during embryonic phases and the first postnatal weeks. The program coordinated by Prof. 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 Prof. María Dominguez investigates how environmental factors, pathogens and 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 Dr. 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 Dr. 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.



The fish that wanted to be a dragon
Adrián Cuevas

Research Groups

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders
Ángel Barco

Neurogenesis & cortical expansion
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

Mechanisms of growth control & cancer
Silvia de Santis

Mechanisms of growth control & cancer
María Domínguez

Neuropharmacology, Molecular Immunobiology and Behavior
Teresa Femenía

Ocular Neurobiology
Juana Gallar / María del Carmen Acosta

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
Andrea 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 López-Sánchez

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

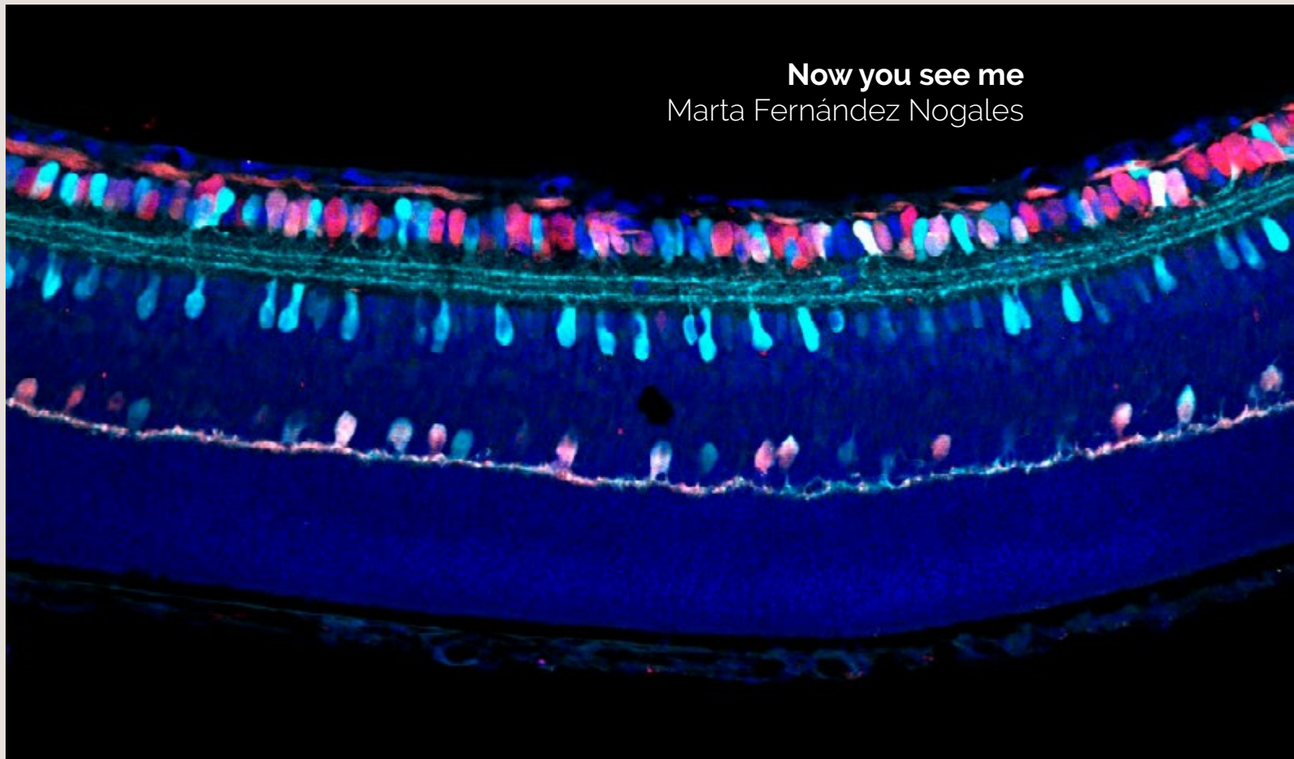
Functional Epi-Genomics of Aging and Alzheimer's Disease
José Vicente Sánchez Mut

Neurogenetic basis of behavior
Juan A. Sánchez Alcañiz

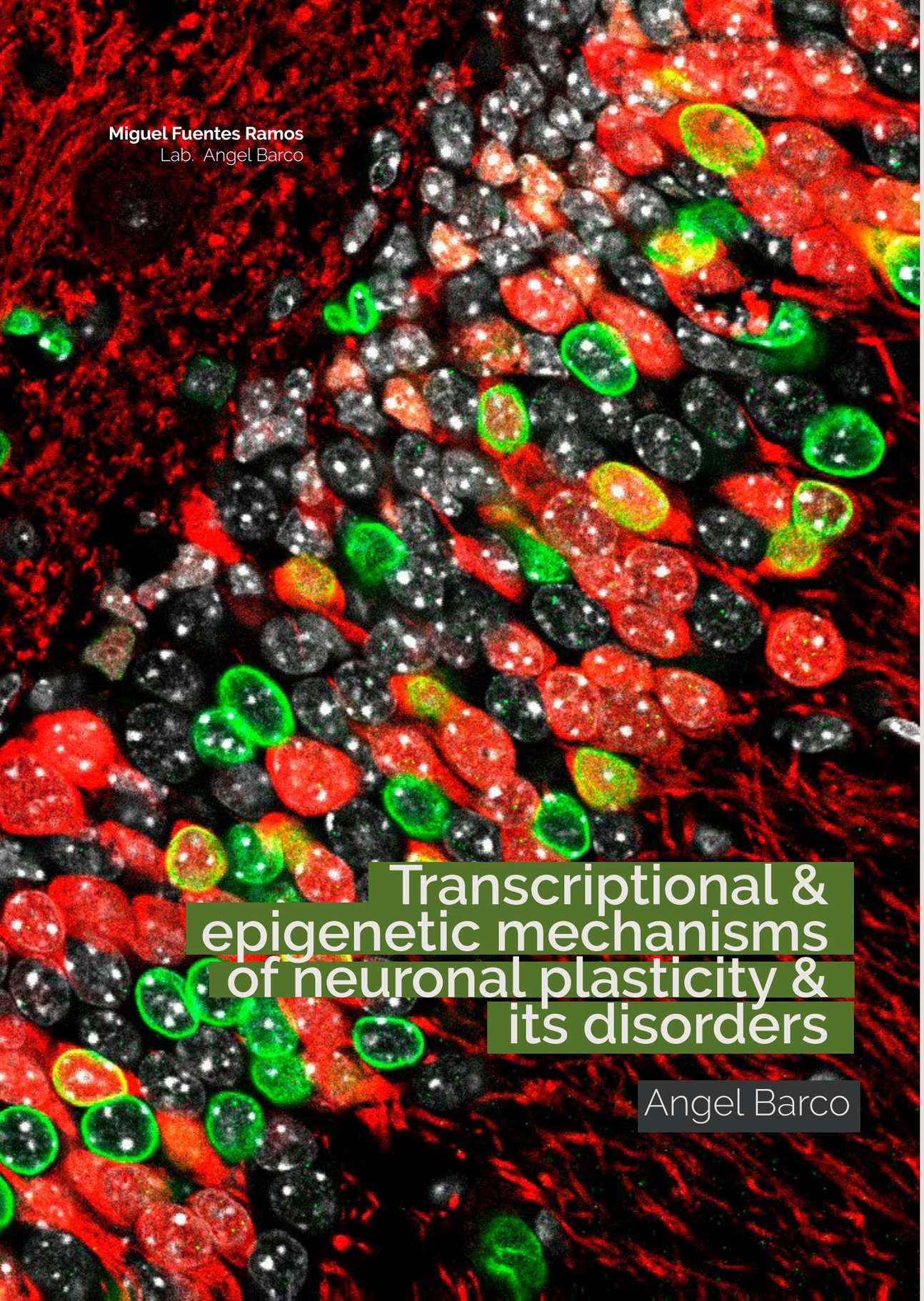
Wiring and Function of Somatosensory Circuits
Francisco J. Taberner Sanchís

Molecular neurogenetics
Fernando J. Tejedor

Molecular and cellular physiology of synaptic transmission
John Wesseling



Now you see me
Marta Fernández Nogales



Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Angel Barco

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:

- 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 of animal's 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

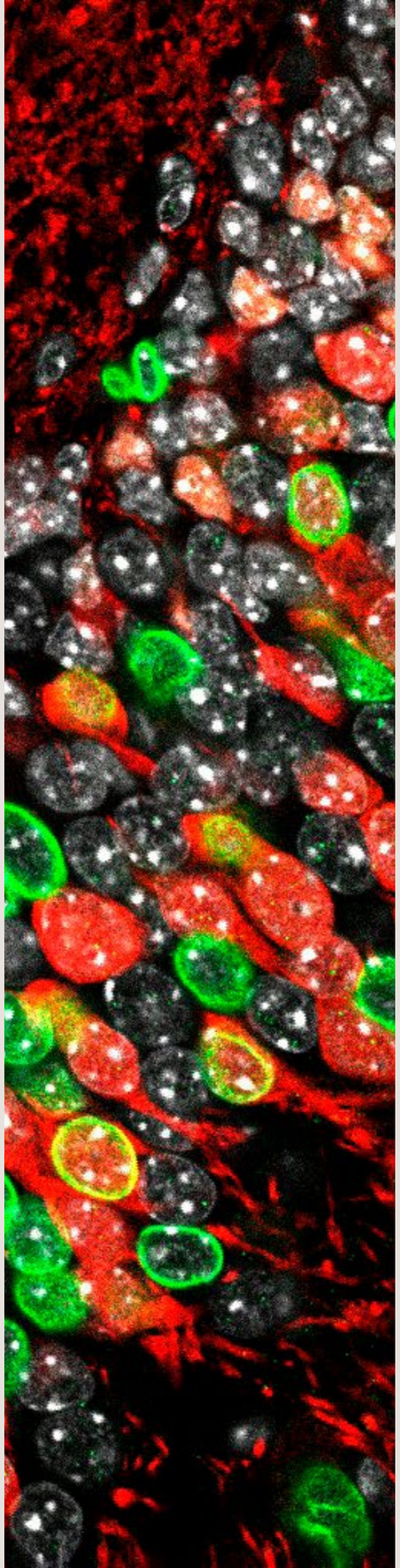
Lipinski, M., Niñerola, S., Fuentes-Ramos, M., Valor, L.M., del Blanco, B., López-Atalaya, J.P. and Barco, A. (2022). **CBP is required for establishing adaptive gene programs in the adult mouse brain.** *Journal of Neuroscience*, 42(42), 7984-8001. https://doi.org/10.1523/JNEUROSCI.0970-22.2022

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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PhD Investigator
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Beatriz del Blanco
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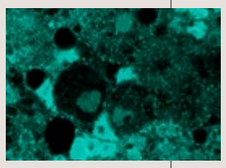
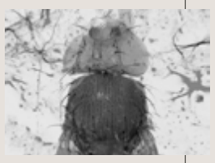
PhD Student
Marta Alaiz Noya
Isabel Bustos Martínez
Miguel Fuentes Ramos
Sergio Niñerola Rives
Master Student
Patricia Torres Raves
Technical Staff
Mirjam Cangonja
Román Olivares
Carina Racovac

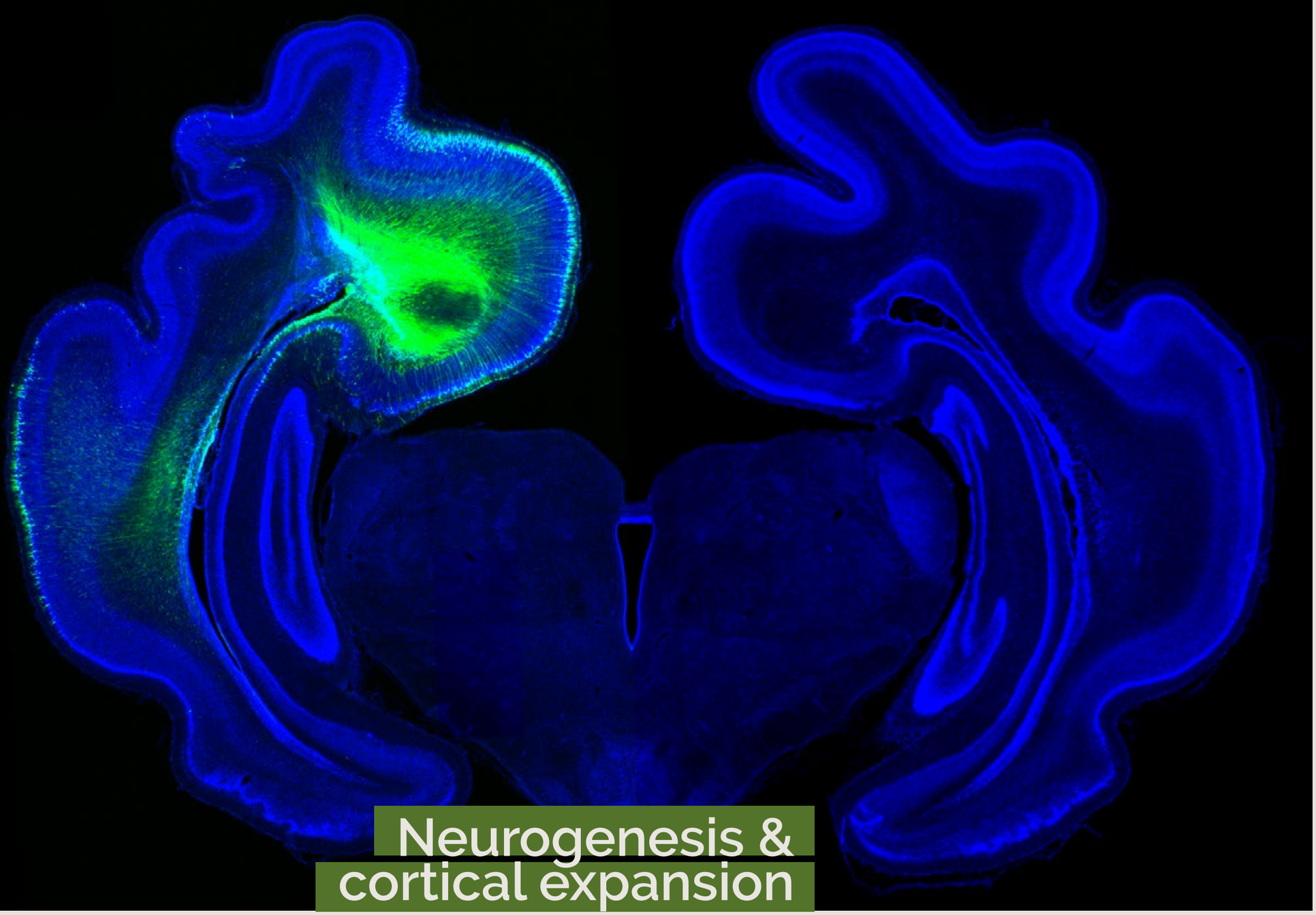
Department:
Molecular Neurobiology and Neuropathology



Sp1_ Neural stem cell regulation and differentiation



Sp6_Genetic & epigenetic basis of Individuality & aging



Neurogenesis & cortical expansion

Víctor Borrell

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 extraordinary growth in size of the cerebral cortex observed across the mammalian evolutionary scale is thought to underlie the concomitant growth in intellectual capacity. This evolutionary expansion of the cerebral cortex is recapitulated during development in higher mammals, when the embryonic cerebral cortex undergoes massive growth in surface area, and folds itself in stereotypic patterns.

Multiple genetic mutations have been identified as the leading cause for intellectual or learning disability and intractable epilepsy in humans. These mutations are consistently linked to defects of cortical development during fetal de 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.

Our research focuses on identifying and understanding the cellular, molecular and genetic mechanisms involved in the expansion and folding of the mammalian cerebral cortex in health and disease, and consequences on the function of cortical circuits. We combine transcriptomic and epigenomic analyses at the level of individual cortical layers and single cells (Dropseq), with a wide variety of experimental animal models (snake, chick, mouse, ferret, human organoids) and strategies for genetic manipulation of the developing brain (including in vitro, in ovo and in vivo electroporation, viral vectors, transgenic and knock-out animals). Our phenotypic analyses range from state-of-the-art imaging techniques on live and fixed tissue, to 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. Following our recently published studies, we are currently studying the evolution of genetic mechanisms that regulate cerebral cortex expansion across amniotes and the establishment of cortical folding patterns, and the impact of these mechanisms on cortical function, as well as the consequences of deregulation of these mechanisms, including the development of pediatric brain cancer.

Relevant publications

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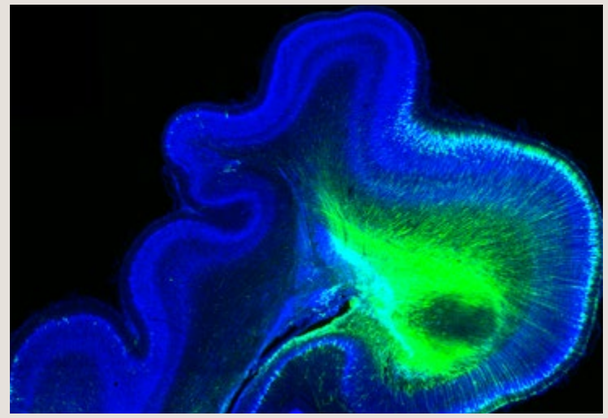

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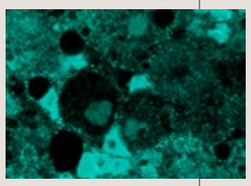
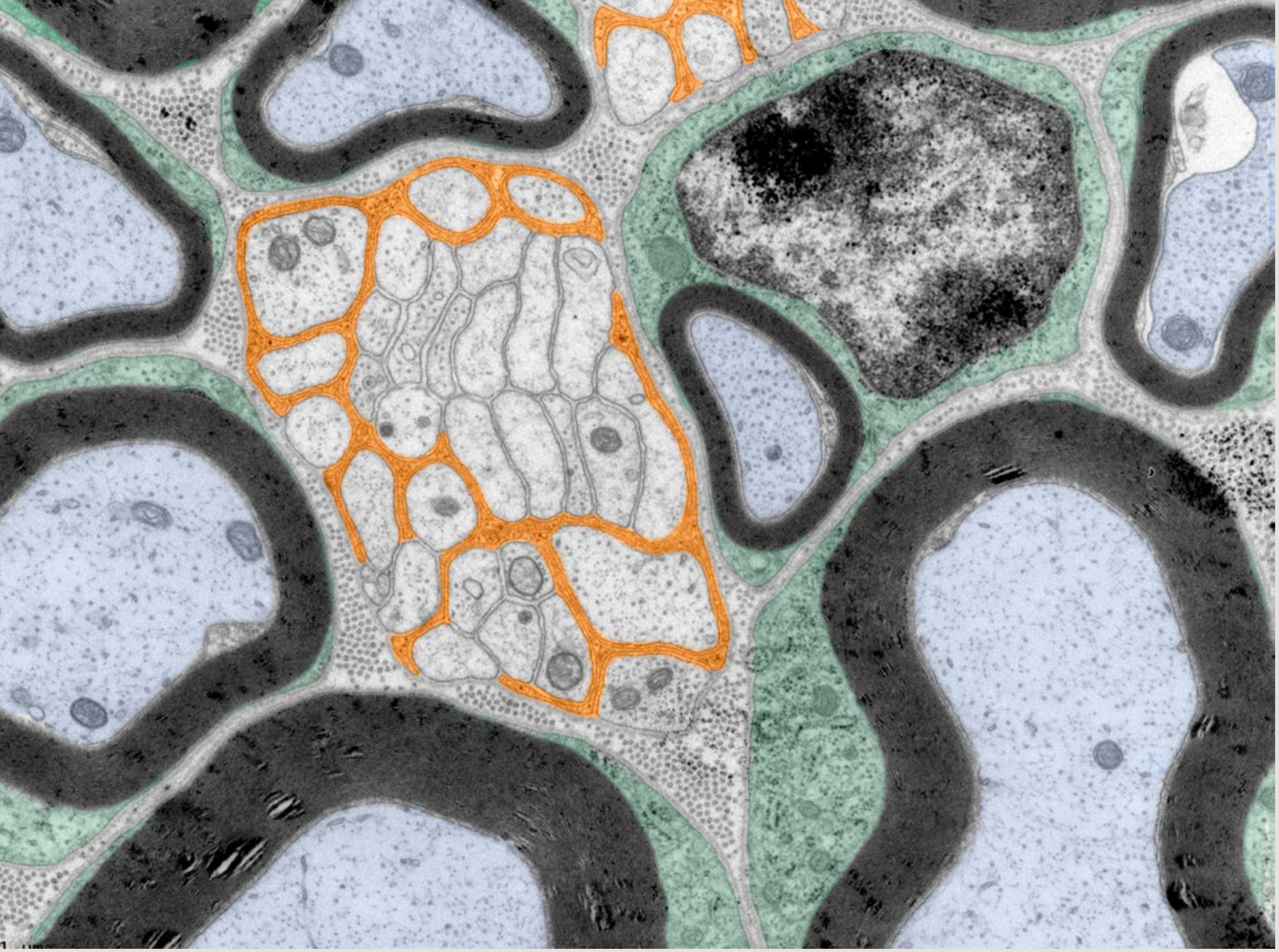


Sp1_ Neural stem cell regulation and differentiation



Molecular control of axonal myelination

Hugo Cabedo

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 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 the 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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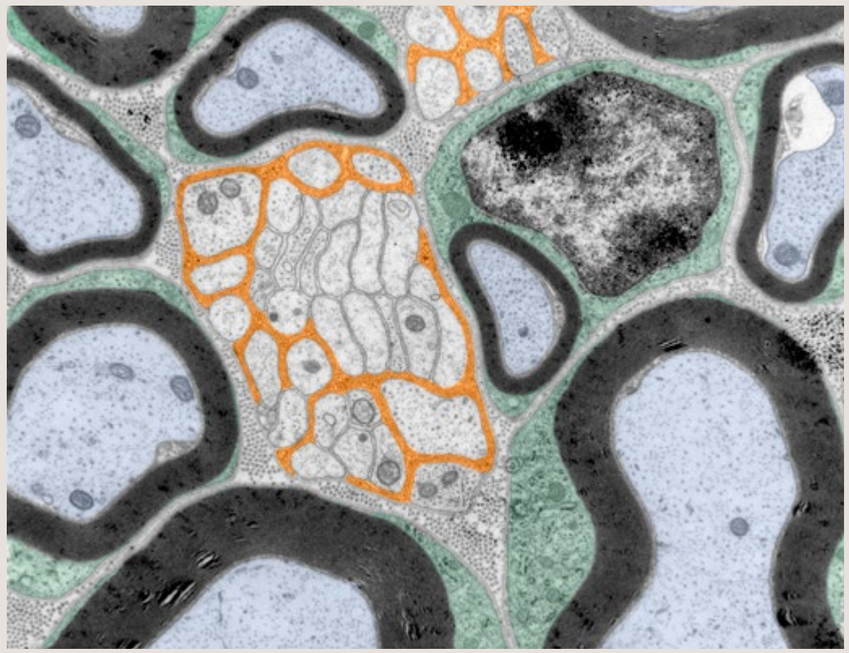

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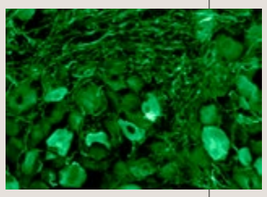
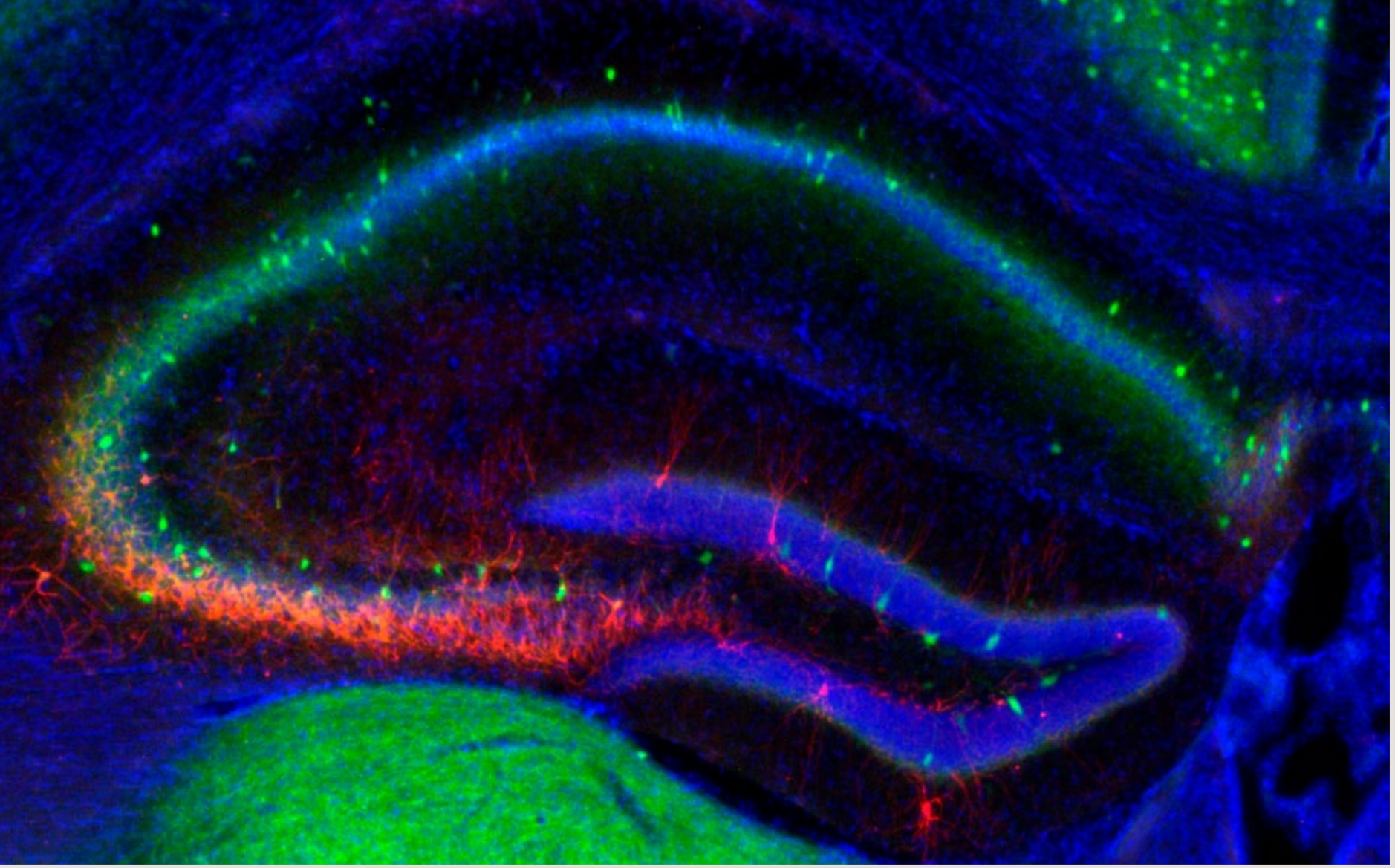


Sp5_Neurobiology of pain & inflammation



Plasticity of brain networks

Santiago Canals

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 behavioural 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 neuromodulation. To this end we combine functional magnetic resonance imaging (fMRI) with electrophysiological techniques and deep brain microstimulation, 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 behaviour becomes hard-wired in the addict's brain. By applying the same multidisciplinary approach, 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

Garcia-Hernandez, R., Cerdán Cerdá, A., Trouve Carpena, A., Drakesmith, M., Koller, K., Jones, D.K., Canals, S. and De Santis, S. (2022). **Mapping microglia and astrocyte activation in vivo using diffusion MRI.** *Science Advances*, 8(21), eabq2923. https://doi.org/10.1126/sciadv.abq2923

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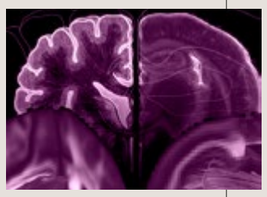
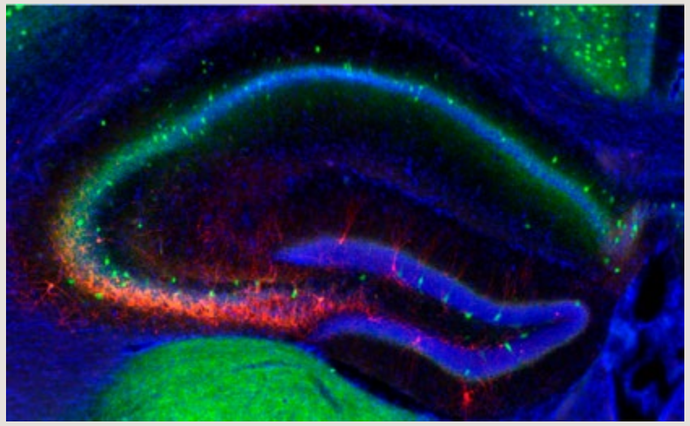
Cellular and Systems Neurobiology



Sp7_Human cognition & behaviour



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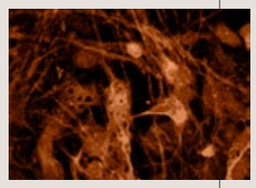

Sp8_ Translational research of neurological and psychiatric disorders

Asymmetric division of neural stem cells in development and tumorigenesis

Ana Carmena

Our lab is currently focused on analysing 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 are 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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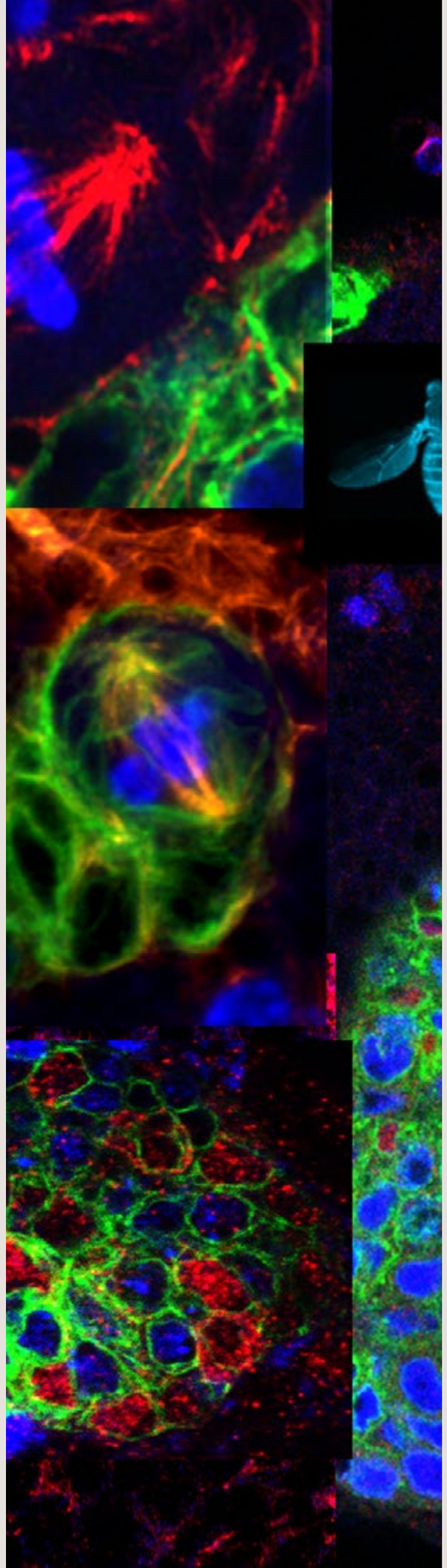

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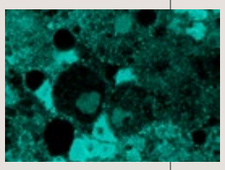
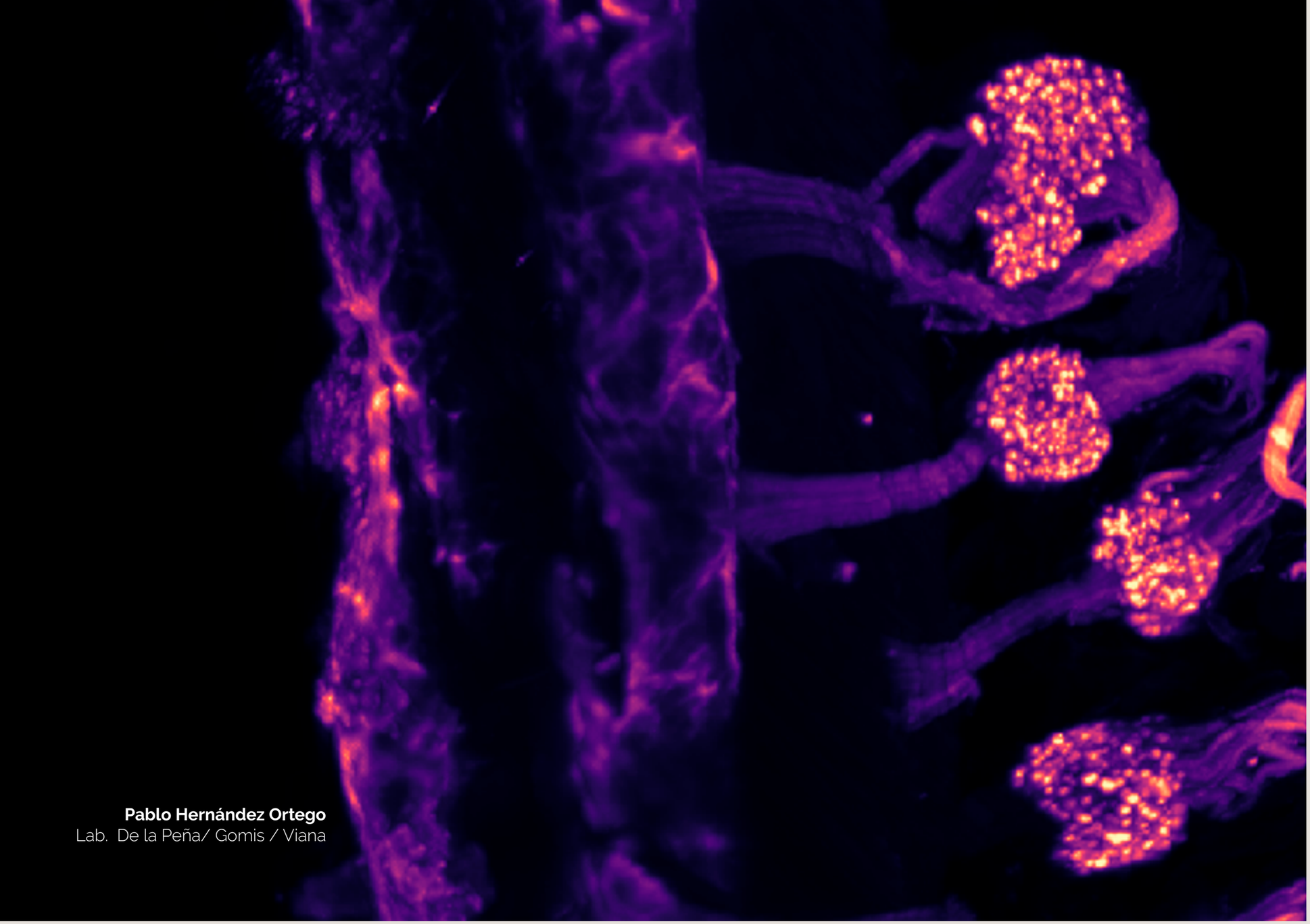


Sp1_ Neural stem cell regulation and differentiation



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

Sensory transduction and nociception

Elvira de la Peña / Ana Gomis / Félix Viana

Our research aims at understanding the cellular and molecular mechanisms involved in the detection and transduction of physical and chemical stimuli by mammalian sensory nerve endings, with an emphasis on 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 eventually use these molecular receptors as analgesic targets.

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

Hernández-Ortego, P., Torres-Montero, R., de la Peña, E., Viana, F. and Fernández-Trillo, J. (2022). **Validation of Six Commercial Antibodies for the Detection of Heterologous and Endogenous TRPM8 Ion Channel Expression.** *International Journal of Molecular Sciences*, 23(24), 16164. https://doi.org/10.3390/ijms232416164

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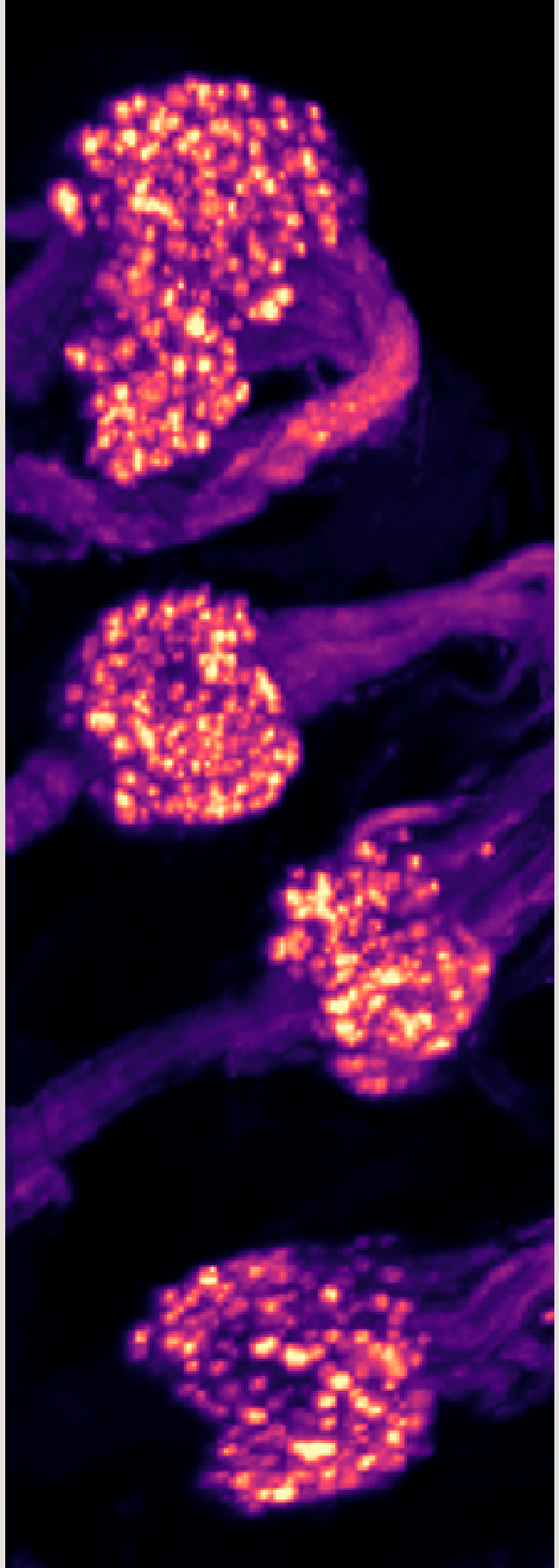

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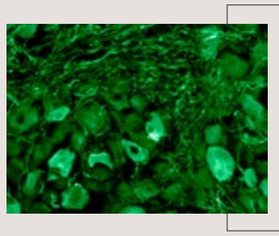
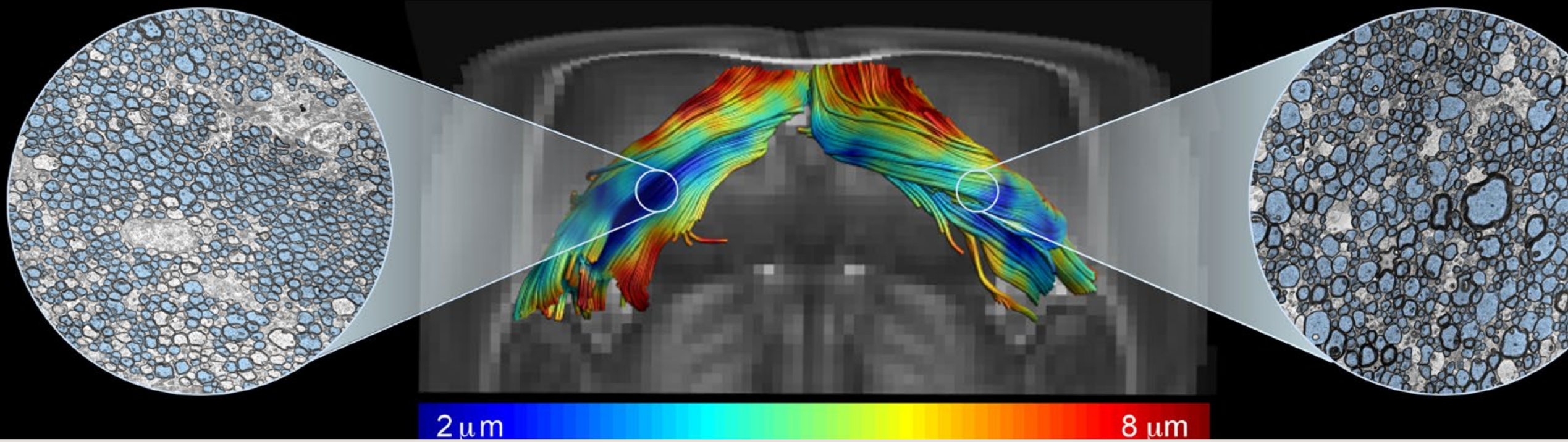


Sp5_Neurobiology of pain & inflammation



Translational Imaging Biomarkers

Silvia de Santis

Neuroinflammation and neurodegeneration are hot topics in brain research, and they have become very promising targets for the development of novel disease-modifying treatments in pathological conditions. In order to characterize there 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: i) transfer the developed framework from the preclinical to the clinical setting by incorporating artificial intelligence tools; ii) investigate the evolution of inflammatory markers throughout life, in rodents and humans and considering the gender dimension; iii) characterize the role of inflammation in animal models and in patients and Alzheimer's disease; and iv) 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

Garcia-Hernandez, R., Cerdán Cerdá, A., Trouve Carpena, A., Drakesmith, M., Koller, K., Jones, D.K., Canals, S. and De Santis, S. (2022). **Mapping microglia and astrocyte activation in vivo using diffusion MRI.** *Science Advances*, 8(21), eabq2923. https://doi.org/10.1126/sciadv.abq2923

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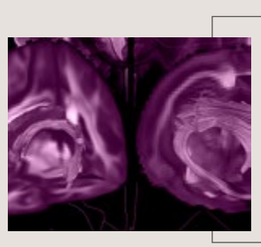
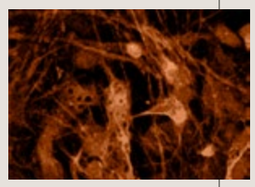
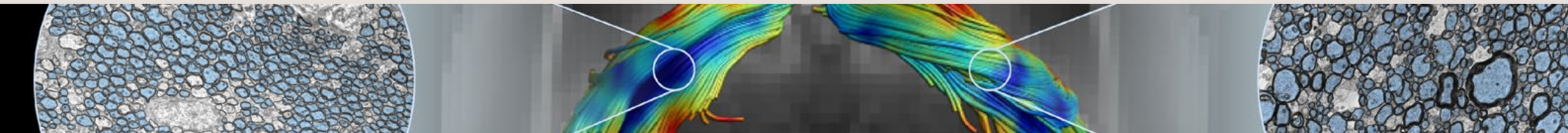


Sp7_Human cognition & behaviour



Sp8_ Translational research of neurological and psychiatric disorders



Mechanisms of growth control & cancer

María Domínguez

Our research primarily focuses on unravelling the molecular mechanisms underlying high-order growth control and tumorigenesis. Within this overarching objective, we concentrate our efforts on two main research areas.

The first revolves around bilateral asymmetry and high-order growth control. We are intrigued by the remarkable constancy of animal size within species. Our focus lies in understanding how the left and right parts of organisms, such as the wings of insects, grow independently and yet manage to achieve an exact match in size. Genetic and environmental factors inevitably cause bilateral asymmetry during development, and uncorrected size variation can significantly impact an organism's locomotion and balance. We utilize geometric morphometric and "fluctuating asymmetry" index to identify factors buffering size variations. Our research has made significant discoveries about the high-order control of growth and its association with perfect bilateral symmetry and constancy in body size. Specifically, we have found that these controls resides within the neuroendocrine system and relies on extensive communication between the left

and right parts of the body and neurons mediated by the ILP8-Lgr3 relaxin system. We recently discovered that compensating for growth deficiency caused by starvation involves a different mechanism via the relaxin ILP7-Lgr4 system. These factors are intimately associated with fitness, genetic quality and resilience.

The second area of our research focuses on cancer and therapeutics. We aim to deepen our understanding of cancer initiation (the black box) and how the innate immune response to cancer cells can be leveraged for potential therapeutic interventions. In pursuit of this goal, we are implementing automated high-throughput screen platforms blended with multiorgan metabolomics and RNA-seq to identify potential therapeutic candidates and interventions for certain human cancers. For instance, we have discovered that FDA-approved anti-asthmatic drugs, Montelukast and Zileuton, could be repurposed to treat leukaemia. Our pharmacogenetic analyses have also shed light on a Nitric oxide (NO)-dependent inflammation pathway, which requires the production of leukotriene LTB4, exerting both local and systemic effects.

In summary, our research efforts aim to advance our understanding of high-order growth control, bilateral asymmetry and tumourigenesis and to identify possible innovative therapeutic strategies to alleviate growth problems.

Relevant publications

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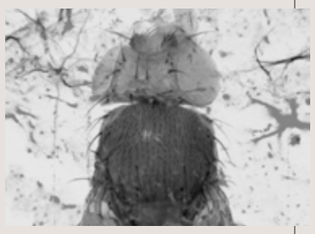
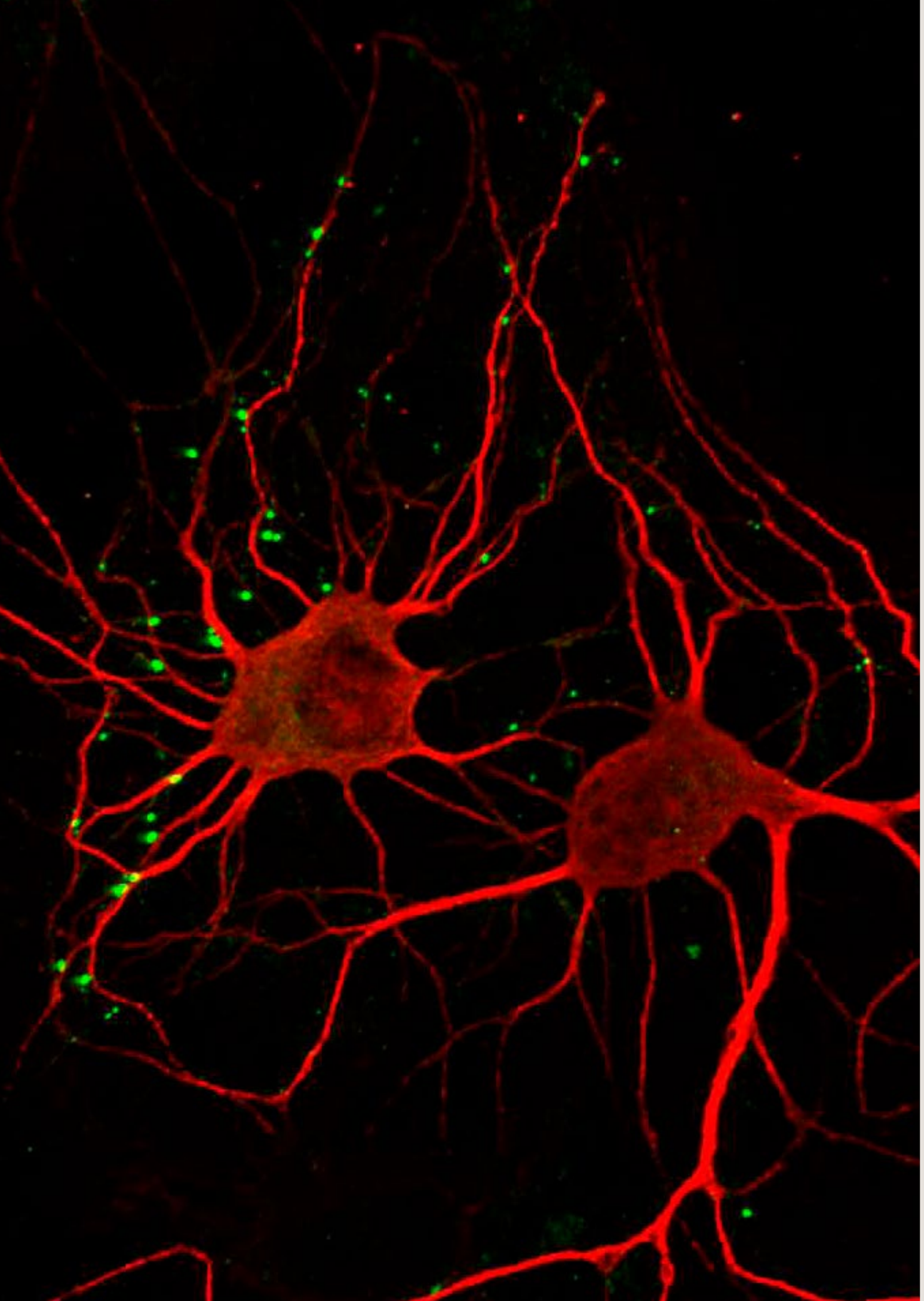


Sp6_Genetic & epigenetic basis of Individuality & aging



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 with 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 with low-grade inflammation such as metabolic disorders, which are commonly associated with mood and anxiety disorders.

Although there has been a long-standing relation 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

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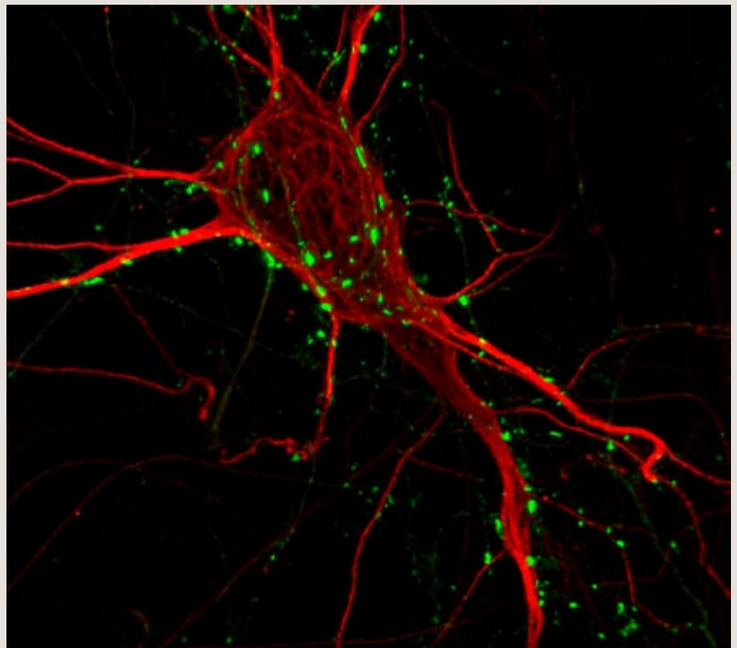

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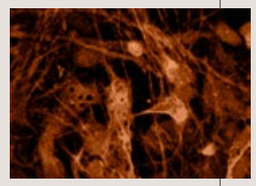
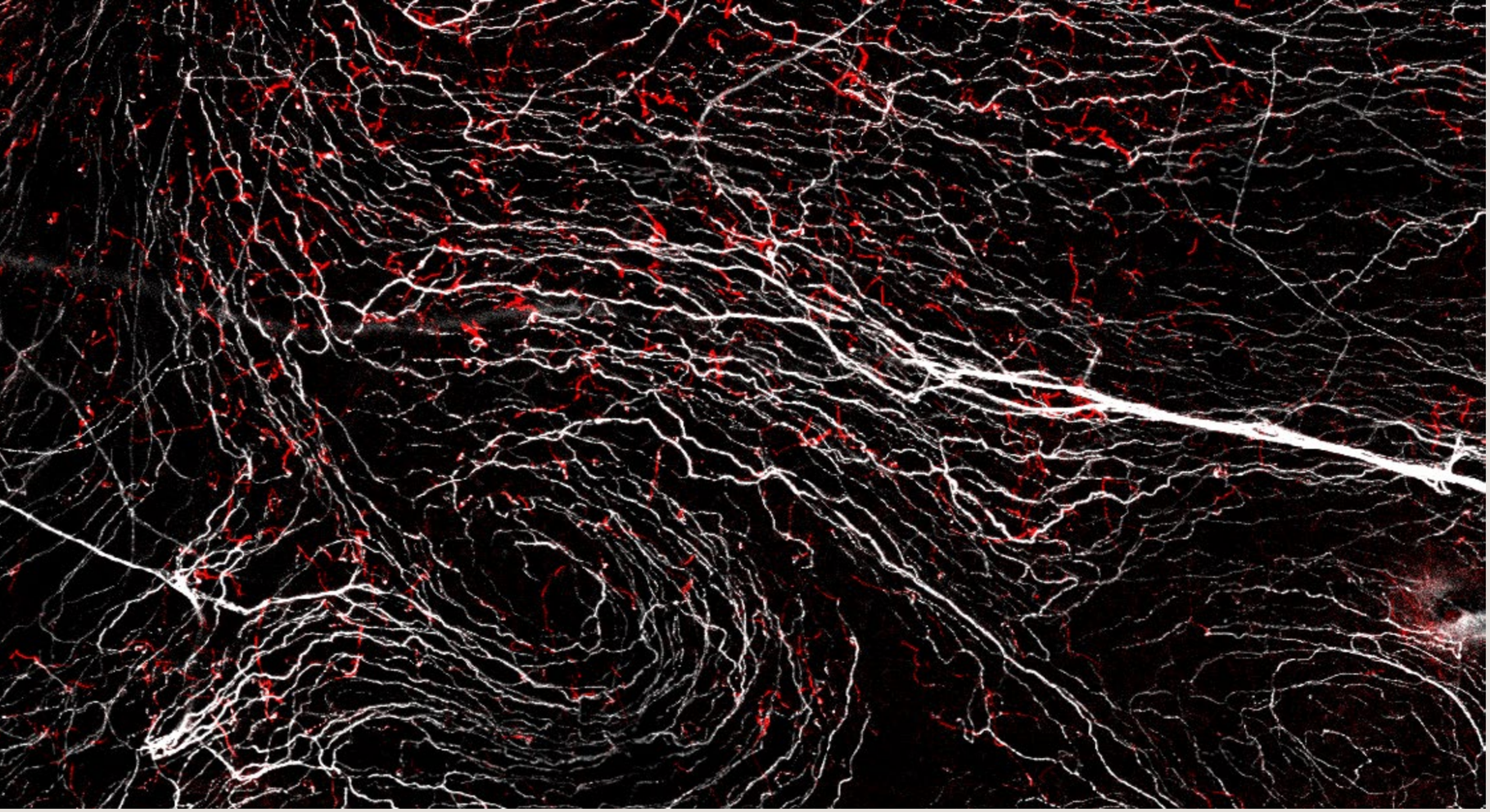


Sp8_ Translational research of neurological and psychiatric disorders



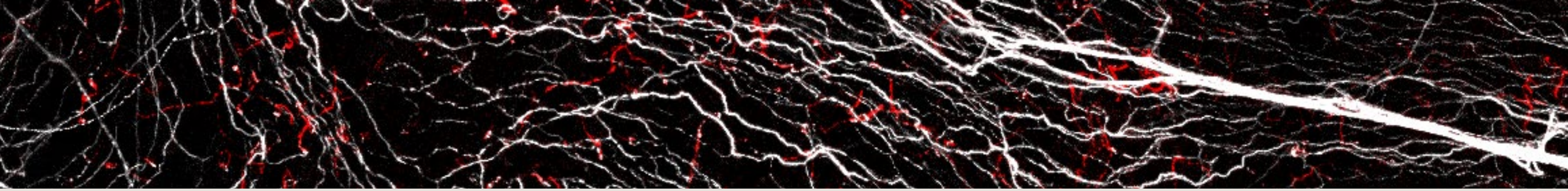
Ocular Neurobiology

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 as well as for the trophic maintenance of ocular tissues. This sensory input is also used by the CNS 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 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 ageing, 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 with the use of different ophthalmic drugs, and 4) the role of the ocular surface nerve activity in regulation by the CNS of basal and reflex tearing, and blinking.

At the present time, the ONG studies the neural mechanisms responsible for the regulation of ocular surface wetness. The group is studying the molecular and cellular mechanisms underlying spontaneous and stimulus-evoked sensory nerve activity, and the role of trigeminal sensory input in the reflex regulation of tear production and blinking, as well as their changes with injury, ageing, dry eye and contact lens wearing.



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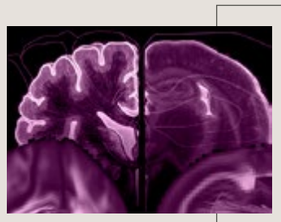
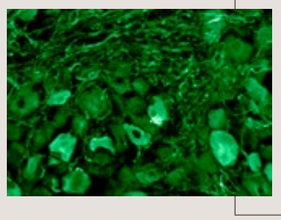


Sp7_Human cognition & behaviour



Sp5_Neurobiology of pain & inflammation

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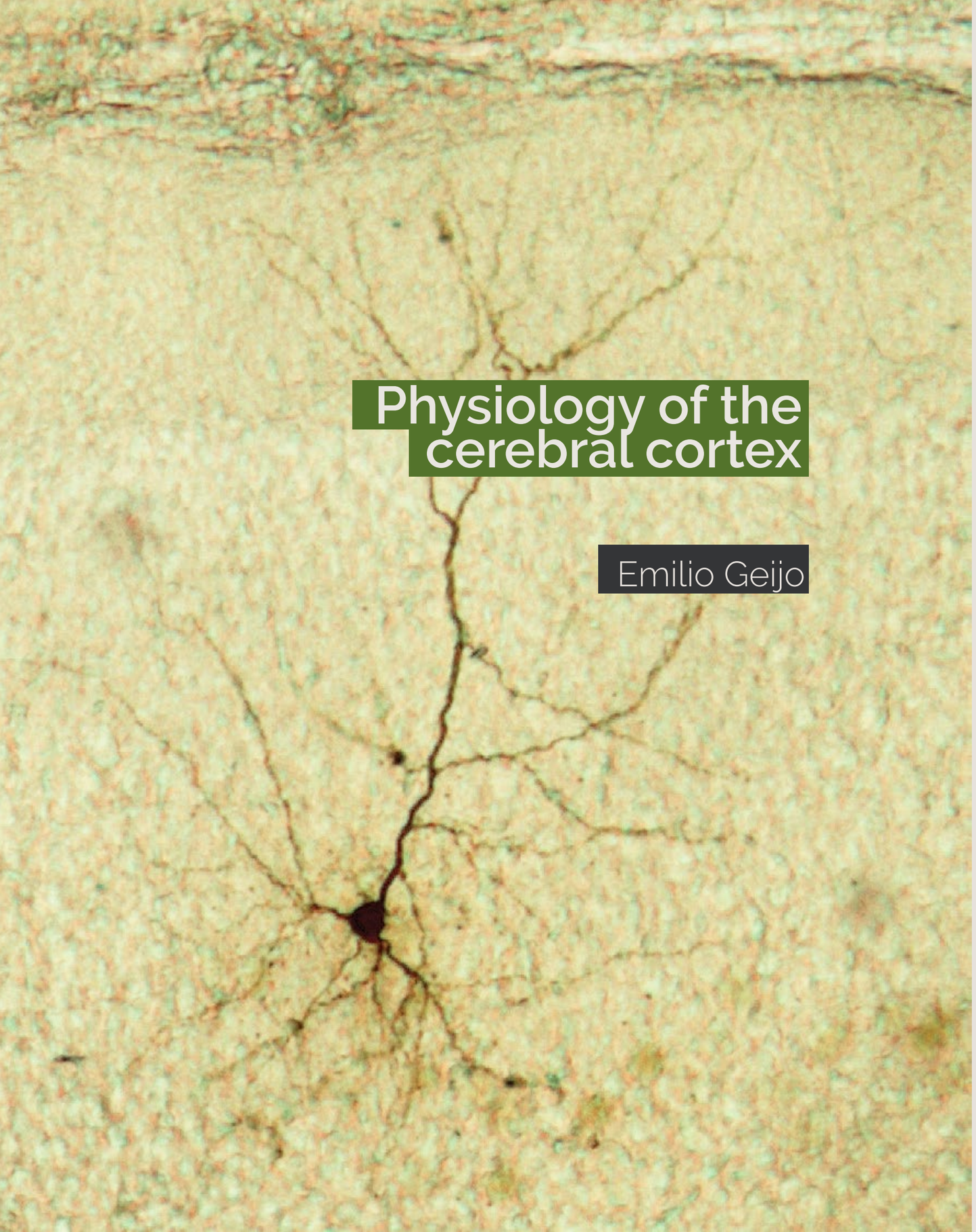

Physiology of the cerebral cortex

Emilio Geijo

Our group is interested in the study of the basic physiological mechanisms of the cortical local microcircuits, in particular of the prefrontal cortex and the anterior cingulated cortex; These cortical areas are implicated in cognitive functions and very specially in short term memory or working memory; also, they are densely innervated by dopaminergic and serotoninergic fibers originated in the diencephalon and brainstem which contribute to the modulation of cortical functions. We use intracellular recording with patch electrodes and microelectrodes in pyramidal and non-pyramidal cortical neurons visually identified with infrared video microscopy and Nomarski optics; in these neurons we record membrane potential and currents and synaptic responses. The specific objectives of our work are the study of:

- The intrinsic electrophysiological properties of pyramidal and non-pyramidal neurons and their modulation by dopamine and serotonin.
- The mechanisms of excitatory and inhibitory synaptic transmission in the cortex, the modulation of these mechanisms by dopamine and serotonin and the role of intrinsic properties in the mechanisms of synaptic integration.
- The electrophysiological responses of a mouse genetically modified that is a model of a human cerebral disease: the Lis1 gene mutant mouse (in man, the mutations of the LIS1 gene produce lissencephaly). The experimental work focused on the last objective is carried out in collaboration with Dr Salvador Martínez (*Instituto de Neurociencias*).

In addition to the above line of work, and in collaboration with members of Service of Clinical Neurophysiology of the San Juan University Hospital, we are developing a clinical research line of work focused on the study of the mechanisms of generation and the diagnostic value of the F-wave, which is a late component of the human electromyogram (EMG); this electrophysiological response is important in the diagnosis of diverse neuromuscular diseases and also it can be used to study the excitability of spinal motor neurons in normal and pathological conditions.

Relevant publications

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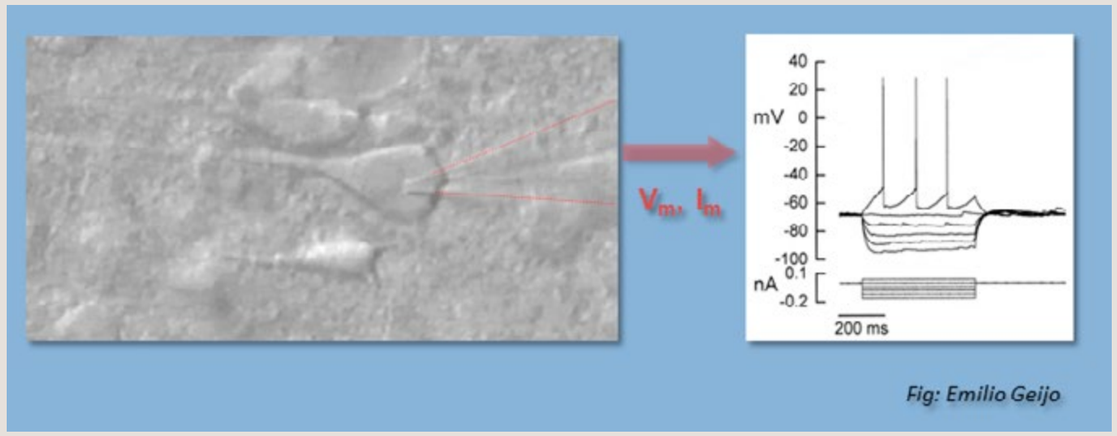

Fig: Emilio Geijo

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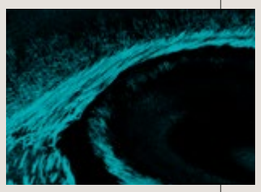
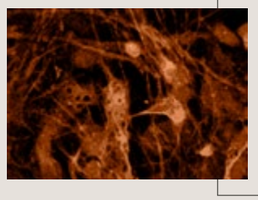


Sp4_Synaptic modulation of neural circuits and behavior



Sp8_ Translational research of neurological and psychiatric disorders

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 vertebrate cognition (rodent individuality and learning), our group currently concentrates 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" and also "frontier" in the scientific study of who we are as human beings. Back to the future, our conceptual umbrella and mission consists in exploring the forgotten grand hypothesis of the brain as "permissive" (rather than "productive") of thought, memory, perception, and consciousness.

Relevant publications

Gómez-Marín, A. (2022). **Transcending reductionism in neuroscience**. *Science*, 378(6620), 606. https://doi.org/10.1126/science.ade8689

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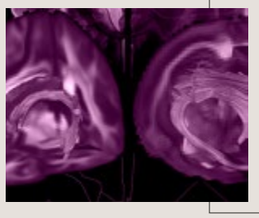

Sp7_Human cognition & behaviour

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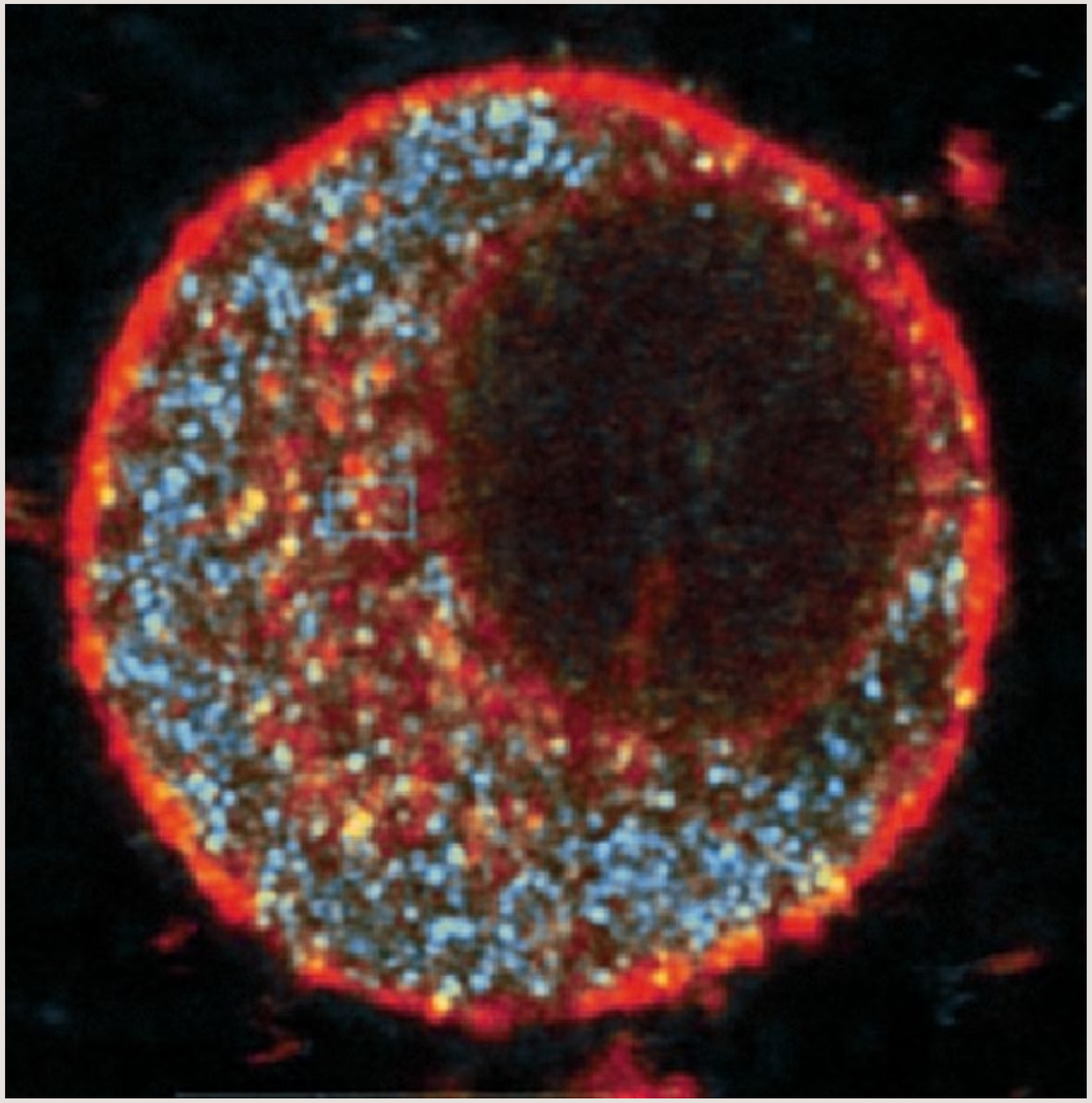
Graduate student
Fernando Casanova
Undergraduate student
Alex Sospedra

Curator and host of **The Future Scientist** conversation series (12 installments with prominent international scholars as guests).

Conversant in **The Matter with Things** dialogue series with psychiatrist, neuroscientist, and philosopher Iain McGilchrist (30 online installments with a total of 460K views on YouTube).

Conversant on science matters with *Rupert Sheldrake* (various recordings with a total of 100K views on YouTube as of May 2023).



Molecular mechanisms of neurosecretion

Luis M. Gutiérrez / Manuel Criado

Institute for Neuroscience UMH-CSIC

Adrenomedullary chromaffin cells have been used as an excellent experimental model to study the exocytosis and therefore the molecular mechanisms of neuro-transmission. 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 in two different aspects of the molecular mechanisms of neurotransmission:

Implication of the cytoskeleton in different aspects of neurosecretion and the determination of 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 on the secretory stages have 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 specially the function of FTY-720, an analog of shingosine, on exocytosis and cancer.

Relevant publications

Villanueva, J., Gimenez-Molina, Y., Davletov, B. and Gutiérrez, L.M. (2021) **Vesicle Fusion as a Target Process for the Action of Sphingosine and Its Derived Drugs.** *International Journal of Molecular Sciences,* 23(3), 1086. https://doi.org/10.3390/ijms23031086

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Darios, F.D., Jorgacevski, J., Flašker, A., Zorec, R., GarcíaMartinez, V., Villanueva, J., Gutiérrez, L.M., Leese, C., Bal, M., Nosyreva, E., Kavalali, E.T. and Davletov, B. (2017). **Sphingomimetic multiple sclerosis drug FTY720 activates vesicular synaptobrevin and augments neuroendocrine secretion.** *Science Reports,* 7, 5958. https://doi.org/10.1038/s41598-017-05948-z

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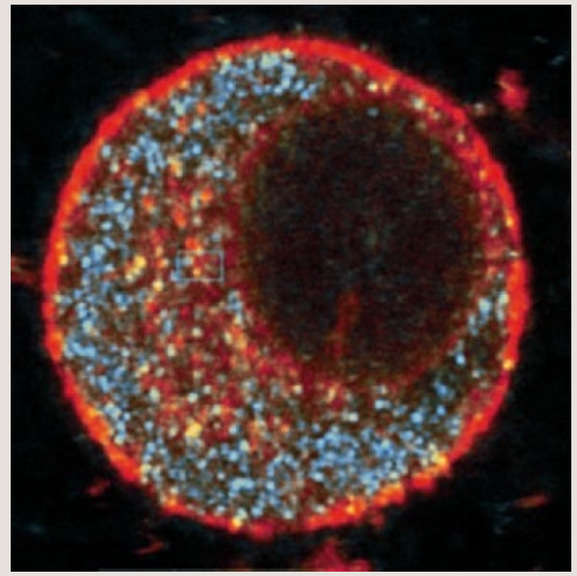

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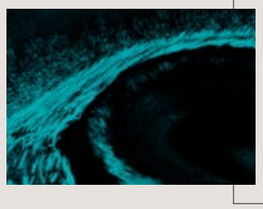
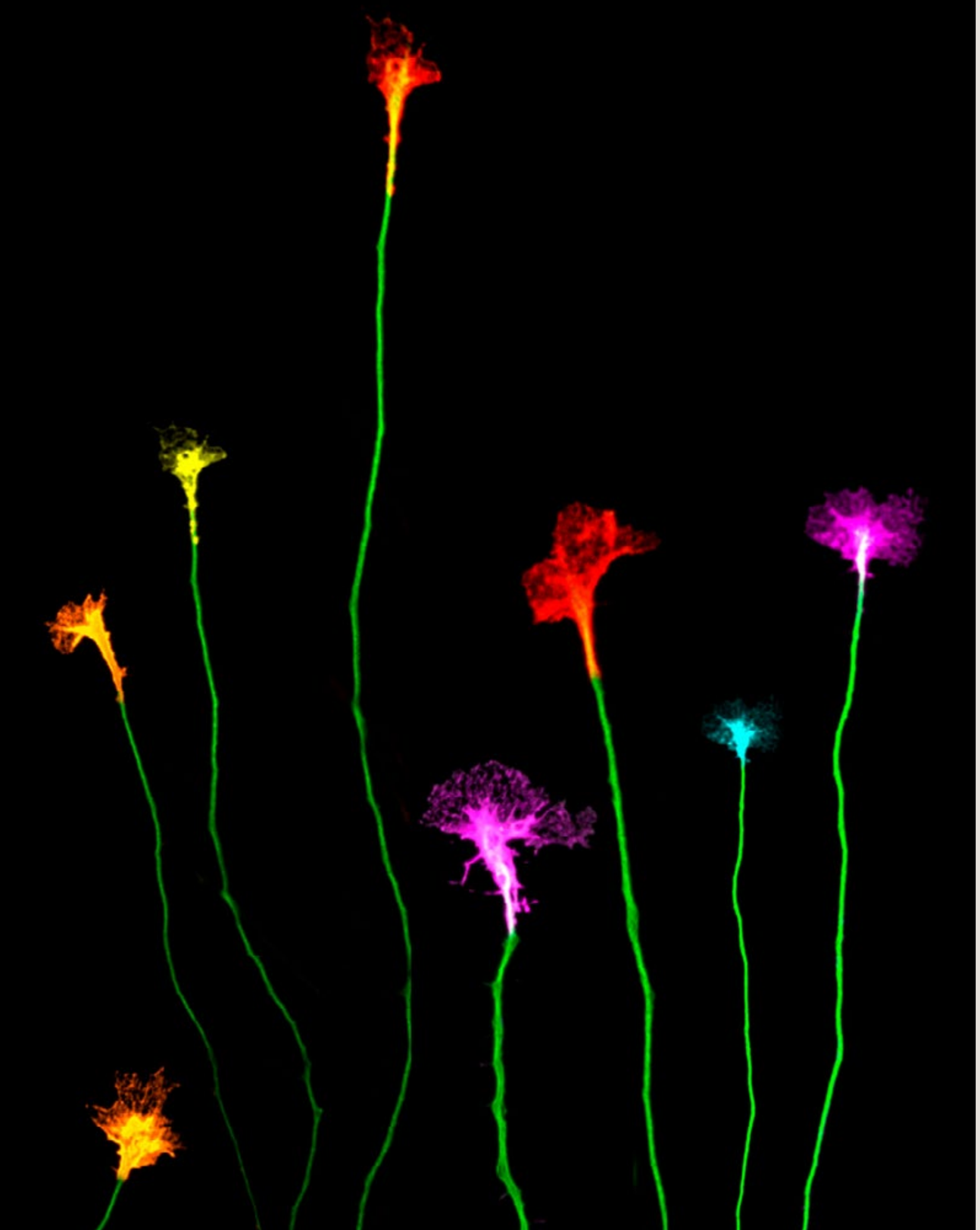


Sp4_Synaptic modulation of neural circuits and behavior

Carnations
Verónica Murcia Belmonte



Institute for Neuroscience UMH-CSIC

Generation and Regeneration of Bilateral Neural Circuits

Eloísa Herrera

For proper development and connectivity of the brain, it is crucial that the axons of the various neuronal types grow and direct themselves towards 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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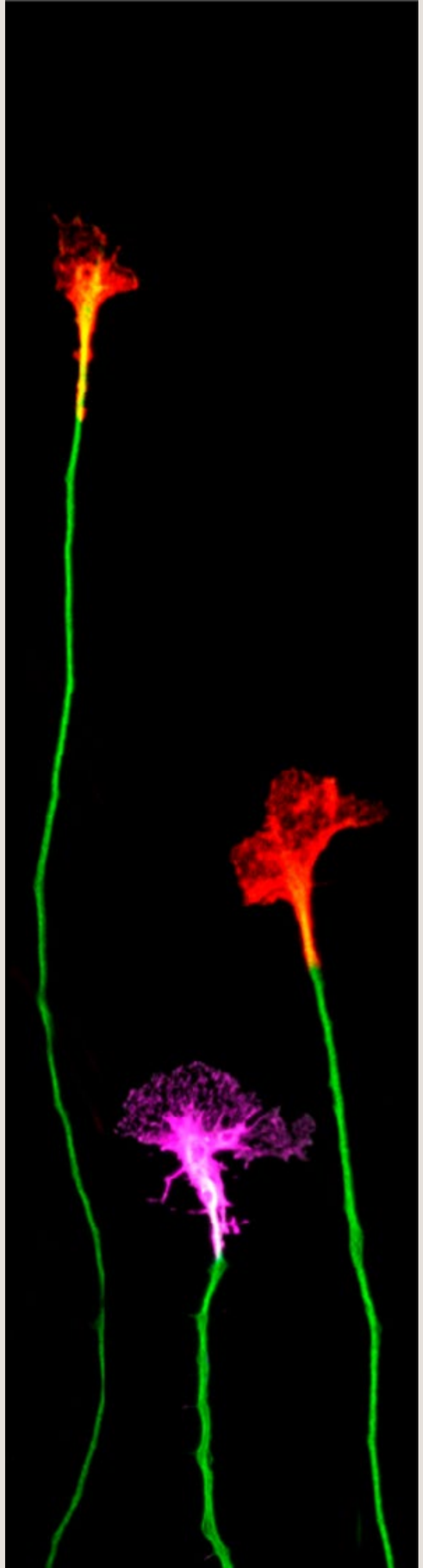
Murcia-Belmonte, V., Coca, Y., Vegar, C., Negueruela, S., de Juan Romero, C., Valiño, A., Sala, S., DaSilva, R., Kania, A., Borrell, V., Martinez, L.M,, Erskine, L. and Herrera, E. (2019). **A Retino-retinal Projection Guided by Unc5c Emerged in Species with Retinal Waves.** *Current Biology,* 29(7), 1149-1160. https://doi.org/10.1016/j.cub.2019.02.052

Fernández-Nogales, M., Murcia-Belmonte, V., Yu Chen, H. and Herrera, E. (2018). **The peripheral eye: A neurogenic area with potential to treat retinal pathologies?** *Progress in Retinal and Eye Research,* 68, 110-123. https://doi.org/10.1016/j.preteyeres.2018.09.001



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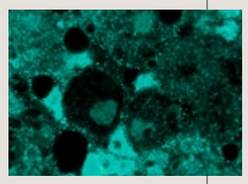
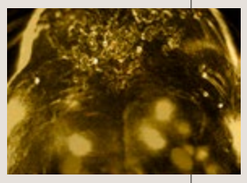
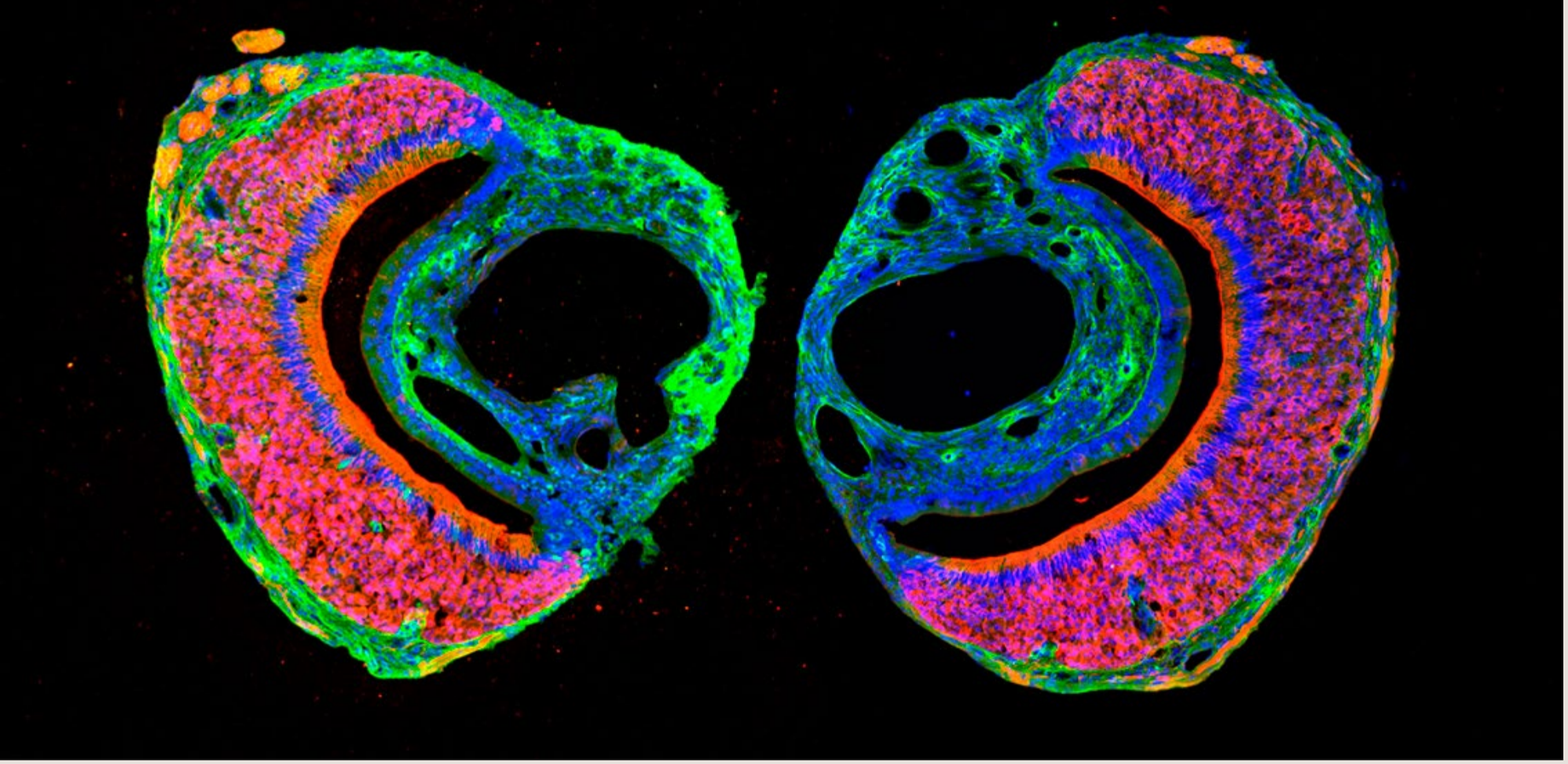


Sp1_ Neural stem cell regulation and differentiation



Sp3_ Building & adapting circuits into functional networks



Synaptic Neuromodulation

Sandra Jurado

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 in 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.

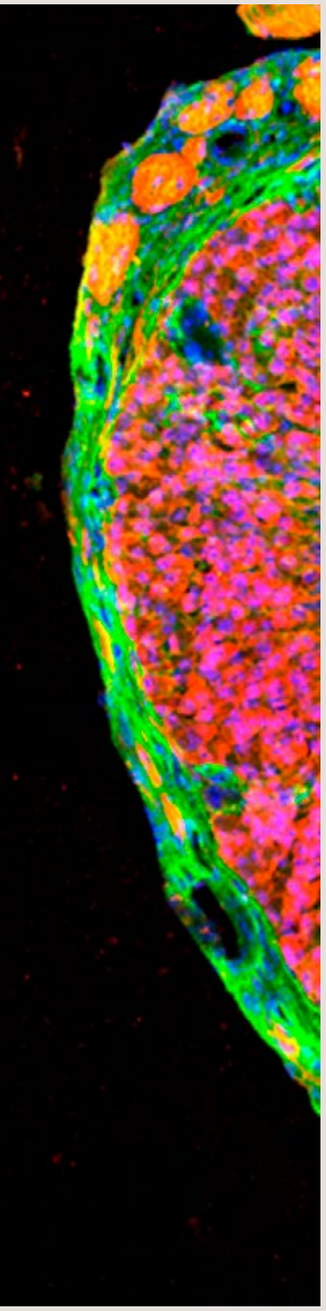
We currently work on three research lines:

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 hypothalamic circuits: 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 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

Royo, M., Escolano, B.A., Madrigal, M.P. and Jurado, S. (2022). **AMPA Receptor Function in Hypothalamic Synapses.** *Frontiers in Synaptic Neuroscience,* 14, 833449 - Review. https://doi.org/10.3389/fnsyn.2022.833449

Madrigal, M.P. and Jurado, S. (2021). **Specification of oxytocinergic and vasopressinergic circuits in the developing mouse brain.** *Communications Biology,* 4, 586. https://doi.org/10.1038/s42003-021-02110-4

Madrigal, M.P., Ballester-Lurbe, B., Gómez, O., Moreno-Bravo, J.A., Puelles, E., Jurado, S., Garcia-Verdugo, J.M,, Pérez-Roger, I. and Terrado, J. (2021). **Rnd3 is necessary for the correct oligodendrocyte differentiation and myelination in the central nervous system.** *Brain Structure and Function*, 227, 829-841. https://doi.org/10.1007/s00429-021-02419-0

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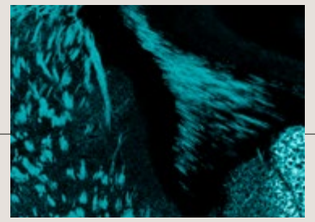
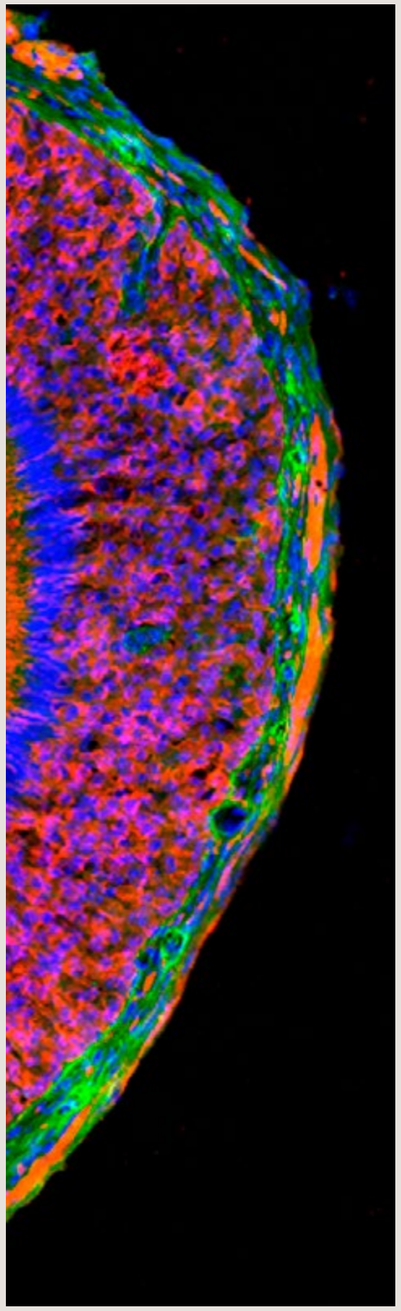
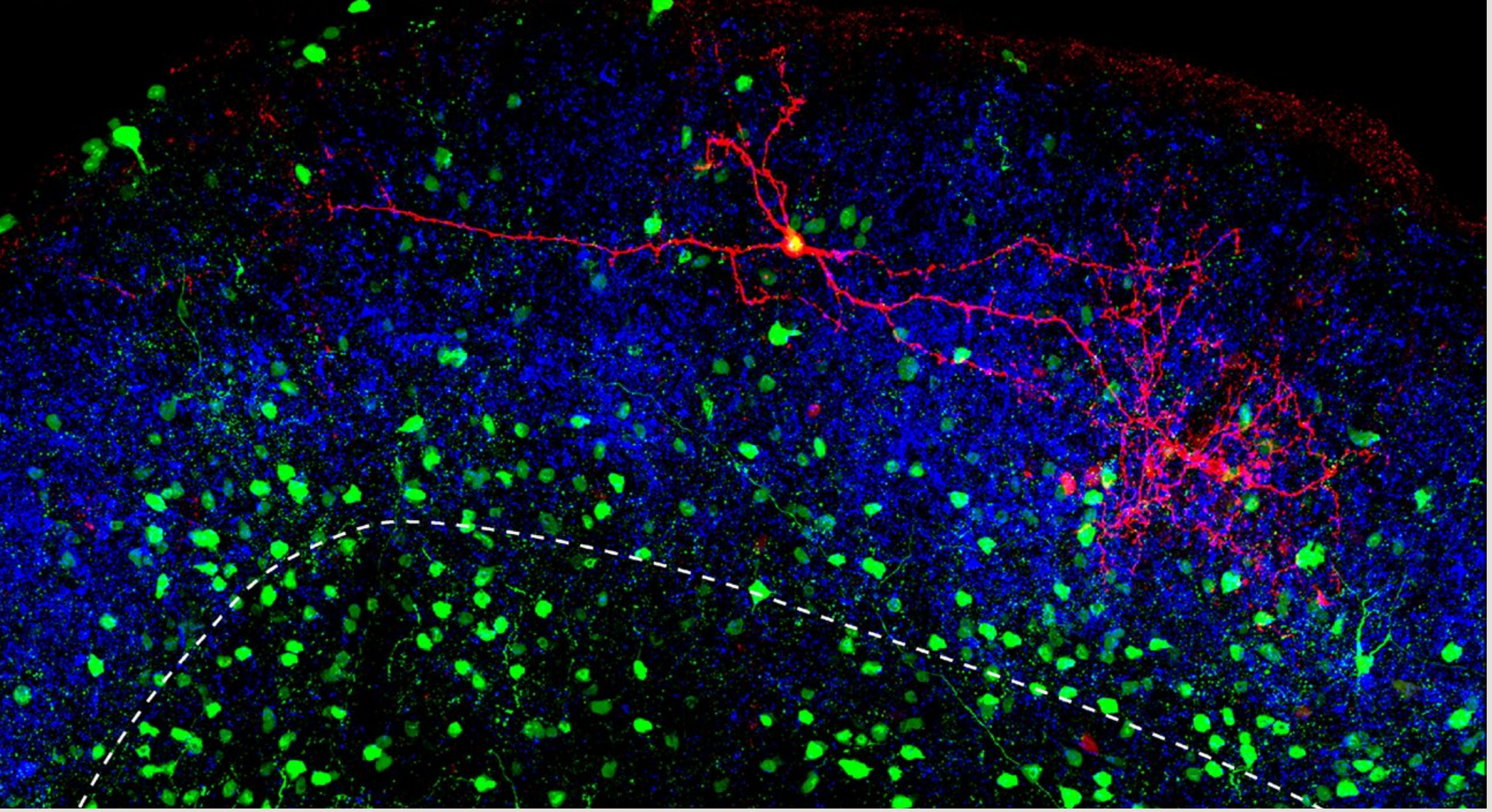


Sp4_Synaptic modulation of neural circuits and behavior





Neural circuits in vision for action

Andrea Kardamakis

How the nervous system achieves versatility in visuospatial behaviour is a fundamental, yet unresolved, question in neuroscience that requires a cross-disciplinary approach. Our group addresses this question in the context of neural circuits controlling visual-based orienting behaviour.

Research focus. Mammalian visuomotor circuit laboratory.

Orienting or 'paying attention' to visual events in our surroundings while ignoring irrelevant ones during various tasks highlights a main feature of selective visual attention, which aims to rapidly and accurately solve this dimensionality reduction and context-dependent classification problem.

One of our main research objectives is to obtain a mechanistic understanding of how neural circuits implement this computation by linking patterned visual input onto selected motor behaviour at: (A) the level of the individual neuron and (B) their synaptic interactions within visuomotor loops involving the retina, superior colliculus, frontocortical networks and substantia nigra. Our expertise lies in microcircuit and systems approaches that involve a combination of electrophysiology, optogenetics, viral-based approaches, behaviour

and computation.

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 computational principles underlying visual search behaviour, thereby, inspiring the creation of brain-like heuristic and learning approaches to real-world applications, such as machine vision and robotics.

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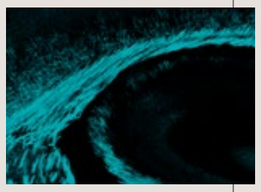

Sp4_Synaptic modulation of neural circuits and behavior

Relevant publications

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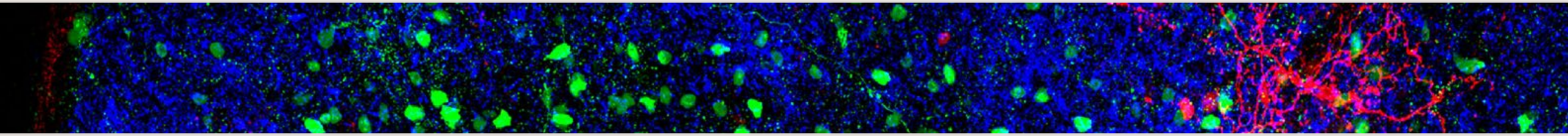

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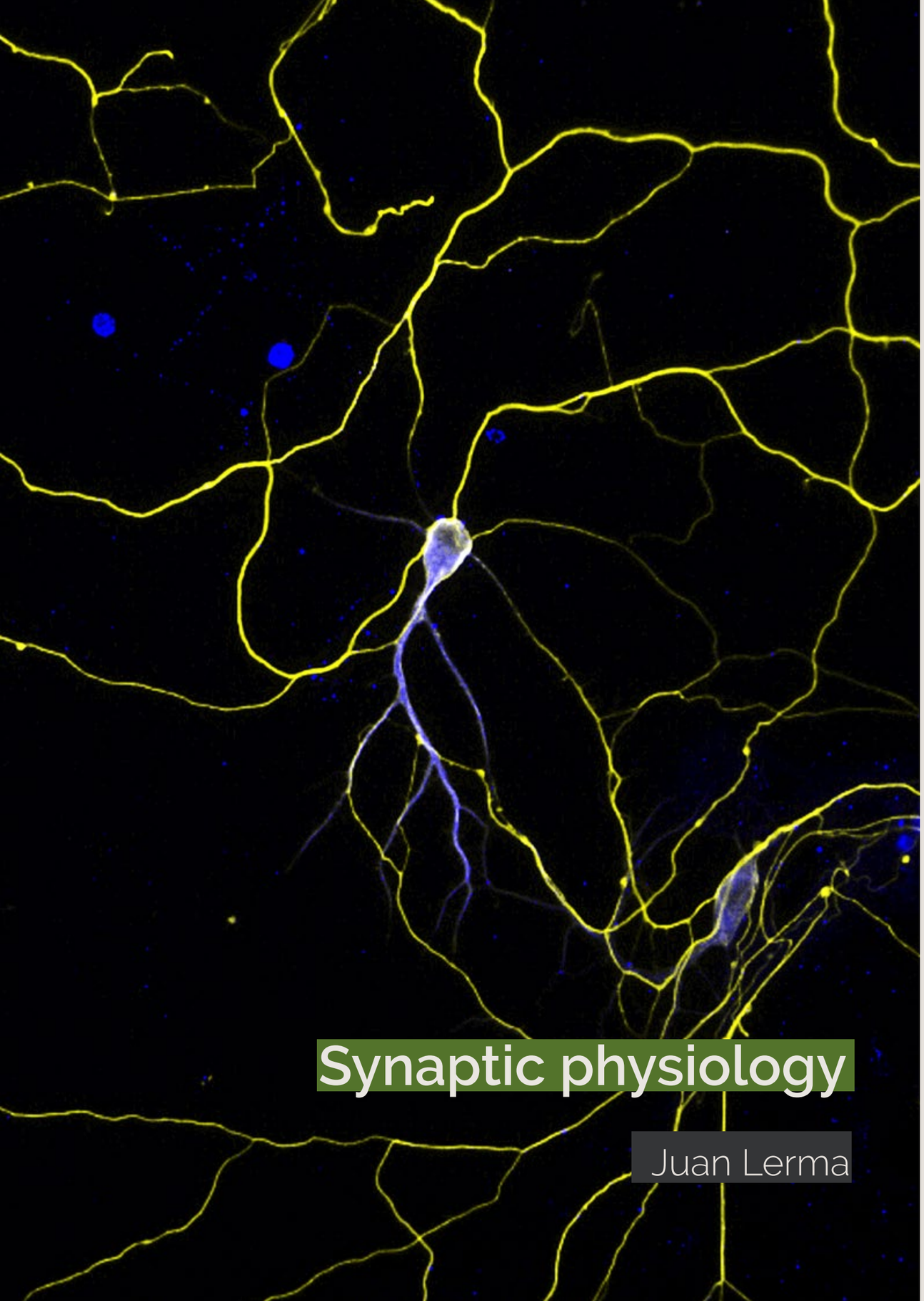
Kuisong Song



Synaptic physiology

Juan Lerma

Neurons communicate with each other by means of 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 signalling 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 receptors, 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 behavioural 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 behavioural 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. and Marques, 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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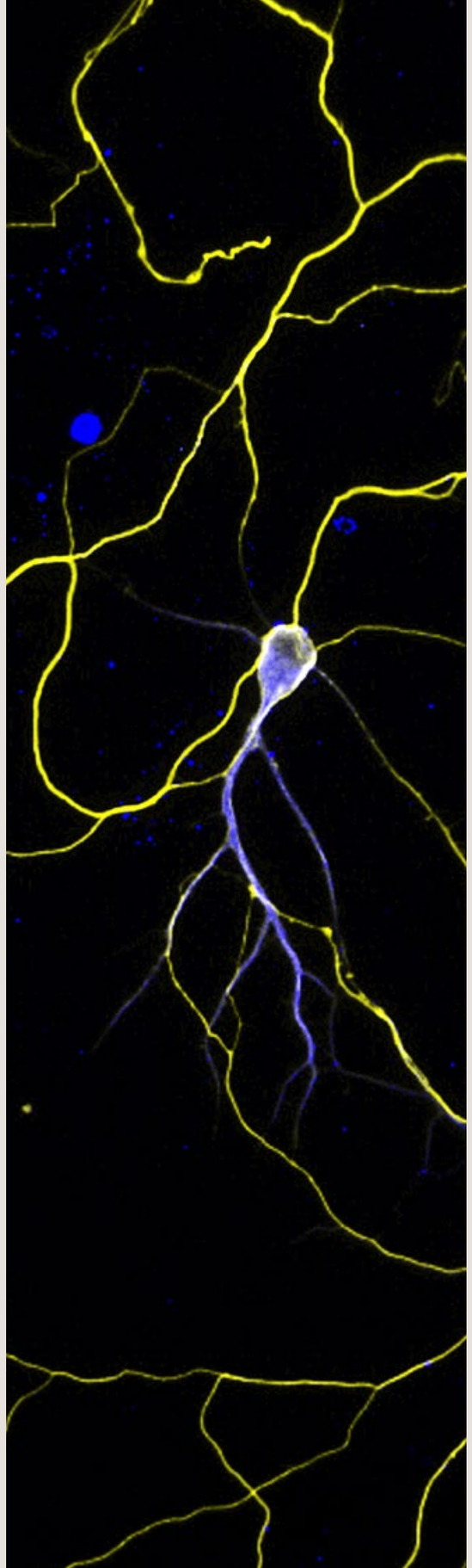

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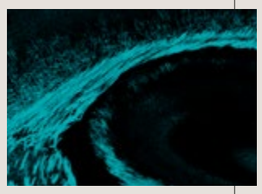

Sp4_Synaptic modulation of neural circuits and behavior

Cognition and social interactions

Felix Leroy

The cognition and social interactions laboratory investigate how cognitive information (past experiences and decisions) prioritize, determine and calibrate 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 and the Brain and Behavior Foundation.

Relevant publications

Merseburg, A., Kasemir, J., Buss, E.W., Leroy, F., Bock, T., Porro, A., Barnett, A., Tröder, S.E., Engeland, B., Stockebrand, M., Moroni, A., Siegelbaum, S.A., Isbrandt, D. and Santoro, B. (2022). **Seizures, behavioral deficits and adverse drug responses in two new genetic mouse models of HCN1 epileptic encephalopathy.** *eLife*, 11, e70826. https://doi.org/10.7554/eLife.70826

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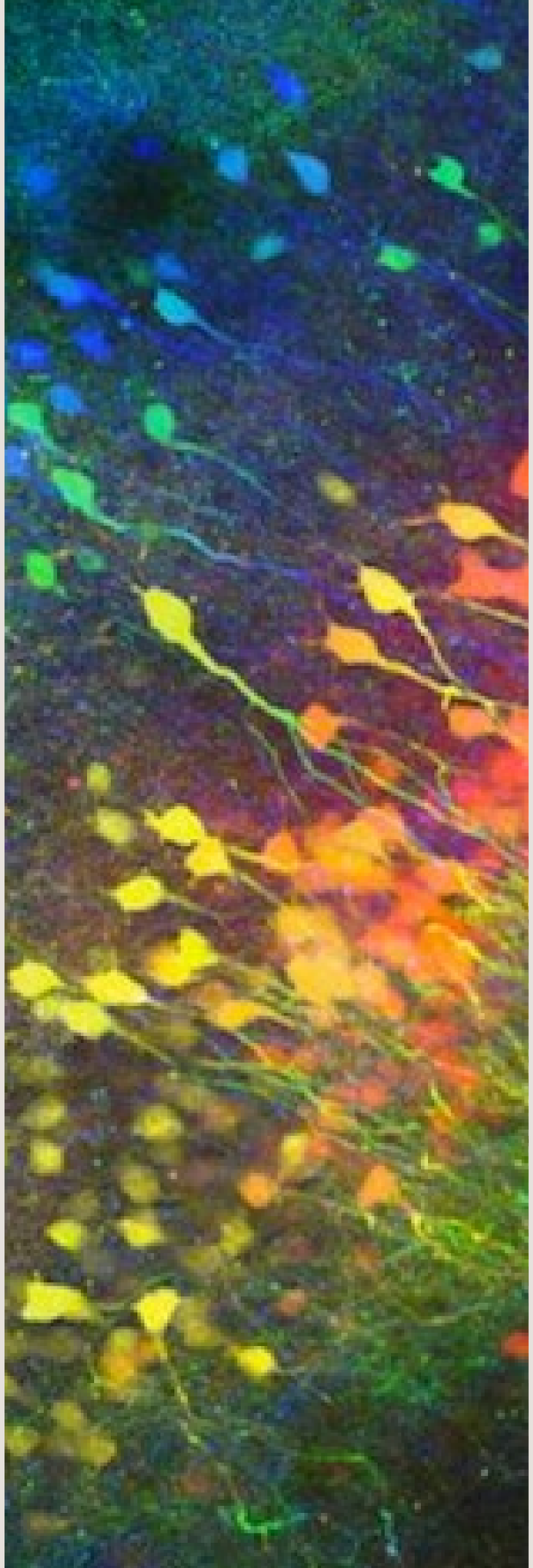

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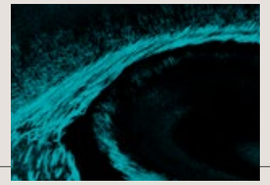
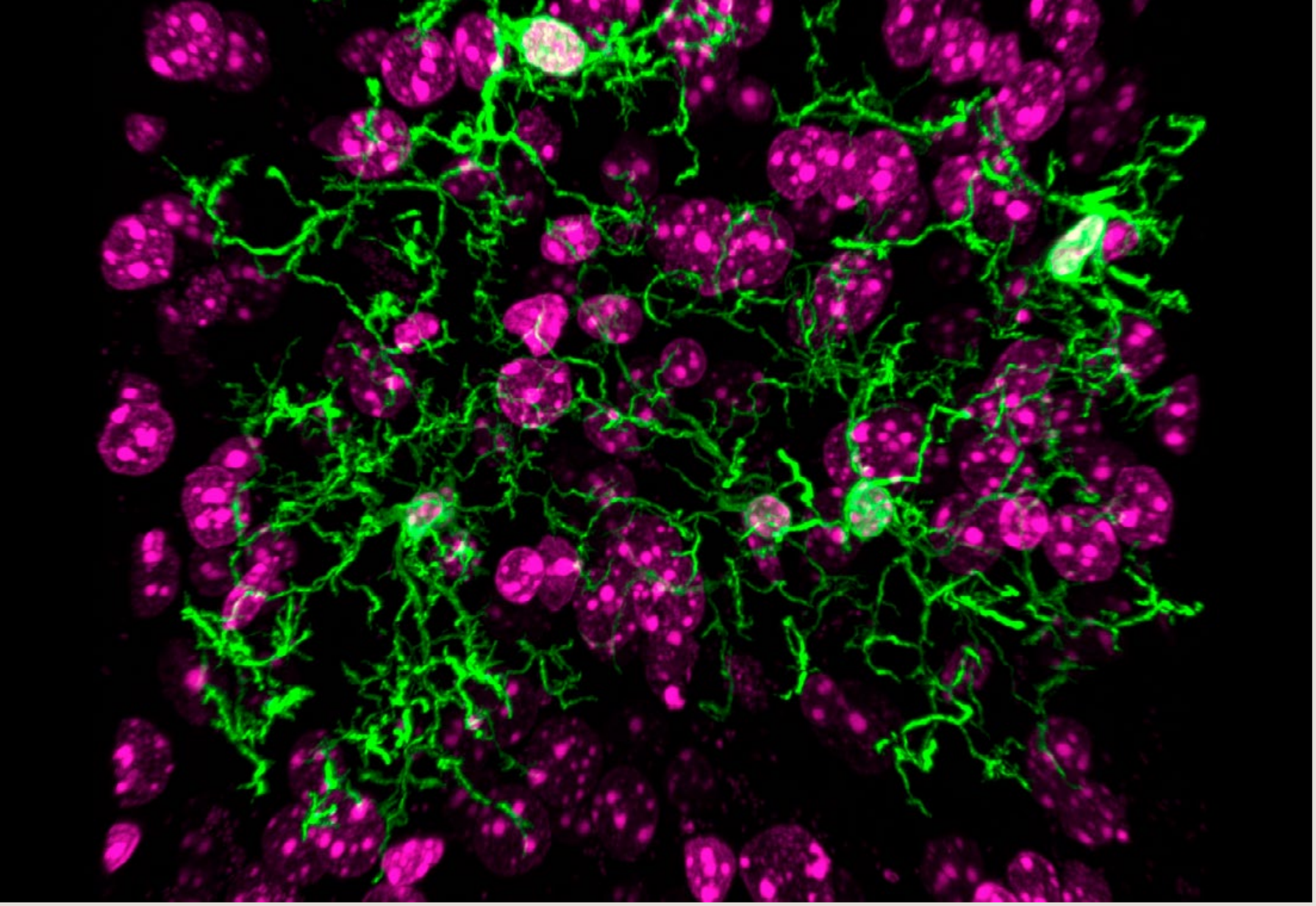
Sidonie Bourgoin
Technical Staff
Antonia Ruiz Pino
Yuki Nomura
Administration
Javier Paniagua Paniagua

Departamento:

Neurobiología celular y de sistemas



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 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 have particular interest in unveiling the core gene regulatory networks regulating the transitions and maintenance of distinct phenotypic and functional states of brain's innate immune cells. To this aim we combine genetic mouse models of Alzheimer's disease and postmortem brain samples from patients, genome-wide 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 most prevalent neurodegenerative conditions.

Relevant publications

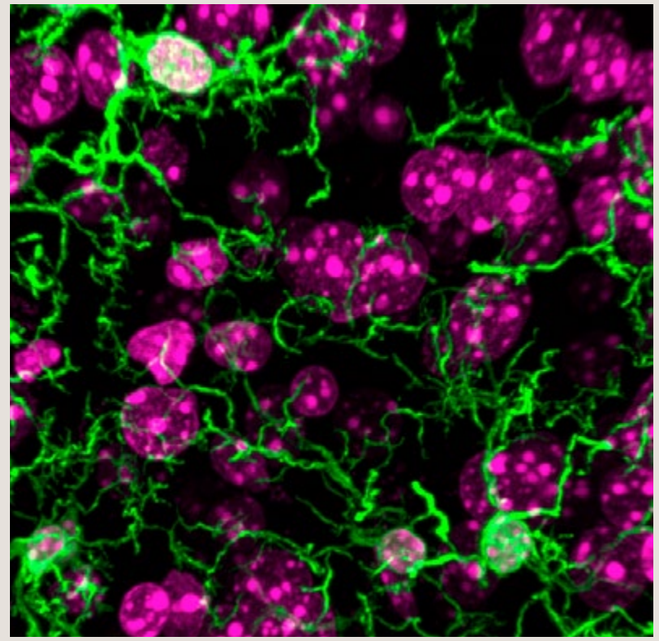
González-Martínez, R., Márquez-Galera, A., Del Blanco, B., López-Atalaya, J.P., Barco, A. and Herrera, E. (2022). **CBP and p300 jointly maintain neural progenitor viability but play unique roles in the differentiation of neural lineages.** *Cells*, 11(24), 4118. https://doi.org/10.3390/cells11244118

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

Marquez-Galera, A., de la Prida, L.M. and Lopez-Atalaya, J.P. (2022). **A protocol to extract cell-type-specific signatures from differentially expressed genes in bulk tissue RNA-seq.** *STAR Protocols,* 3(1), 101121. https://doi.org/10.1016/j.xpro.2022.101121

Linares, R., Gutiérrez, A., Márquez-Galera, Á., Caparrós, E., Aparicio, J.R., Madero, L., Payá, A., López-Atalaya, J.P. and Francés, R. (2022). **Transcriptional regulation of chemokine network by biologic monotherapy in ileum of patients with Crohn's disease.** *Biomedicine & Pharmacotherapy,* 147, 112653. https://doi.org/10.1016/j.biopha.2022.112653

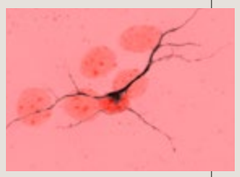
Chinnappa, K., Cárdenas, A., Prieto-Colomina, A., Villalba, A., Márquez-Galera, Á., Soler, R., Nomura, Y., Llorens, E., Tomasello, U., López-Atalaya, J.P. and Borrell, V. (2022). **Secondary loss of miR-3607 reduced cortical progenitor amplification during rodent evolution.** *Science Advances,* 8(2),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



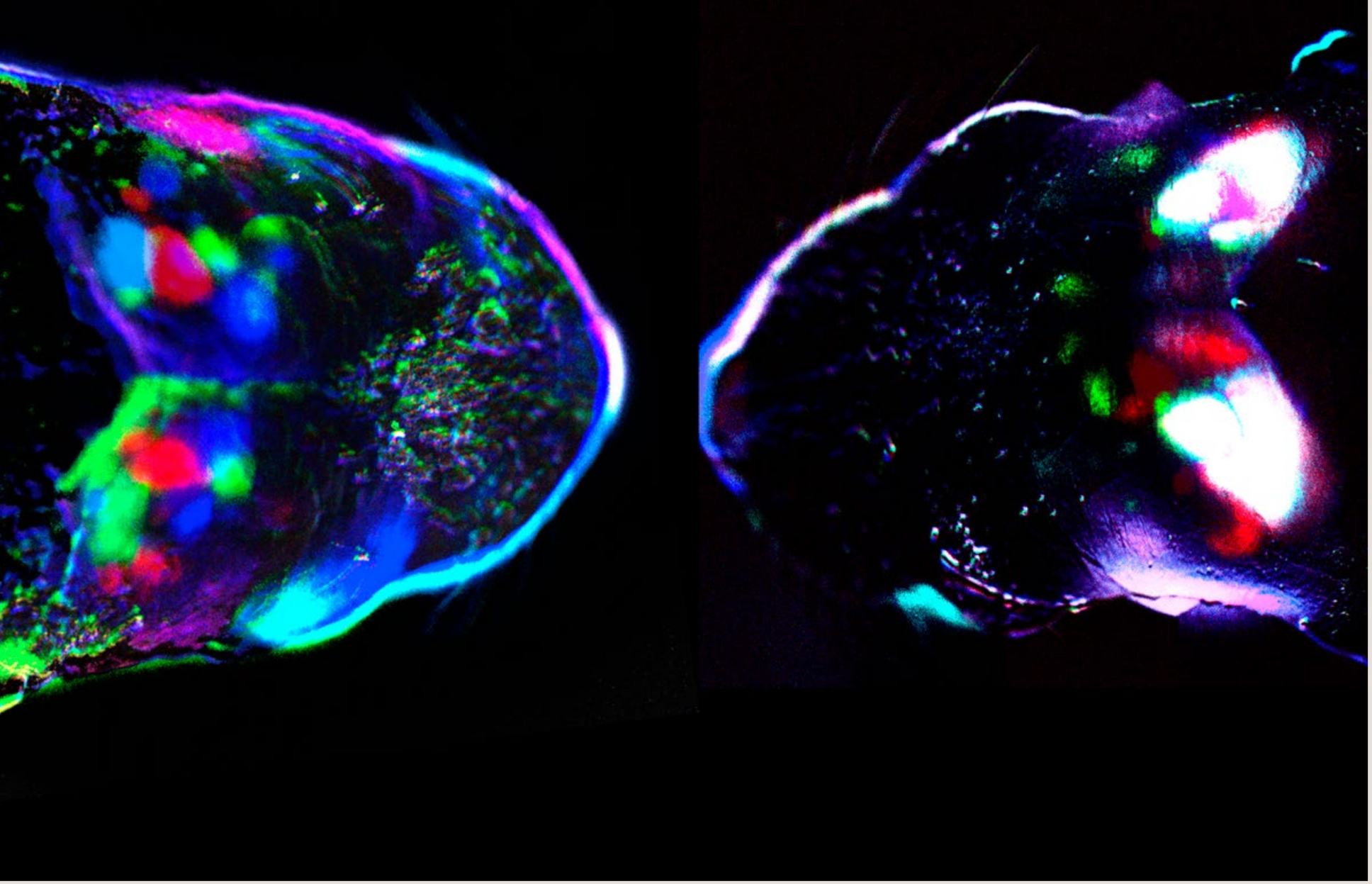
Principal Investigator
José P. López-Atalaya
PhD Investigator
Ángel Márquez Galera (desde 20/07/2022)
PhD Student
Angel Márquez Galera (hasta 19/07/2022)
Aysha M. Bhojwani Cabrera
Verónica López López
Master Students
Daniel Oppermann Peixoto
Technical Staff
Manuel Alejandro Expósito Coca

Department:

Molecular Neurobiology and Neuropathology



Sp2_Cell plasticity in brain disease and repair



Development, Plasticity and Reprogramming of Sensory Circuits

Guillermina López-Bendito

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 designing tools to restore defective neuronal connections in patients with sensory deficits, such as blindness or deafness).

Relevant publications

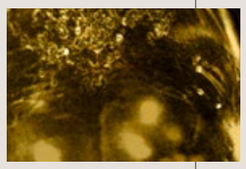
Guillamón-Vivancos, T., Aníbal-Martínez, M., Puche-Aroca, L., Moreno-Bravo, J.A., Valdeolmillos, M., Martini, F.J. and López-Bendito, G. (2022). **Input-dependent segregation of visual and somatosensory circuits in the mouse superior colliculus.** *Science*, 377(6608), 845-850. https://doi.org/10.1126/science.abq2960

Herrero-Navarr,o 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

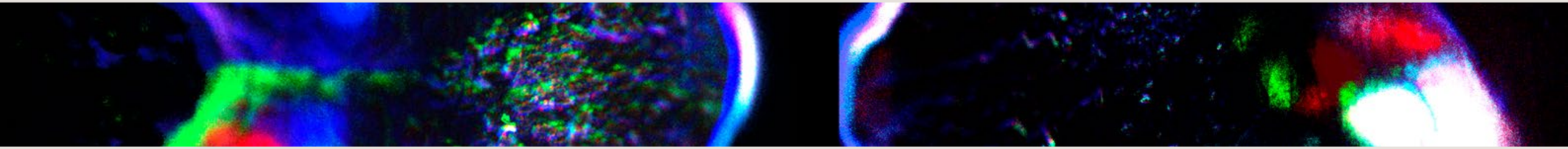
Martini, F.J., Guillamón-Vivancos, T., Moreno-Juan, V., Valdeolmillos, M. and López-Bendito, G. (2021). **Spontaneous activity in developing thalamic and cortical sensory networks.** *Neuron*, 109(16), 2519-2534. https://doi.org/10.1016/j.neuron.2021.06.026

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



Sp3_ Building & adapting circuits into functional networks



Department:

Developmental Neurobiology

Relevant information for the year 2022

Dra. López-Benditoco-organized the Spontaneous Activity in Brain Development SPONT22 Meeting in Alicante.

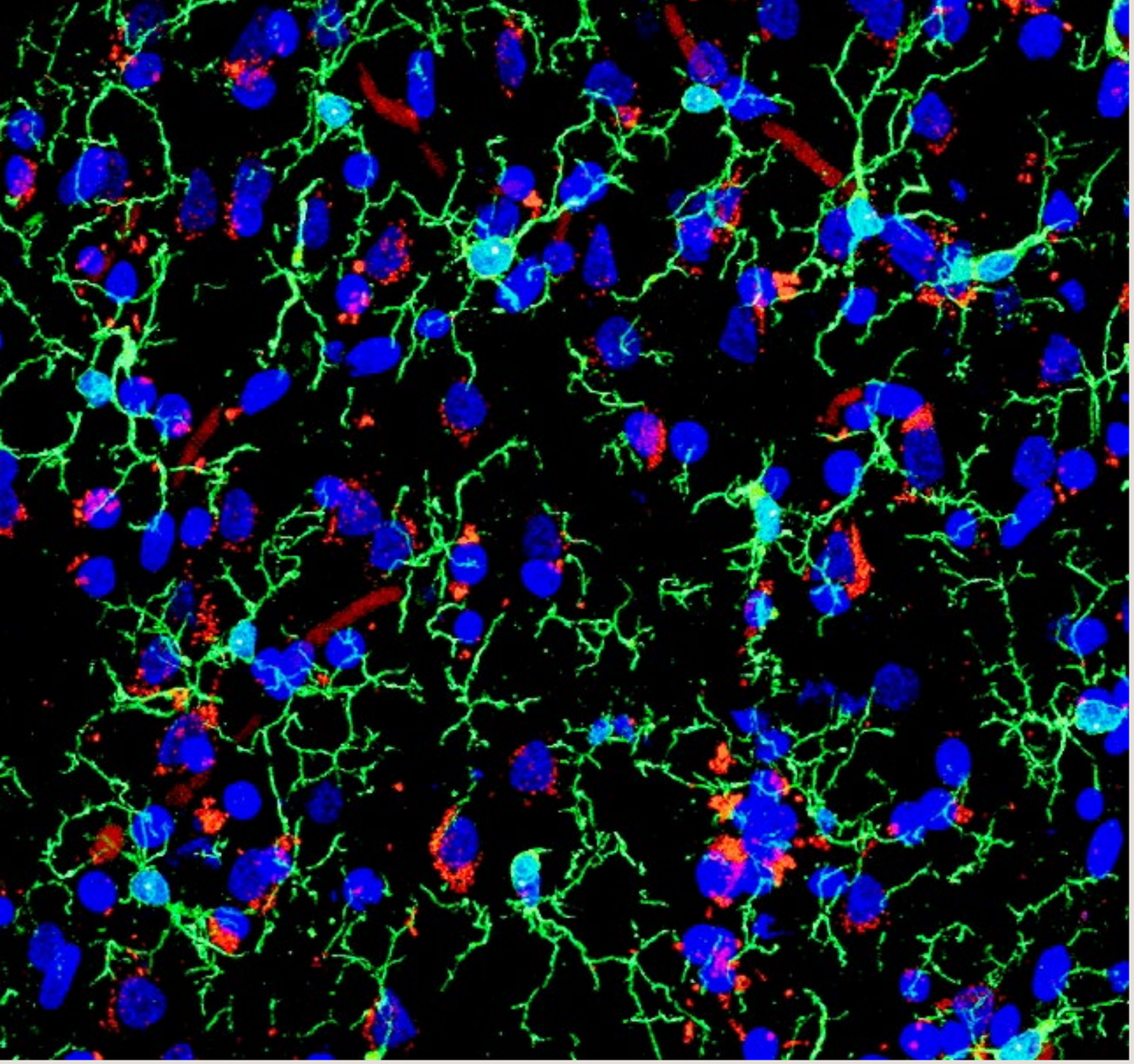
The team was awarded an ERC Advanced grant (€2,494,220) and a Ministry of Science & Innovation grant (€584,000), in addition to publishing 2 scientific articles and 1 review:

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

Genescu, I., Aníbal-Martínez, M., Kouskoff, V., Chenouard, N., Mailhes-Hamon, C., Cartonnet, H., Lokmane, L., Rijli, F.M., López-Bendito, G., Gambino, F. and Garel, S. (2022). **Dynamic interplay between thalamic activity and Cajal-Retzius cells regulates the wiring of cortical layer 1.** *Cell Reports,* 39(2), 110667. https://doi.org/10.1016/j.celrep.2022.110667

López-Bendito, G., Aníbal-Martínez, M. and Martini, F.J. (2022). **Cross-Modal Plasticity in Brains Deprived of Visual Input Before Vision.** *Annual Review of Neuroscience,* 45, 471-489. https://doi.org/10.1146/annurev-neuro-111020-104222

Principal Investigator
Guillermina López Bendito
Senior scientist
Francisco J. Martini
Miguel Ángel Valdeolmillos López
Investigador doctor
María Teresa Guillamón Vivancos
Daniel Torres Romero
Dorien Vandael
Emily Wilson
PhD Investigator
María Del Mar Aníbal Martínez
Irene Huerga Gómez
Chrysoula Giasafaki
Lorenzo Puche Aroca
Pablo Castellano Ruiz
Francesco Dori
Technical Staff
Luis Miguel Rodríguez Malmierca
Belén Andrés Bayón
María Aurelia Torregrosa Mira
Administration
Helena Campos Martín



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 in relation to 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 by means of real-time PCR techniques, as well as procedures for analysing protein expression by means of 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 benefit to patients.

Relevant publications

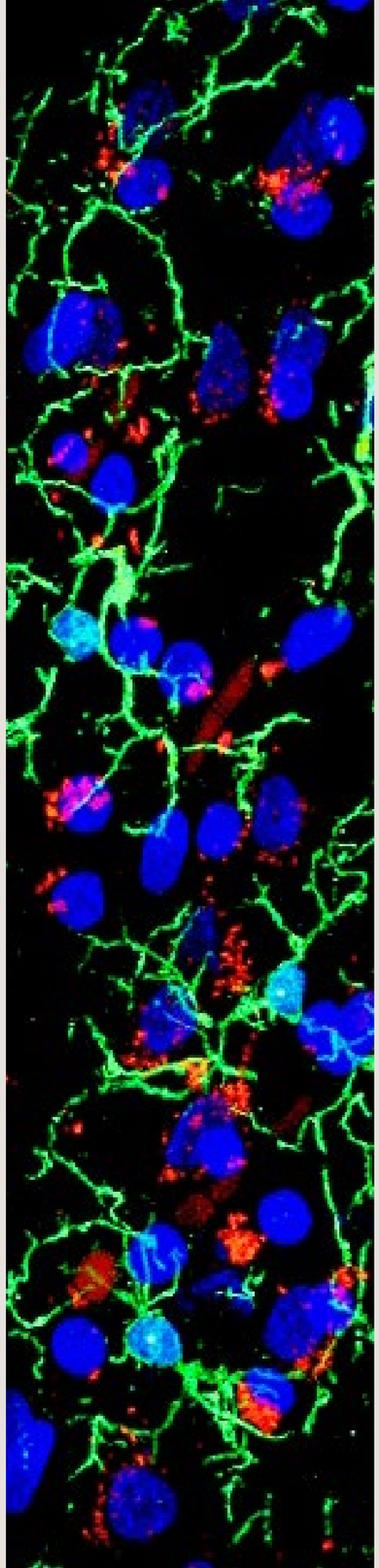
Gasparyan, A., Navarro, D., Navarrete, F. and Manzanares, J. (2022). **Pharmacological strategies for post-traumatic stress disorder (PTSD): From animal to clinical studies.** *Neuropharmacology*, 218, 109211 - Review. https://doi.org/10.1016/j.neuropharm.2022.109211

Navarro, D., Gasparyan, A., Navarrete, F., Torregrosa, A.B., Rubio, G., Marín-Mayor, M., Acosta, G.B., García-Gutiérrez, M.S. and Manzanares, J. (2022). **Molecular Alterations of the Endocannabinoid System in Psychiatric Disorders.** *International Journal of Molecular Science*, 23(9), 4764 -Review. https://doi.org/10.3390/ijms23094764

Navarrete, F., Gasparyan, A. and Manzanares, J. (2022). **CBD-mediated regulation of heroin withdrawal-induced behavioural and molecular changes in mice.** *Addiction Biology*, 27(2), e13150. https://doi.org/10.1111/adb.13150

Fernández-Miranda, J.J., Pascual-Pastor, F., Díaz-Fernández, 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

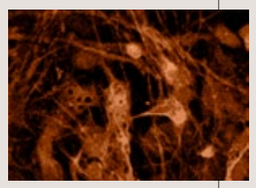
García-Gutiérrez, M.S., Navarrete, F., Gasparyan, A., Navarro, D., Morcuende, Á., Femenía, T. and Manzanares, J. (2022). **Role of Cannabinoid CB2 Receptor in Alcohol Use Disorders: From Animal to Human Studies.** *International Journal of Molecular Science,* 23(11), 5908 -Review. https://10.3390/ijms23115908



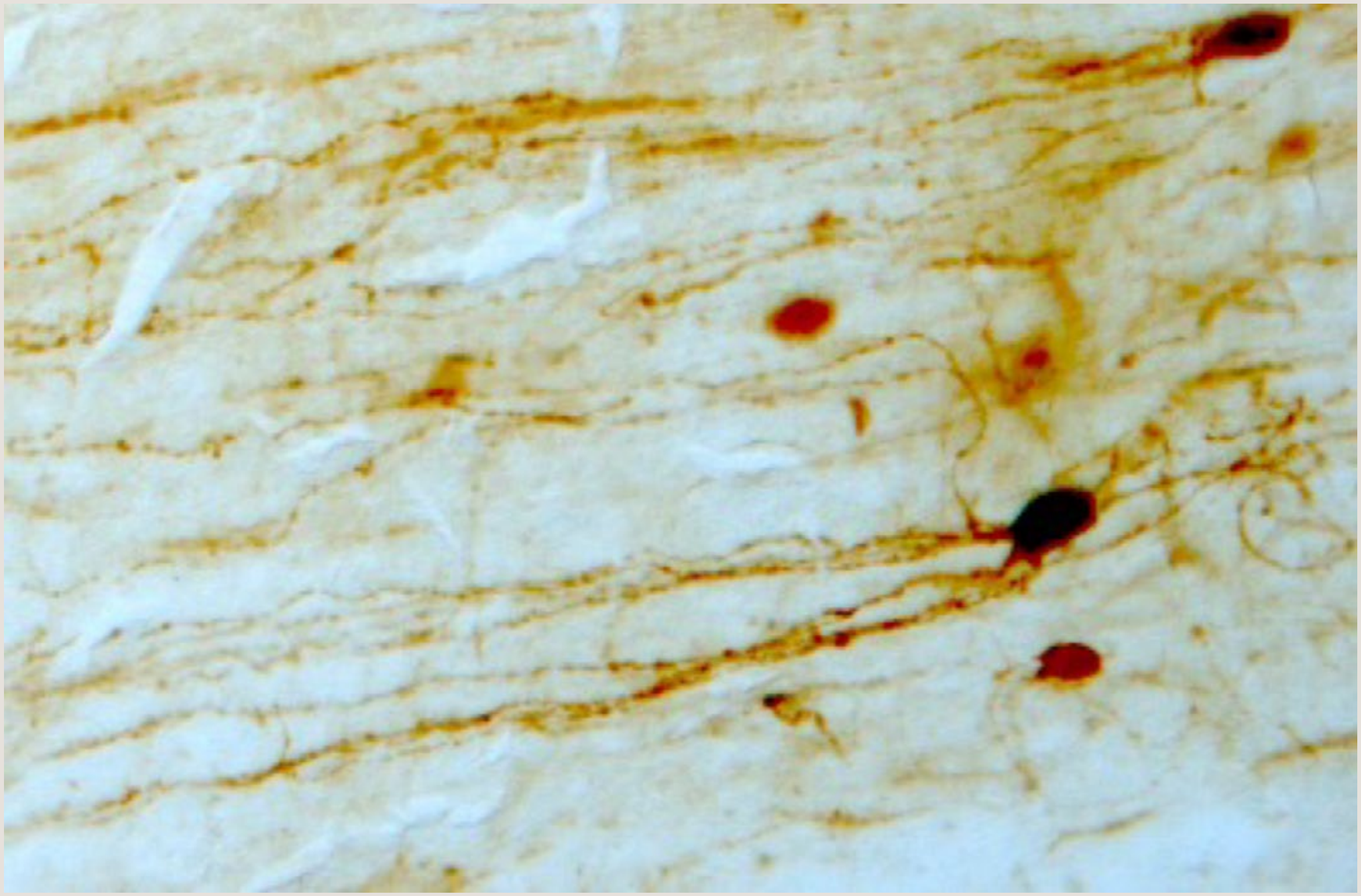
Principal Investigator
Jorge Manzanares
Professor Colaborator
María Salud García Gutiérrez
Francisco Navarrete Rueda
Daniela Vanesa Navarro
Ani Gasparyan Hovhannisyan
PhD Student
Amaya Austrich Olivares
Abraham Bailén Torregrosa
Master Student
Luisa Gutiérrez Esteve
Visitor
Przemyslaw Danek (Maj Institute, Polonia)
Dawid Gawlinski (Maj Institute, Polonia)
Kinga Gawlinska (Maj Institute, Polonia)

Departamento:

Neurobiología molecular y neuropatología



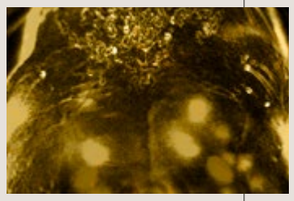
Sp8_Investigación traslacional de las enfermedades neurológicas y psiquiátricas



Neurobiology of mental, neurodegenerative and neuro-oncological diseases

Salvador Martínez / Diego Echevarría / Eduardo de Puelles

We have continued with the study of the structural and functional alterations mediated by Lis1 expression deficits in the cerebral cortex of animal models. Two electrophysiological studies have showed that Lis1/sLis1 heterozygous mice (with deletion of exon1 of Lis1) present alterations in the position of interneurons in the cerebral cortex, with a clear functional translation in the electrical properties of cortical circuits (1,2). These results have served to strengthen our hypothesis of using e Lis1 expression as an experimental approach to develop mental illness animal models. On the other hand, we have continued our work on the neurobiological mechanisms of immunological tolerance and tumor infiltration of glioblastoma multiforme cells in the cerebral cortex, by studying the secretome of pericytes with a molecular blockade of chaperone-mediated autophagy. Given that this autophagy is controlling the process of vascular coaptation, conditioning vascular coaptation underlay immune conditioning and blocking the secretion of antitumor molecules by these cells (3). In relation to our activity in the clinical trial of new therapeutic drugs for ALS, we have participated in the publication of a participated in the publication of a consensus article at the level of European groups interested in this disease (4). Finally, the work on the development of limbic system tracts and regions, with special attention to the habenular region and the retroflex fasciculus have led to two original publications (5,6).



Sp3_ Building & adapting circuits into functional networks

Relevant publications

Domínguez-Sala, E., Andreu-Cervera, A., Martín-Climent, P., Murcia-Ramón, R., Martínez, S. and Geijo-Barrientos, E. (2022). **Properties of the epileptiform activity in the cingulate cortex of a mouse model of LIS1 dysfunction.** *Brain Structure and Function,* 227, 1599-1614. https://doi.org/10.1007/s00429-022-02458-1

Domínguez-Sala, E., Valdés-Sánchez, L, Canals, S, O. Reiner, A. Pombero, R. Garcia-López, A. Estirado, D. Pastor, E. Geijo Barrientos and S. Martínez. (2022). **Abnormalities in Cortical GABAergic Interneurons of the Primary Motor Cortex Caused by Lis 1 (Pafah 1b1) Mutation Produce a non-drastic functional phenotype.** *Frontiers in Cell and Developmental Biology,* 10, 769853. https://doi.org/10.3389/fcell.2022.769853

Molina, M.L., Garcia Bernal, D., Salinas, M.D., Martínez, S. and Valdor, R. (2022). **Chaperone-Mediated Autophagy Ablation in Pericytes Reveals New Glioblastoma Prognostic Markers and Efficient Treatment Against Tumor Progression.** *Frontiers in Cell and Developmental Biology*, 10, 797945. https://doi.org/10.3389/fcell.2022.797945

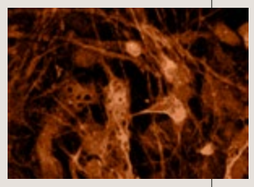
Mitrečić, D., Hribljan, V., Jagečić, D., Isaković, J., Lamberto, F., Horánszky, A., Zana, M., Foldes, G., Zavan, B., Pivoriūnas, A., Martinez, S., Mazzini, L., Radenovic, L., Milasin, J., Chachques, J.C., Buzanska, L., Song, M.S. and Dinnyés, A. (2022). **Regenerative Neurology and Regenerative Cardiology: Shared Hurdles and Achievements**. *International Journal of Molecular Science*, 23(2): 855. https://doi.org/10.3390/ijms23020855

Company, V., Murcia-Ramón, R., Andreu-Cervera, A., Aracil-Pastor, P., Almagro-García, F., Martínez, S., Echevarría, D. and Puelles, E. (2022) **Adhesion molecule Amigo2 is involved in the fasciculation process of the fasciculus retroflexus.** *Developmental Dynamics*, 251(11): 1834-1847. https://doi.org/10.1002/dvdy.513

Callejas-Marin, A, Moreno-Bravo, J.A., Company, V., Madrigal, P., Almagro, F., Martinez S and Puelles E. (2022). **Gli2-Mediated Shh Signaling is required for thalamocortical projection Guidance**. *Frontiers in Neuroanatomy*, 16, 830758 http://doi.org/10.3389/fnana.2022.830758

Department:

Developmental Neurobiology



Sp8_ Translational research of neurological and psychiatric disorders

Principal Investigator
Salvador Martínez Pérez
Eduardo de Puelles Martínez de la Torre
Diego Echevarria Aza
Collaborating professor
Mari Carmen Lillo
PhD Investigator
Raquel García López
Ana Isabel Pombero García
Diego Pastor Campos
María Luisa Molina
Pilar Madrigal Verdú
Nicanor Morales
Verónica Company Devesa
Marta Martínez
Abraham Andreu Cervera
PhD Student
Iris Juárez
Claudia García
Antonio Guillermo Almenar Such
Technical Staff
Francisca Almagro García
Mónica García Abad
Graduate students
Lucia Serralta Ferrer
José Martín Murciano López
Paula Aracil Pastor
Lorena Martínez Hostyn
Candela Palimera Beneiro
José Manuel Hernández López
Cristina Medina Hernández
Administration
María Jesús Arencibia Rojas

Presentation of the following posters

Name: Claudia Garcia
Poster: Therapeutical approach for a novel in vitro model of X-linked adrenoleukodystrophy
Author/s: Claudia Perez Garcia, Maria Luisa Molina-Gallego, Carlos Bueno, Emilio Geijo-Barrientos, Salvador Martínez,

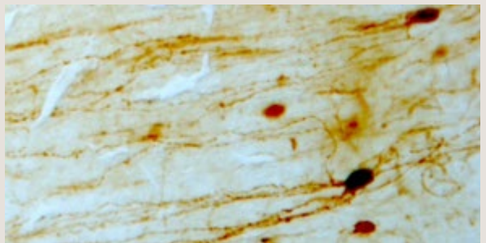
Name: Emilio Geijo Barrientos
City: Paris, France
Poster: Effects of Lis1 gene loss in parvalbumin expressing cells on the mouse cerebellar cortex
Author/s: Emilio Geijo-Barrientos, Abraham Andreu-Cervera, Ana María Jiménez, Francisca Almagro-García, Diego Echevarría, Salvador Martínez

Name: Raquel García López
Poster: Alterations in the Anterior Cingulate area and Dentate Gyrus in Lis1 Mutant Mouse Underlies A Schizophrenia-Like Phenotype
Author/s: Raquel Garcia Lopez, Ana Pombero, Alicia Estirado, Emilio Geijo-Barrientos, Salvador Martínez

Name: Ana Pombero
Poster: Potential role of fibroblast growth factor receptor 1 (fgfr1) in the development of the retrosplenial cortex.
Author/s: A.Pombero, R.García-López, A.Estirado and S.Martínez.

Participation in the following Meetings

Congress: FENS Forum 2022
Date: 9-13 July 2022
City: | Paris, France



Visual Analogy Laboratory

Luis M. Martínez Otero

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

Criado-Boado, F., Alonso-Pablos, D., Blanco, M.J., Porto, Y., RodríguezPaz, A., Cabrejas, E., Del Barrio-Álvarez, E. and Martínez, L.M. (2019). **Coevolution of visual behaviour, the material world and social complexity, depicted by the eye-tracking of archaeological objects in humans.** *Scientific Reports*, 9, 3985. https://doi.org/10.1038/s41598-019-39661-w

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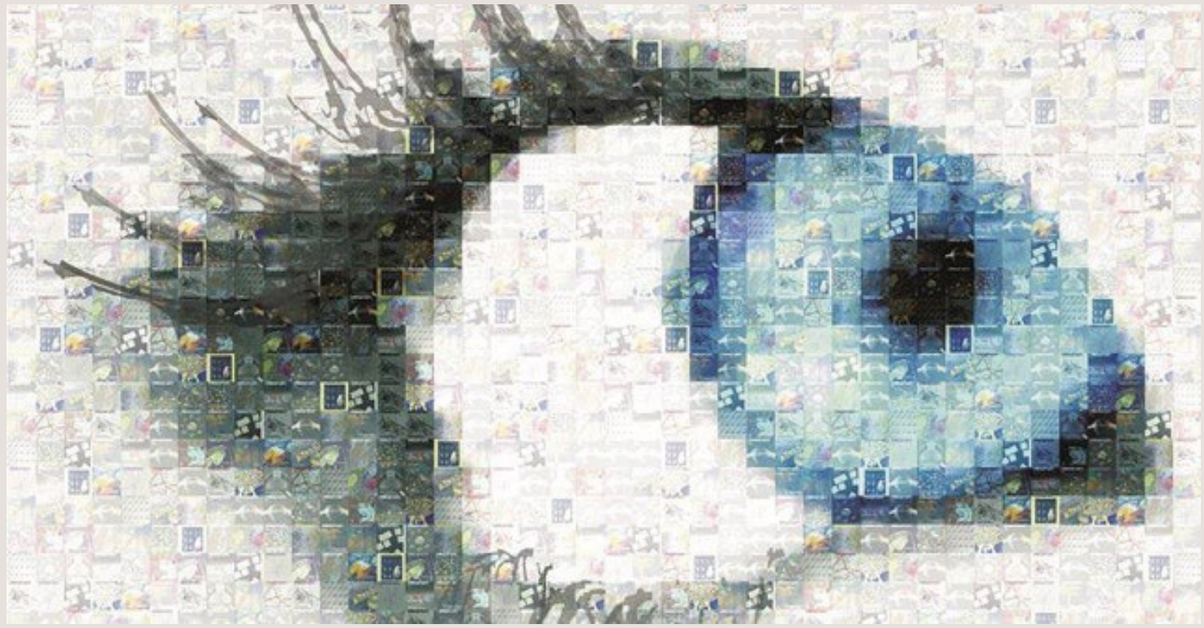
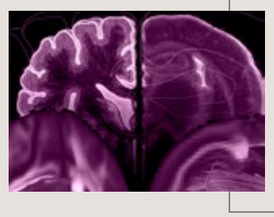
Principal Investigator
Luis M. Martínez Otero



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, remains a fascinating mystery. 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 stores 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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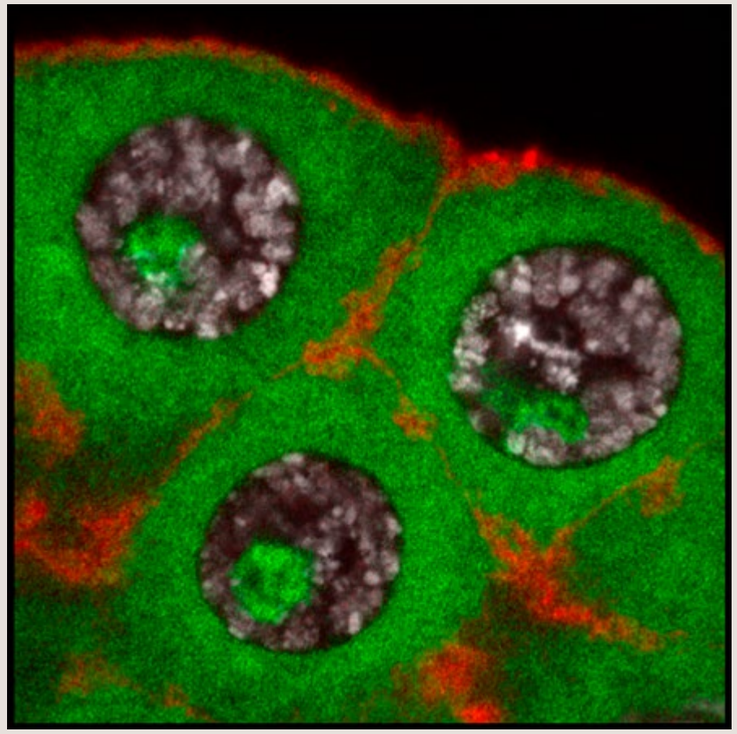

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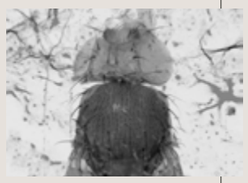
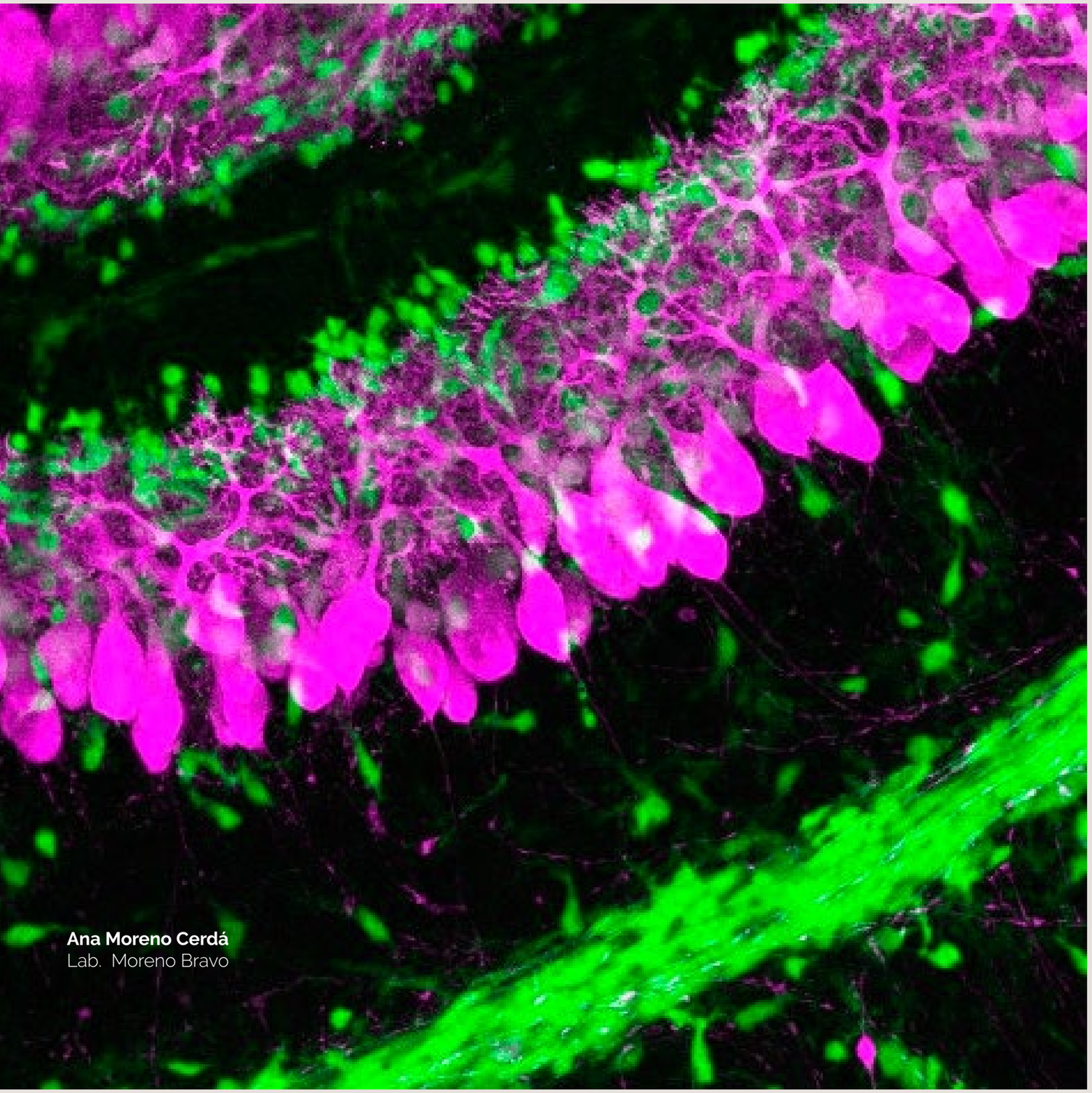


Sp6_Genetic & epigenetic basis of Individuality & aging



Ana Moreno Cerdá
Lab. Moreno Bravo

Development, wiring and function of cerebellar circuits

Juan Antonio Moreno Bravo

The goal of the lab is understanding 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 on the brain function.

We combine mouse genetics to develop animal models with cerebellar alterations, state-of-the-art histological, cellular, 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 in 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 on 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 derive in an abnormal function of the cerebellum.

Relevant publications

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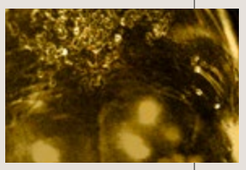
Department:

Developmental Neurobiology



Sp3_ Building & adapting circuits into functional networks

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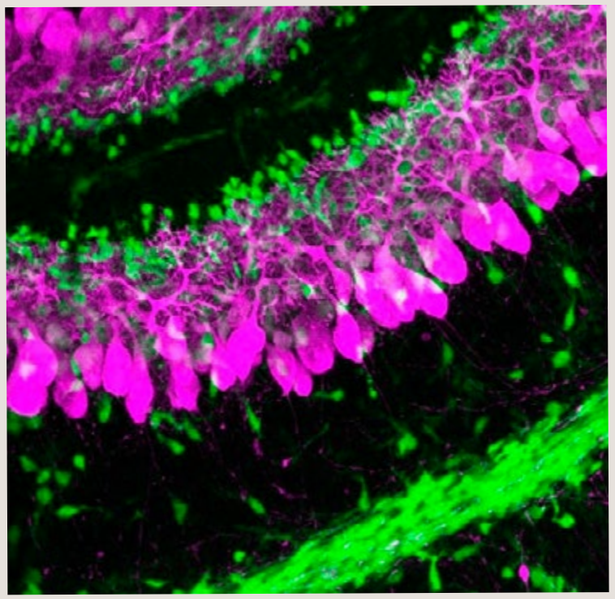

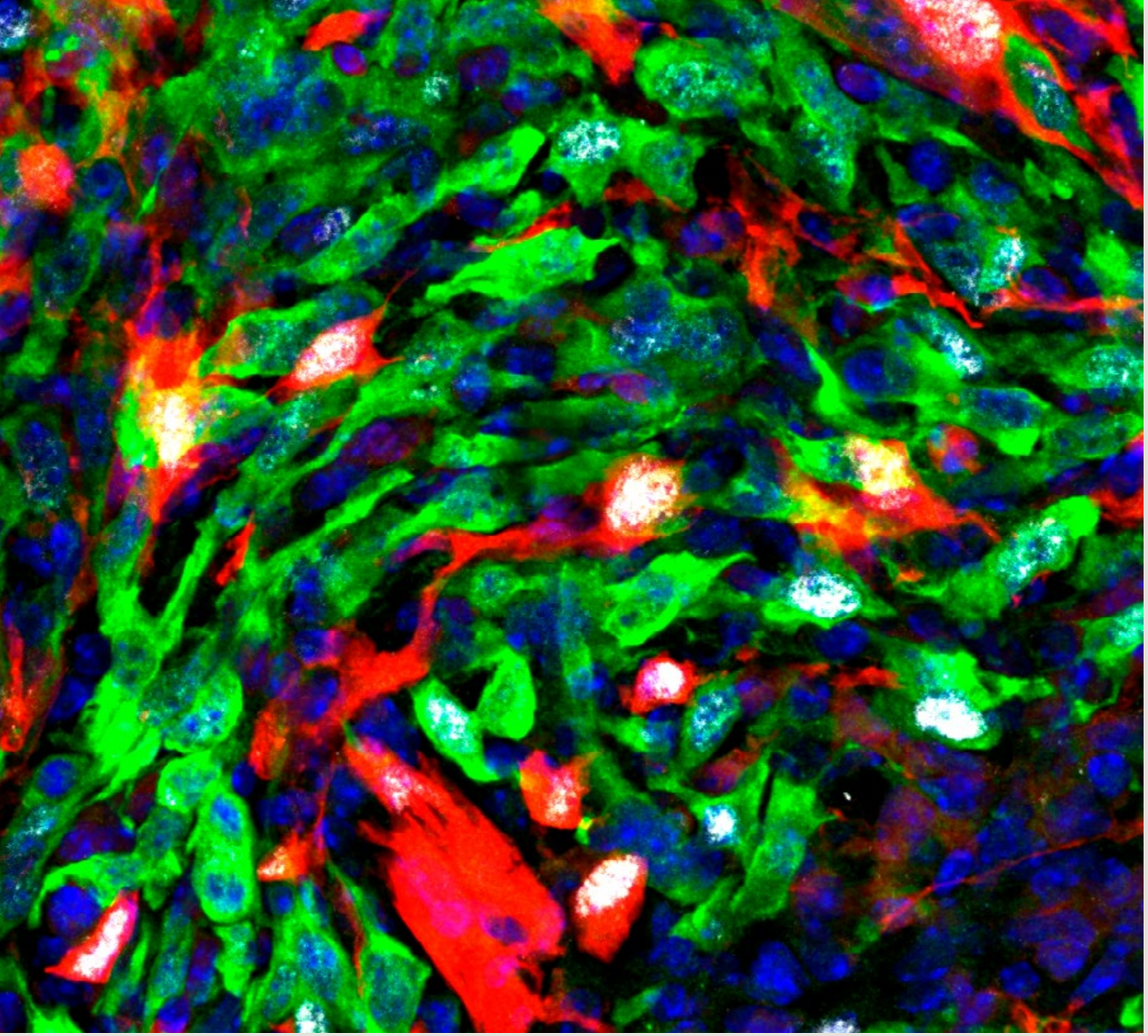

Cell Plasticity in Development & Disease

Ángela Nieto / Berta López-Sánchez

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 to allows cells to delaminate and migrate towards 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 the adult leads to several prominent pathologies, including cancer and fibrosis. As such, an aberrant activation of the EMT programme in tumours leads to 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, specially, 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 programmes induced by different EMT-TFs and have developed new models to investigate EMT-TF expression codes and signalling pathways that can discriminate EMT states and predict cell behaviour 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 reactivation of developmental programmes in the adult 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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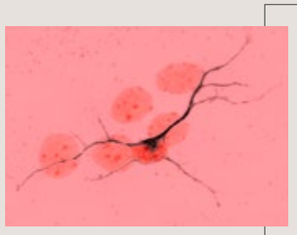
Department:

Developmental Neurobiology



Sp2_Cell plasticity in brain disease and repair

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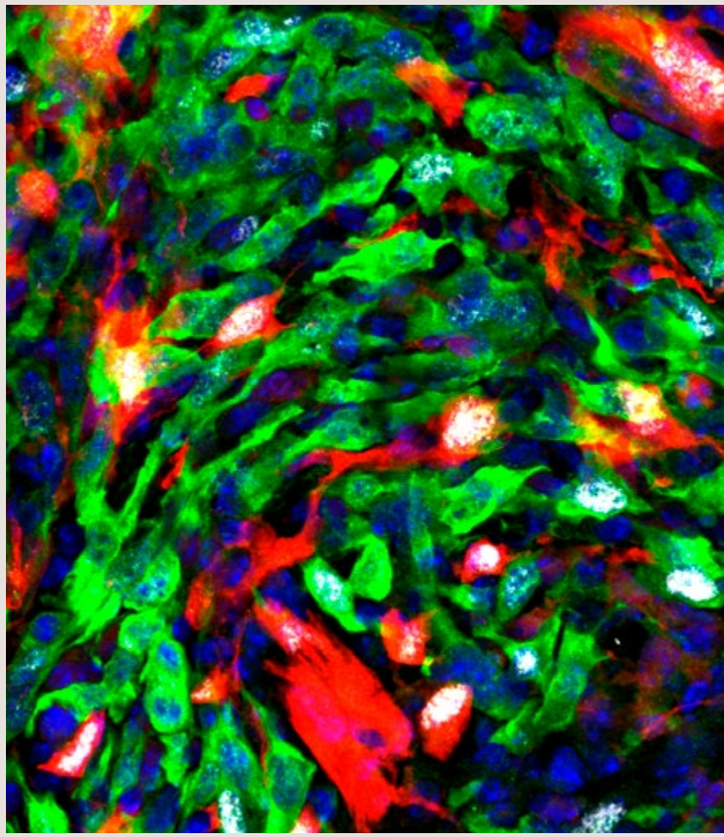

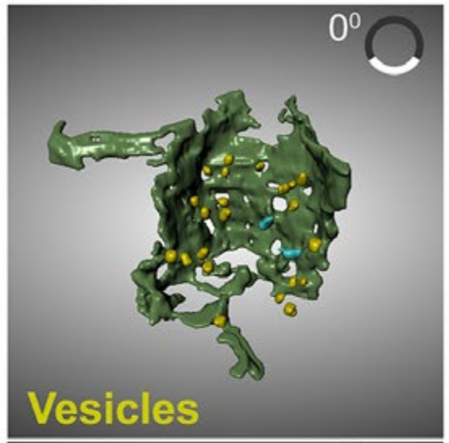

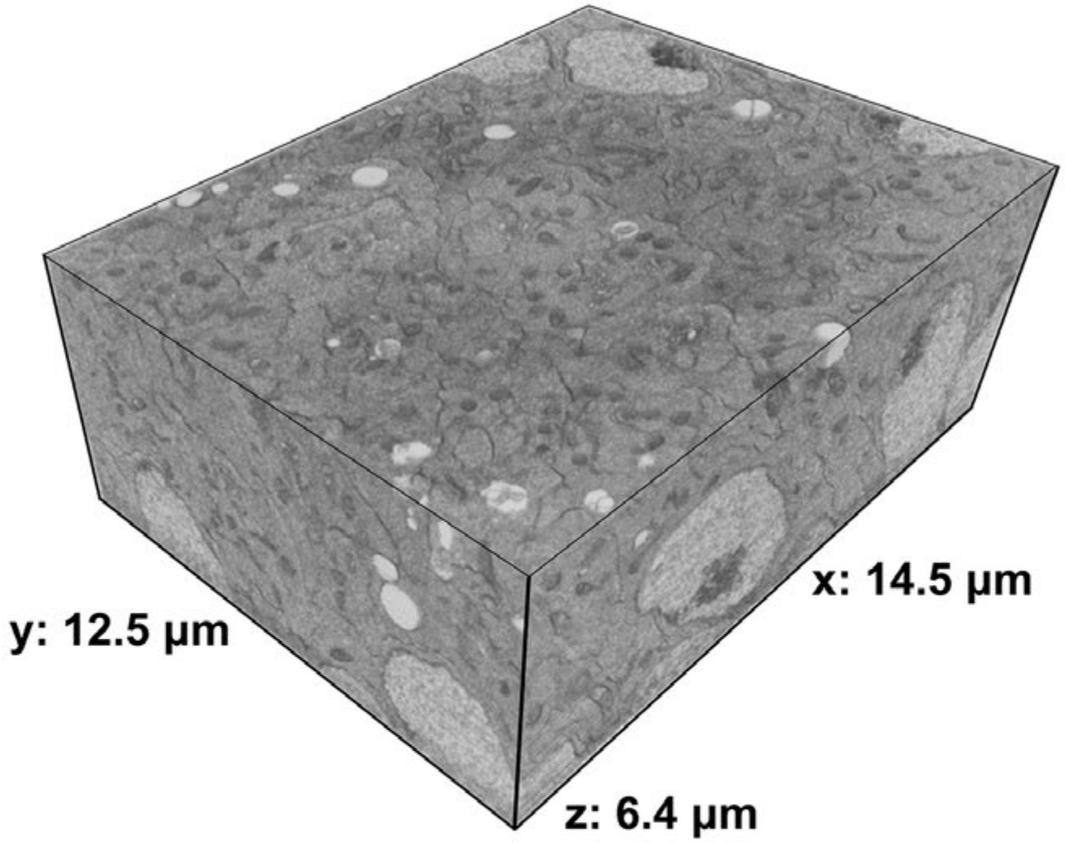

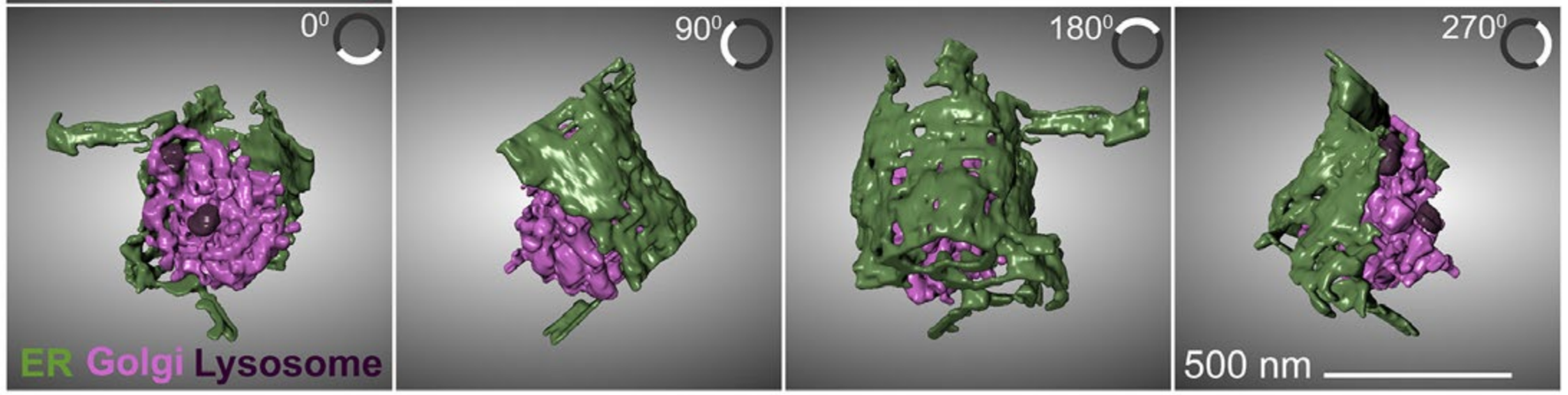

Cell-to-tissue architecture in the nervous system

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 age-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

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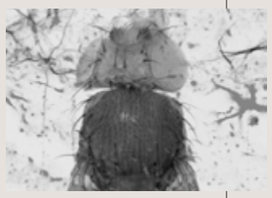
Department:

Developmental Neurobiology



Sp6_Genetic & epigenetic basis of Individuality & aging

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Technical Staff
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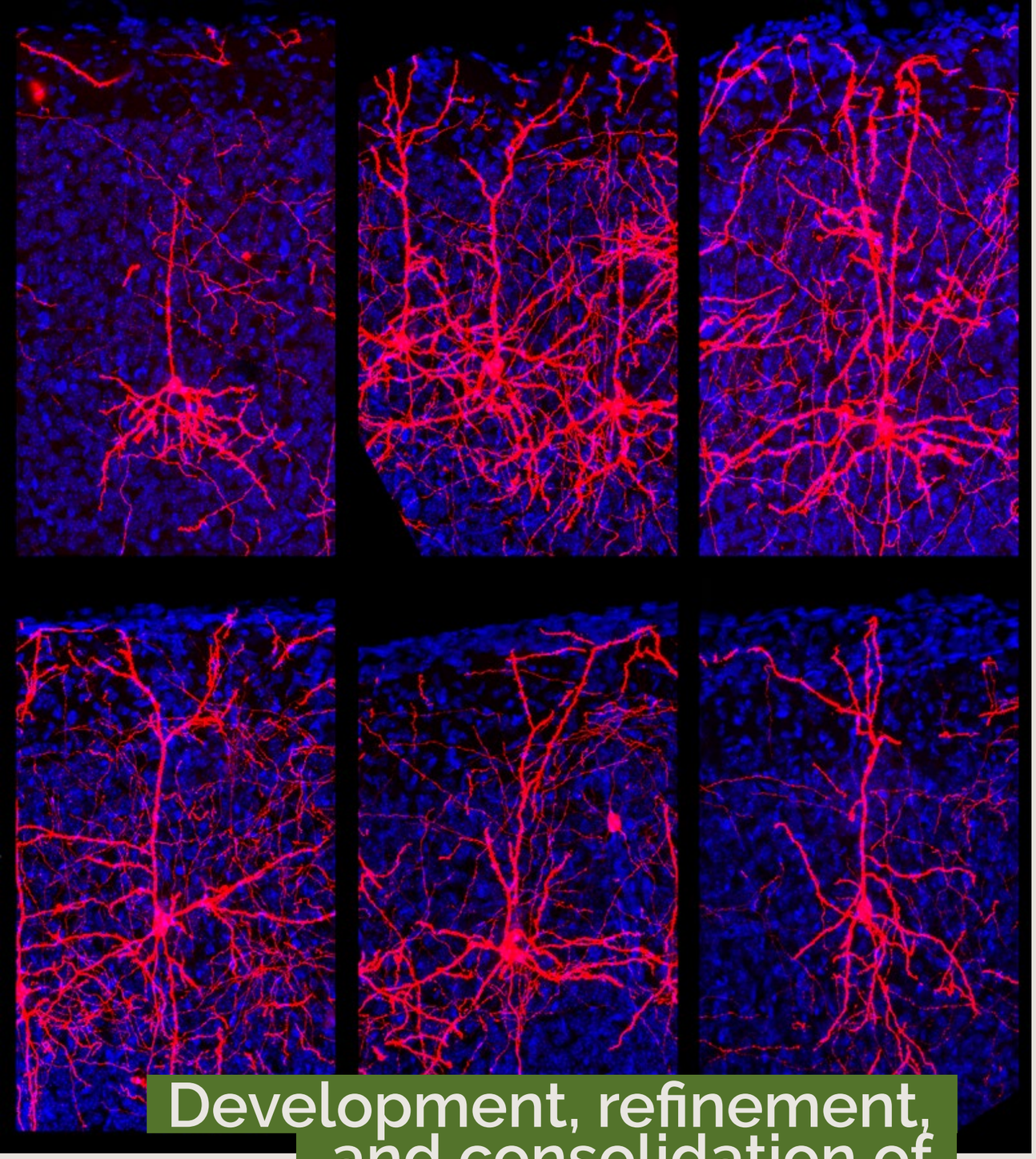


Development, refinement, and consolidation of neural circuits

Isabel Pérez Otaño

Brain function generates 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 its environment. Synaptic remodeling occurs throughout life but is maximal during "so-called" critical periods—a stage 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 during postnatal circuit refinements and to support precise learning and cognitive-guided behaviors. Understanding how this is achieved is one major goal of our lab.

A central research theme stems from our discovery of a 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 Rev 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 behaviours that rely on GluN3A plasticity and understand its role in juvenile and adult plasticity as well on the control of functional integration.

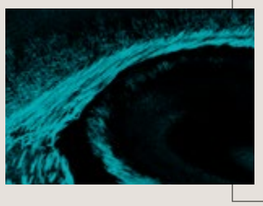
Other areas of investigation include:

1) *Targeting circuit plasticity and cognition:* Neurons rely on translational control to direct persistent modifications to selected synapses. We have discovered a novel signaling complex formed by the postsynaptic scaffold GIT1 and the mammalian target of rapamycin complex 1 (mTORC1) that nucleate 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 moeries, opening an entry point for modulating cognition (*eLife* 2021).

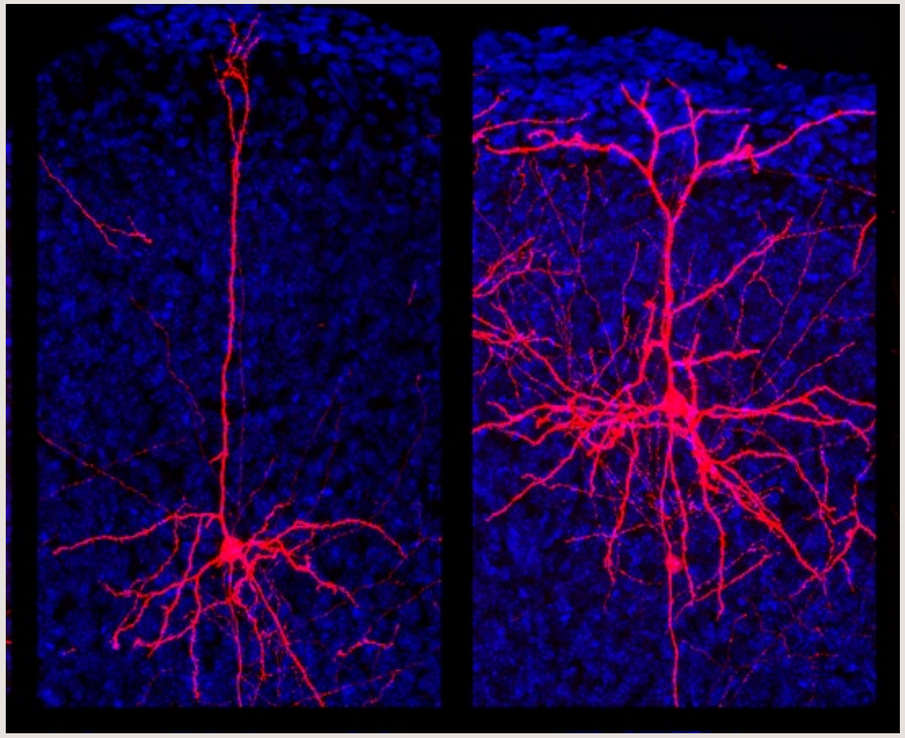
2) Identifying plasticity niches in non-neuronal cells, with a focus on the ability of GluN3A to control adaptive myelination and targeting for functional restoration.

Department:

Cellular and Systems Neurobiology



Sp4_Synaptic modulation of neural circuits and behavior



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Carlos Parras, collaborator

Relevant publications

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 Perez-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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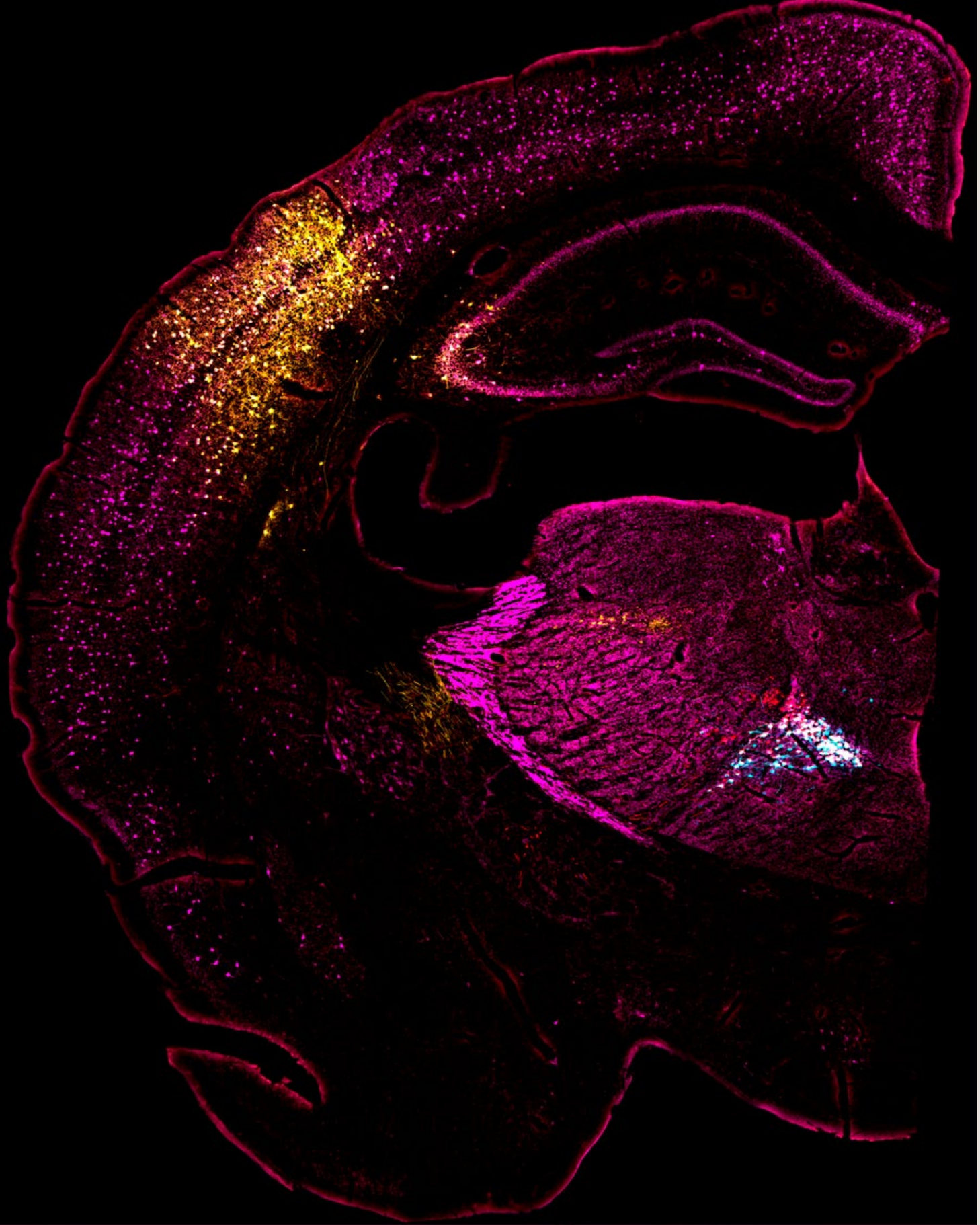

Sensory-motor processing by subcortical areas

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 for example 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 as prefrontal, motor or sensory, and thalamus. The striatum also receives massive dopaminergic innervation from the substantia nigra pars compacta. These afferent inputs interact with the striatal microcircuit to result in meaningful output to the downstream nuclei of the basal ganglia by striatal projection neurons, via the direct and indirect pathways. 95% of the striatal neurons are GABAergic projection neurons called medium spiny neurons (MSNs). This population is subdivide in two groups depending of their axonal targets and defining two different circuits (D1-MSNs, direct pathway and D2-MSNs indirect pathway). The remaining 5% are different types of GABAergic (FSI, SOM+/NPY/NOS+, CR+, TH+…) and cholinergic (Chl) interneurons that modulate the activity of the MSNs.

The striatum is best known for its role in planning and selecting motor sequences. But 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 with the striatal function. To answer this question we use complementary electrophysiological, behavioral, optical and anatomical methods.

Relevant publications

Alegre-Cortés, J., Sáez, M., Montanari, R. and Reig, R. (2021). **Medium spiny neurons activity reveals the discrete segregation of mouse dorsal striatum.** *eLife,* 10, e60580. https://doi.org/10.7554/eLife.60580

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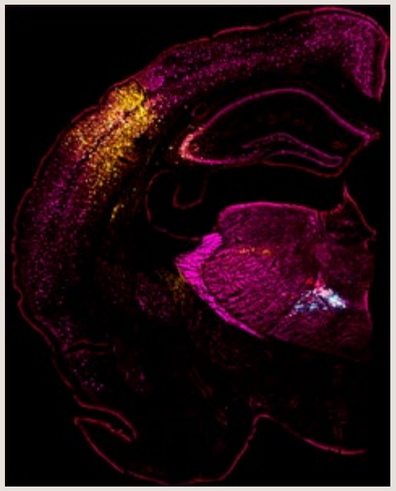

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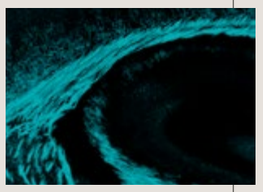
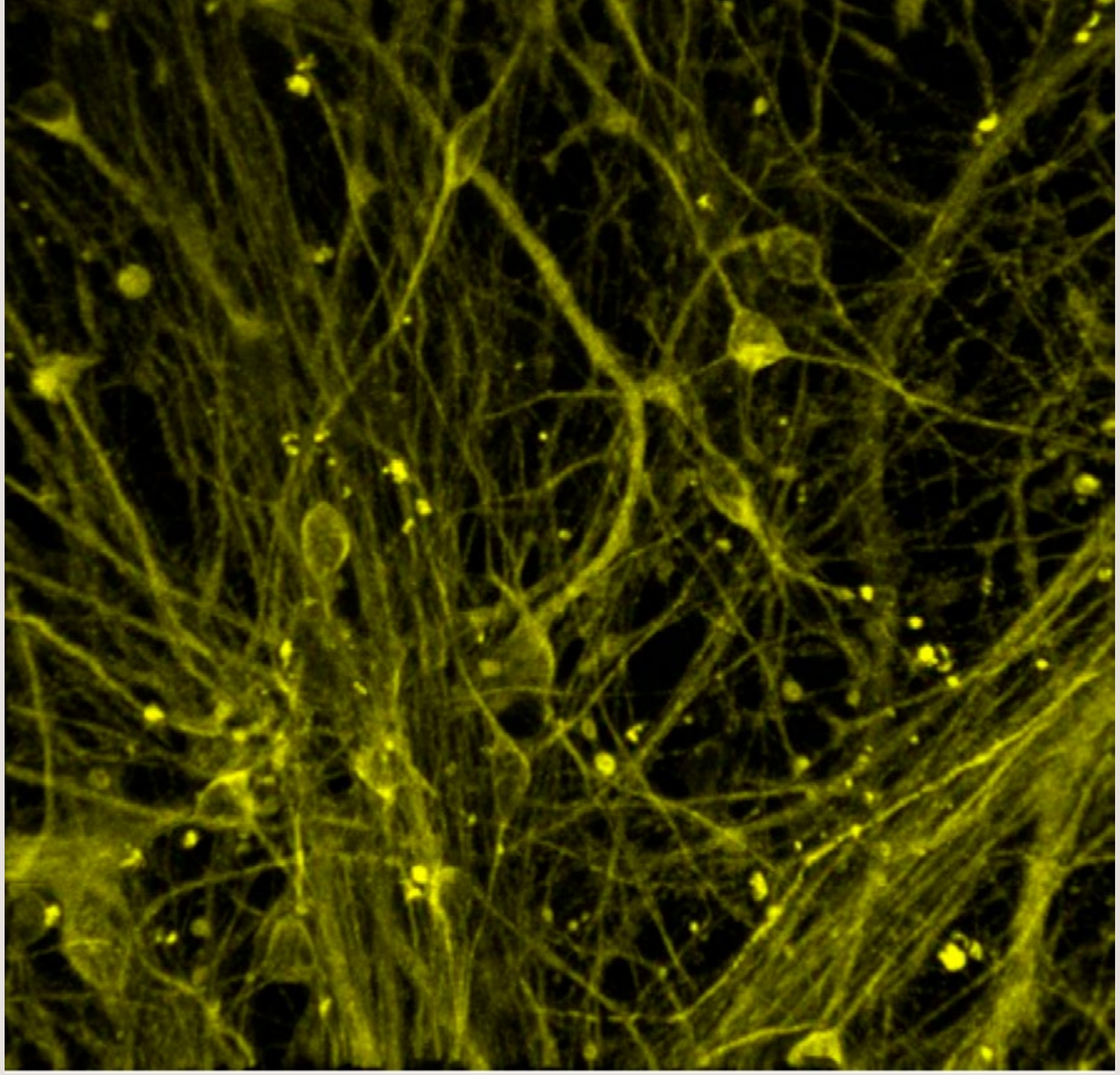
Sp3_ Building & adapting circuits into functional networks



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 in Alzheimer's disease (AD), but with interest in other neurodegenerative disorders. Our research lies in we aim to clarify the pathological mechanisms which underlie the disease searching potential diagnostic tools and/or processes with therapeutic relevance. Our group is part of CIBERNED (Center for Networked Biomedical Research in neurodegenerative diseases) with members from Institute of Health and Biomedical Research ISABIAL and FISABIO. Our expertise comprises i) biochemical characterization of PTM for brain/CSF/plasma proteins, including glycosylation, phosphorylation, characterization of proteolytic processing and localization in extracellular vesicles (EVs); ii) characterization of ligand-receptor interaction associated to signaling pathways; iii) assessment of sustained inhibition of key enzymes. We validate our findings in cell models, including human stem cells (iPSc).

Among the recent studies there are: i) aberrant patterns of reelin and apolipoprotein E (apoE) protein in CSF from AD patients. Reelin is a signaling protein that modulates synaptic function in the brain. ApoE is the major genetic risk factor for sporadic AD, being also a ligands for the same receptors than reelin. We demonstrated that apoE is altered in AD CSF, displaying altered content in immature glycoforms and aberrant aggregates, suggesting that the function may be compromised. Interestingly reelin also display aberrant aggregates in AD CSF and altered balance of proteolytic fragments, again suggestion altered function. ii) Recently we demonstrated that the SARS-CoV-2 host cell receptor, the angiotensin-converting enzyme 2 (ACE2), display changes of particular ACE2 species in virus infected humans. We further explore the potential of serum ACE2 as a biomarker to test SARS-CoV-2 infection and vaccine efficacy in virus susceptible transgenic K18-hACE2 mice expressing human ACE2. Noticeably, we demonstrated that immunization with the MVA-CoV2-S vaccine candidate prevented ACE2 cleaved changes in serum of animals challenged with a lethal dose of SARS-CoV-2. These findings highlight that ACE2 could be a potential serum biomarker for disease progression and vaccination against SARS-CoV-2. iii) We also reported detailed protocols for the characterization and analysis of brain EV preparations; and hosted the Workshop "Neuroglycoproteins in health and disease" as part of the UE-Cost Action "Innovation with glycans: new frontiers from synthesis to new biological targets".

Relevant publications

Lennol, M.P., García-Ayllón, M.-S., Esteban, M., García-Arriaza, J. and Sáez-Valero, J. (2022). **Serum angiotensin-converting enzyme 2 as a potential biomarker for SARS-CoV-2 infection and vaccine efficacy.** *Frontiers in Immunology*, 13: art 1001951. https://doi.org/10.3389/fimmu.2022.1001951

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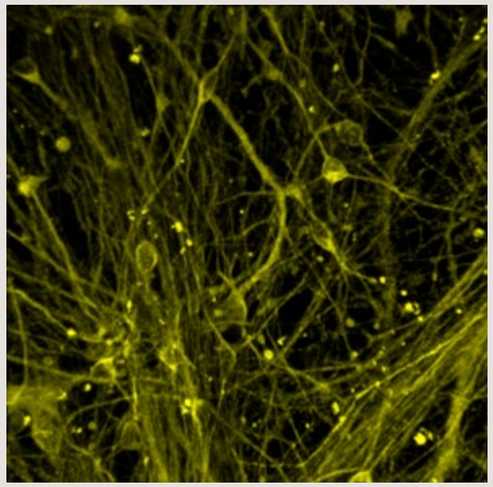

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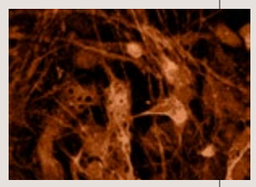
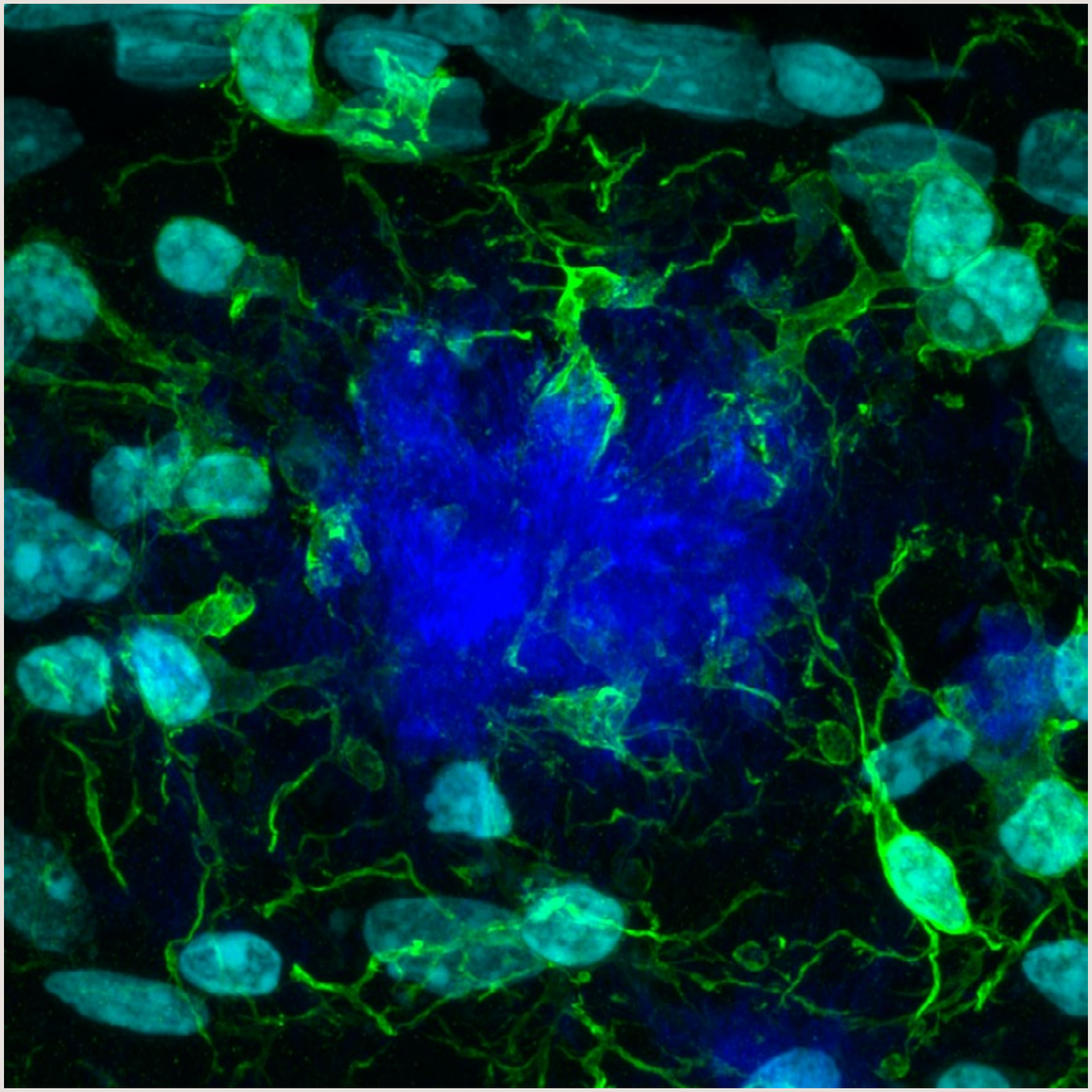


Sp8_ Translational research of neurological and psychiatric disorders



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.** *Proc Natl Acad Sci*, 119: e211679711. https://doi.org/10.1073/pnas.2116797119

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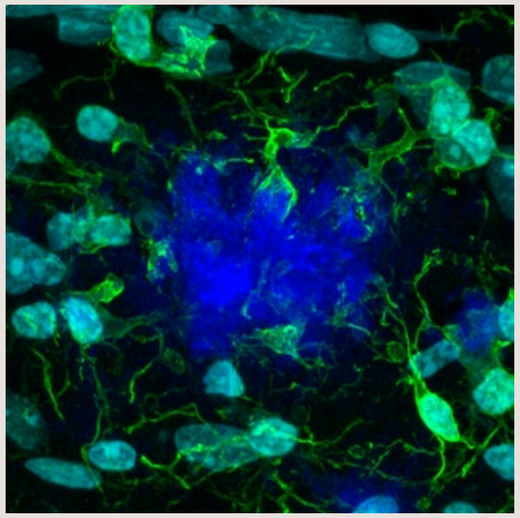

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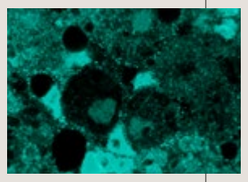
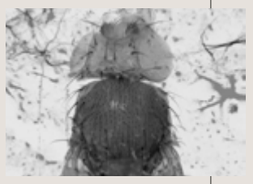
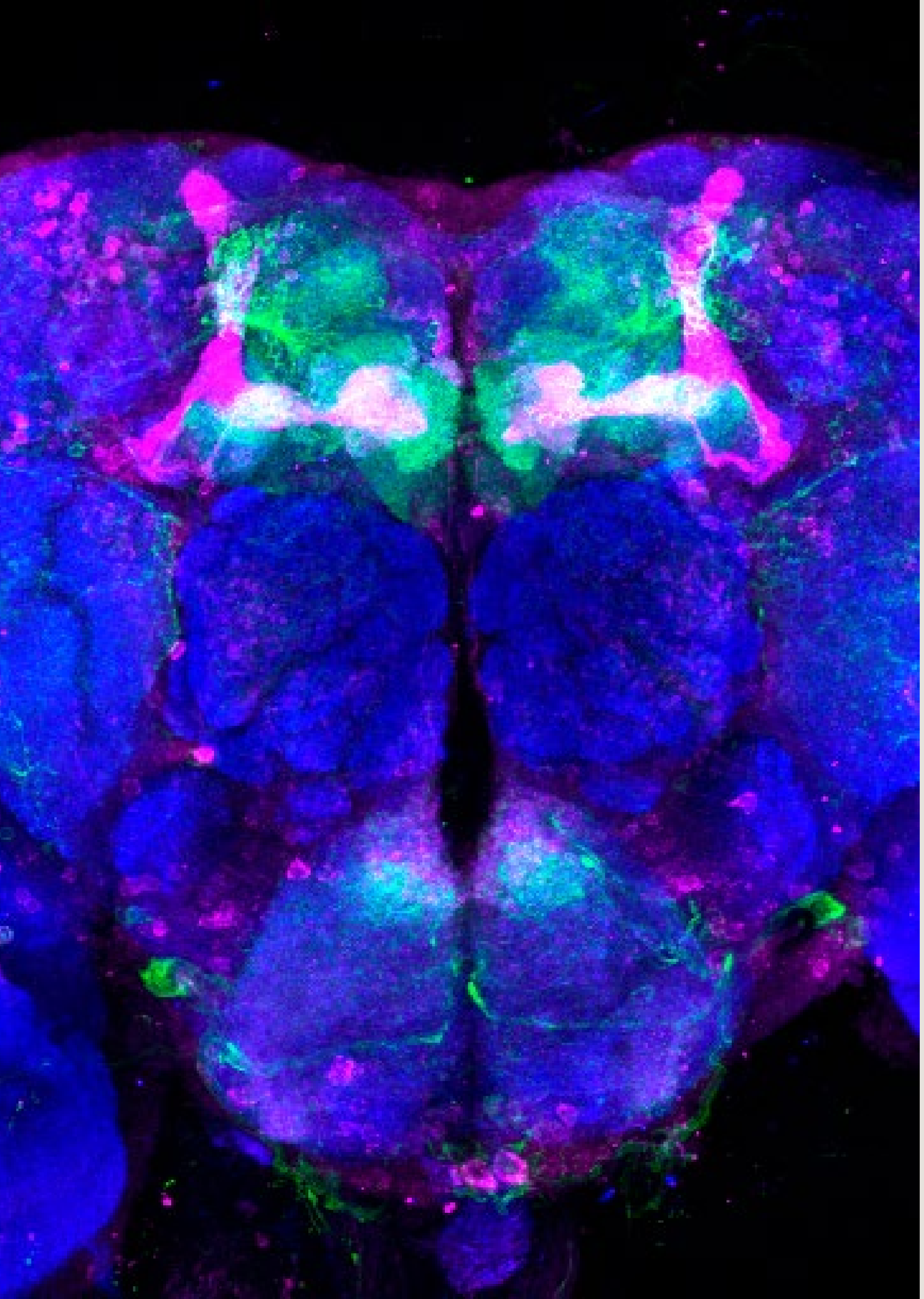


Sp1_ Neural stem cell regulation and differentiation



Sp6_Genetic & epigenetic basis of Individuality & aging



Institute for Neuroscience UMH-CSIC

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, D. melanogaster is a great biological system where to study those processes due to its accessibility to image and manipulate neural circuits, modify genetically and ease to study its behavioural 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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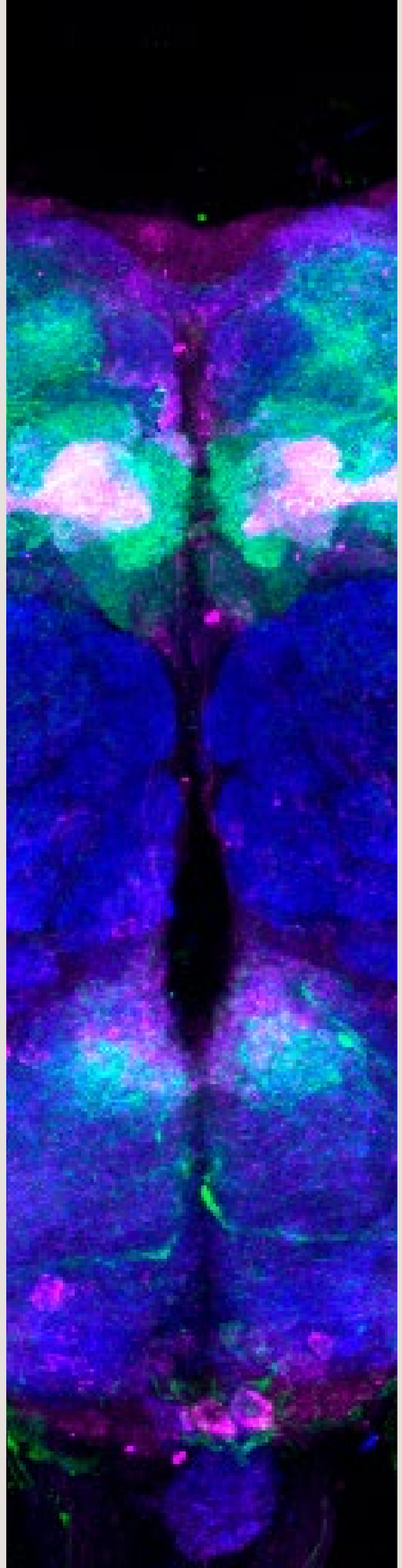

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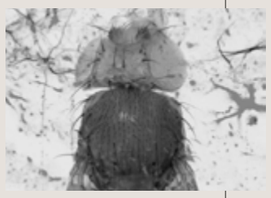
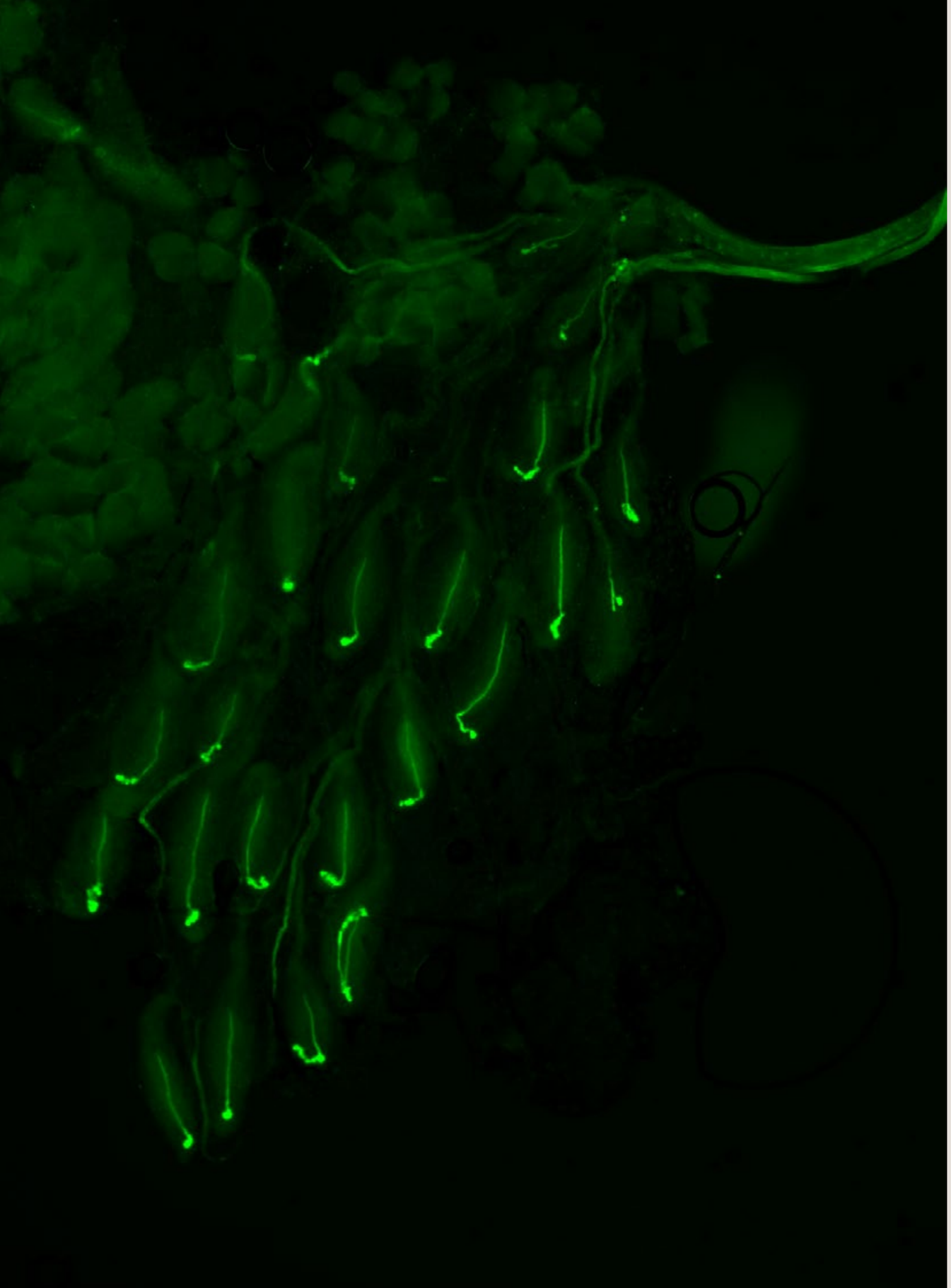


Sp6_Bases genéticas y epigenéticas de la individualidad y el envejecimiento



Institute for Neuroscience UMH-CSIC

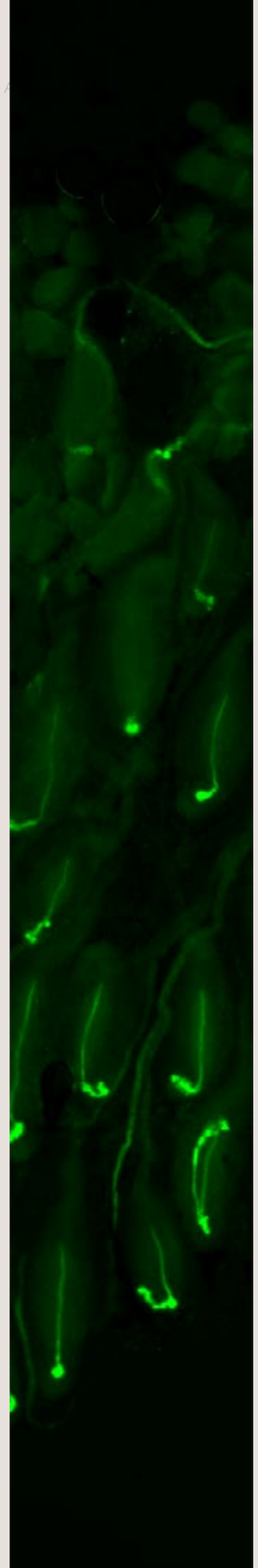
Wiring and Function of Somatosensory Circuits

Francisco J. Taberner Sanchís

Specialized subsets of primary sensory neurons innervating different body tissues detect and transduce different environmental cues into itch, touch, temperature or pain information. When these signals eventually reach the brain, they generate the sensory percept and evoke the convenient physiological and behavioural responses for the survival of the animal. On its way to the brain, this sensory information undergoes an initial processing at 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 to 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 on 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 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 defining 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-stablished electrophysiological techniques.



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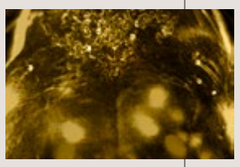

Sp3_ Construcción y adaptación de los circuitos neuronales en redes funcionales

Relevant publications

Gangadharan, V., Zheng, H., Taberner, F.J., Landry, J., Nees, T.A., Pistolic, J., Agarwal, N., Männich, D., Benes, V., Helmstaedter, M., Ommer, B., Lechner, S.G., Kuner, T. and Kuner, R. (2022). **Neuropathic pain caused by miswiring and abnormal end organ targeting.** *Nature*, 606 (7912): 137-145. http://doi.org/10.1038/s41586-022-04777-z

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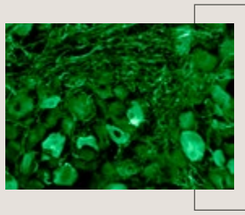
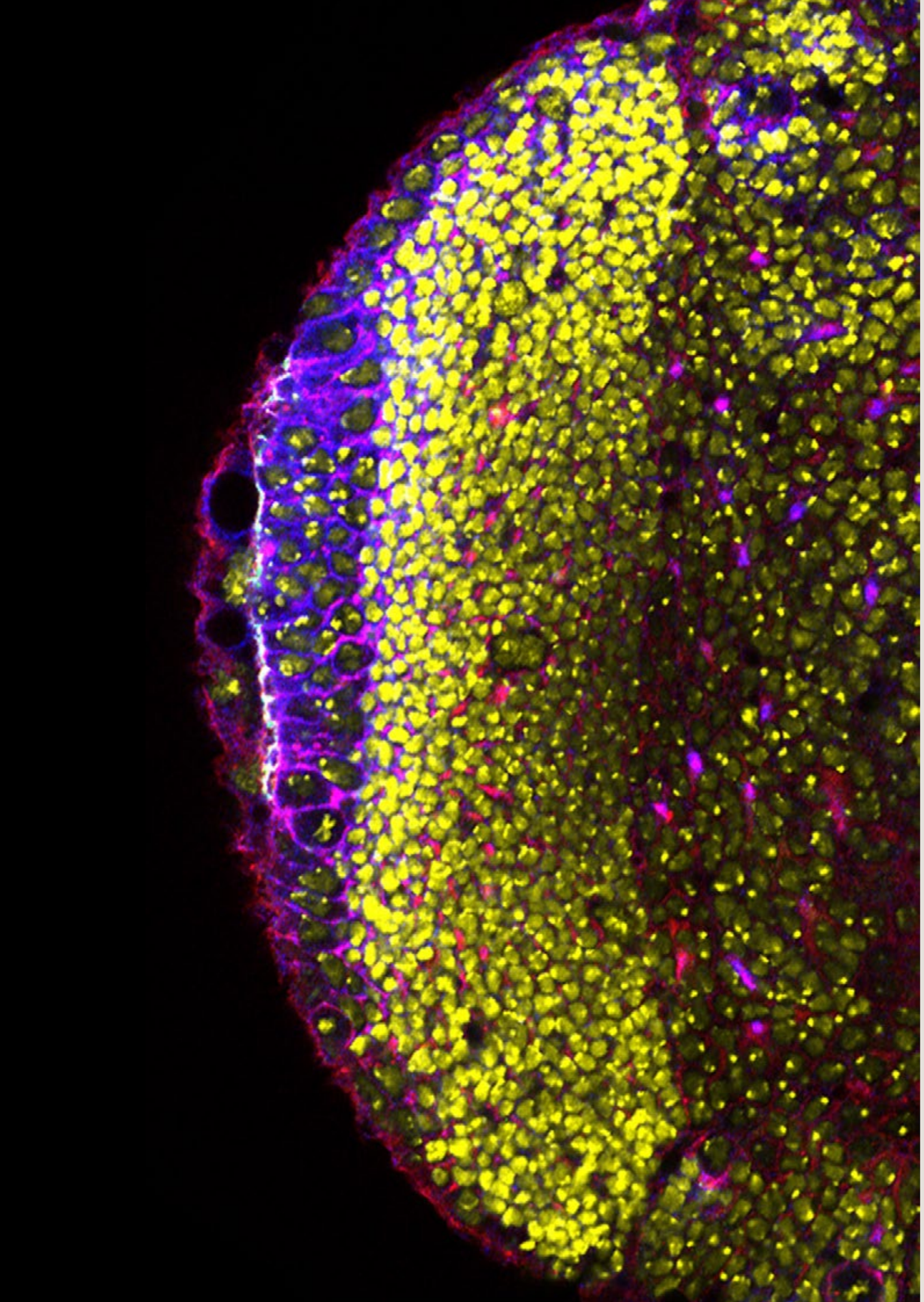


Sp5_Neurobiology of pain & inflammation



Molecular neurogenetics

Fernando 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 cells proliferation and neurogenesis. We are particularly interested on 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 to unravel molecular mechanisms underlying these cellular processes. At this end, we are using the proliferation centres of the larval optic lobe (OL) of Drosophila melanogaster as an experimental model system. At the same time, we are interested on how genetic alterations of these genes may contribute to developmental neuropathologies.

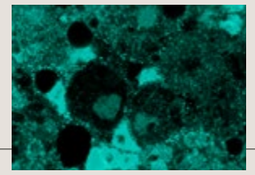
Following this approach, we identified the gene minibrain (mnb, also called Dyrk1A in vertebrates) as a major regulator of neural progenitor cell proliferation and neurogenesis in Drosophila melanogaster. Mnb/Dyrk1A encodes a very well evolutionary conserved protein-kinase, which play several functions through brain development. We are focusing on its roles in the regulation of neural proliferation, cell cycle, neurogenesis, and neuronal differentiation, unravelling the underlying molecular mechanisms. Remarkably, haploinsuficiency 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 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.

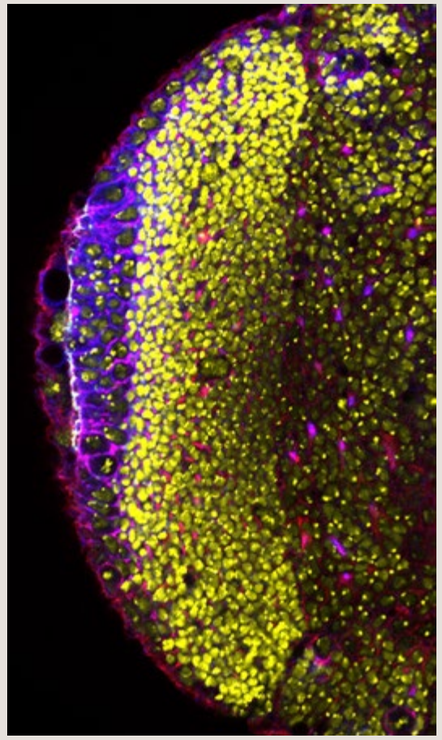
Finally, we are studying the integration of Mnb/Dyrk1A, proneural genes and Notch signaling pathways in the regulation of the neuroepithelial-neuroblast transition at the larval OL.

Department:

Developmental Neurobiology



Sp1_ Neural stem cell regulation and differentiation



Publicaciones destacadas

Viard, J., Loe-Mie, Y., Daudin, R., Khelfaoui, M., Plancon, C., Boland, A., Tejedor, F., Huganir, R.L., Kim, E., Kinoshita, M., Liu, G., Haucke, V., Moncion, T., Yu, E., Hindie, V., Bléhaut, H., Mircher, C., Herault, Y., Deleuze, J.F., Rain, J.C., Simonneau, M., Lepagnol-Bestel, A.M. (2022) **Chr21 protein-protein interactions: enrichment in proteins involved in intellectual disability, autism, and late-onset Alzheimer's disease.** *Life Sci Alliance*, 5(12):e202101205. http://doi.org/10.26508/lsa.202101205

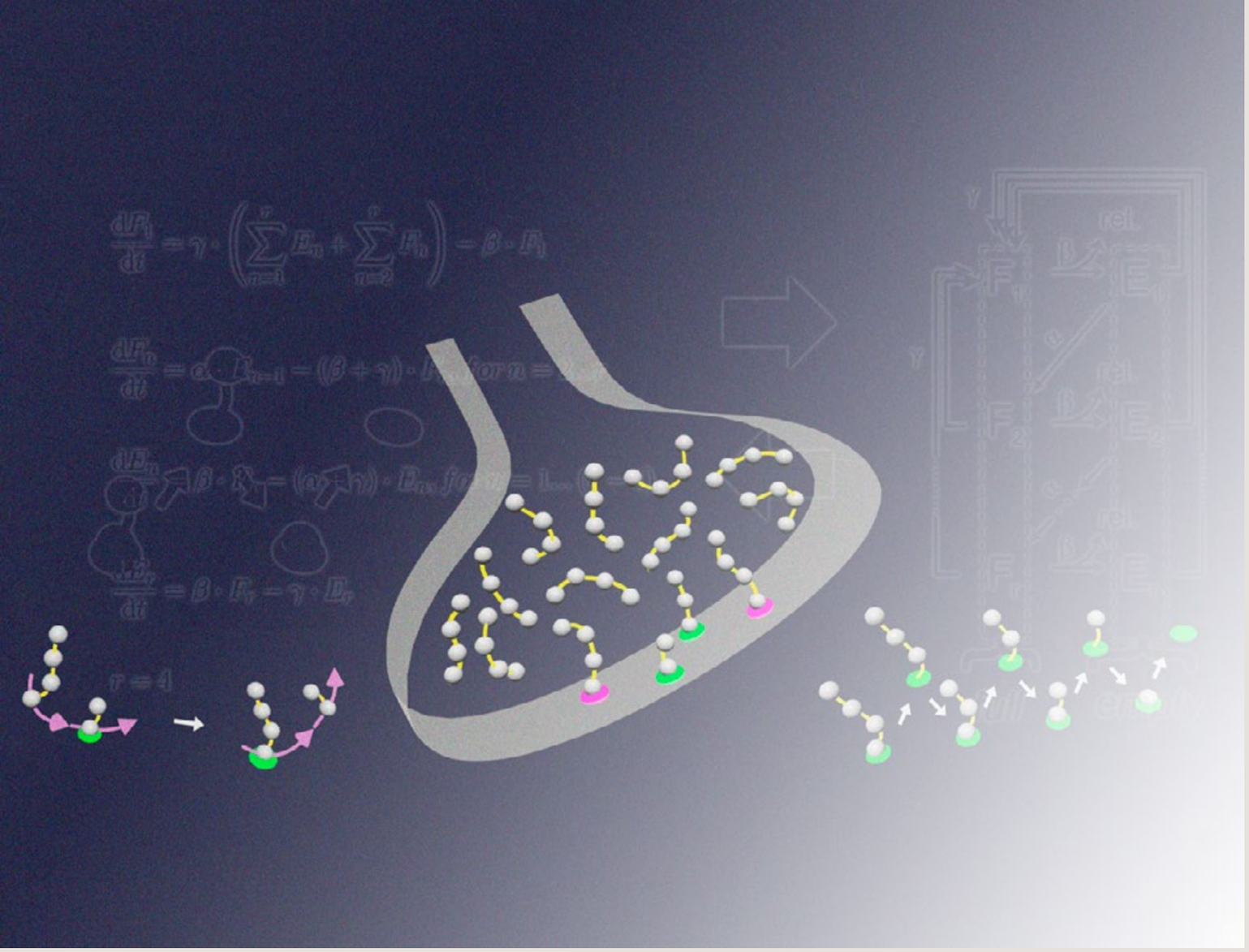
Martin, M., Shaikh, M.N., Gutierrez-Avino, F., Tejedor, F.J. (2021). **A novel proneural function of Asense, integrated with L'sc and Notch, promotes the Neuroepithelial to Neuroblast transition.** *bioRxiv*. https://doi.org/10.1101/2021.04.15.440037

Shaikh, M.N. and Tejedor, F.J. (2018). **Mnb/Dyrk1A orchestrates a transcriptional network at the transition from self-renewing neurogenic progenitors to postmitotic neuronal precursors.** *J. Neurogenet,* 32(1) 37-50. https://doi.org/10.1080/01677063.2018.1438427

Shaikh, M.N., Gutierrez-Aviño, F., Colonques, J., Ceron, J., Hämmerle, B. and Tejedor, F.J. (2016). **Minibrain drives the Dacapo-dependent cell cycle exit of neurons in the Drosophila brain by promoting asense and prospero expression.** *Development*, 143(17):3195-205. https://doi.org/10.1242/dev.134338

Becker, W., Soppa, U., Tejedor, F.J. (2014). **DYRK1A: a potential Drug Target for Multiple Down Syndrome Neuropathologies.** CNS Neurol Disord-Drug Targets, 13(1):26. https://doi.org/10.2174/1871527311312660186

Principal Investigator
Francisco J. Tejedor



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

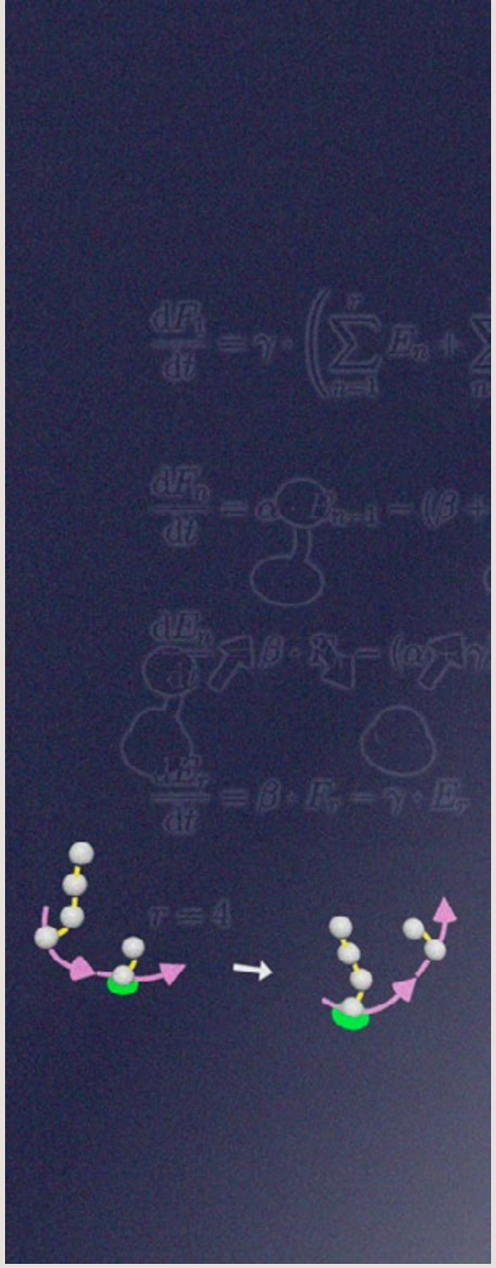
Wesseling, J.F., Phan, S., Bushong, E., Marty, S., Pérez-Otaño, I. and Ellisman, M.H. (2019). **Sparse force-bearing bridges between synaptic vesicles.** *Brain Structure and Function,* 224(9):3263-3276. https://doi.org/10.1007/s00429-019-01966-x

Raja, M.K., Preobraschenski, J., Del Olmo-Cabrera, S., Martínez-Turrillas, R., Jahn, R., Pérez-Otaño, I. and Wesseling, J.F. (2019). **Elevated synaptic vesicle release probability in synaptophysin/gyrin family quadruple knockouts.** *eLife*, 8:e40744. https://doi.org/10.7554/eLife.40744

Pérez-Otaño, I., Larsen, R.S., Wesseling, J.F. (2016). **Emerging roles of GluN3A-containing NMDA receptors in the central nervous system.** *Nature Reviews Neuroscience*, 17:623-635. https://doi.org/10.1038/nrn.2016.92

Mahfooz, K., Singh, M., Renden, R., and Wesseling, J.F. (2015). **A Well-Defined Readily Releasable Pool with Fixed Capacity for Storing Vesicles at Calyx of Held.** *PLoS Computational Biology*, 12: e1004855. https://doi.org/10.1371/journal.pcbi.1004855

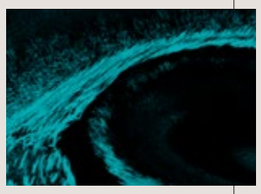
García-Pérez, E., Mahfooz, K., Covita, J., Zandueta, A., and Wesseling, J.F. (2015). **Levetiracetam accelerates the induction of supply-rate depression in synaptic vesicle trafficking.** *Epilepsia*, 56:535-545. https://doi.org/10.1111/epi.12930



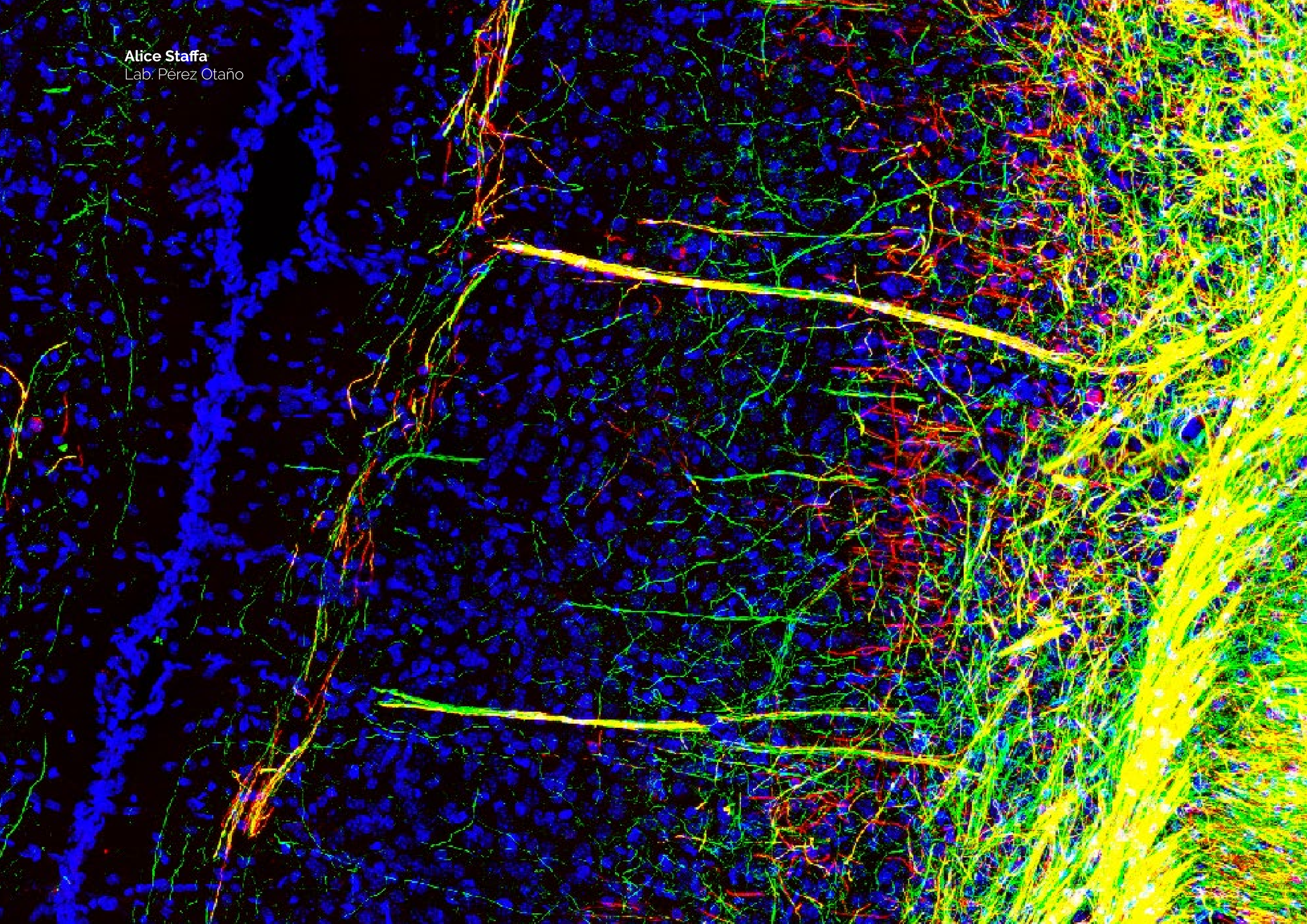
Principal Investigator
John F. Wesseling
PhD Student
Sergio Del Olmo Cabrera
Juan José Rodríguez Gotor
Doris Santiago
Technical Staff
Diana Baeza Soler

Department:

Cellular and Systems Neurobiology



Sp4_Synaptic modulation of neural circuits and behavior

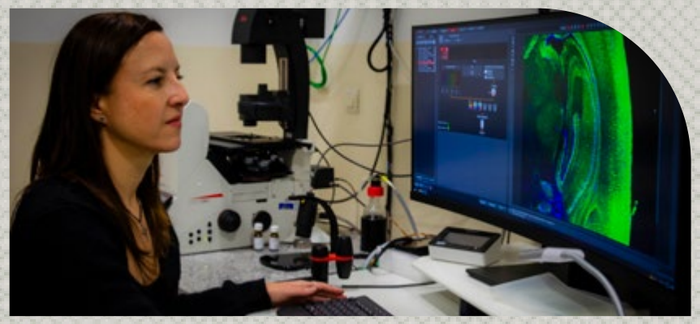


Alice Staffa
Lab. Pérez Otaño

Servicies and Facilities

Microscopy
Molecular Imaging
Animal Housing
Animal Research
Omics and gene analysis
Cell Culture & Sterilization
Neurotropic Vectors
Genotyping
SHARE. Electronic workshop
Administration & management
Support Services

Microscopy



The Instituto de Neurociencias (IN) Microscopy Facility is a platform for microscopy and image analysis that provides services and training to both IN investigators and external users. This core facility includes a set of state-of-the-art equipment that allows to perform a great variety of techniques including confocal microscopy, multiphoton, light-sheet (*in vivo* and clarified) or super-resolution microscopy (Airyscan, SR-SIM, PALM / dSTORM). Images and videos from fixed samples, living tissues, cell cultures, slices or even intact animals can be acquired. The service also counts with high-performance workstations and software packages for image processing and analysis.

Technician staff

Giovanna Expósito Romero
Verona Villar Cerviño

Molecular Imaging

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

The facility was created in 2011 as a central service in the Instituto de Neurociencias (CSIC/UMH). The service has a Bruker BioSpec 7Tesla (30 cm internal diameter) fully equipped to perform in vivo and ex vivo MR Imaging and Spectroscopy. The service is equipped with volume coils for rodent whole body imaging and single voxel spectroscopy. Also it has a special set up for brain imaging using a phase array coil, optimized for functional Magnetic Resonance Imaging (fMRI).

The Unit of Functional Magnetic Resonance Imaging provides necessary instrumentation to anesthetize the animals using inhalation or injectable anesthesia. Equipment for non-invasive and fully MR-compatible physiology monitoring during imaging acquisition is also available, including body temperature, arterial pressure, heart and breath rate and oxygen saturation. A 4 channel electric stimulation device for stimulation-driven fMRI is available. Additional equipment to perform surgery and artificial ventilation could be provided upon request.

Technician staff

Luis Tuset Sanchís

Animal Housing

SPF *Animal House*

The Unit for Genetically Modified Mice is one of 3 animal facilities at the Animal Experimentation Service of the UMH. It is a specific pathogen free facility with capacity for around 15,000 mice. The IN has full control of this facility and set up a service for in-house embryo cryopreservation, mouse genotyping and to generate 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. We are maintaining transgenic lines as well as wild type fish and we can produce embryos from all of them for developmental and genetic studies.

Drosophila Unit

Specialized personnel and equipment of the IN Drosophila Unit support research and genetic experiments in the model organism Drosophila melanogaster (common fruit fly). The IN Drosophila Unit prepares medium for fruit fly culture (fly food), and provides it in vials to the six laboratories currently using Drosophila in the IN. In addition, the IN Drosophila Unit houses over 10,000 wild type, mutant and transgenic strains in two walk-in climatic chambers (18oC) under temperature- and humidity-controlled conditions for optimal, pathogen-free growth of the different fly lines. It also provides space for storing experimental crossings (25oC) in two large incubators.

Animal Research

Platform to study rodent behavior

The SPF animal house also houses an area for studying mice behavior. Specifically, there are eight fully equipped rooms to explore the usual behavior of mutant lines and wild types and specific aspects of social behavior, anxiety and depression, sleep, learning and memory, and simple or complex motor performance. For these purposes, the platform to study rodent behavior (PEC) has numerous mazes, including a Morris water maze; operant conditioning chambers for studying both fear conditioning and the startle reflex; 24-hour monitoring equipment and the Erasmus ladder, among others, available for IN researchers.

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
Raúl Pardo Mérida
Mª Ángeles Soler Ripoll
Darío Carratalá Sánchez

Omics and gene analysis

The Instituto de Neurociencias (IN) Omics Facility is a platform for Genomic and Transcriptomic analysis that provides services and training to both IN and external users. This core facility includes a set of state-of-the-art equipment that allows to perform a great variety of techniques including Cell Sorting (populations and single cell), Single Cell platform, QPCR, DNA and RNA quality control, Library construction, DNA sonication, Bioinformatics platform for data analysis and storage. Genomic and Transcriptomic issues from fixed cells, disaggregated living tissues, cell cultures and cellular organelles can be analyzed.

The service also counts with high-performance workstations and software packages for data analysis.

Technician staff
Antonio Javier Caler Escribano
José Mulet Soler

Cell Culture & Sterilization

The Cell Culture Unit is the Insituto de Neurociencias Service that provides researchers the environment for getting healthy viable cell cultures. This Service is composed by three different and spatially separated Areas in order to carry out different types of cell cultures: Cell Lines, Primary Cultures and Organotipic Cultures.

Each of these facilities are well equipped with class I and/or class II laminar flow cabinets, incubators, inverted phase contrast and fluorescence microscopes and all the material necessary to perform specialized cell culture techniques. Bio-safety level 2 areas are included to work with high risk material (human samples, virus). The Unit also have available a new generation system for real-time quantitative live-cells analysis.

Technician staff

Sara Carratalá Gosálbez
Mar Francés Pérez

Sterilization

Washing and sterilization technician

Trinidad Guillén Carrillo

Neurotropic Vectors

The Neurotropic Vectors Unit is devoted to the production of delivery vectors of viral origin for the study of the nervous system in health and disease.

In recent years the delivery of molecular tools into neurons has become an essential approach to understand the mechanisms underlying brain function and brain disorders.

Genetically engineered viruses have become ideal vectors for introducing these tools into brain cells allowing neuroscientists unprecedented control over cells and circuits.

To facilitate the use of these state-of-the-art methodologies by our neuroscientists, the Vector Unit centralizes the process of producing and distributing neurotropic vectors.

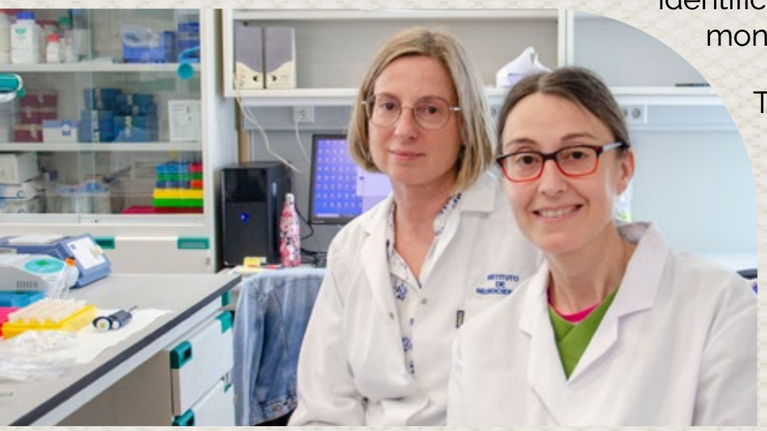
Technician staff

Cristina Gracía Frigola
María de los Ángeles Hernández Vellisca

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

SHARE. Electronic workshop

The Scientific HARdware and Electronics service (SHARE) provides services to adapt and create instruments and experimental devices according to the specific needs of the IN groups. It has state-of-the-art precision machinery for the prototype and manufacturing of new scientific devices and to perform local reparations of equipment, and is intimately related to the innovation unit (UCIE).

Reparations of scientific and laboratory equipment. Provide knowledge and tools for technology innovation. Promote a “do it yourself” culture.

Technician staff

Victor Javier Rodríguez Milán

David Cerverón Morales

Scientific equipment

Molecular Biology & Microbiology

Histology Area

Ultra freezers rooms - Microelectrodes rooms

Cold rooms

Centrifuges

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 Martinez Fitor
Isabel Ortega Castillo
David Rodríguez Dueñas
Raul Romero Garrido
José Sánchez Ardila
Antonio Valero Villar

Staff management CSIC
Mª José Soria Pedrera

Internationalization
Julio Barbas González

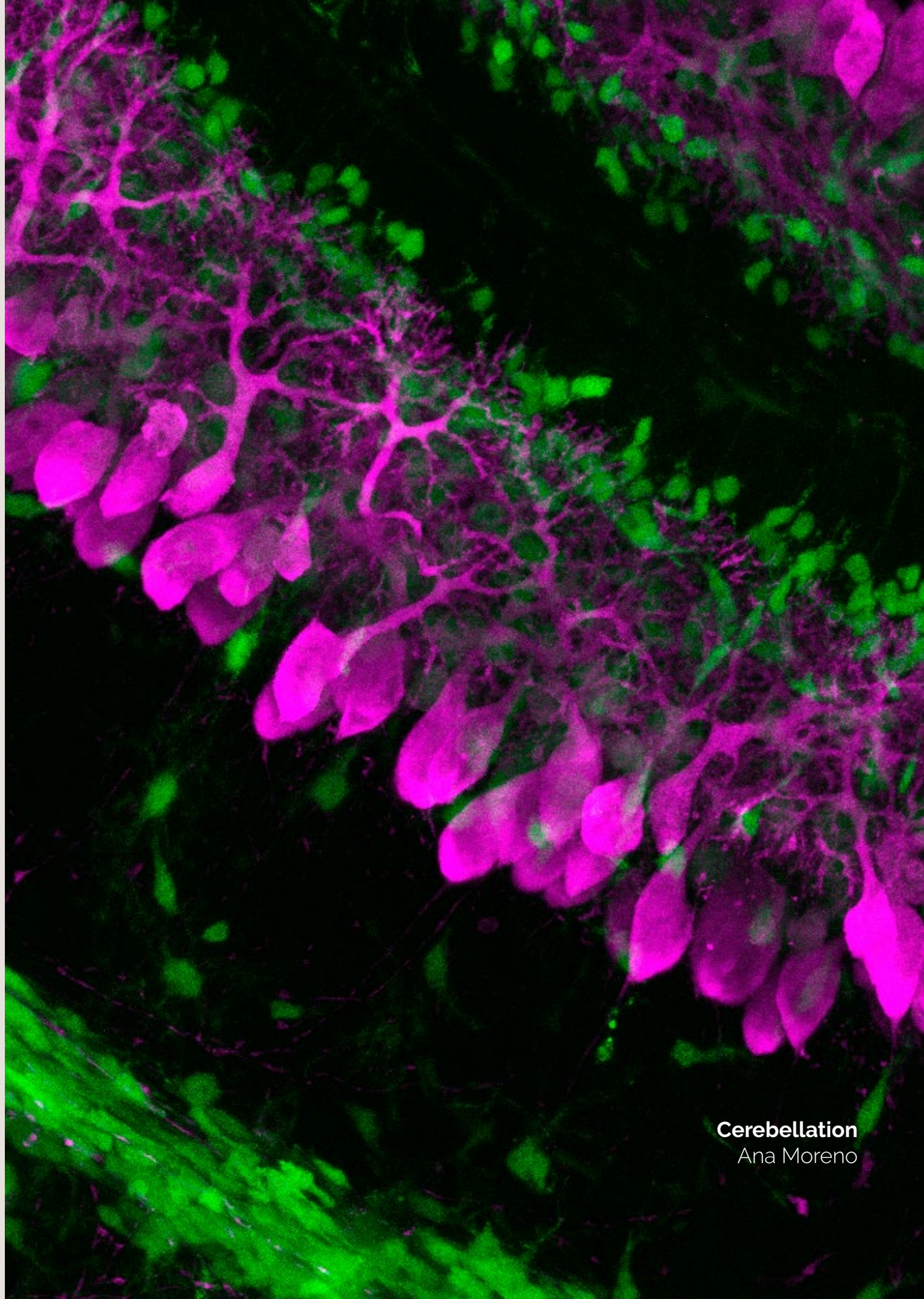
Warehouse
Mª Teresa García Hedo

Support Services

Audiovisual Service / Graphic Design
Sergio Javaloy Ballesteros
Rebeca de las Heras Ponce

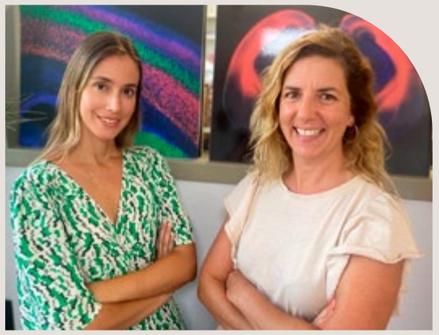
Maintenance
Jesús Campos Roldán
Alvaro Daniel Fenoll Esclapez

IT / Webmaster
Mª Isabel Sánchez Febrero

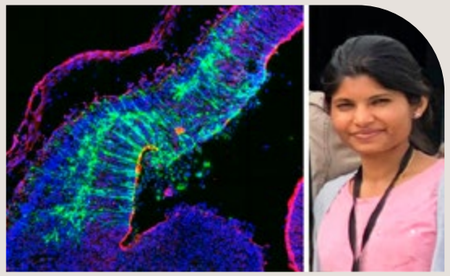


Cerebellation
Ana Moreno

Research Highlights

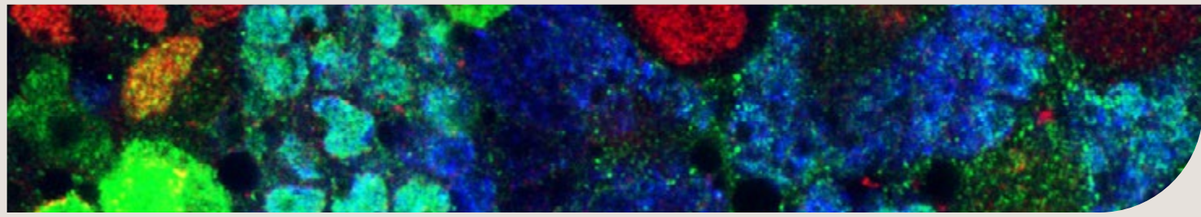


A study led by **Guillermina López-Bendito**, published in *Science*, showed that the touch and sight circuits are not independent in the embryo, but are intermingled. This work verified for the first time in vivo in mice that, during embryonic development, a tactile stimulus not only triggers the expected response in the primary somatosensory cortex but also triggers a response in the primary visual cortex of both hemispheres.

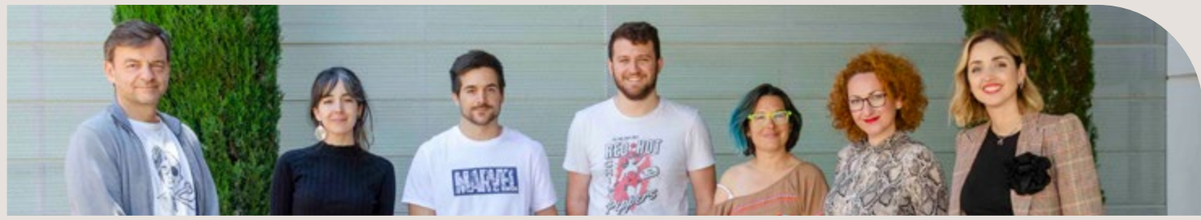


The group led by **Víctor Borrell** published in *Science Advances* a study that describes the role of the small genetic fragment of RNA called MIR3607 in the human cerebral cortex. Its main function is to increase the number of neural stem cells to enhance the formation of neurons.

An investigation led by **Hugo Cabedo** and published in *eLife* identified a series of genetic mechanisms that are activated sequentially to ensure that myelin is formed. This process ensures the functioning of peripheral nerves when they develop and during their regeneration after injuries.



The research group led by **Ana Carmena** published a study in *Current Biology* that revealed an unknown function of Netrins, axonal guidance molecules capable of regulating the excess proliferation of neural stem and progenitor cells.



A joint investigation led by **Silvia De Santis** and **Santiago Canals** made it possible to visualize brain inflammation using diffusion-weighted magnetic resonance imaging (MRI). This detailed and pioneering "x-ray", published in *Science Advances*, would allow a non-invasive and longitudinal study of the role of inflammation brain in Alzheimer's, Parkinson's, or multiple sclerosis.

The group led by **Cristina Márquez** published in *Current Biology* a study in rodents that suggests that good leaders are more willing to help. These altruistic behaviors favor the development of positive social interactions such as cooperation, which support individual and group well-being. In addition, the importance of the attitude of the subordinates to encourage this helping behavior in the leaders was observed.

Elvira de la Peña and **Félix Viana** published in *Brain* a study carried out in mice that shows how to prevent neuropathic pain associated with chemotherapy in colon cancer treatments. Pretreatment with an antagonist of the sigma 1 receptor, a key protein in pain control, largely prevents the development of neuropathic symptoms associated with oxaliplatin, a component of chemotherapy.

A study led by **Eloísa Herrera in collaboration with Angel Barco**, published in Advanced Science, identified, through a multiomic analysis, new regulatory proteins involved in the formation of neural circuits or networks during the development of the nervous system.

A study led by **Angel Barco in collaboration with José López-Atalaya** and published in *The Journal of Neuroscience* examined the role of the epigenetic regulator CBP in establishing adaptive genetic programs in the adult mouse brain. The role of two transcriptional coactivators involved in cognitive processes and intellectual disability, CBP and p300, was examined as their specific roles in adapting adult hippocampal circuits to experience were not fully understood.

The group led by **Javier Sáez Valero** collaborated with the CSIC's National Center for Biotechnology (CNB) in a study, published in *Frontiers in Immunology*, which demonstrated that the detection of ACE2 fragments or complete proteins in blood serum is a biomarker that would allow the determination of the efficacy of vaccines for COVID-19.

This same research group published a joint study in *Alzheimer's Research & Therapy* describing the changes experienced by apolipoprotein E (apoE) with the development of Alzheimer's disease. Comparing the different variants of this protein, alterations present in patients were determined, regardless of whether they were carriers of the apoE4 risk variant, which represents a further step in the direction of an early diagnosis of the disease.

A study led by **Santiago Canals** showed in an animal model that chronic alcohol consumption increases redundant activity in brain structures, and that specific communication is reduced to a set of pathways. This work, published in *The Journal of Neuroscience*, causally links chronic alcohol consumption with an early readjustment of the functional balance of the brain, which persists even during abstinence.

Scientific Events

Researchers at the *Instituto de Neurociencias* are very active in organizing scientific meetings, outreach activities, and scientific culture events. Thanks to these initiatives, Alicante has established itself as a key European center 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.

Esta semana hacemos Ciencia – Ciudad Ciencia CSIC

One Tuesday of each month high school students from our region take a guided tour to see the main technological facilities of the IN, they also enjoy informative lectures by our researchers. This is an activity promoted by the Spanish Research Council (CSIC) with the support of the Ministry of Science and Innovation.

International Day of Women and Girls in Science at the IN #11F

On February 11th, a conference was held, coordinated by Sandra Jurado, in which IN researchers Raquel García, Mar Aníbal, Rita Mariana, María Sáez and Encarni Marcos participated, as well as Christiana Dalla, from the University of Athens. During the day they presented the results of their research and discussed the main challenges that women face in their professional careers.

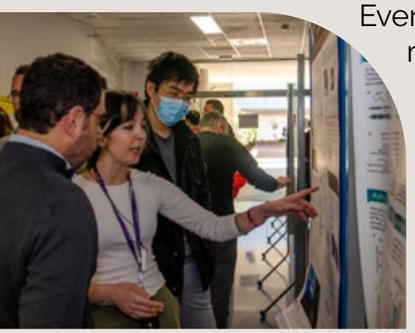
IN Sessions

This annual event took place on November 2nd, 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 researchers of the center.

Pint of Science

On May 9th, researchers Silvia De Santis and Luis Miguel Gutiérrez participated in this informative activity, held in various bars in the city of Alicante, in which they explained some of the research carried out at the IN.

XIX 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 20th and 21st and was coordinated by Teresa Femenía and Félix Leroy.

2nd IN Annual Retreat

On May 16th and 17th, a meeting was held to promote interaction between principal researchers, postdoctoral researchers, doctoral students, and common service technicians. During the meeting, science issues and scientific strategies were discussed, experiences were shared and various scientific activities were carried out.

World Alzheimer's Day

On World Alzheimer's Day, on September 21st, the groups of researchers Salud García, Javier Sáez, José V. Sánchez-Mut, and José López-Atalaya explained the pioneering studies they are carrying out on this type of neurodegenerative dementia. They work around improving their diagnosis, determining the genetic risk of suffering from the disease and even preventing or slowing down the progression of the disease.

I Research Meeting: Buscando sinergias

On June 7th, a meeting was held between the Alicante Health and Biomedical Research Institute (ISABIAL) and the IN at the Dr. Balmis General Hospital in Alicante, aimed at promoting collaboration between the two institutions.

NeuroArte 2022

From September 30th to October 14th, Adif Alicante Station hosted the exhibition "NeuroArte 2022", organized by the IN in collaboration with Adif and the European project MEDNIGHT (Mediterranean Researchers Night). The exhibition showed microscopy images captured by IN researchers.

Congress of Neurobiology of Pain and Inflammation

On September 29th and 30th, a scientific congress coordinated by Félix Viana was held in Sant Joan d'Alacant, which brought together a good number of international researchers, and leaders in the study of pain and inflammation.

Global Day Against Pain

Coinciding with the World Day of Pain, October 17th, the groups of researchers Félix Viana, Ana Gómis, Elvira de la Peña, Juana Gallar, M.C. Acosta, and Francisco Taberner presented their lines of research focused on understanding the changes that occur in the transition from acute pain to chronic pain and on finding new therapies in this field.

II Concurso de Fotografía IN #SciencePhoto_IN

On December 13th, the decision of the prize of the photography contest that the IN summons among its researchers was announced.

Ciencia Viva. La historia de la neurociencia española contada en primera persona

To recognize relevant researchers who have had a great impact on the advancement of Neuroscience in our country, on July 1st, professors Carlos Belmonte and Luis Puelles offered seminars on their outstanding careers, as part of a series of conferences promoted by the Spanish Society of Neurosciences.

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 Neurocienciass, 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 and, in particular, Virtudes García.

The student representatives of this course were: Manuela de las Casas and Juan José Rodríguez.

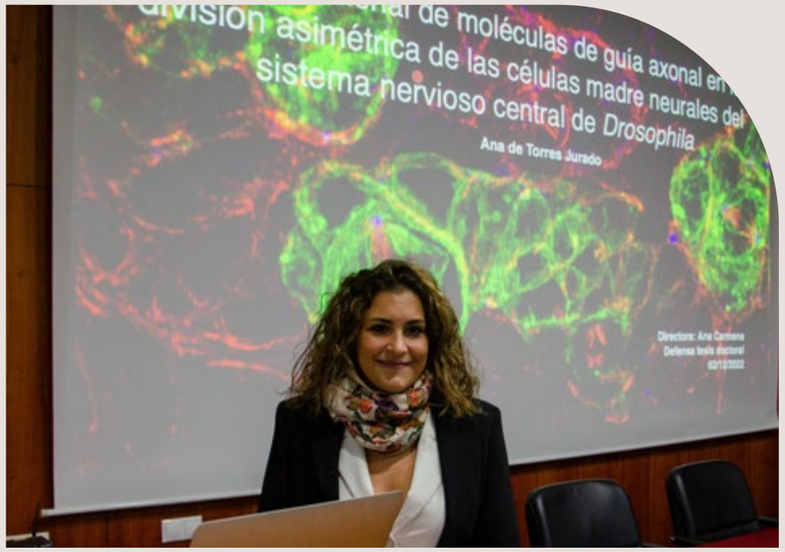
There have been 108 students enrolled in the PhD Program in Neurosciences (54 women and 54 men), 25% of whom are foreigners. 30% completed the Master's in Neurosciences at the UMH, for which the *Instituto de Neurociencias* is also responsible. There were 20 new students.

During the 2021-22 academic year, the Extraordinary Doctorate Award for the 2020-21 academic year were awarded to doctors: Álvaro Herrero Navarro, Ana Villalba Requena, Sergio Velasco Avilés, María Sáez García.

During this course, **56 researchers, members of the IN, have been directing Doctoral Theses** (30 male directors and 16 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 3 male PhD students and 11 female PhD students.** Seven of them with an international mention (6 female PhD students and 1 male PhD student) (Annex Defended Theses). All doctoral theses presented at least one quality indicator recognized by CENAI/ANECA in the field of evaluation to which the thesis belongs.

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 Neurocienciass, 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.

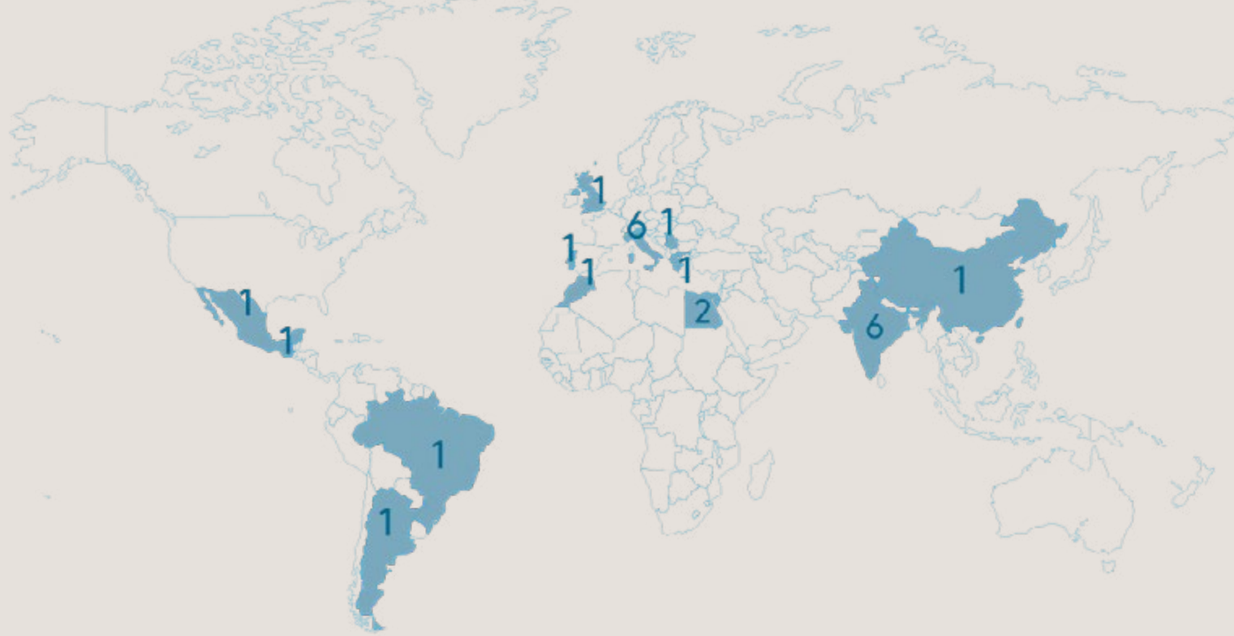
They took an introductory programming course entitled **"Cocinando IA con Python"** taught by Fernando Borrás, a UMH professor, the Applied Statistics course " Apoyo continuado a problemas estadísticos en el laboratorio," taught by Victoria Fornés, a statistician from the Oficina of Responsible Research of the UMH, in addition to an **advisory course for writing research articles** taught online by the prestigious journal Nature. They attended Congresses and Workshops, in person whenever possible or online.

They also participated in the **II Annual Congress of PhD Students** organized by the UMH, in which the student Mariángeles Cortés was part of the organizing committee, together with the Vice Chancellor for Research. The coordinator, Cruz Morenilla, along with Francisco Navarrate (CAPD-Neurosciences) were part of the Scientific Committee. The student Laura Frutos is part of **NeurotechEU** and participated in the organization of the "Students and NeurtechEU" symposium, as a representative of UMH students.

Regarding scientific dissemination, doctoral students are very involved in **Brain Awareness Week**, an activity organized by the Instituto de Neurocienciass, coordinated by the professor of the PhD Program, Juan Antonio Moreno (CSIC Researcher) that is held every year during the month of March at the Sant Joan d'Alacant Campus of the UMH. During this academic year, **61 students have been involved in holding 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).** Javier Morante, professor of the PhD Program, attended the biannual meeting held in Paris to present the program.

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 Neurocienciass: **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.

In the 2021-22 academic year, **the master's degree had 10 students enrolled** (6 women and 4 men). One of the students of the master's degree postponed the Master Research Project (MRP) to the following academic year, 2022-23 because she is a graduate in Medicine who obtained a MIR training place in 2022, which prevented the start of the laboratory work necessary to carry out the MRP.

During the 2021-22 academic year, teaching activities at the UMH were normalized and the master's degree was taught in its entirety in person.

Nine of the enrolled students took the **training course for the use of laboratory animals**, organized by the Office of Responsible Research of the UMH and 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.

The students Luis Felipe Hernández Villamizar (Mexico) and AlbaMarina Lucart Sánchez (Venezuela) enjoyed a scholarship from the Carolina Foundation, and the students Daniel Oppermann Peixoto (Brazil) and Víctor Martín Aguiar (Spain) obtained one of the Severo Ochoa Program scholarships. In the 2021-22 academic year, three scholarships were awarded within the Severo Ochoa Program, as there were very few candidates, possibly because the call was still made within the period of restrictions due to COVID-19. The third scholarship was awarded to a German student (Barbara Henning) who gave up taking the master's degree when it was just starting due to personal/family problems.

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

Undergraduate training

During the 2021-22 academic year, members of the IN have participated in 6 degrees from the UMH and 3 degrees from other universities. Also 24 Final Degree Projects have been carried out and have been participated in 2 Highly Specialized CSIC Courses.

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:

NeurotechEU Summit 2021 Pre-selection Event

Date: 10/23/2021 (virtual)

Neural basis of rodent social behaviour (IN and NeurotechEU)

Location: IN and virtual

NeurotechEU Virtual Summit

Date: 01/31/2022 (virtual)

Synapses Lecture Series: meet our universities! Session 1: UMH

Date: 02/24/2022

Location: IN

Celebrating NeurotechEU Women

Date: 03/08/2022 (virtual)

Course for PhD students "The Vascular Brain"

Date: 07/13/2022-07/17/2022

Location: Karolinska Institutet (Solna, Sweden)

NeurotechEU and Donders Cognitive Brain and Technology Summer School

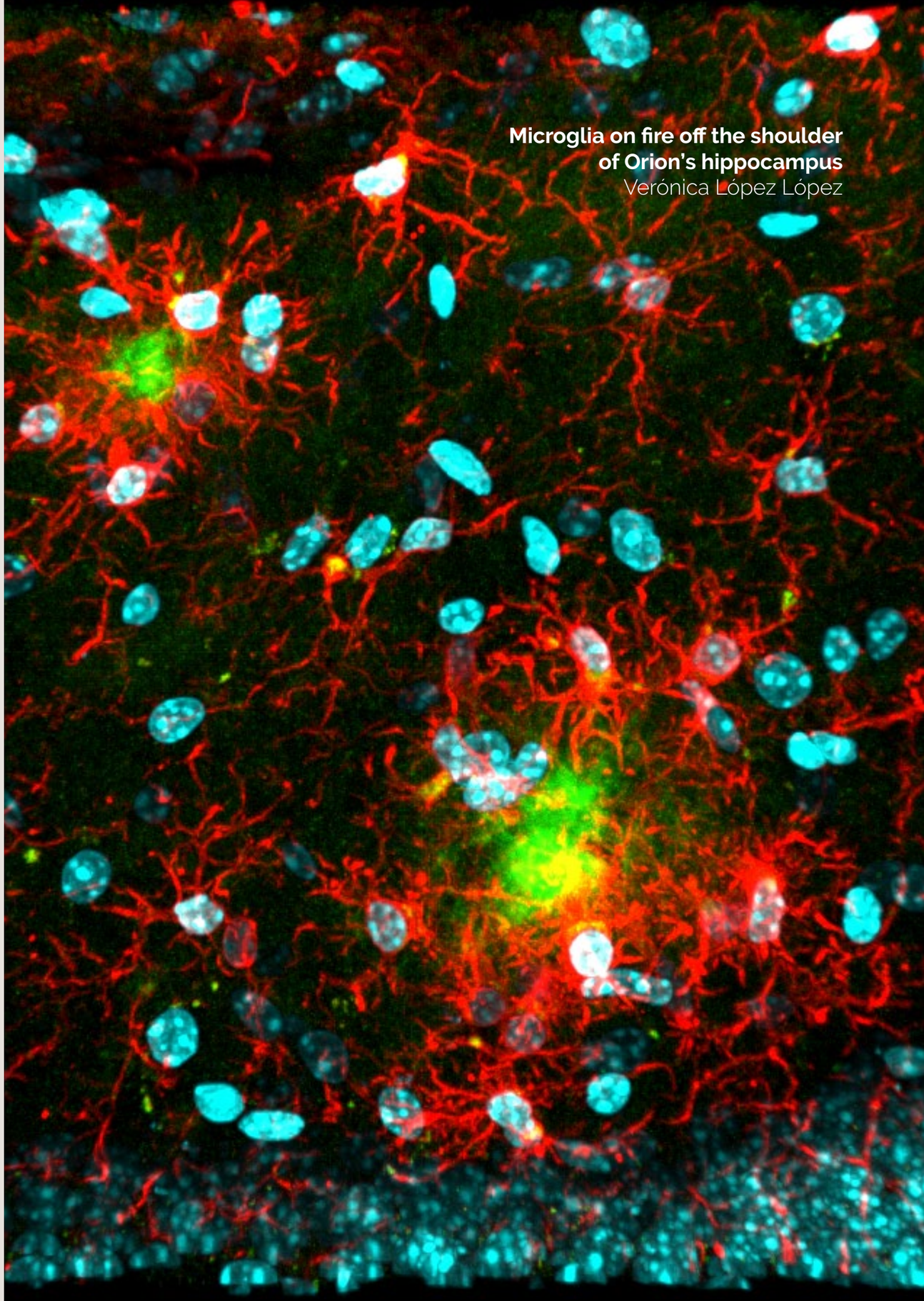
Date: 09/05/2022-09/16/2022

Location: Nijmegen (Netherlands)

NeurotechEU Summit 2022

Date: 09/12/2022-09/13/2022

Location: Nijmegen (Netherlands)



Microglia on fire off the shoulder of Orion's hippocampus
Verónica López López

Innovation UCIE

In order to encourage research applied to productive activity, the Agencia Valenciana de Innovación (AVI) promoted and supports 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. Ongoing projects are related to healthy aging.

IN.pulse
UNIDAD CIENTÍFICA DE INNOVACIÓN EMPRESARIAL

Staff

José Manuel del RíoVerona
Andrés Giner Antó
Visi Navarro Robledillo

Translation

Translational research at the Instituto de Neurociencias UMH-CSIC

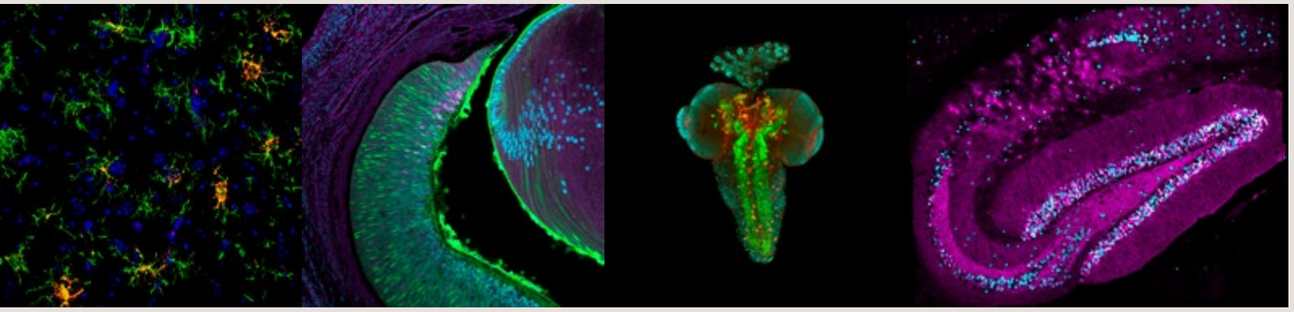
One of our main objectives is to turn the research carried out at the IN into novel therapies for diseases of the nervous system. To do this, we conduct research on nerve regeneration, demyelinating diseases, Parkinson's disease, Alzheimer's, ALS and chronic pain, among others. IN researchers have developed 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

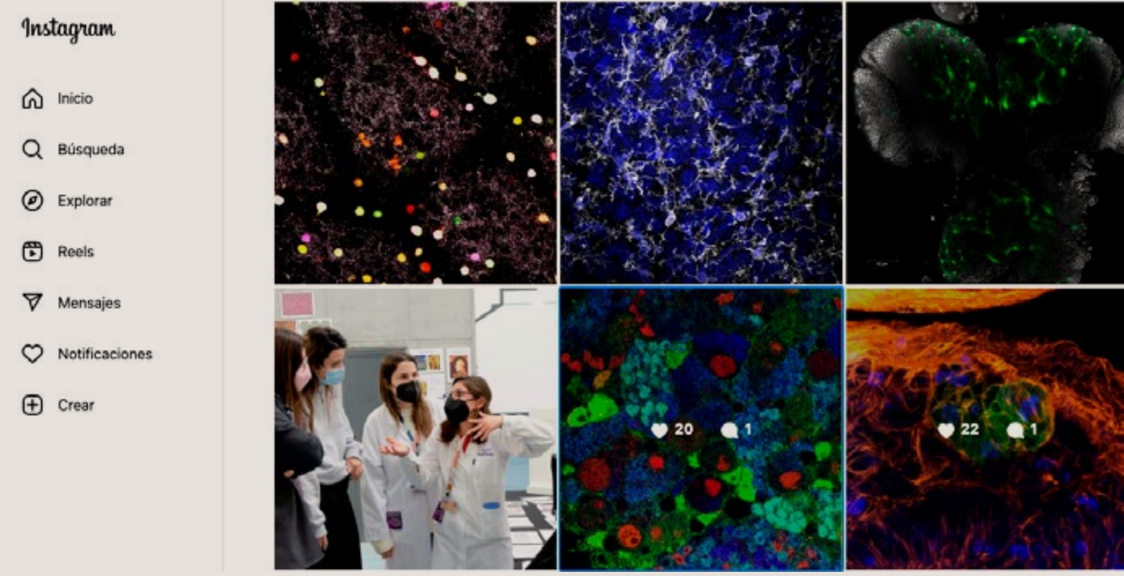
During 2022, we carried out several initiatives to get closer to society:

Open doors activities

Annually, we organize the Brain Awareness Week (BAW) in collaboration with the European DANA Alliance for the Brain. The main activity is an open-door day and a science fair in which the entire institute is involved, from PIs and doctoral students to administrative staff. After being forced to cancel in-person activities in 2020 and 2021 due to COVID-19 restrictions, we carried out our initiatives in 2022 with some restrictions. Nevertheless, the open-door activities were well-received, and we received visits from around 2000 people.



In addition to these days, a photographic exhibition NEUROARTE 2022 was held at the Renfe Station in Alicante to announce the winners of the I Scientific Photography Contest. We also celebrated the International Day of Women and Girls in Science by organizing several outreach activities (talks and round tables) to increase the visibility of women in Science. We also ran a program of visits for schools that attracted hundreds of students, and received a visit from the CSIC Science City Program on two occasions.



Presence in social media

Our social media channels continue to make excellent progress in terms of followers (Twitter: 6600, Facebook: 2200, LinkedIn: 1600, Instagram: 600, and YouTube: 500) and we strive to create engaging content regularly. Having a strong presence on social media is crucial for staying connected with our community and keeping them informed about the latest developments in neuroscience research. In addition, the 2nd IN Scientific Photography Contest took place, organized by the postdoctoral organization of the Institute of Neurosciences (OPINA) in collaboration with the IN social media team, with the aim of creating among the whole IN community a joint catalog of scientific photography..

Presence in the media

The Instituto de Neurociencias UMH-CSIC appeared 619 times in the media in 2021, slightly exceeding that registered in 2019 (607). The trend of increasing impacts that began in 2017 seems to be recovering. These impacts have been the result of 14 press releases sent to the media in 2021. The *Instituto de Neurociencias* has maintained a constant presence in the traditional media (press, television, radio) with the participation of its researchers in multiple interviews and appearances in both local (Diario Información) and national media (El Pais, ABC, La Vanguardia, etc,...).

Website

We continue to improve our website, enhancing its attractiveness and accessibility by adding multimedia material and new content both for public access and on our intranet.

Awards & distintions 2022

Ángel Barco Guerrero

XIX Alberto Sols Prize to the best scientific publication for the paper published in Nature Communications journal in 2020 "KAT3-dependent acetylation of cell type-specific genes maintains neuronal identity in the adult mouse brain".

Guillermina López Bendito

Hipatia Award for Scientific Career by elEconomista.

Ángela Nieto

L'Oreal-UNESCO for Women in Science Award (for Europe).

Foreign member of th**e French Academy of Sciences** (Académie des Sciences).

Honorary Doctor from the University of Jaén.

Santiago Grisolía Valencian Science Prize (first edition exaequo with Avelino Corma).

Salvador Martínez

On December 15th, 2022, he was named **Full member of the Royal Academy of Medicine** of the Valencian Community.

Álvaro Herrero Navarro (Lab. Guillermina López-Bendito)

Research Award from the Federico Olóriz Institute for Neurosciences (University of Granada) for young researchers in basic neurosciences (2022).

Extraordinary **PhD award** from the UMH.

María Sáez Garcia (Lab. Ramón Reig)

CSIC relevant **PhD thesis award**

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.

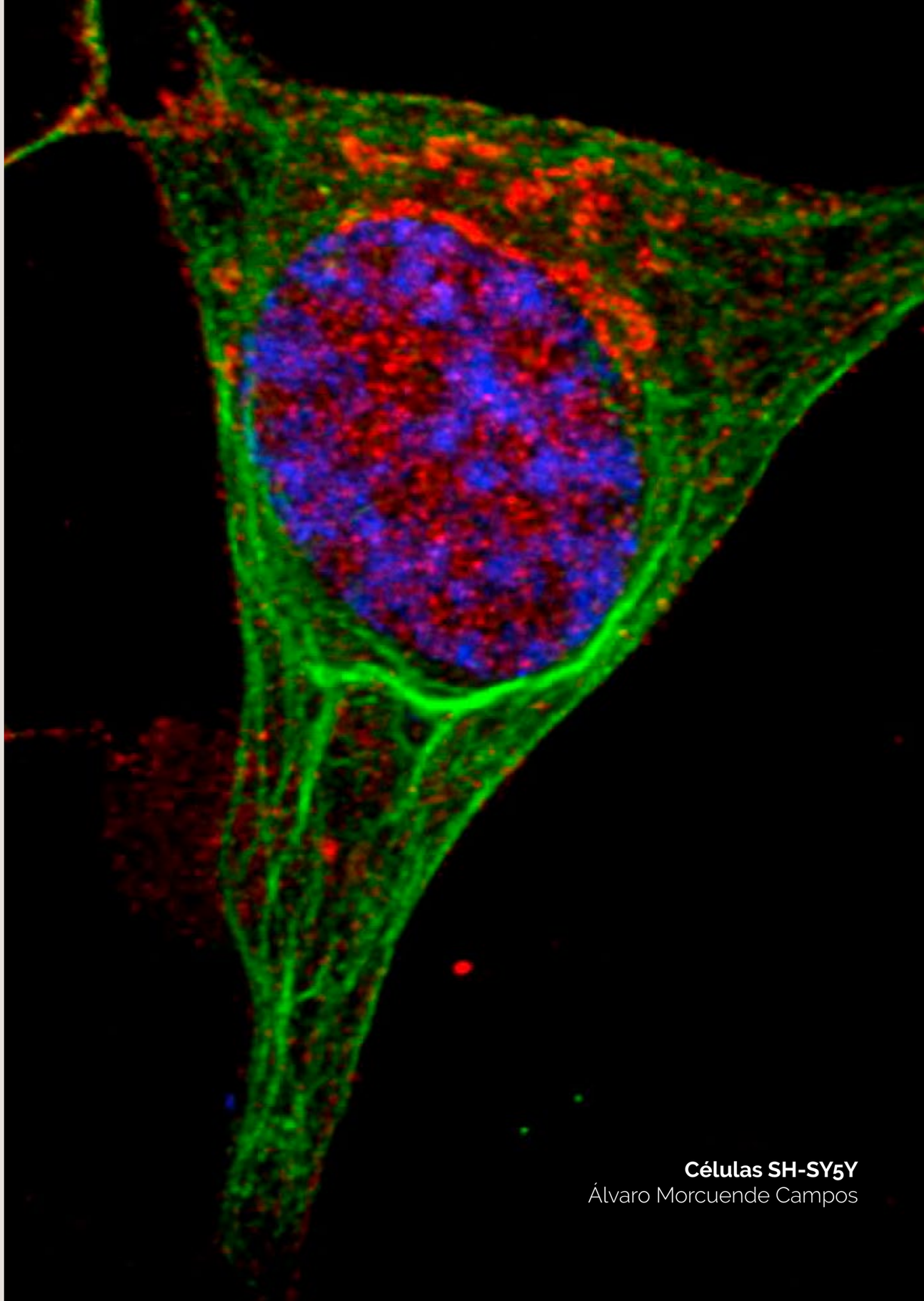
Visits 2022

Nobel Prize 2021

The American biochemist David Julius received the Nobel Prize in Medicine or Physiology in 2021 for his pioneering contribution to the analysis of the molecules that allow us to sense pain and temperature. As part of the jury for the Rei Jaume I Research Awards, Julius visited the Institute for Neurosciences on Monday, June 6th, 2022.

Minister of Science and Innovation

Visit of the Minister of Science and Innovation, Diana Morant, last December to the facilities of the Institute for Neurosciences (IN, CSIC – UMH), located in the Santiago Ramón y Cajal building on the Sant Joan d'Alacant campus of the UMH.



Células SH-SY5Y
Álvaro Morcuende Campos

Accreditations and distinctions

Renewal of the "Severo Ochoa" Centre of Excellence accreditation

The Instituto de Neurociencias (IN) ended 2022 with the pleasure of having its application for renewal of accreditation as a "Severo Ochoa" Centre of Excellence approved. **The IN thus becomes one of the few Spanish research centres to have renewed this accreditation of excellence twice in a row.** The "Severo Ochoa" accreditation of excellence, granted by the State Research Agency (AEI) as part of the Institutional Reinforcement Sub-programme, distinguishes the country's leading public R&D&I centres. This recognition involves an investment of four million euros over the next four years, in addition to several pre-doctoral contracts associated with this support.

In this context, the IN reorganised its strategic lines of research into 8 Scientific Programmes covering the most relevant fields of Neuroscience, which provided the basis of the Strategic Plan presented for the renewal of the Centre of Excellence accreditation.

Gender Equality Distinction

In 2022, the IN also received one of the accesits of the 4th edition of the Distinction for Gender Equality, awarded annually by the CSIC, "for the elimination of barriers that hamper the equality of women and men in the workplace". The director of the IN, Ángel Barco, received the award at a ceremony held in Madrid on 8 March 2022, which was also attended by the manager of the Institute, Maite García Hedo, Professor Ángela Nieto, National Research Award 2019, and the researcher and coordinator of the IN's Equality Commission, Sandra Jurado.

Renewal of the "Remedios Caro Almela" Chair in Neurobiology

The Universidad "Miguel Hernández" (UMH), the Instituto de Neurociencias and the Martínez-Caro family have renewed for the second time the "Remedios Caro Almela" Chair of Neurobiology. Created in 2000, the Chair aims to promote research on the nervous system at the molecular, cellular and organic levels, both in normal and pathological conditions, with a particular focus on the study of the development of the nervous system.

This third agreement will be in place until 2025 and will allow the continuity of activities such as the biennial "Remedios Caro Almela" Scientific Award for Research in Developmental Neurobiology, as well as the promotion of scientific dissemination activities and the sponsorship of travel grants for young researchers from the Institute to attend international scientific congresses. The Chair has contributed enormously to the visibility and promotion of the Institute as a centre of reference in Neurosciences both nationally and internationally.

Cátedra de Neurobiología Remedios Caro Almela

The Remedios Caro Almela Chair in Neurobiology was created in the year 2000 as a result of the philanthropic initiative by Fernando Martínez Ramos and his family to honor the memory of his deceased wife Remedios Caro Almela. After several renewals, the funding provided by the Martínez-Caro family seeks to keep alive the memory of their beloved mother and to promote the investigation of the nervous system, both in normal and pathological conditions, with a focus on the study of nervous system development.

Since its creation and until his retirement in 2012, Professor Constantino Sotelo was the Chairman, developing an excellent job for more that 10 years. In 2013, Professor Richard Morris was appointed as the new Chairman. Professor of Neurosciences of the University of Edinburgh and fellow of the Royal Society, Richard Morris has made countless contributions to the neurobiology of learning and memory. Some of his major scientific achievements include the development of the water maze, known as Morris Water Maze, the discovery of the role of NMDA receptors in learning and memory, the development of the hypothesis of synaptic labeling and capture, and discoveries about the neurobiology of previous knowledge (schema), etc.

Richard Morris & Constantino Sotelo

Profesor 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.

Profesor 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.

Anexos

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Books chapters 2022

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Seminars 2022

4/2/22 Eduardo Fernández Jover
Instituto de Bioingenieria, Elche
Towards a bidirectional communication with the brain in the blind: Challenges and future prospects

18/2/22 Antonia Gutiérrez
Universidad de Málaga
Glial pathology in Alzheimer's disease: from transgenic models to human brains

25/2/22 Antonio Ferrer Montiel
Universidad Miguel Hernández, Elche
Role of thermoTRPs in chronic migraine and its sexual dimorphism

4/3/22 Heidi Johansen-Berg
Wellcome Centre for Inegrative Neuroimaging, University of Oxford
Imaging and stimulating adaptive brain plasticity

11/3/22 Ángel Nadal
Universidad Miguel Hernández, Elche
Endocrine disruptors as environmental determinants of diabetes

25/3/22 Bassem Hassan
Paris Brain Institute, Paris
The neuroscience of fly personality

22/4/22 Sergio Casas Tinto
ISCIII/Instituto de Investigación de Enfermedades Raras(IIER), Madrid
Cell to Cell communication mediates neurodegeneration caused by glioblastoma

6/5/22 Richard Benton
Center for Integrative Genomics, University of Lausanne, Switzerland
The making of a specialist fly: investigating the neurobiology of ecological niche adaptations

13/5/22 Stanislav Zakharenko
St. Jude Research, Memphis, USA
Teasing-Out Schizophrenia Mechanisms via Models of 22q11.2 Deletion Syndrome

3/6/22 Marta Costa
Department of Zoology, University of Cambridge, Cambridge, UK
Mapping neural circuits in the fly with connectomics

10/6/22 Robin Franklin
Wellcome-Medical Research Council Cambridge Stem Cell Institute, U. Cambridge, UK
The regenerative biology of adult CNS progenitors - reversing the ravages of time

17/6/22 Amanda Sierra
Achucarro Basque Center for Neuroscience, Zamudio, España
Not just corpse removal: how microglial phagocytosis maintains brain tissue homeostasis

16/9/22 Manuel Tena-Sempere
Universidad de Córdoba/IMIBIC, Córdoba, Spain
Novel mechanisms for the brain control of mammalian puberty: Roles of Kiss1 neurons, miRNAs and energy/nutrient sensors

23/9/22 Ana Pombo
MDC, Berlin, Germany
Long-lasting memory of cocaine exposure is encoded in the 3D genome structure of dopamine neurons

30/9/22 Gary Lewin
Max Delbrück Center for Molecular Medicine, Berlin, Germany
Ion channels and tethers for touch

7/10/22 Javier Burgos y Juan Lerma
Universitat Jaume I de Castelló
El cerebro y las enfermedades del alma

14/10/22 Michael Heneka
Luxembourg Centre for Systems Biomedicine (LCSB), Belvaux, Luxembourg
Innate Immunity in chronic neurodegeneration

17/10/22 Tom Blanpied
University of Maryland Medical School, Baltimore, USA
Synaptic nanoarchitecture that controls receptor activation

21/10/22 Victoria Moreno
CIPF, Valencia
Cell Therapy for Spinal Cord Injury regeneration

11/11/22 Henrique Veiga-Fernandes
Champalimaud Center for the Unknown, Lisboa, Portugal
Neuroimmune interactions in health and disease

18/11/22 Christian Mayer
Max Planck Institute of Neurobiology, Martinsried, Germany
Single-cell characterisation of lineage and genetic identity in the mouse brain

PhD Thesis 2022

Universidad Miguel Hernandez de Elche (UMH)

Ana Maria de Torres Jurado
Análisis funcional de moléculas de guía axonal en la división asimétrica de las células madre neurales del sistema nervioso central de Drosophila
Ana Carmena De La Cruz

Maria Empar Blanco Cantó
Descripción clínica y genética de los pacientes con diagnóstico de charcot-marie-tooth en el área de alicante e identificación de nuevas mutaciones en CMT1
Hugo Cabedo Marti

Noemi Castroviejo Jiménez
Genetic robustness of emt-tfs in zebrafish heart laterality
M. Ángela Nieto Toledano

Almudena Iñigo Portugués
Identificación Molecular y Morfodinámica de las Fibras Sensoriales de Frío Corneales en el Ratón Adulto
Carlos Belmonte Martinez, Victor Manuel Meseguer Vigueras, Juana Gallar Martinez

Adam Matic
Invariances and controlled variables in human arm movement
Alejandro Gomez Marin

Ángel Márquez Galera
Neurodegeneratie trajectories in a model of epilepsy with hippocampal sclerosis
José Pascual López-Atalaya Martinez

Laura Frutos Rincón

Neuroimmune interactions in the cornea: Effects of resident dendritic cell depletion on cold nerve terminal activity, basal tearing, and pain

Juana Gallar Martinez, Maria Del Carmen Acosta Boj

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Novel Competition Test For Food Rewards Reveals Stable Dominance Status In Adult Male Rats

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The role of KAT3 proteins in neural development

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Translational investigation in humans and animal models of alcohol use disorders

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Using spontaneous and evoked activity to identify subregional specialisations of corticorecipient areas

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Evaluation Of Jun Overexpression In Schwann Cells On Motoneurons Feasibility And Myelination In The Peripheral Nervous System

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Cristina Hernandez Medina

A Functional Study Of Anterior Cingulate And Retrosplenial Cortex After Lis1 Selective Deletion In Somatostatin-Expressing Interneurons

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