Annual Report

2019 - 2020

CSIC UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS


CSIC
Consejo Superior de Investigaciones Científicas


UNIVERSITAS
Miguel Hernández


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EXCELENCIA
SEVERO
OCHOA

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Saludation

Salvador Martínez
Director until September 2020

Ángel Barco
Director since October 2020

The Instituto de Neurociencias (IN) recently celebrated its 20th anniversary as the largest research center dedicated to brain research in Spain and as an international benchmark. Our story is a story of vision, effort, perseverance and success that started 35 years when a group of neuroscientists, working at that time in the Universidad de Alicante, had the idea to create an international institute dedicated to the study of the structure and function of the nervous system at the Mediterranean shore. Thanks to the effort of many people, this idea became a reality and the successful path traced by the IN previous directors, Professors Carlos Belmonte (1999-2007) and Juan Lerma (2007-2016), stimulating quality research and scientific excellence as a guiding principle, has led our center to reach high levels of international leadership. The IN has maintained throughout its trajectory a growing level of publications with high scientific impact in internationally prestigious journals. Many of the established IN groups are leaders in their respective fields of research. In the last two years, IN researchers have published more than 160 articles that received thousands of citations, including very relevant findings presented in journals of the highest impact. Thanks to the accreditation as a "Severo Ochoa Center of Excellence" we have been able to develop an ambitious and multidisciplinary research program, undertake new methodological initiatives and recruit talented young researchers. This has been the case even in a particularly difficult period such as the one covered in this report. The difficulties confronted in 2020 due to the COVID-19 pandemic did not slow down our researchers in their ambitious goals of generating knowledge about the function and development of the brain and its pathologies. Two new research groups initiated their trajectory in our institute in 2019, and three more joined in 2020, shortly after the lockdown. The talent, energy and creativity of the new hires represent an exceptional asset that guarantee the future of the IN. These achievements also depend on the excellent work and professionalism of the research and administrative support staff, which makes the experimental work and the financial resources of the researchers more efficient. For all these reasons, we would like to thank and congratulate all the researchers and employees of the IN, as well as to all the people who have contributed and contribute to the excellence and vitality of our institution. We also want to thank the Institutions to which we belong, CSIC and UMH, for the continuous support of our activity and growth.

Salvador Martínez, Director (until September 2020)

Ángel Barco, Director (since October 2020)

Who We Are

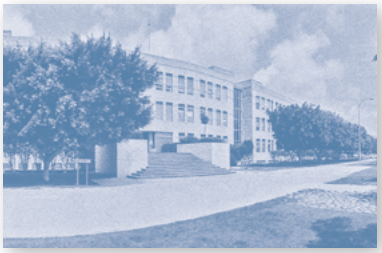
The IN, a joint center of the Spanish Research Council (CSIC) and the Universidad Miguel Hernández de Elche (UMH), is today the largest publicly funded center dedicated to brain research in both normal and pathological conditions in Spain. This is achieved through a multidisciplinary approach towards the study of the structure, function and development of the nervous system at the molecular, cellular and integrative levels. More than 300 people dedicate all 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 that we are committed to increase to become an international center of reference in neuroscience. 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. Moving beyond the typical university departmental structure, 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

A bit of history

1985 — **University of Alicante**
group of researchers dedicated to studing the structure & function of the nervous system



1990 — **University Insitute**
formally recognised at the University of Alicante

1995 — **Asociated Unit**
of the Instituto Cajal CSIC

1996 — **University Miguel Hernández**
transferred to the newly created University Miguel Hernández of Elche

1999 — **Joint Centre**
UMH and CSIC

2001 — **Construction**
of the new building

2004 — **Occupation**
of the new building

2005 — **Inauguration**
by Her Royal Majesty

2007 — **Consolider-Ingenio grant**
received by the IN

Consolider

2014 — **Severo Ochoa Distinction**
received by the IN

EXCELENCIA SEVERO OCHOA

Ph.D. Program was created to train young scientists in the 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.

EXCELENCIA SEVERO OCHOA

2018 Renewal of SO Distinction received by the IN

20 Years UMH & CSIC 2019

1999 - 2019

AÑOS

INSTITUTO DE NEUROCIENCIAS

IN 20th Anniversary

In 1999, the IN was formally created as a Joint Centre of the UMH and CSIC. Since then, the IN has gathered scientists belonging to both institutions and actively recruited young researchers providing a favorable environment for the creation and consolidation of new groups. In 2001, 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 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 have seen an important period of expansion, resulting in the IN becoming the largest Spanish institute monographically 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 IN currently host 33 research groups with more than 250 researchers (See graphic IN in Numbers: Personnel).

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 acreditation as “Center of Excelence Severo Ochoa” in 2014 and its renewal in 2018 have enabled the consolidation of our project through the development of an ambitious and multidisciplinar research program. In 2019, we celebrated our 20th Anniversary with the strong vocation of continuing growing and progressing towards 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.

L.M. Gutiérrez

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).

PERSONNEL

TENURE
Full tenure research staff
43

SUPPORT
Administrative & technical staff
100

NON-TENURE
Non- tenure research staff
11

POSTDOC
Postdoctoral staff
56

PREDOC
Predoctoral staff
118

GENDER

60% Female staff

40% Male staff

ORIGIN

Non-Nationals 12%

Spanish nationals 88%

PUBLICATIONS

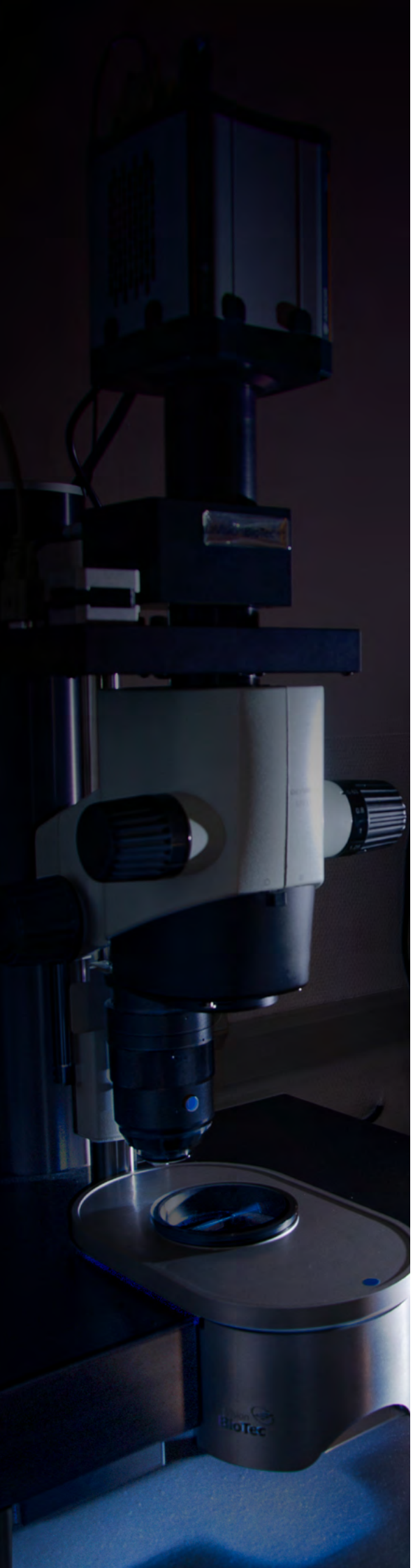
Web of Science

In the period 2019 to 2020

174

7

IMPACT
Mean IF



What We Do

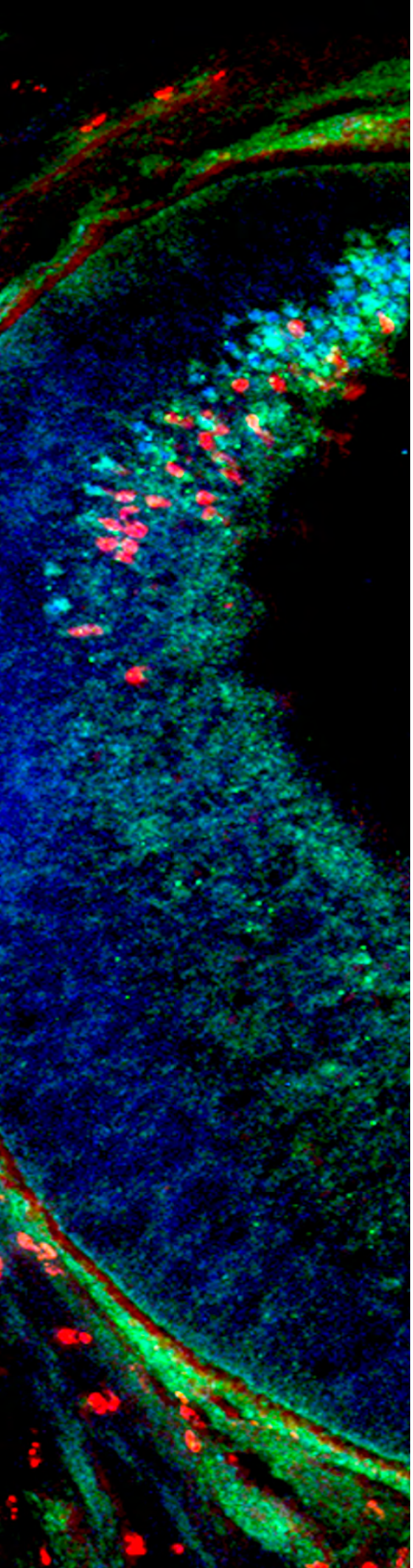
Our main activity is **RESEARCH**. The IN has contributed throughout its trajectory to many key discoveries presented in publications in internationally prestigious journals with high scientific impact. Thanks to the scientific talent and the quality of their projects, our researchers obtain a high degree of competitive funding that allows us, as an institute, to maintain technologically advanced research support services. The joint participation in the calls for infrastructure, articulating needs and efforts, have served to incorporate the most modern techniques and technologies into the Center, which allow our researchers to carry out the most advanced experiments and progress in the knowledge of the brain on equal terms with our European and American colleagues. The repercussion of a better understanding of the brain in the construction of the society of the future is enormous. Neuroscience is called to modify human attitudes and customs towards higher levels of well-being, as well as improve adaptation to the new circumstances that humanity faces. The IN aspires to contribute to this task.

We have an external Scientific Advisory Board (SAB) that evaluates our scientific production and advises on the research activity and strategies of the Institute. Our current SAB is chaired by Claudio Sterm (UCL, UK) and includes Ranulfo Romo (UNAM, Mexico), María Blasco (CNIO, Spain), Magdalena Götz (MCN, Germany) and Michael Häusser (UCL, UK).

The IN researchers are not only committed to the challenge of understanding how the brain works; the research of many groups has a strong translational orientation. The IN aspires to become a reference in terms of **TRANSLATION** and collaboration between basic and clinical researchers in different disciplines.

One of the greatest challenges facing today's science and society is to understand the brain

The IN is also firmly committed to **INNOVATION**. The initiative of the Generalitat Valenciana to create a Valencian Innovation Agency (AVI) to stimulate the transfer of research results to industry and society, has allowed the creation of an associated Scientific Unit for Business Innovation (UCIE) to the IN, called IN.PULSE, which we hope will contribute to increasing the social impact of our research on the Valencian economy and industry, as well as the well-being of citizens. The first results have begun to be evident in this period. The IN is also a teaching institution that wants to spread excellence



in academic and technical education in neuroscience. The IN has a strong vocation for **TRAINING** and **EDUCATION** and aspires to train new generations of neuroscientists. Our researchers together with the UMH maintains very attractive international Master and PhD programs in Neuroscience. Our PhD program has been awarded with a mention as “Programme of Excellence” by the Ministry of Education and has ran for more than 20 years forming hundreds of neuroscientists, some of which are today leaders in their fields. In addition, during the Academic Year 2015-2016 we started the International Master in Neuroscience: from bench to bedside. This is a one-year course totaling 60 ECTS on both basic and advanced aspects of neuroscience taught by University and CSIC lecturers in collaboration with the Developmental Biology Master of the Institute Pasteur and the University Paris VI (Pierre et Marie Curie).

The training vocation of the IN extends to society in general. The IN organizes various scientific **OUTREACH** activities, the most notable of which is the celebration of World Brain Week with a week of open doors that in 2019 reached record participation figures (more than 2,500 visitors) and had live radio and television broadcasts of UMH and RNE. In 2020, the pandemic situation caused by COVID-19 forced us to cancel this activity, already very popular in Alicante society, which we hope to resume when possible.

The IN is very active in the establishment of **COLLABORATIONS & ALLIANCES** with prestigious international institutes, which allows interchange of researchers, achieve a critical mass of international leadership and access to complementary technologies, and with other institutions and active forces in our society interested in promoting research and education in neurosciences.

Research Lines & Strategic Plan

One of the greatest challenges facing today's science and society is to understand the brain and the biological basis of human behavior, including functions as diverse as movement control, language, sensations, emotions or consciousness. The promotion of adequate educational programs based on a better understanding of brain maturation, the increasing requirement for resilience to compensate brain fragility during life, together with the necessity of combat high prevalent psychiatric and neurodegenerative illnesses, represent growing health problems and an important social burden in developed western countries. Unfortunately, there is still relatively little knowledge about the cellular and molecular underpinning of complex brain functions and the causes of mental illnesses, and for this reason there is an increasing interest on the study of the nervous system.

The IN wrote its first strategic plan in 2005. Since then, we have designed an implemented four 4-year strategic plans that shaped the research and growth if our Institute and enable our positioning as a center of excellence in the European research area. We moved towards multi-disciplinary approaches and strengthened research around pathologies of the nervous system. The acquisition of cutting-edge technology platforms, such as imaging techniques and omic methodologies aimed at studying and exploring the brain, is another goal of IN. The institute has an international vocation and continues to seek the incorporation of leading scientists from all countries, and intensive collaboration with other research centers, particularly in Europe. The increase of our scientific impact, the international teaching offer and the interaction with technological institutes to stimulate innovation platforms, are three lines of work to drive new challenges in the current Action Plan of the IN for 2018-2021.

SCIENTIFIC OBJECTIVES

In addition to the organization in three Departments, there is a second level of organization based on the seven research lines defined in The Strategic Research Plan of the IN (IN-SRP). These constitute a horizontal organization gathering members of different Departments around more specific research subjects. This horizontal (research lines)-vertical (Departments) structure favors synergistic interactions between our researchers, through an understanding of the brain from different viewpoints, disciplines and techniques.

The main objective of the IN-SRP is to increasing knowledge about normal brain function and the biological roots of brain diseases, to improve prevention, diagnostics, therapies and prognosis.

The main research lines in the IN-SRP are:

IN-SR line 1.- Determining the genetic and epigenetic mechanisms that regulate and coordinate morphogenesis in the central and peripheral nervous systems.

IN-SR line 2.- Towards a better understanding of axon guidance and migratory cell movements during development.

IN-SR line 3.- Deciphering the molecular and functional mechanisms orchestrating neuronal connectivity and brain wiring.

IN-SR line 4.- Systems neuroscience: to study the molecular and functional mechanisms controlling synapsis formation, maturation and sensory transduction.

IN-SR line 5.- To shed light onto the pathophysiological mechanisms causing degenerating brain diseases and cancer.

IN-SR line 6.- Understanding the role of inflammation in normal and pathological brain function.

IN-TSR line 7: A transversal SR line is to shed light on the pathophysiological mechanisms of mental diseases at molecular, cellular, and system levels and to implement ultra-high-throughput functional screening platforms for gene and drug discovery in diseased animal models.

These lines represent a multidisciplinary approach to study the molecular and cellular mechanisms underlying brain morphogenesis, synaptic establishment and maturation in sensorial, motor, social and emotional neuronal circuits; to finally understand how combinatory function of these circuits explain perception, cognition and behavior. We must face the challenges that lie ahead for the neuroscience of the future, fundamentally based on the holistic knowledge of development and maturation of brain activity throughout all periods of life, to understand the neurobiological mechanisms of normal and altered behavior. It is necessary to integrate the genetic, molecular and structural study of the brain with the dynamism of time, progressively applied to all levels, neurons and glia, from synaptic function to connectome, as well as to gender differences. The time setups the hierarchical order in the processes that underlie mental activity, defining biomarkers and their dynamic evolution, and identifying values of normality with their margins of confidence. Biomarkers are also needed to explore the mechanisms of neuroplasticity and resilience, whose knowledge will allow clear diagnoses to address better therapeutic strategies. Therefore, we have to incorporate time in our research designs in both senses, exploring organisms along their life periods and visualizing neural processes in real-time sensitive technological devices. The IN during the last few years has increased technology to visualize in vivo processes and approach real time experiments.

In parallel to the accomplishment of our scientific project we plan to increase the quality of the scientific production and international impact of our publications, in order to improve our capacity to obtain grants and technical contracts. A requirement to properly achieve this program, and also as a consequence of its results, is to promote specialization, stabilization and promotion of our worker's categories, looking for higher quality in technical services and a more coherent equilibrium between research and technical staff in the IN.

Research Units

The Institute is organized in three research Departments. Each Department is formed by scientists that share general research interests and technical approaches.

Developmental Neurobiology

The Developmental Neurobiology Department consists of ten research groups devoted to study the development, evolution and repair of the nervous system and to understand the developmental origin of pathologies using both vertebrate and invertebrate animal models. This research includes pattern formation, growth control and cancer, neurogenesis, cell migration and plasticity, differentiation, reprogramming, axonal guidance and synaptogenesis. We combine genetic, cellular, molecular and experimental embryology approaches with state-of-the-art imaging techniques and single cell “omics”, and apply cross-level integration from cells to the whole organism.

Cellular & Systems Neurobiology

Research groups in the Cellular and Systems Neurobiology Unit study the integrative processes of the nervous system combining molecular, electrophysiological, optogenetics, brain imaging and behavioral tools in a variety of animal models (Drosophila, mouse, rats) and human studies. Specific topics cover investigations on synaptic transmission and synaptopathies, functional organization of brain networks and its plasticity, sensory transduction and perception, sensory-motor integration, memory formation and the neurobiological underpinnings and organizational principles of behavior.

Molecular Neurobiology and Neuropathology

The Molecular Neurobiology and Neuropathology Unit investigates the biological basis of brain disorders. We study rare and prevalent psychiatric and neurological diseases using a combination of behavioral and electrophysiological analyses, cellular and molecular biology techniques, and high-throughput “omics” approaches. Our collective effort seeks to better understand the molecular and environmental grounds of brain malfunction to improve current therapeutic strategies for brain disorders.

C. García Frigola

Research Groups

Developmental Neurobiology

V. Murcia Belmonte

Cellular & Systems Neurobiology

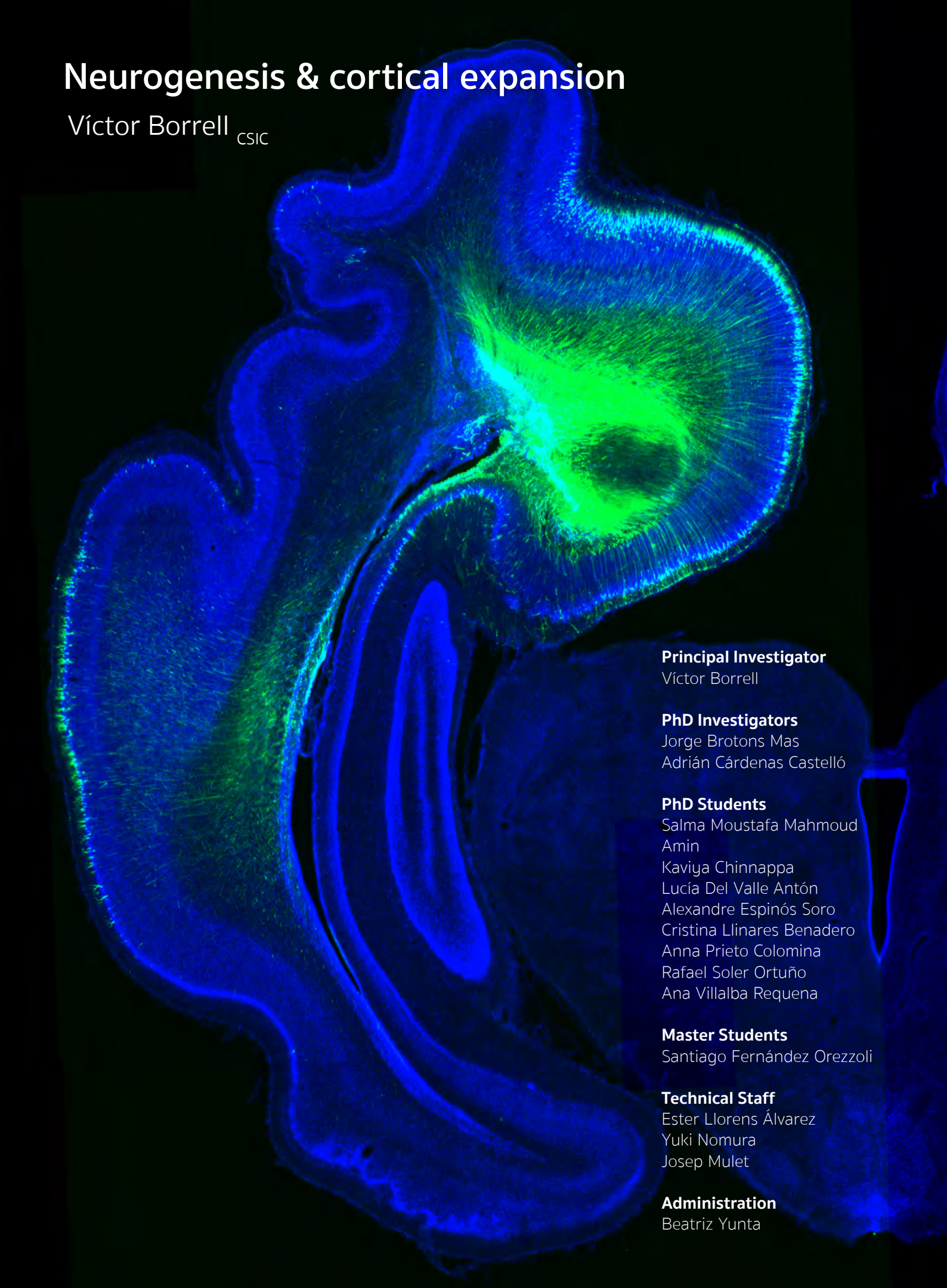
J. Gallar Martínez

Molecular Neurobiology and Neuropathology

A. Giner de Gracia

Neurogenesis & cortical expansion

Víctor Borrell CSIC



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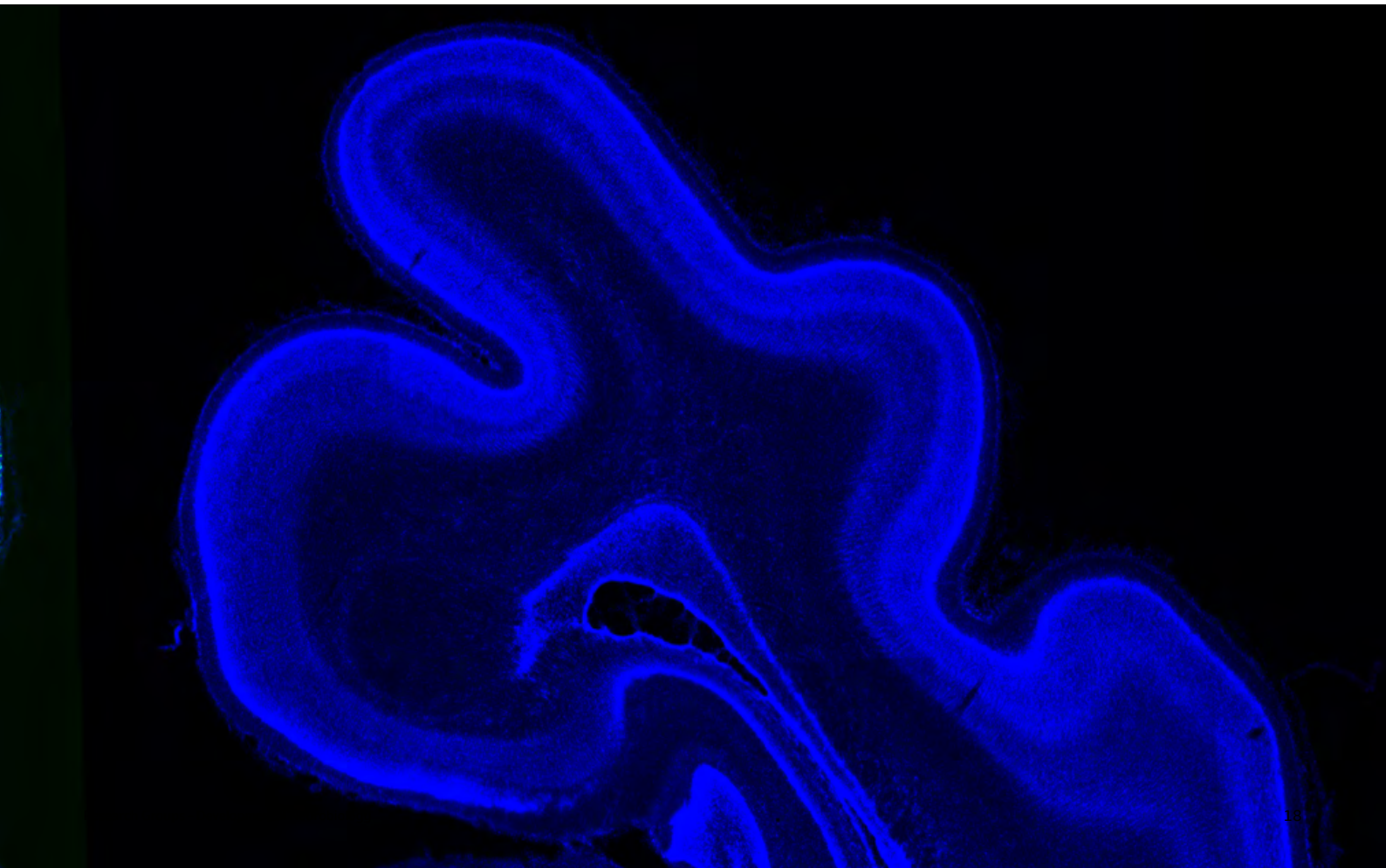
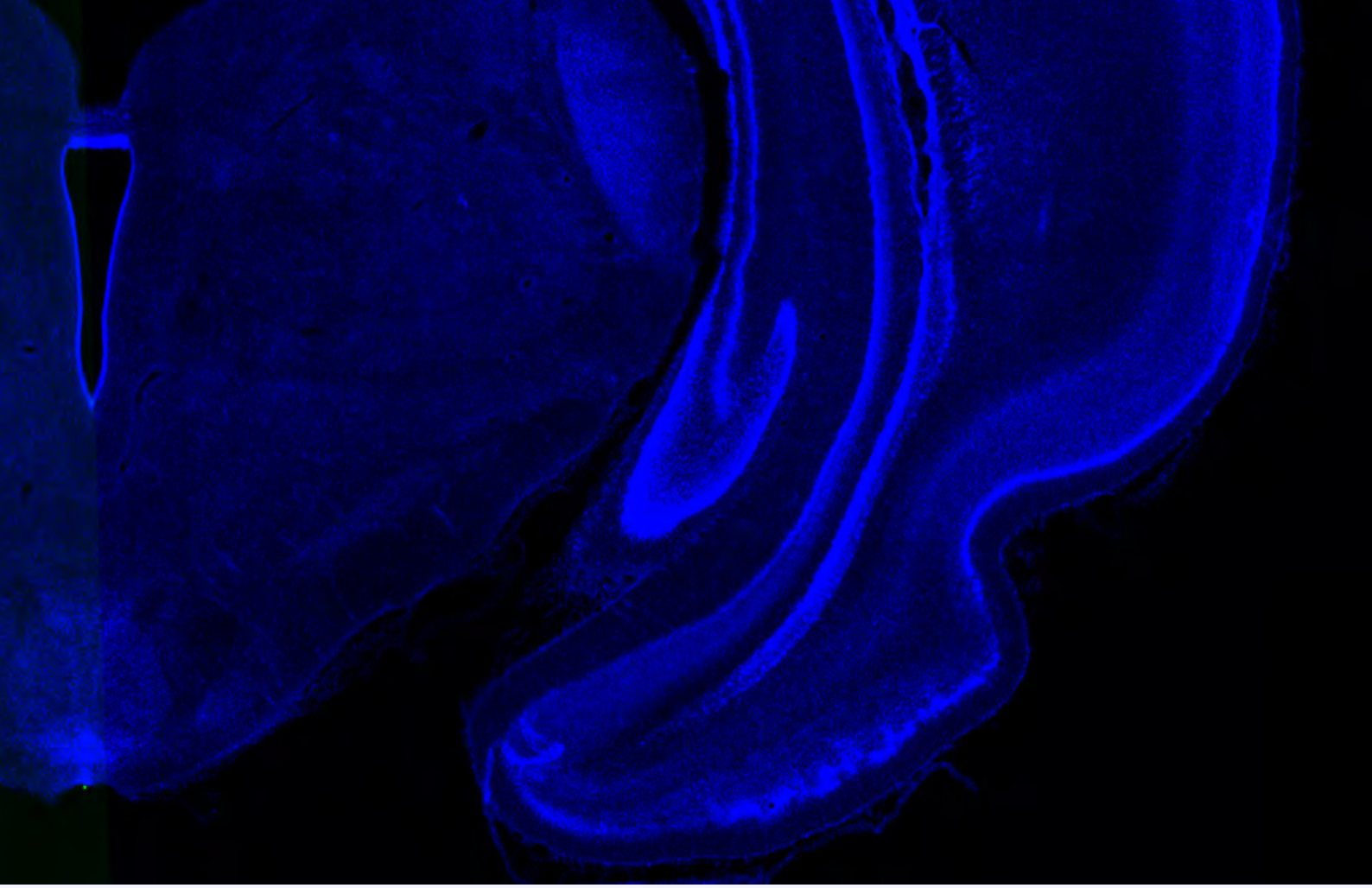
Our laboratory is interested in understanding the cellular and molecular mechanisms governing the expansion and folding of the cerebral cortex observed across mammalian evolution. The cerebral cortex is the largest structure in the brain and is responsible, among others, for the higher cognitive functions 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.





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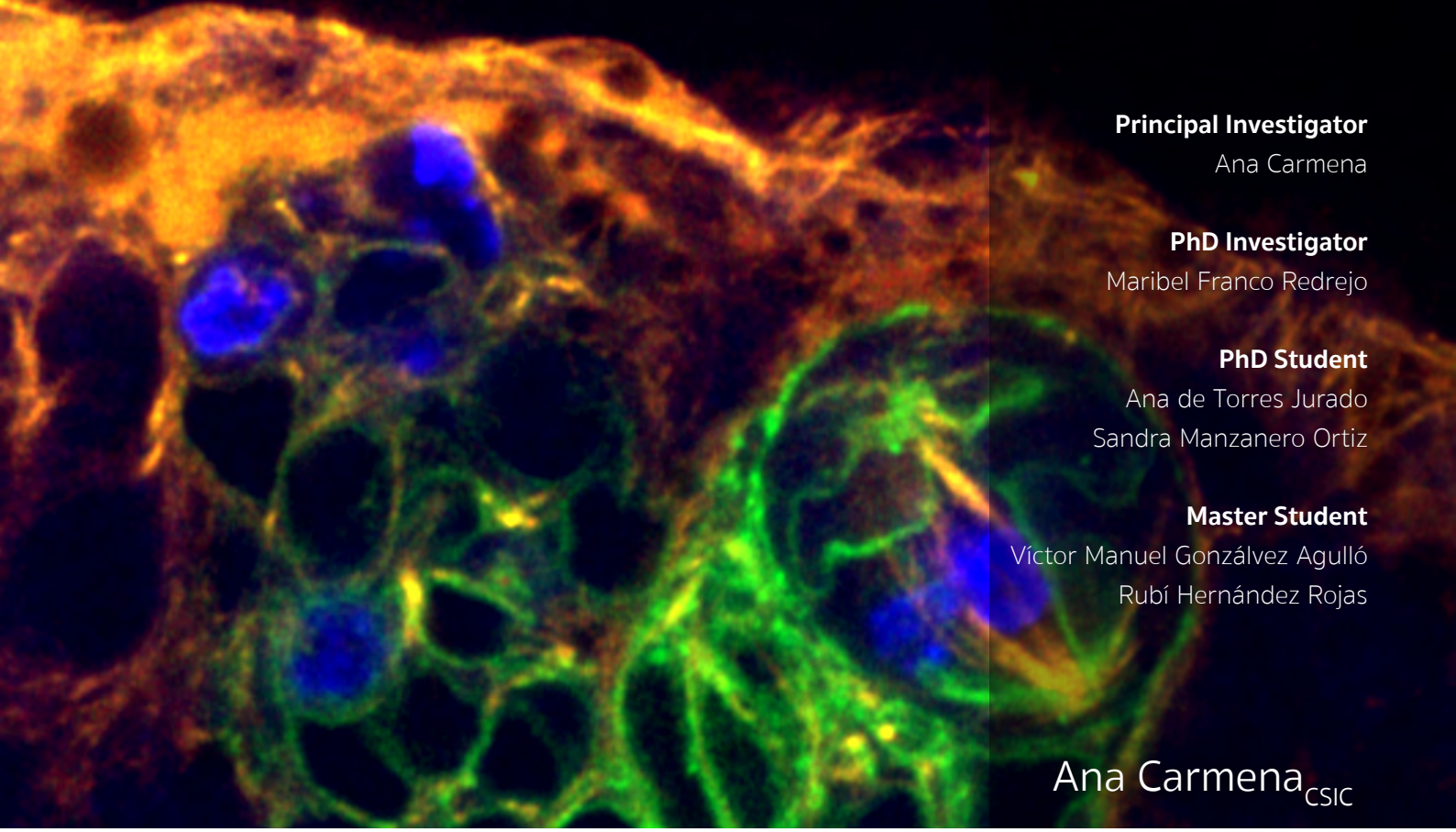

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Ana Carmena$_{CSIC}$

Asymmetric division of neural stem cells in development and tumorigenesis

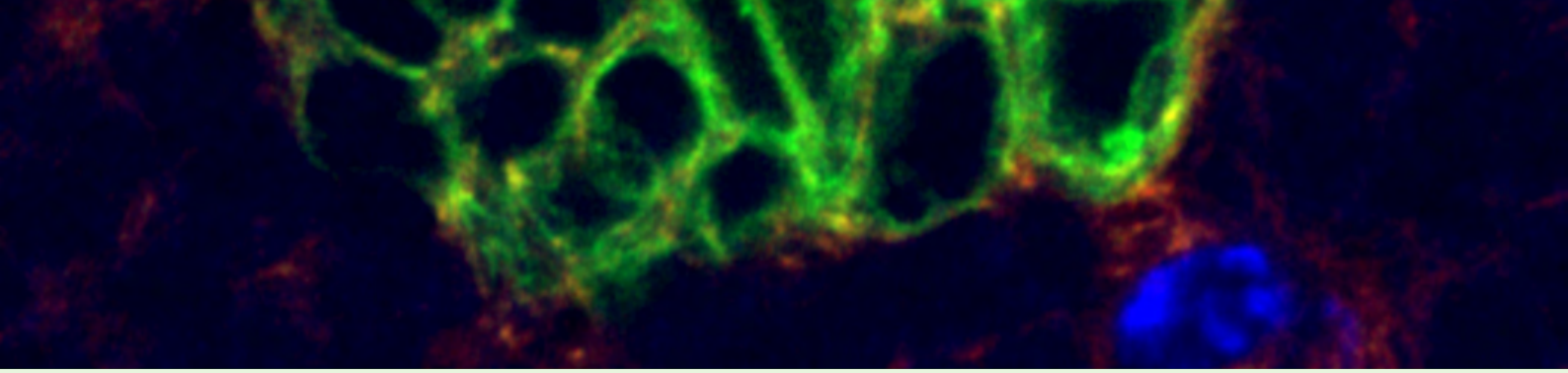
One of the big challenges in Developmental Neurobiology is to understand how the immense variety of neural types that constitute the nervous system is generated. Asymmetric cell division is a universal and key mechanism to generate cell diversity during Development, and it is also an important process in Cancer and Stem Cell Biology. Our lab is currently focused on analyzing in depth this process both during development and in tumorigenesis. The aim of our research is to unveil the functional signaling networks underlying the autonomous and non-autonomous mechanisms that regulate asymmetric cell division. In this context, we consider PDZ (PSD-95, Dlg, ZO-1) domain-containing proteins, including the proteins Canoe/Afadin and Scribble, excellent candidates as hubs of cross-talk between signaling pathways during this process. We achieve our research combining Genetic, Cell Biology, Biochemistry, Molecular Biology and Proteomic techniques.

Specifically, we are interested in studying and contributing to answering three fundamental questions in the field:

1.- What 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.- What are the mechanisms that control the “switch” between a symmetric to an asymmetric mode of cell division? Our model system for answering this question is the “Optic Lobe of the Drosophila larval brain”.

3.- What are the connections between asymmetric cell division and tumorigenesis? Our model system is the type II neuroblasts of the Drosophila larval brain.



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Mechanisms of growth control & cancer in Drosophila

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Our studies are focused on three complementary research projects:

The brain keeps body size in check: The final animal size is remarkably constant within species and this constancy is more striking when we consider how the left and right parts such as our legs or arms, or the wings of an insect, are precisely matched in size and shape. The importance of bilateral symmetry, or more specifically, the lack of symmetry is evident as it relates to effective vision, coordinated locomotion, for example, and is a significant predictor of some diseases. Genetic and environmental noise, diseases and physical stress all can perturb developmental growth programs that may cause deviations and variability, and imperfect bilateral symmetry and proportion. In order to limit the resultant variation, juvenile organisms have the capacity to buffer variability through homeostatic mechanisms, so that the correct final size is attained. Our work has defined the first molecular mechanism underlying such homeostatic control and identified a novel insulin-like peptide, we called Dilp8, and its receptor Lgr3, a member of the relaxin hormone receptor family. Lgr3 is required in neurons and we show that Lgr3 neu-

rons act as 'hub' neurons receiving Dilp8 signals and distributing 'growth' information to other neuronal populations (insulin-producing cells and PTTH-producing neurons) thereby adjusting the levels of insulin, ecdysone, and juvenile hormones, in a manner that stabilizes body and organ size in response to size asymmetries and growth perturbations.

At the organ level, the proper control of growth is governed by specialized signalling centres within the developing organs, known as "organizers" as well as mechanical forces and cell autonomous factors. We had focused on the Notch and Hedgehog signaling pathways, which have crucial roles in establishing growth-promoting organizers along the dorsal-ventral (DV) and anterior-posterior (AP) axes, respectively. These organizers emit signals that promote global organ growth also influencing large-scale patterns and cell fate specification via mechanisms incompletely understood. Our work has revealed, for example, how signalling through the Notch receptor is used reiteratively in organ growth control, individual cell fate specification, apoptosis/survival and cell differentiation to ensure proper organ size and shape and also redefined the relationship with other growth and fate specification pathways, which might be universal interactions relevant in growth regulation in other species including humans.

Genome-wide screen for novel cancer genes and mechanisms: We have pioneered high-throughput genetic screens for identifying novel gene cooperation in tumour initiation and progression. Through these screens, we have identified novel nexus of cancer including the synergism between Notch and epigenetic silencers in malignant transformation or the cooperation between Notch and the Pten/PI3K/AKT pathway in promoting tumour invasion that are also conserved during human leukaemogenesis. In collaboration with Dr. Borggrefe, we have shown that the histone demethylases and methyltransferases as core components of Notch silencing complex in tissue growth and tumorigenesis. Our screens also identified conserved microRNAs miR-8 (called miR-200 in humans) and miR-7 in the regulation in space and time of Notch, Hedgehog, and and EGFR signalling pathways during development and tumorigenesis and their participation in adult tissue homeostasis.

In vivo high-throughput screening for anticancer drug discovery: The fruit fly Drosophila melanogaster has been a workhorse of genetics and developmental biology for almost a century, but its true potential for the genetic and cell biology analysis of tumour metastasis has only recently been realized. Recently we have been implemented a low cost and highly effective Drosophila-based high-throughput platform for drug screening using flies with eye tumours induced by defined genetic manipulations. As a proof of concept, we have screened a commercial drug library for compounds effectively blocking tumorigenesis induced by the cooperation of Notch and the PI3K/Akt with less side effects than current pathway inhibitors. The screen platform and the novel tools for drug discovery and cancer studies in vivo we have developed has paved the way for future drug screens aimed at identifying alternative strategies for cancer metastasis, and cancer-related inflammation.

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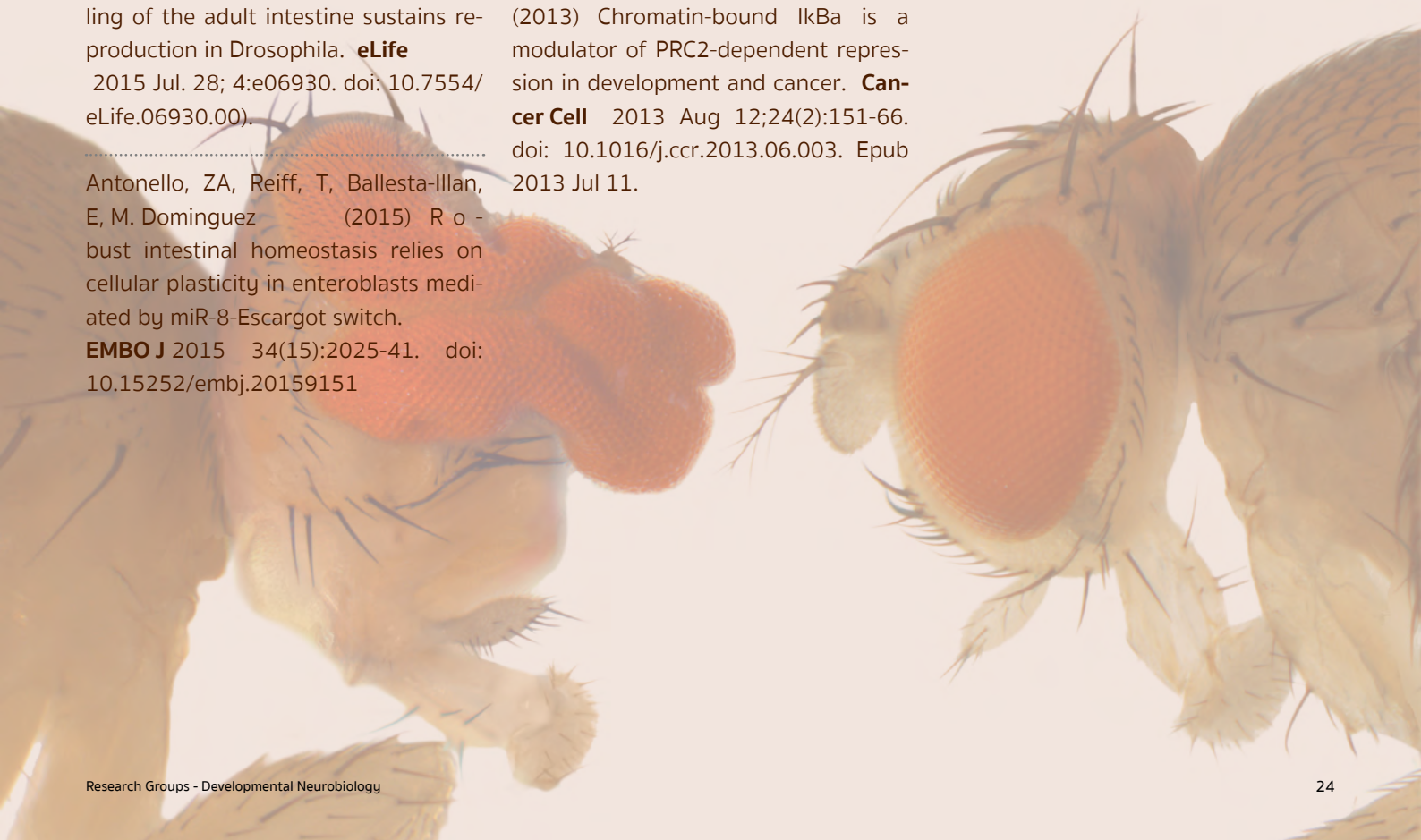
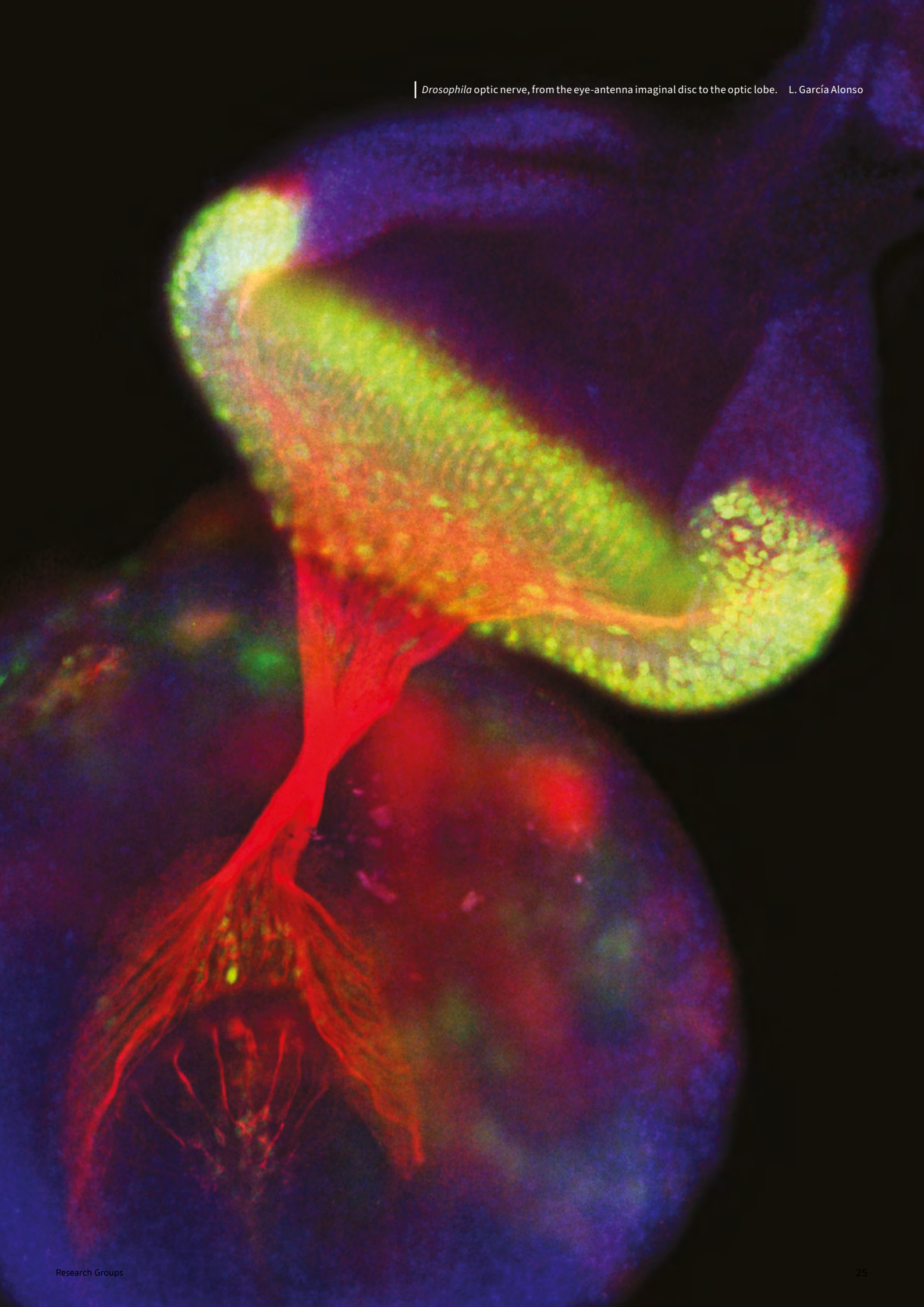
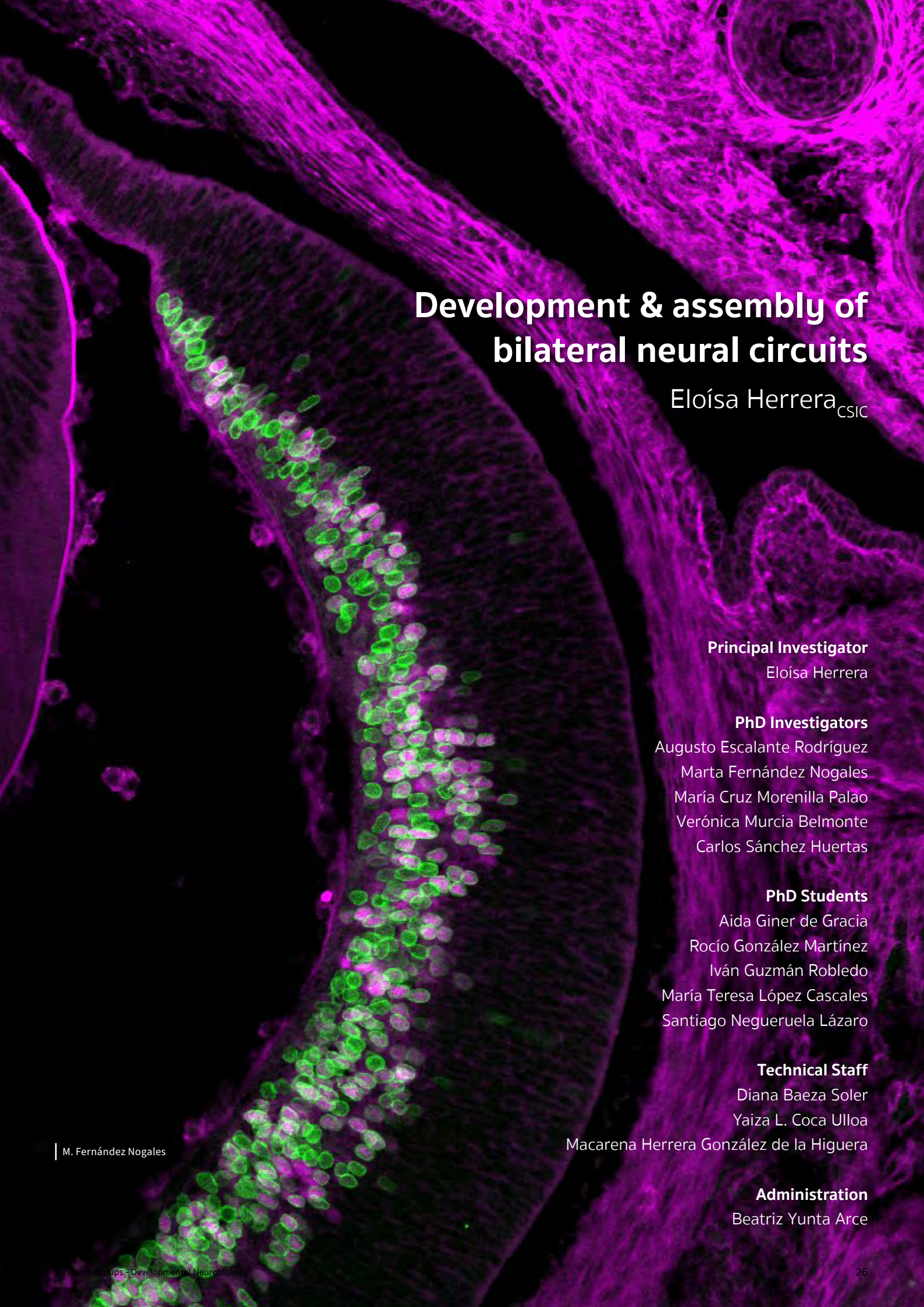




Drosophila optic nerve, from the eye-antenna imaginal disc to the optic lobe. L. García Alonso



Development & assembly of bilateral neural circuits

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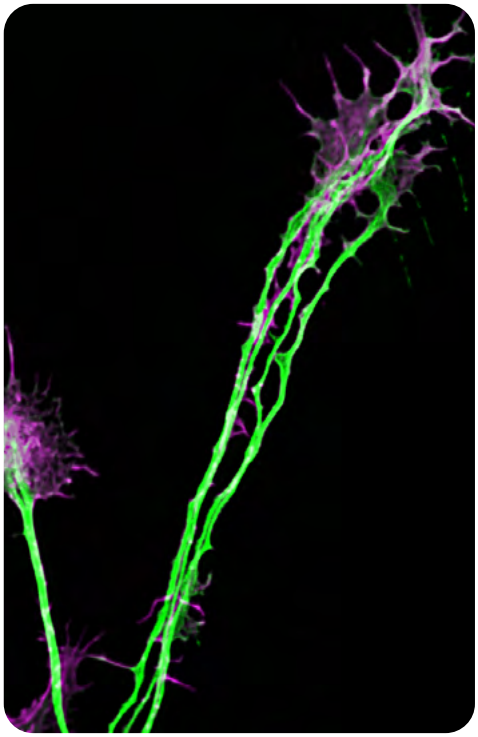
The precise wiring of the nervous system relies on the proper navigation of neuronal axons when they are trying to reach their final targets in the developing brain in order to establish precise connections with other neurons. Guided by the concerted action of attractive and repulsive molecules, axon growth cones change rapidly their response as they grow and move from one intermediate target to the next one. Many of the main families of axon guidance molecules and their respective receptors involved in this process have been described but the regulatory mechanisms triggering axonal reprogramming from a decision point to the next one are poorly characterized. Growth cone plasticity is at play all over the developing nervous system and we use the mammalian visual system as a model to uncover the transcriptional, epigenetic (context-specific) and activity-dependent mechanisms that regulate axon pathfinding and circuit assembly. We also investigate to what extent our discoveries in the visual system apply to other circuits in the CNS.



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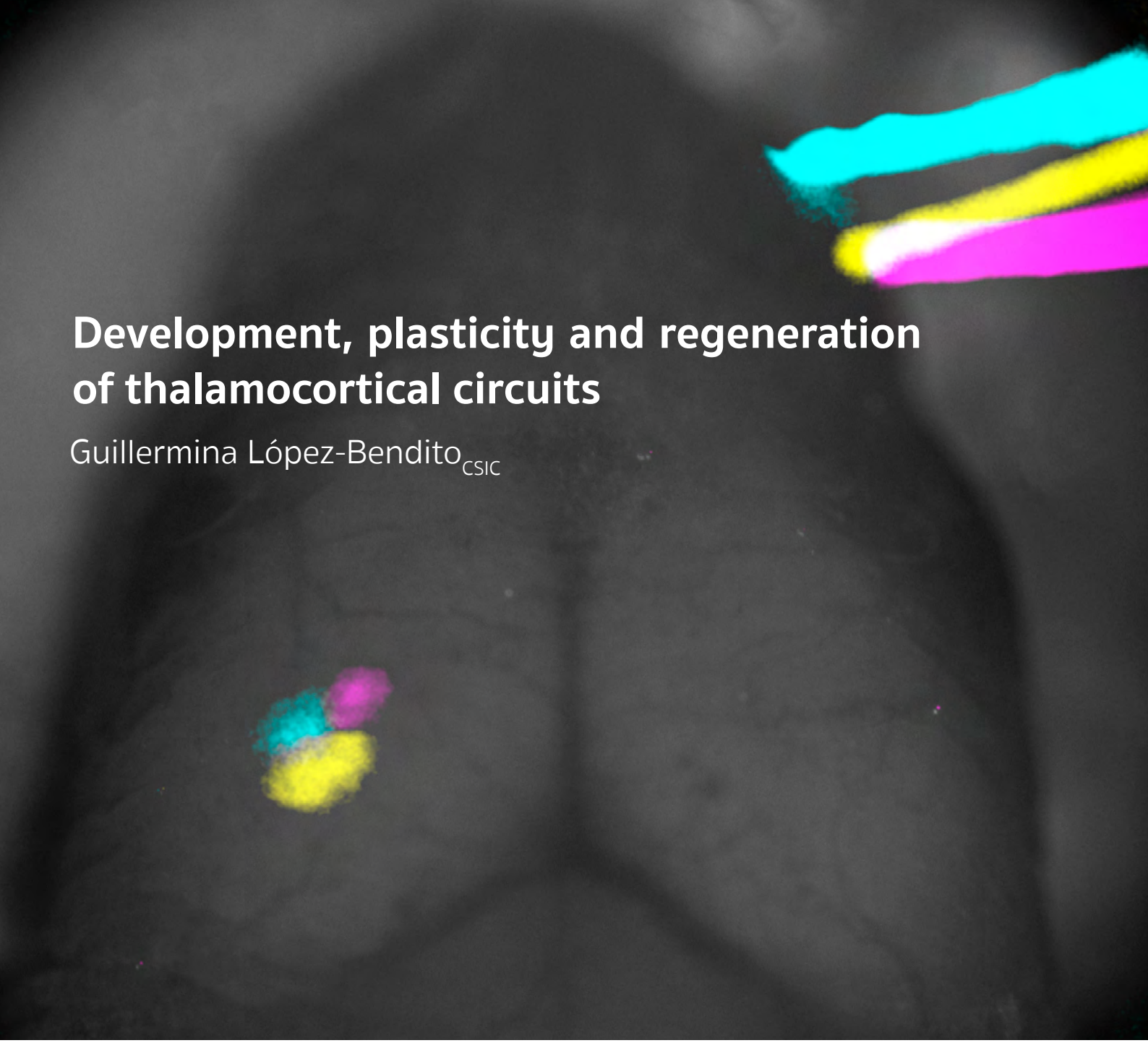

Development, plasticity and regeneration of thalamocortical circuits

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Our research team runs several related projects studying the cellular and molecular mechanisms involved in the development of axonal connections in the brain. In particular, our aim is to uncover the principles underlying thalamocortical axonal wiring, maintenance and ultimately the rewiring of connections, through an integrated and innovative experimental programme.

The development of the thalamocortical wiring requires a precise topographical sorting of its connections. Each thalamic nucleus receives specific sensory information from the environment and projects topographically to its corresponding cortical. A second level of organization is achieved within each area, where thalamocortical connections display an intra-areal topographical organization, allowing the generation of accurate spatial representations within each cortical area. Therefore, the level of organization and specificity of the thalamocortical projections is much more complex than other projection systems in the CNS. The central hypothesis of our laboratory is that thalamocortical wiring influences and maintains the functional architecture of the brain. We also believe that rewiring and plasticity events can be triggered by activity-dependent mechanisms in the thalamus.

Two major questions are been focused in the laboratory: i) the activity-dependent mechanisms involved in thalamocortical wiring,

ii) the role of the thalamus and its connectivity in the neuroplastic cortical changes following sensory deprivation, and iii) reprogramming thalamic cells for circuit and sensory restoration. We are also developing novel animal models for determining the role of thalamocortical input in cortical functional specification and plasticity.

Within these projects we are using several experimental programmes, these include: functional neuronal imaging, manipulation of gene expression in vivo, cell and molecular biology, biochemistry, cell culture and electrophysiology. We have also used gain- and loss-of-function experiments to help unravel new mechanisms involved in the development and rewiring of this major axonal tract (see Science 2019; CurrOpiNeurob 2018; NatComm 2017; Cerebral Cortex 2016; EMBO Reports 2015; Current Biology 2014, Nature Neuroscience 2012, Journal of Neuroscience 2012, Current Biology 2011, Neuron 2011, PLoS Biology 2009, J Neurosci 2007, Cell 2006, Nat Rev Neurosci 2003).

We expect that the results derived from our investigations will contribute to our understating of how reprogramming of cortical wiring takes place following brain damage and how cortical structure is maintained.

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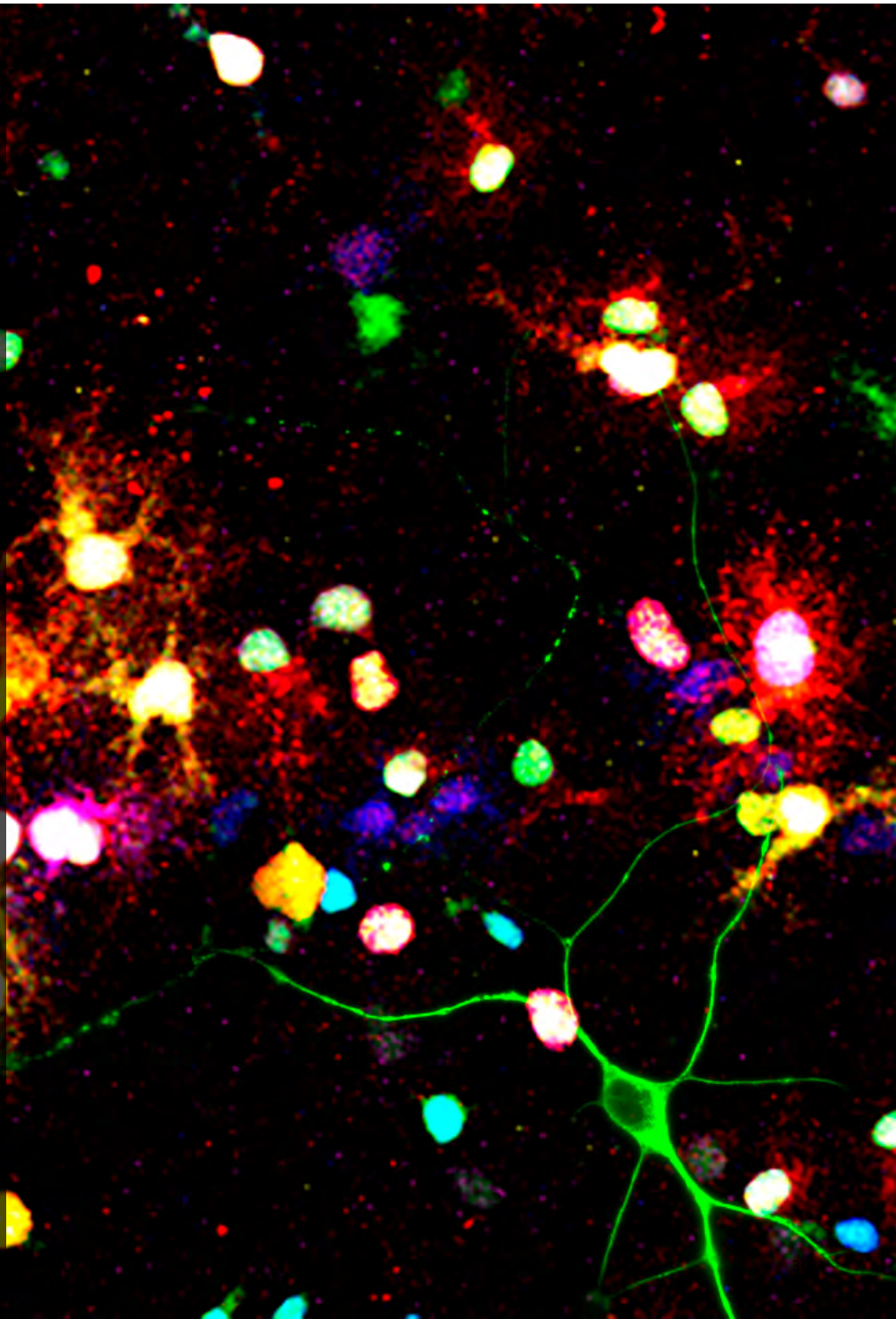

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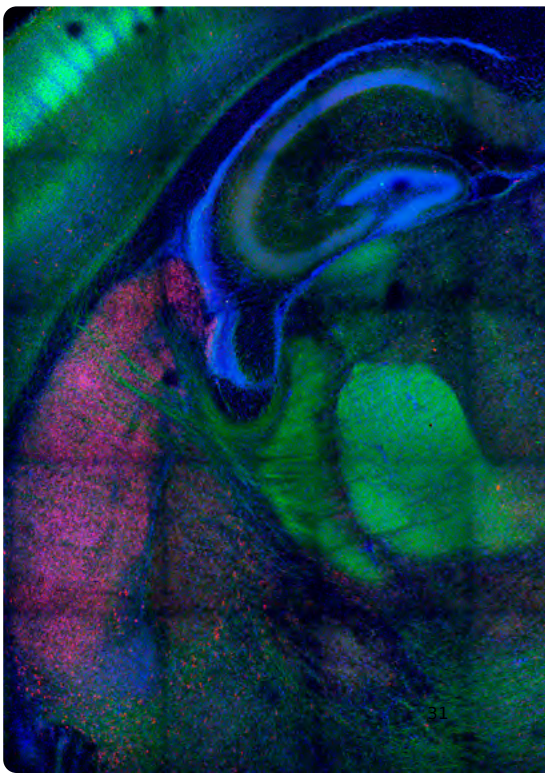

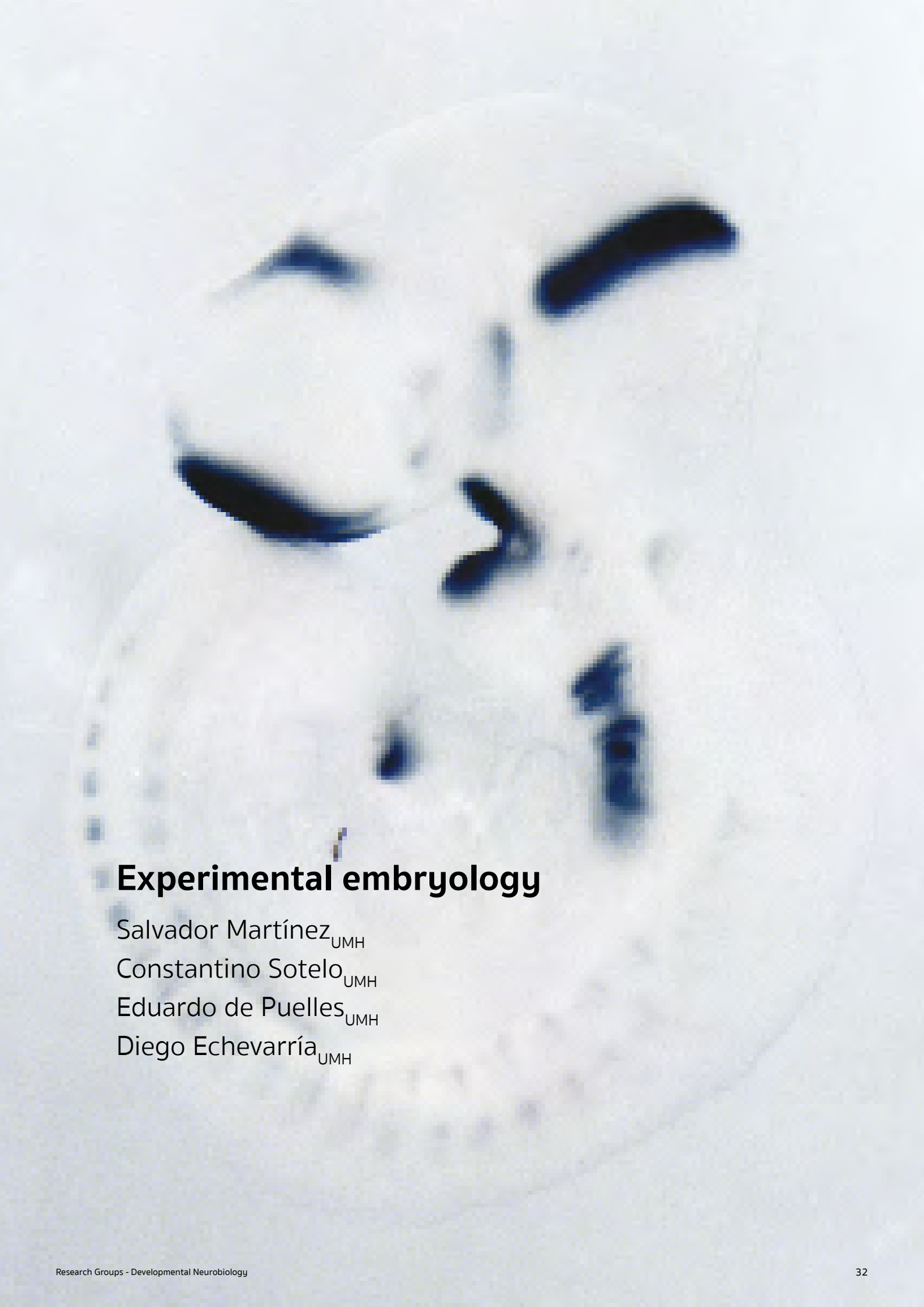

Experimental embryology

Salvador Martínez$_{UMH}$
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Our studies are focused on four research projects:

Experimental Embryology: manipulations in mouse and chick embryos allow us to study cellular and molecular factors that control the regionalization, segmentation, proliferation, differentiation and cellular migration processes of the Central Nervous System. We concentrate our research work in the understanding of the molecular factors that control the development and morphogenetic activity of the secondary organizers of the anterior neural tube of vertebrates. Our work explores particularly the molecular action of signalling molecules like SHH, WNTs and FGFs in the Isthmic organizer, the zona limitans intrathalamic (ZLI) and the anterior neural ridge (ANR).

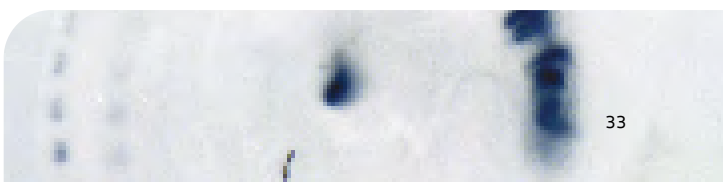
Experimental methodology: (i) Interspecific transplants of neural tissue between quail and chick embryonic brain areas. (ii) Explant cultures of mouse anterior neural tube will permit to make experimental embryological techniques on genetically altered mouse models.

Neurogenetics: We are studying expression patterns of important genes related to the structural organization of the brain through its development. This research line is part of the Allen Institute Brain Development project in which we pretend in a large-scale manner to analyse the expression pattern genes at several embryonic stages of mice (www.brainmap.org). The further genetic manipulation by homologous recombination will help us to elucidate the functional role of these genes. Currently we are also interested in genes important of human neuropathogenesis. Thus, we have created a line of research investigating the alterations of lisencephaly, several cortical heterotopies, multiple sclerosis and peripheral senso-motoral neuropathologies as well as Down syndrome. Related to this research line we are analysing the genetic alteration associated to functional psychosis (squizophrenia and bipolar disorder), particularly genes related to alteration in cortical architectural development.

Experimental methodology: (i) detection of genetic pattern expression by in situ hybridization; (ii) structural and functional analysis of natural mutant mice and genetically manipulated (knockouts); (iii) genetic and molecular analysis of patient blood and tissue samples with suspicious genetic cortical alterations and structural anomalies of the cortex and psychosis.

Limbic system connectivity: study of the molecular and cellular mechanisms involved in the axon guidance during the Limbic system development. Our aim is centered in the afferent and efferent tracts of the Habenula as central station between the telencephalic and rombencephalic components. This approach is complemented with functional analysis through optogenetics and animal behaviour techniques.

Stem Cell Research: We are developing experimental models that permit to demonstrate the neurotrophic potentiality of stem cells of derived from blood marrow (hematopoyetic stem cells). We are currently observing that injection of HSC into animal brain models of multiple sclerosis, cerebellar ataxia (lateral amiotrophic sclerosis) has a trophic effect and in many cases is a further partial regeneration of damage.



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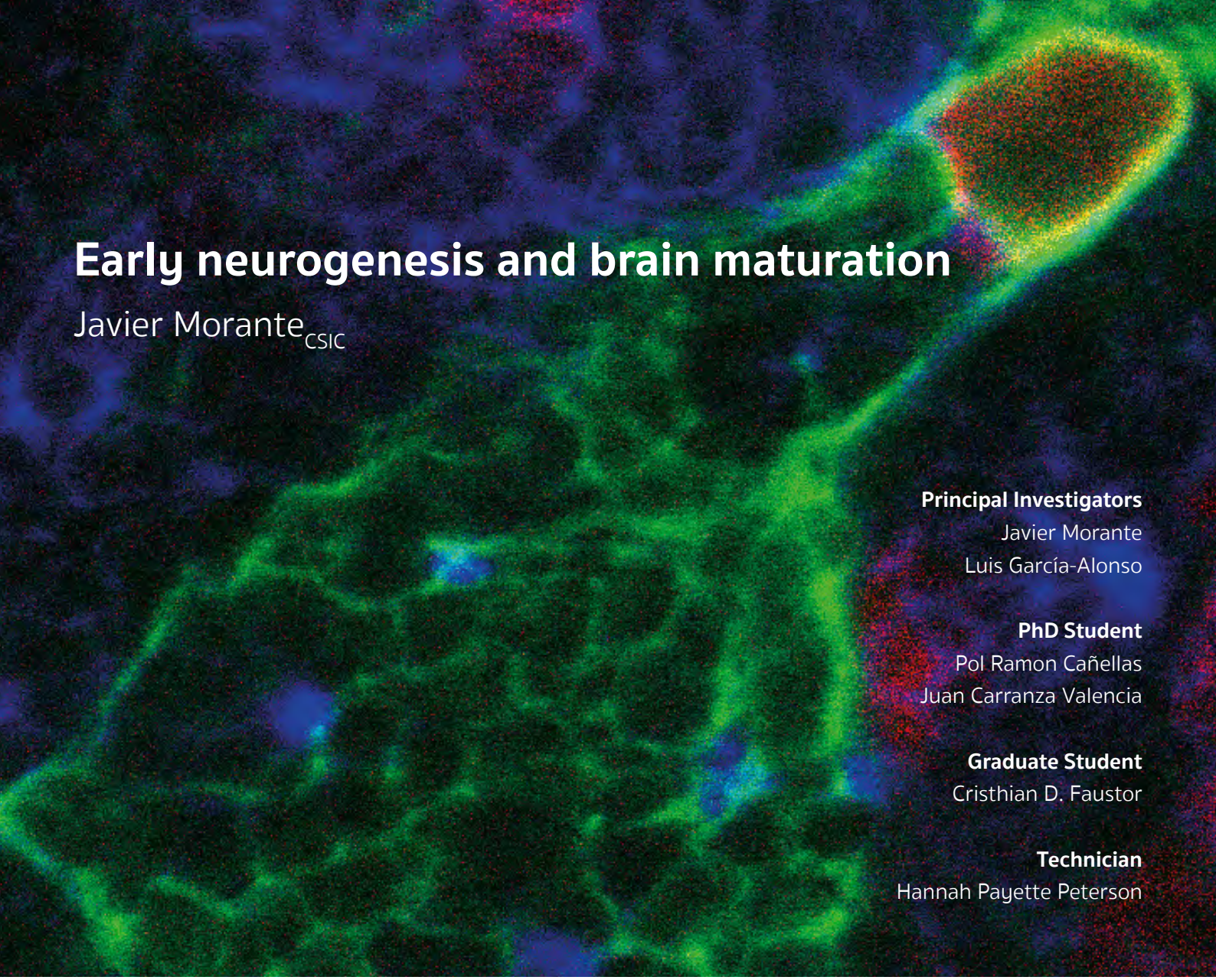

Early neurogenesis and brain maturation

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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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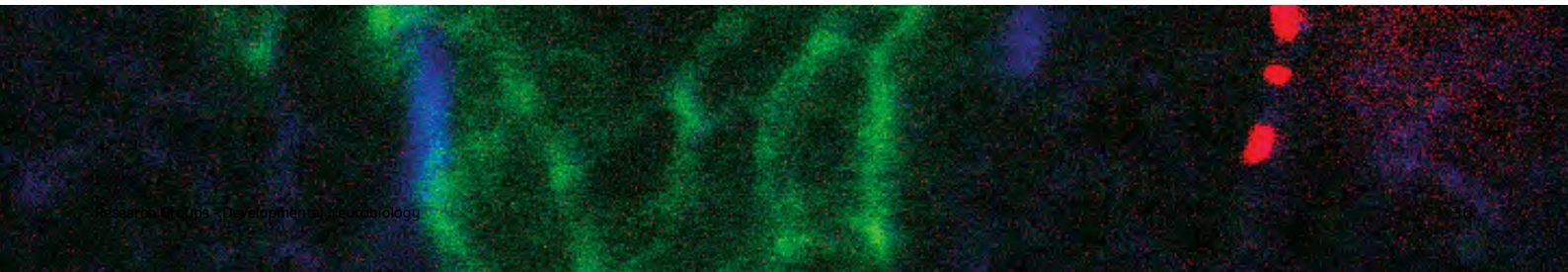

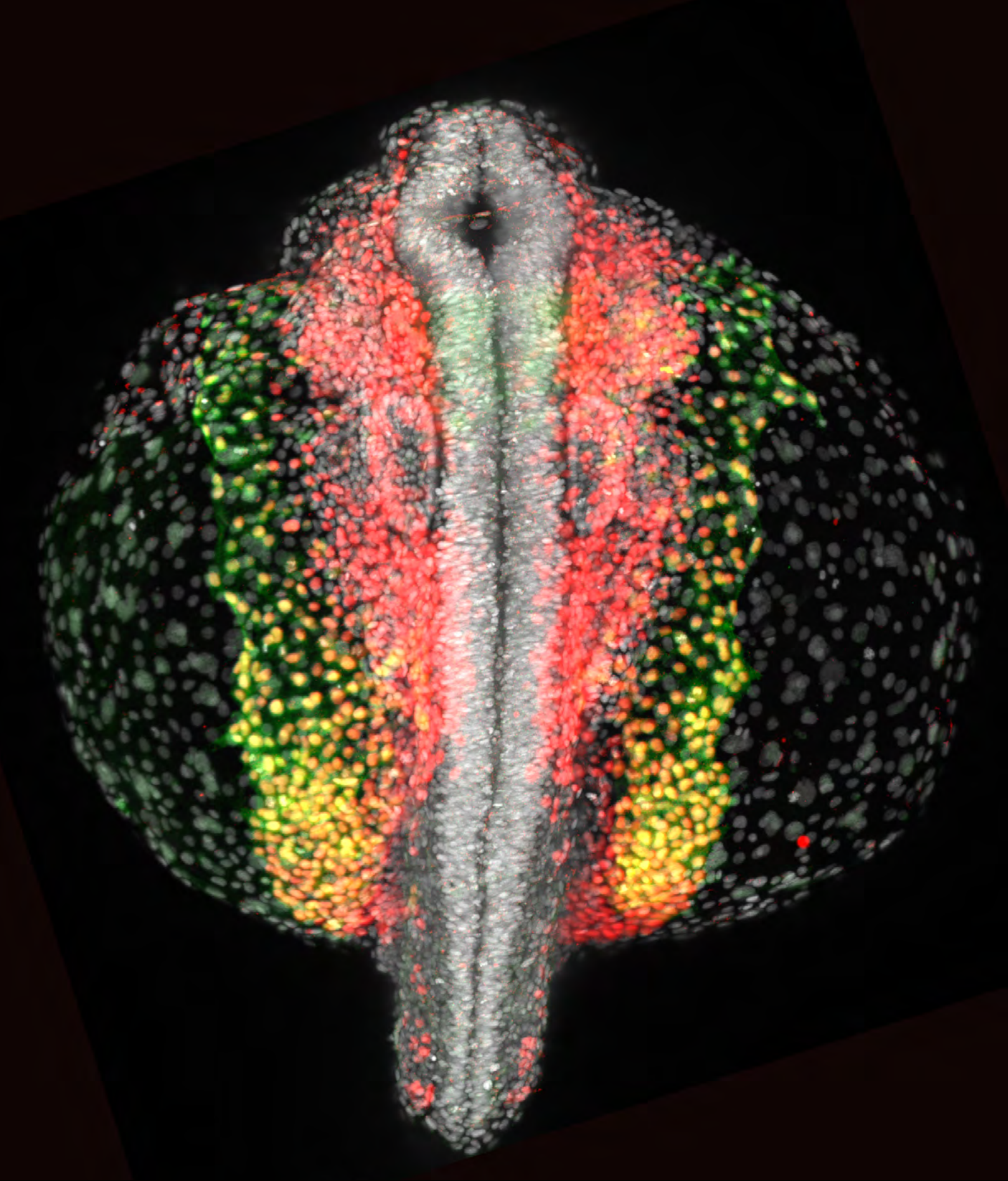

Cell plasticity in development & disease

M. Angela Nieto[CSIC]
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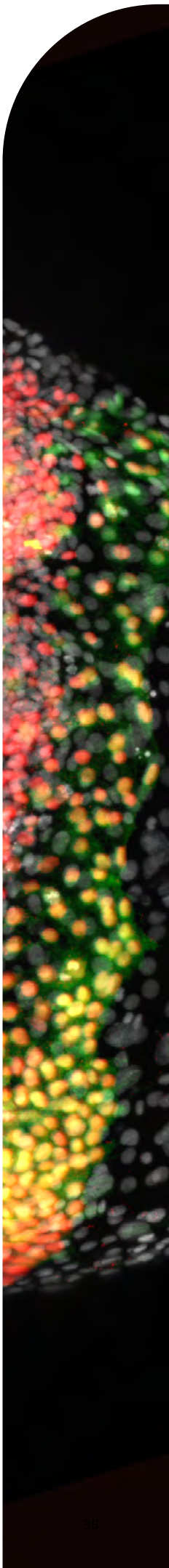
For the last almost 30 years, the group has been studying cell movements and plasticity in health and disease. We have been working on the epithelial to mesenchymal transition (EMT), a fundamental process during embryonic development to allow cells to migrate and reach their final destinations. We described how different transcription factors, the so-called EMT-TFs, are activated in different vertebrates to fulfill their function regulating massive cell movements during gastrulation, neural crest migration or organ positioning. We 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 the acquisition of invasive and migratory properties, required for cancer dissemination and progression to the metastatic disease. Along the years, we have witnessed different phases in which the EMT process has been debated. Widely accepted by developmental biologists, pathologists did not initially consider the EMT relevant for cancer progression or organ fibrosis. However, it later became a leading research field in cancer and nephrology that was challenged again due to its complexity and the lack of optimal animal models.

One of the reasons for the complexity of EMT is that different EMT-TFs promote different programmes in embryonic and cancer cells. Indeed, the behavior of cells varies depending on their EMT-TF expression code. As important as it is that cells maintain some contacts while migrating in a coordinated manner, it is also important that they repel each other to achieve cell spreading. In this regard, we have recently proposed that Eph receptors and their ligands, a signaling pathway that is activated during some EMT programmes, already had an ancestral function that could contribute to the emergence of multicellular organisms precisely to promote the segregation of distinct populations.

How the EMT-TFs orchestrate the adhesive/repulsive migratory programmes and, specially, how the highly plastic partial EMT states can influence metastatic potential and therapy resistance is not well understood. We are now characterizing the EMT programmes induced by different EMT-TFs and the circuits in which they are integrated. We have unveiled two novel gene regulatory networks (GRN) involving Snail1 and Prrx1, one associated with different prognoses in cancer patients and the other affecting organ positioning. In the first, these EMT-TFs are expressed in complementary patterns due to a reciprocal repression relationship, providing a mechanism to select between different EMT programmes that we have validated in embryos and tumour cells. The second GRN operates during the process we had described of left-right differential cell movements toward the midline of the embryo, more prominent from the right, shifting the posterior pole of the heart to the left. A wave of the signaling molecule Nodal advances from the posterior of the embryo regulating the expression of several microRNAs that attenuate Prrx1 and Snail1 levels on the left side, explaining the predominance of the right side, and ensuring the correct position of the heart. In addition, we are investigating novel functions of these EMT-TFs, during neural crest development and vascular integrity and how other members of the Snail superfamily with expression in the nervous system control neuronal differentiation.

Another layer of complexity to understand EMT processes is the lack of optimal animal models, which are now being developed in multiple labs highlighting the crucial role of EMT in health and disease. Our new models aim at investigating EMT-TF codes and signalling pathways that can discriminate partial from full EMT states and predict cell behaviour and prognosis in pathological contexts, including organ fibrosis and breast cancer.

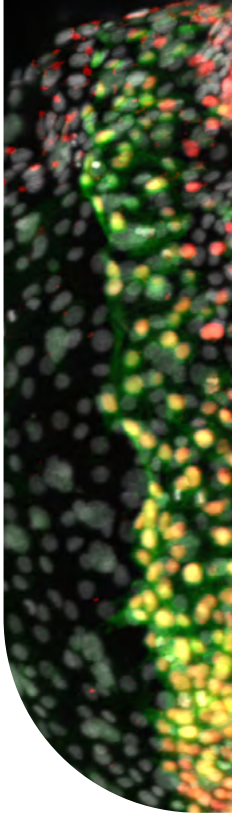
We have also extended our studies to melanoma, the most aggressive skin cancer. Melanoma arises from melanocytes that derive from



highly motile neural crest progenitors. Melanoma high metastatic abilities and resistance to therapies can be attributed to its high intrinsic plasticity, reminiscent of neural crest plasticity. In fact, melanoma cells express EMT inducers and we are investigating their contribution to melanoma progression. We have also observed an activation of developmental programmes in cells from the melanoma microenvironment and we are currently characterizing the contribution of these programmes to tumour progression. In addition, melanoma metastasizes very frequently to the brain. Brain metastases are difficult to treat since they behave differently to metastases in other organs and this is mostly due to their unique tumour microenvironment. To investigate the biology of brain metastases we have developed several preclinical models and performed transcriptome analyses of these in order to understand the mechanisms by which brain cell populations promote metastasis progression.

In summary, we have contributed to characterize EMT as a highly dynamic and reversible process that lies at the heart of cellular plasticity in development and in pathological situations. Our main contribution has been how reactivation of developmental programmes in the adult can lead 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, as well as in other conditions in which EMT-TFs also play an important role, such as achondroplasia. 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 promote tissue regeneration.



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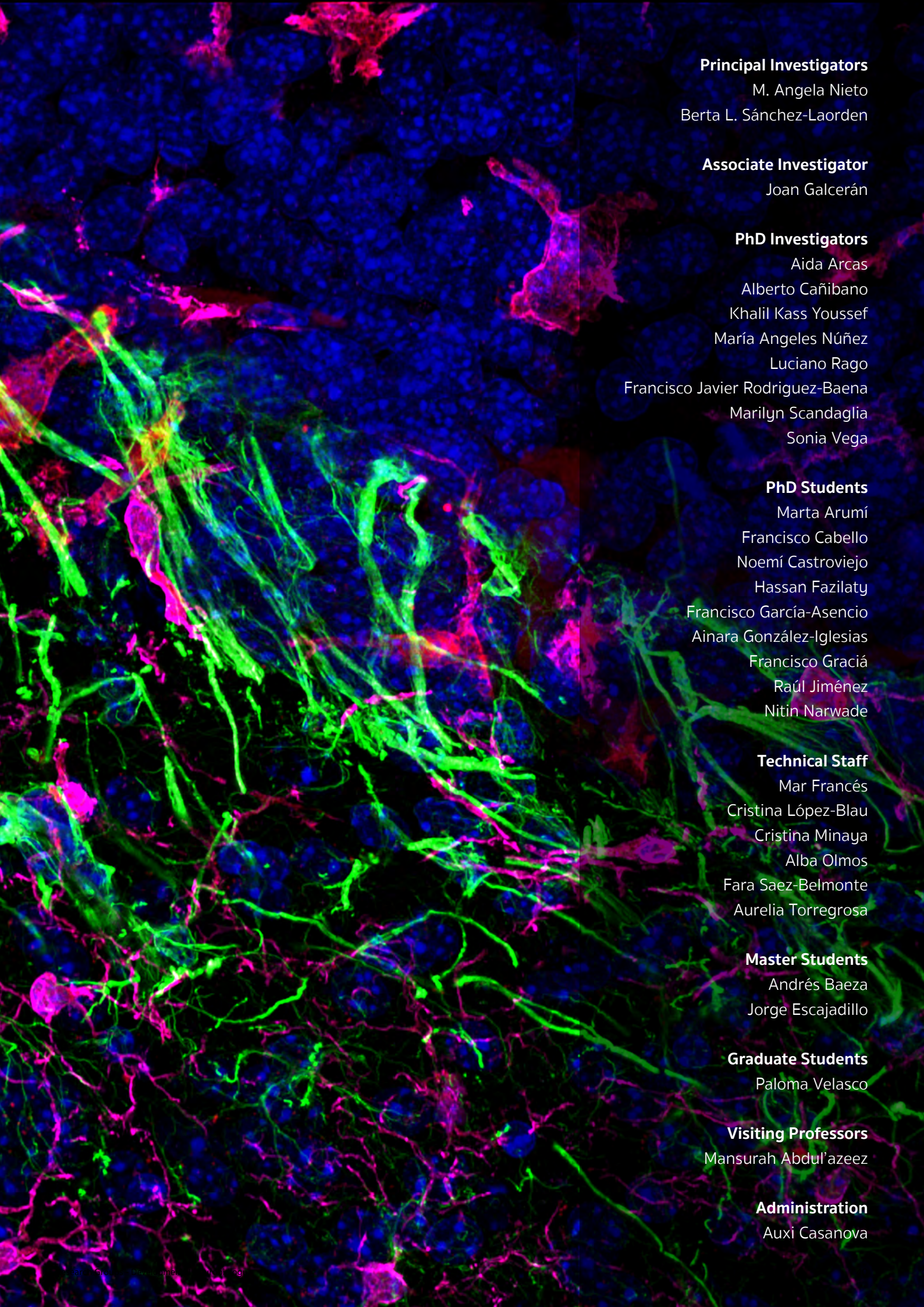

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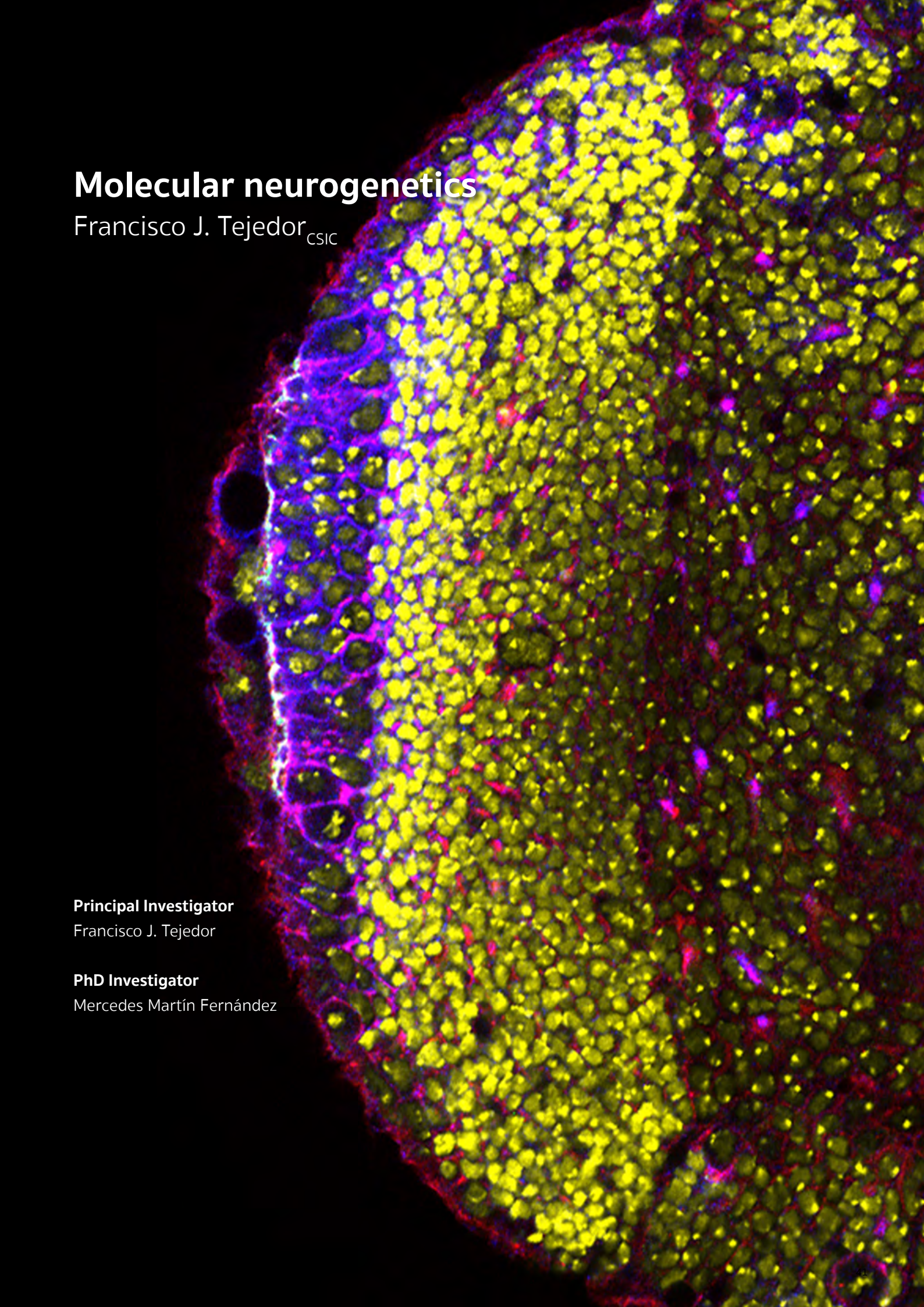

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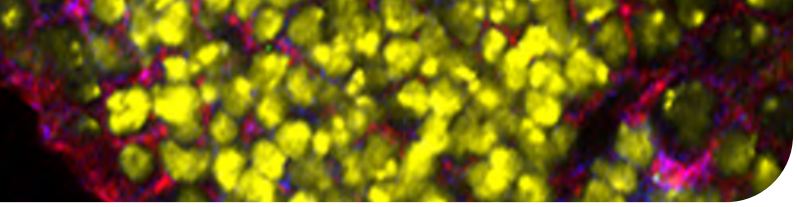
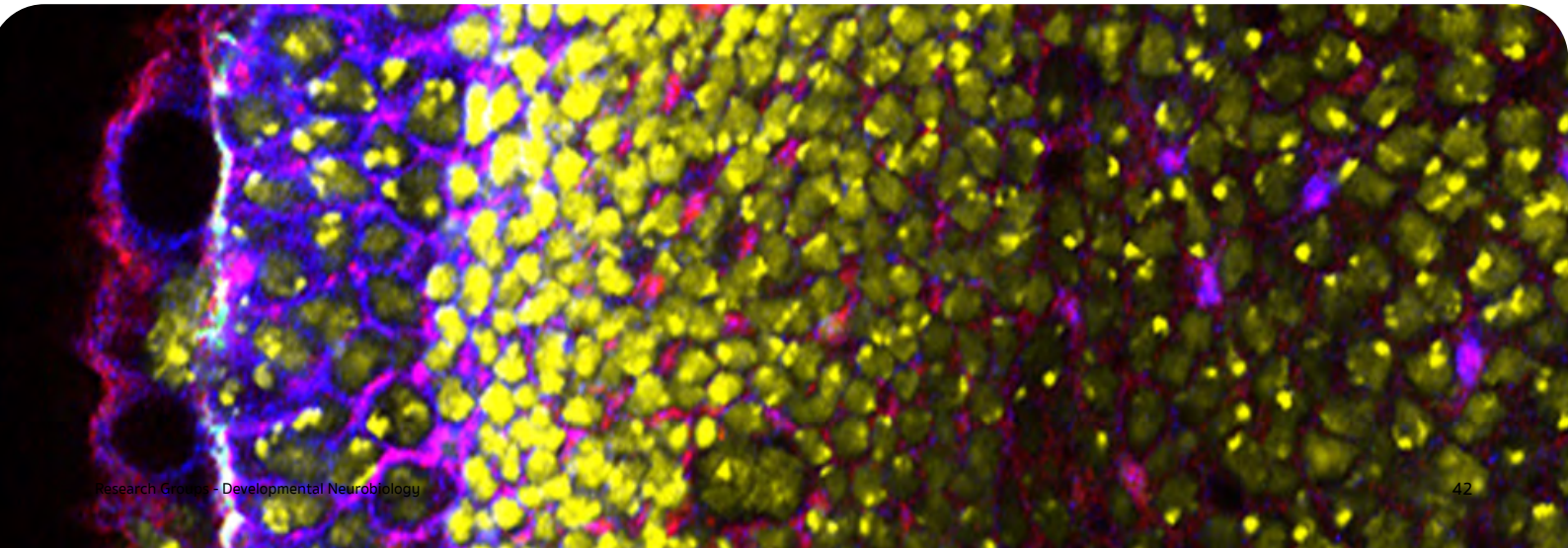


One of the most important issues in Developmental Neurobiology is to elucidate how the large number and rich cellular diversity of the brain is generated in such a precise spatio-temporal manner. Our work focuses on the regulation of neural progenitor cells proliferation and neurogenesis. We are particularly 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 of *Drosophila melanogaster* as an experimental model system. The evolutionary conservation of the genes/functions and molecular mechanisms identified in this system are subsequently assessed in vertebrates (chick and mouse) using embryology and reverse genetics tools. 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*. *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) and it has been implicated in neurodegeneration. As a matter of fact, the MNB/DYRK1A kinase is presentely considered a suitable drug target for DS neuropathologies. Since DS is originated by the triplication of chromosome 21, we are using experimental models to determine what cellular functions and molecular mechanisms are altered by an excess of *Mnb/Dyrk1* function to generate neurobiological alterations reminiscent of DS neuropathologies, particularly, neuronal deficit, dendritic atrophy and neurodegeneration. 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.



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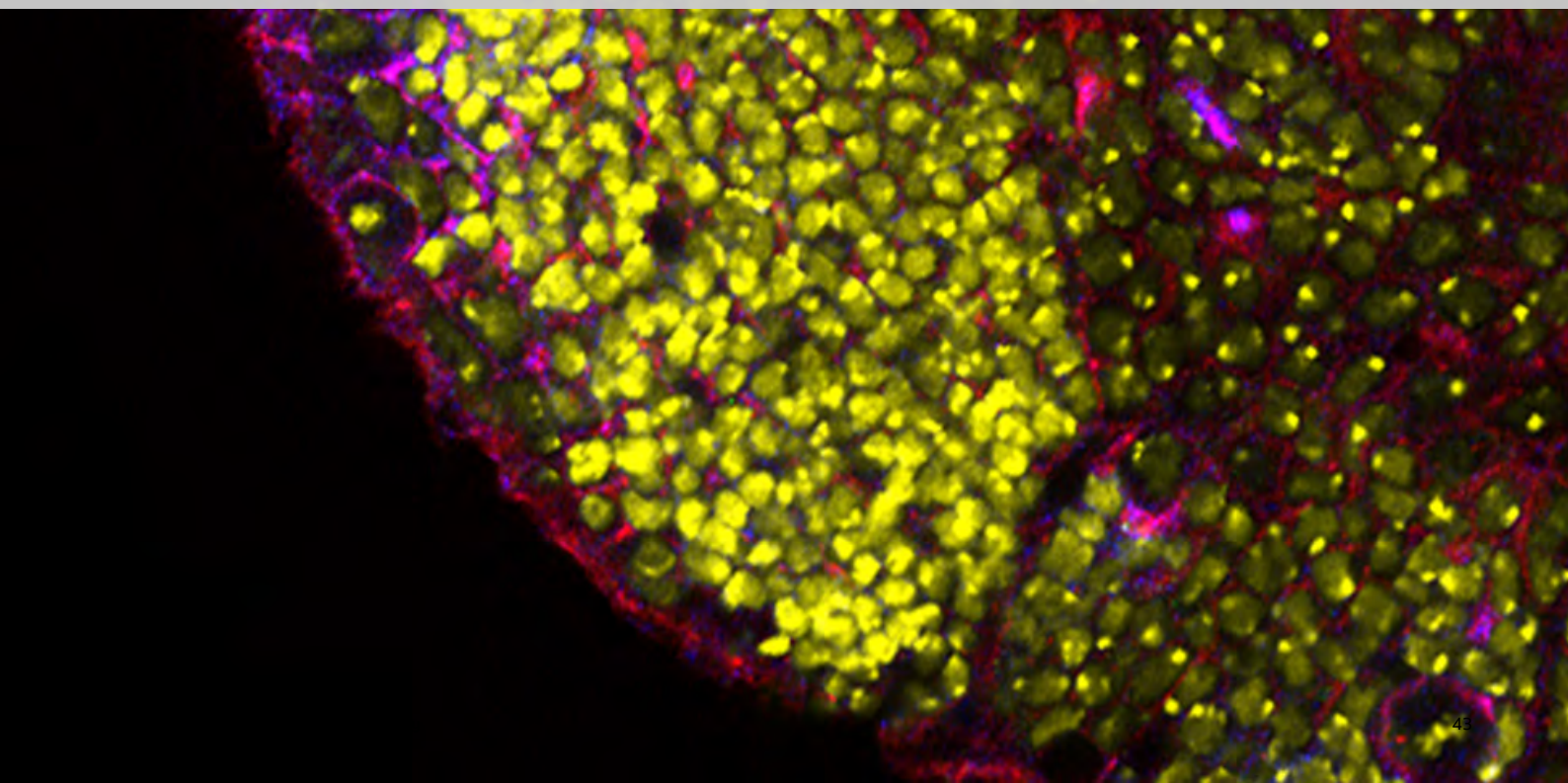
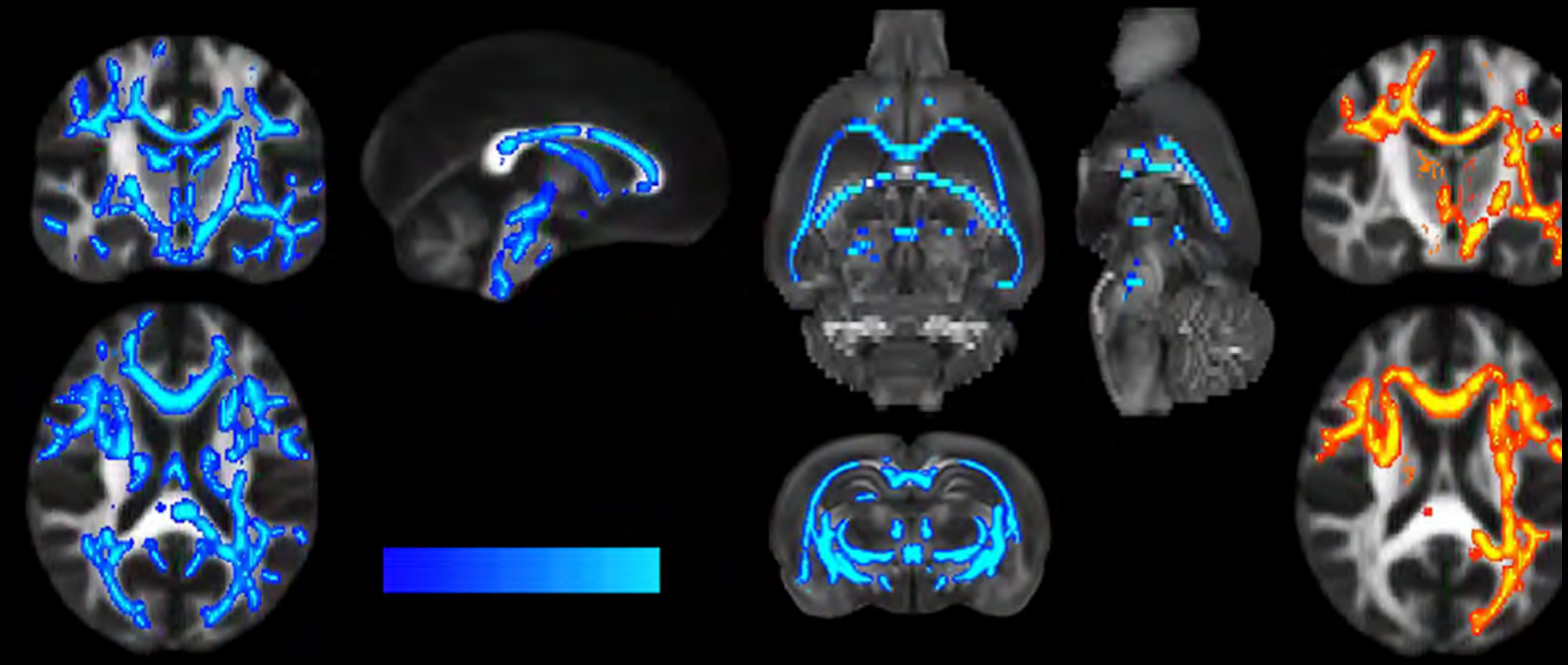
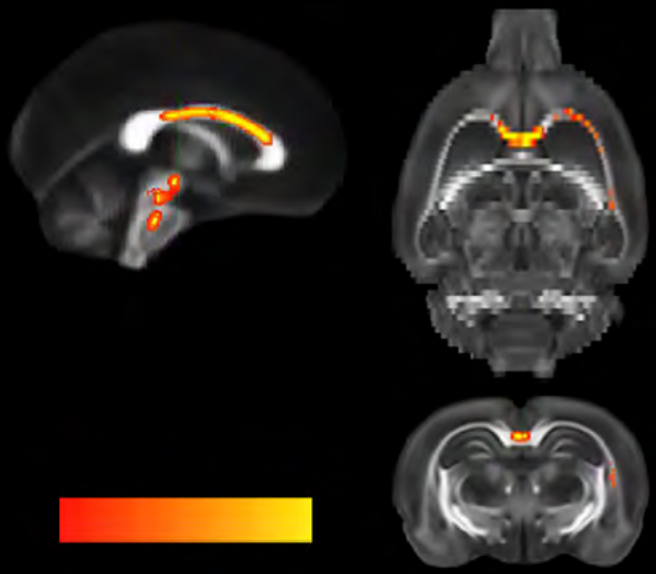
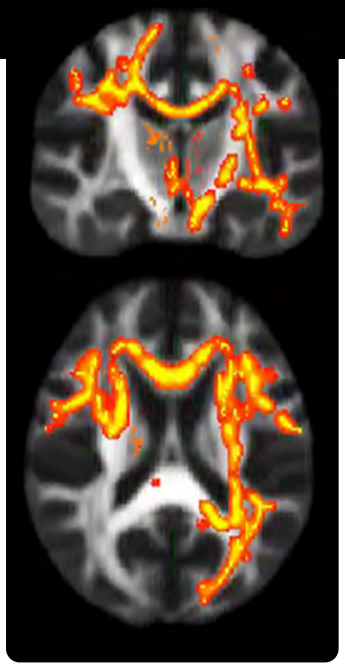




Plasticity of brain networks

Santiago Canals$_{CSIC}$





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.

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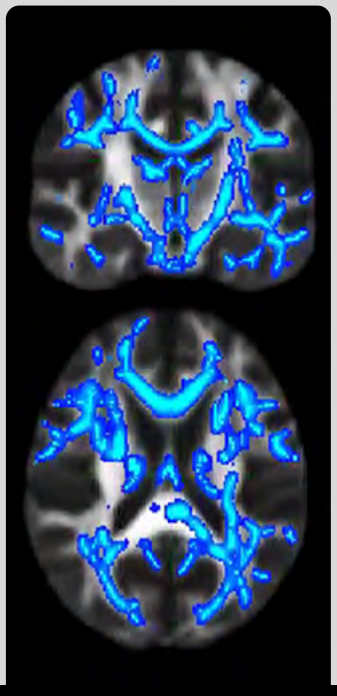

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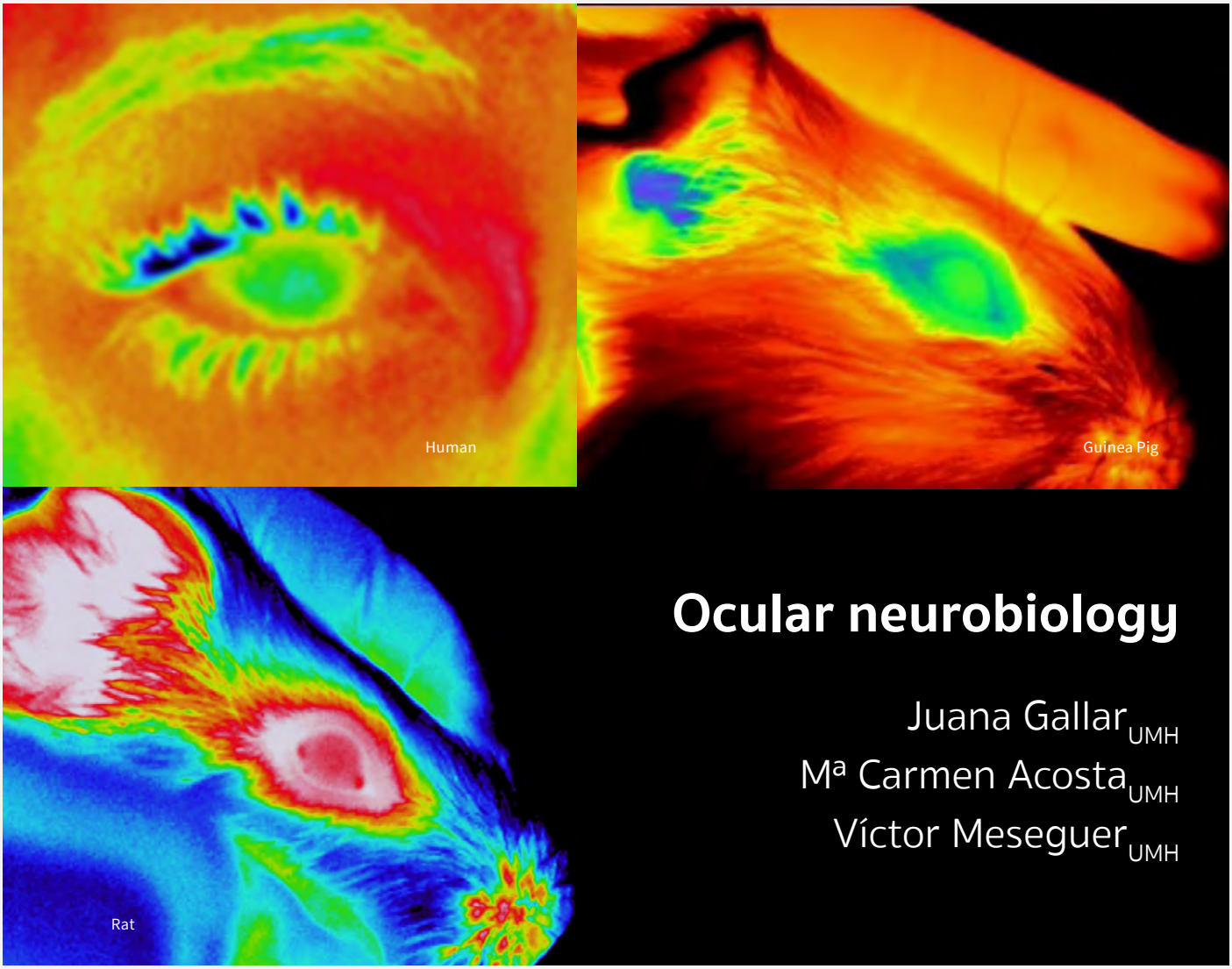

Ocular neurobiology

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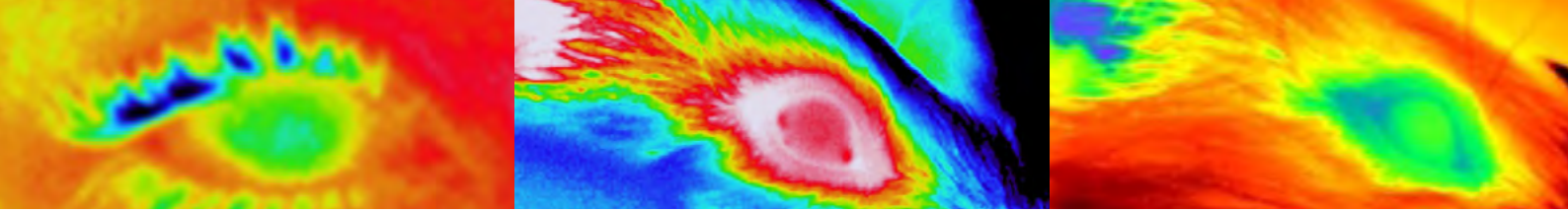

The main interest of the Ocular Neurobiology Group (ONG) is to study the functional activity of sensory nerves from the ocular surface, responsible for the genesis of sensations evoked by stimulation of ocular tissues as well as for the trophic maintenance and protective reflexes ensuring the correct 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 nerve endings and axons, as well as extracellular recording of trigeminal ganglion neurons and CNS neurons along the trigeminal pathway) and pharmacological and opto-pharmacological tools to modulate 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, thalamic and cortical neurons innervating the anterior surface of the eye with particular attention to those neurons participating in 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 in different pathologies, 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 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, studying the molecular and cellular mechanisms underlying sensory transduction, and the role of trigeminal sensory input in the reflex regulation of tear production and blinking, as well as their changes with ageing, dry eye and contact lens wearing.

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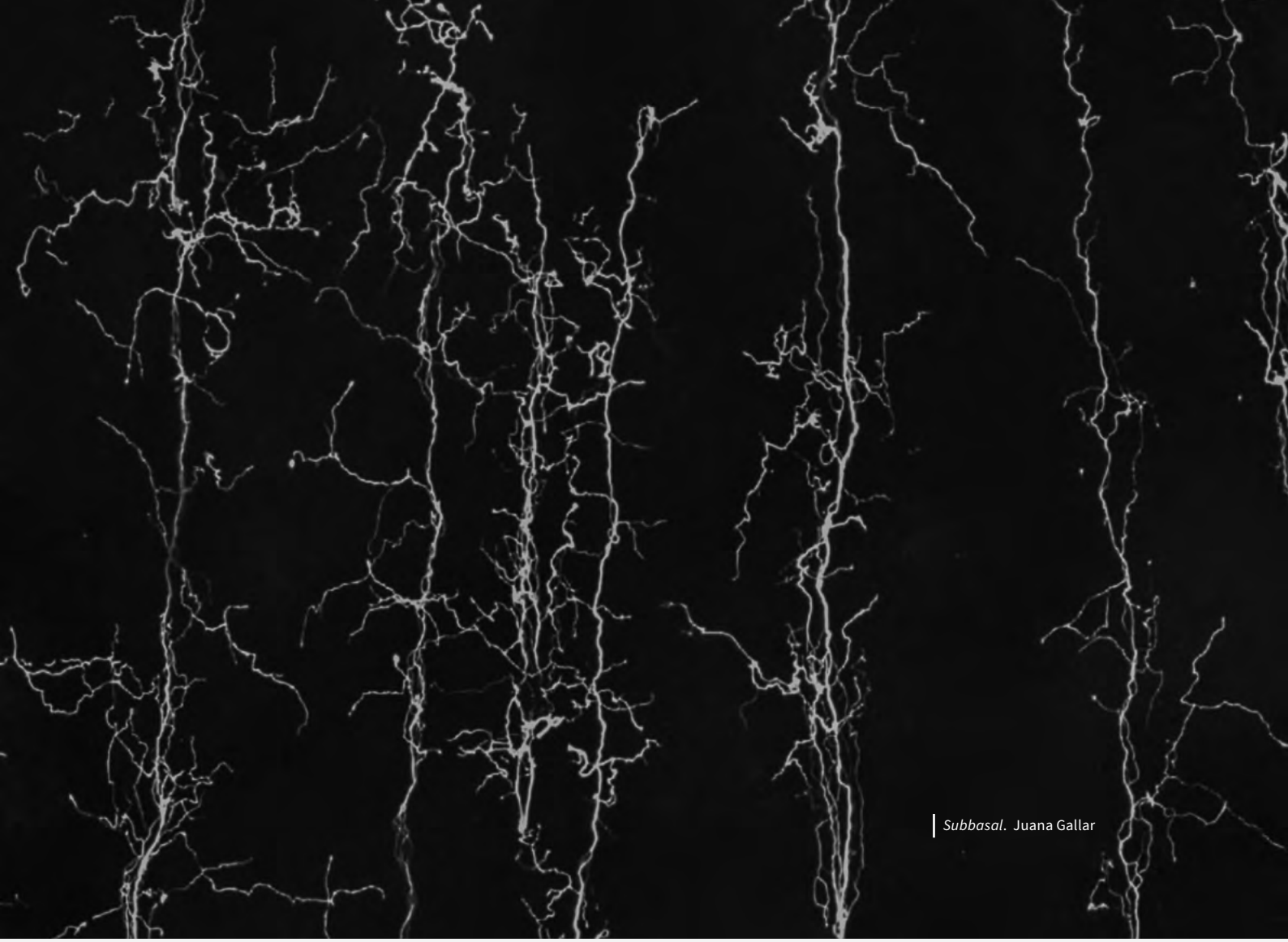

Subbasal. Juana Gallar

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Physiology of the cerebral cortex

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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: i) the intrinsic electrophysiological properties of pyramidal and non-pyramidal neurons and their modulation by dopamine and serotonin. ii) 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. iii) 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 (Institute of Neurosciences).

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.

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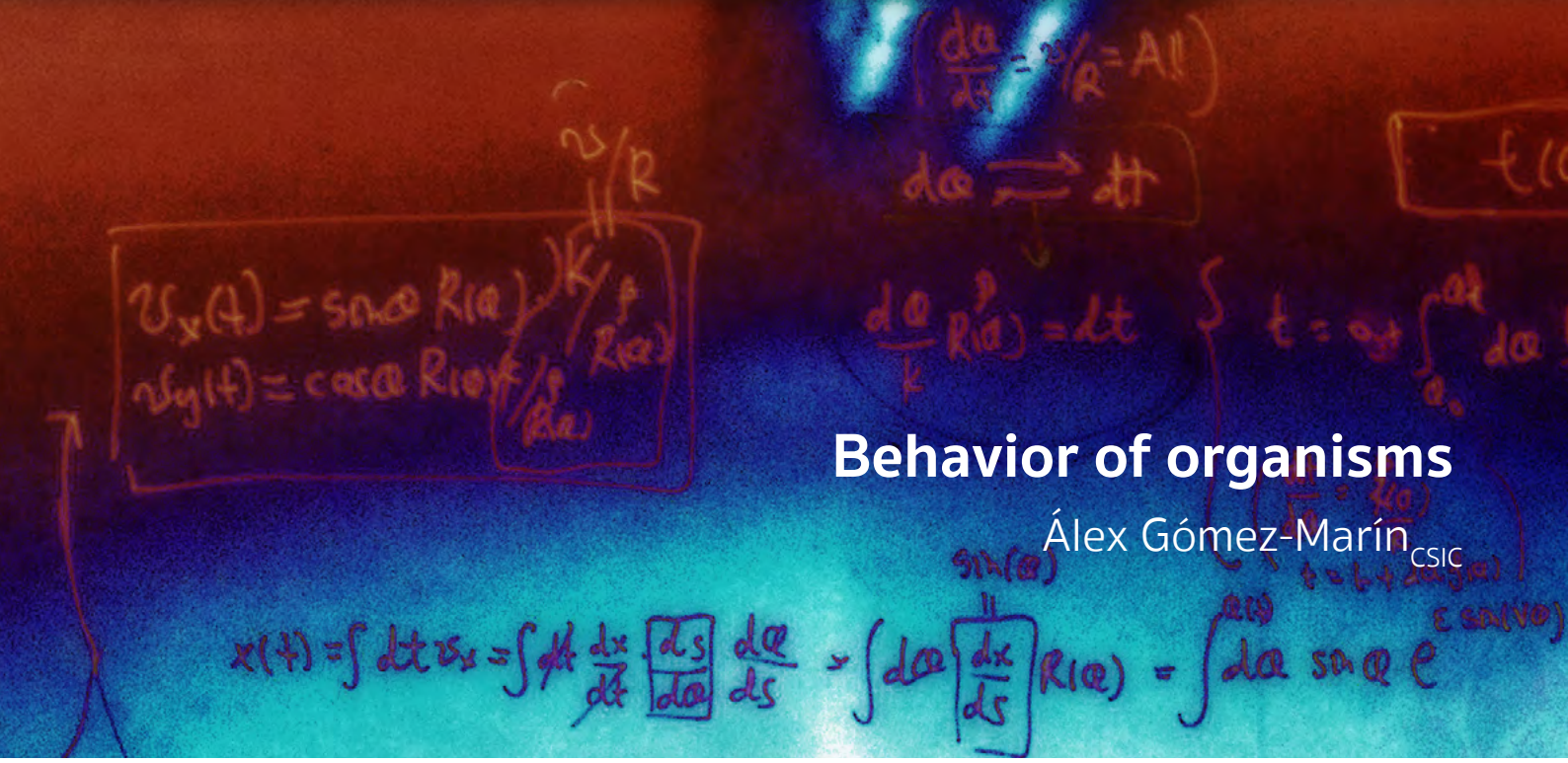

Behavior of organisms

Álex Gómez-Marín CSIC

The behavior of animals is not the behavior of their brains, but the processes emerging from the interaction between neural activity, body biomechanics and environmental constraints. Recent advances in neuroscience comprise a wide range of "big tools" enabling the collection of "big data", both being promissory notes for understanding the brain and explaining behavior. This has lead to much emphasis on techniques and causal accounts of explanation in the flavour of the latest interventionist techniques and reductionist views, thus giving the impression that detailed studies of behavior and its algorithmic composition are less important. However, dissecting "necessary and sufficient" neural circuits for behavior is no shortcut to the proper study of behavior itself. After all, to ask how the brain works is different than (and requires) to ask what it is for — neurons indeed compute information yet nervous systems evolved to produce adaptive behavior. Thus, in the lab we try to avoid missing the forest for the trees.

We advocate for a more pluralistic notion of neuroscience where the dissection of neural processors ("hardware explanations") are best investigated after a careful decomposition of behavioral processes ("software explanations"). This has lead us to pursue a theoretical/computational approach to animal behavior, and across species. From worms and flies to mice and humans, we study shared principles of animal movement from which the fundamental properties of these complex systems should be derivable, interpretable and explainable. We perform high-resolution measurements in virtual reality experiments, and frame our interpretation of the data in descriptive frameworks (bottom-up analyses) and normative theories (top-down principles). Our current efforts target three fronts: (i) seeking the perceptual origins of the speed-curvature power-law in human drawing and maggot locomotion, (ii) exploring the organization of posture sequences in foraging worms and fish, and (iii) establishing behavioral homologies in the unfolding of locomotor degrees of freedom in flies and rodents.

We are hopeful that searching for principles of animal behavior across species will offer general insights into the neurobiology, ecology and evolution of animal behavior. In particular, to deepen into what behavior is (via perceptual control theory), how it is organised (searching for hierarchical organization in postures and actions) and how it evolved (testing the principle of connections to establish behavioral homologies). Seeking to fulfill the promise of nowadays "big science", our more abstract complementary approach moves towards a grounded integrative grasp of animal behavior. Quoting Woese, "without the proper technological advances the road ahead is blocked, without a guiding vision there is no road ahead". Or, as Gallistel put it: "No Mendel, no Watson & Crick".

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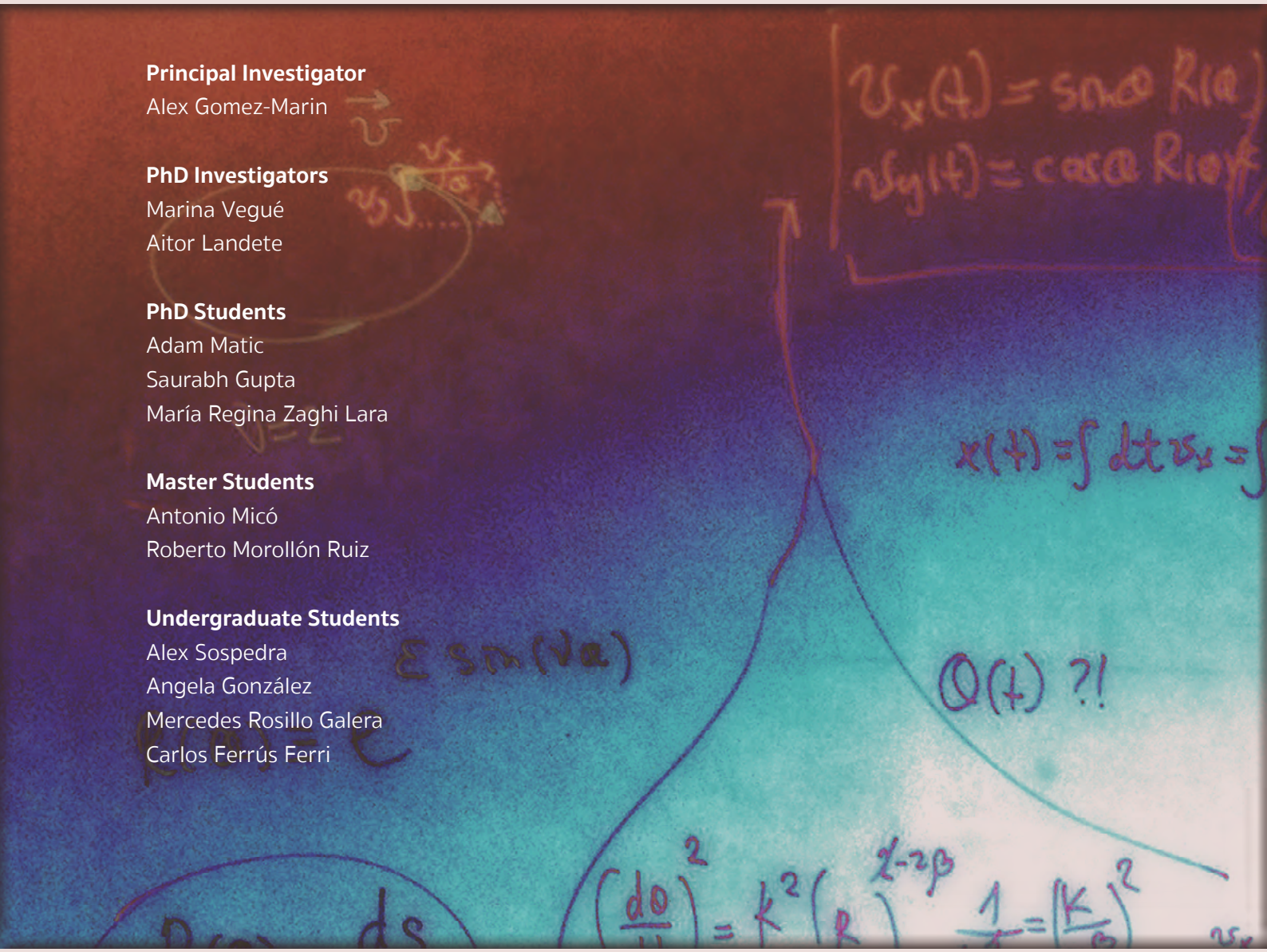

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Mechanotransduction in mammals

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Sensory receptors are cells specialized in sensing diverse physical and chemical stimuli. Their performance has been shaped by millions of years of evolutionary pressure. Nociceptors are primary afferent fibers of the somatosensory system specialized in the detection of noxious stimuli. They are critically involved in the initial steps of pain sensation. Transient Receptor Potential (TRP) channels have been recognized as key molecular detectors of thermal and chemical stimuli in the somatosensory system. Upon activation, these polymodal cationic channels depolarize sensory terminals and bring them to the threshold for action potential discharge. In contrast, the molecular identity of mechanosensitive channels responsible for low and high threshold mechanodetection is not completely known. In addition to several TRP channels, other ion channels, including the family of Piezo proteins may play important roles.

Altered sensitivity of nociceptive neurons to physicochemical stimuli during many pathological conditions, including neuropathies secondary to diabetes or cancer chemotherapy, is one of the established mechanisms underlying pathological pain. However, the molecular and cellular correlates of these alterations in nociceptor excitability, known as peripheral sensitization, are still poorly characterized.

We are interested in identifying the receptor molecules expressed in specific populations of sensory neurons and asking how they participate in

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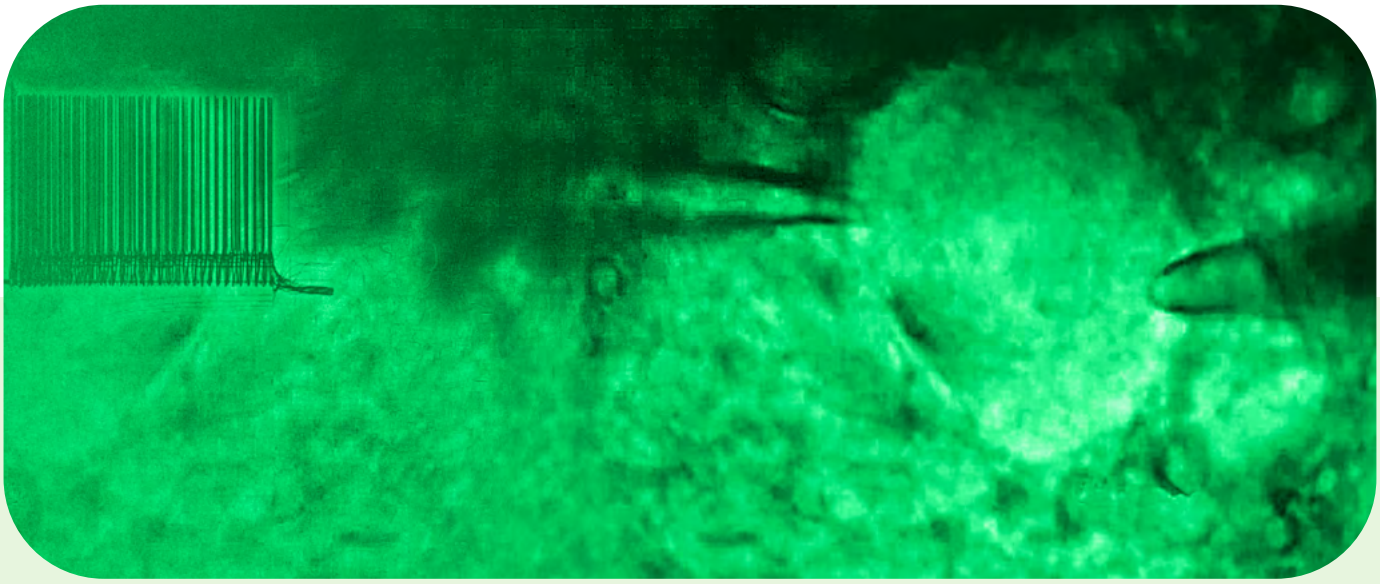
mechanosensation in physiological and pathophysiological conditions. A second goal is to study the interaction of ion channels involved in nociception and mechanotransduction with defined components of the extracellular matrix. Finally, we also study the effects of drugs and blockers of sensory channels on sensory afferents of the knee joint recorded in anesthetized rats. This last step is very important in the establishment of new therapies against pain.

We use whole-cell and single-channel patch-clamp recordings, piezoelectric activation of mechanosensitive channels, intracellular calcium measurements, live confocal microscopy, q-RT-PCR, single-cell PCR, fluorescent-activated cell sorting of sensory neurons and behavioral approaches.



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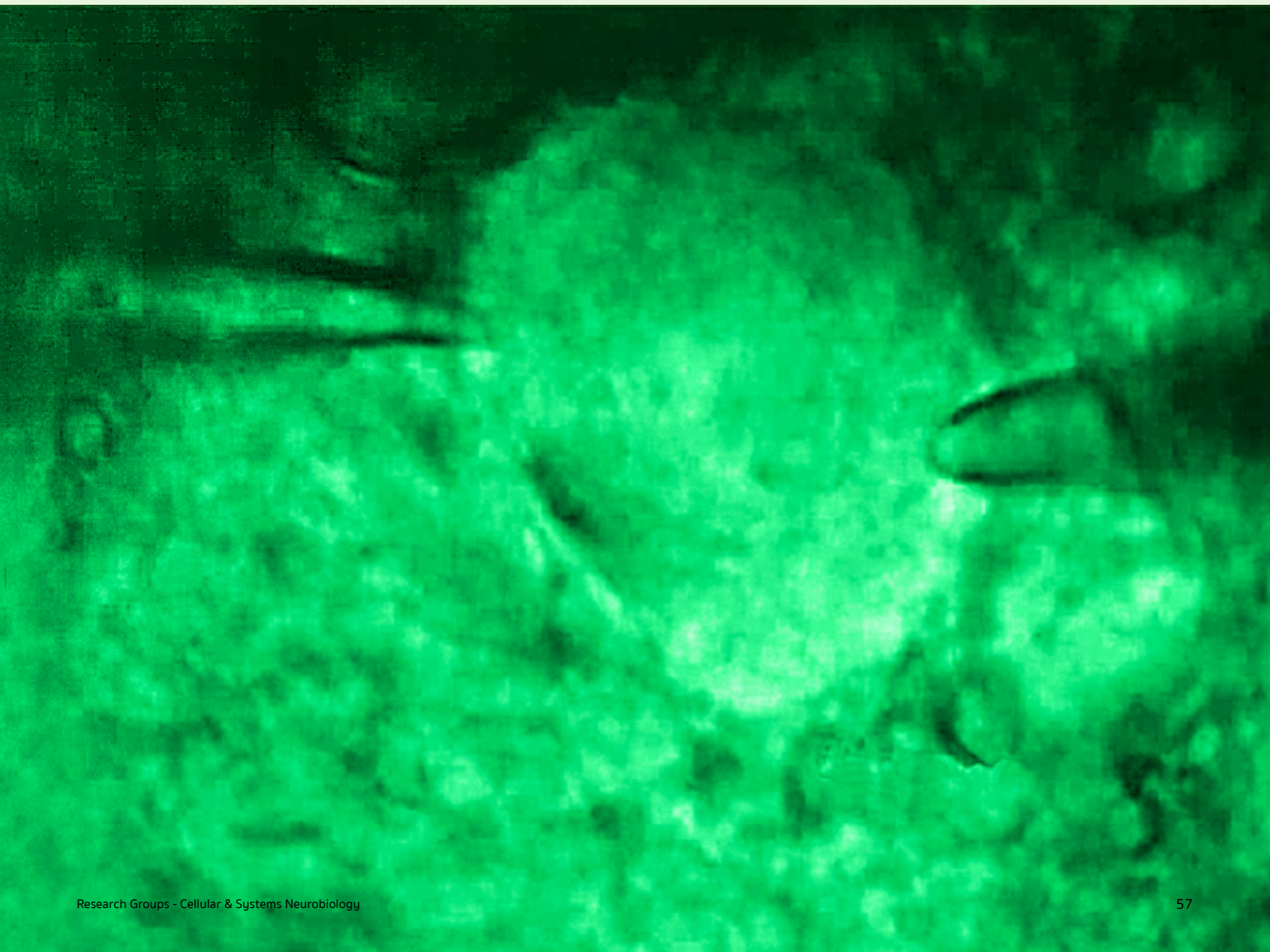

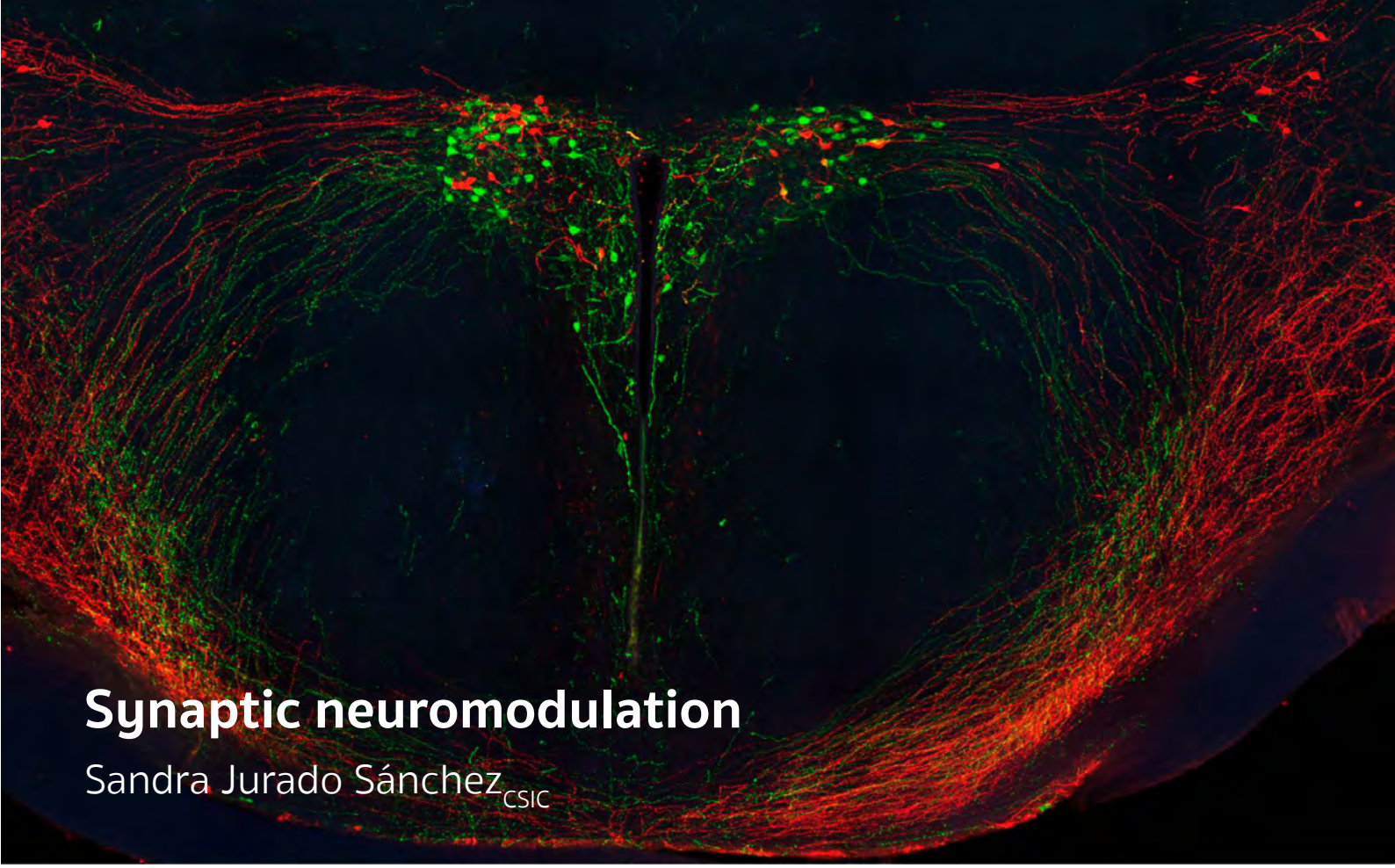

Synaptic neuromodulation

Sandra Jurado Sánchez CSIC

After the intensive refinement process that occurs during the developmental stages, the mature brain retains the ability of undergoing rapid adaptations in response to external stimuli by the means of a cellular phenomenon known as synaptic plasticity. Our goal is to understand how synaptic plasticity is regulated in discrete neural circuits, and how alterations of this process can lead to neurodegenerative and neuropsychiatric diseases. In particular, our laboratory is currently identifying susceptible circuits during early stages of neurodegeneration by using viral-based circuit mapping techniques. We are also interested in understanding how critical neuromodulators such as cathecolamines and endogenous neuropeptides are secreted and how their exocytosis impacts synaptic plasticity and ultimately behavior. To improve the resolution of our molecular studies and manipulations, we plan to develop novel tools to regulate neuronal signaling and function. In particular, we are interested in exploring photo-activatable molecules to control vesicle dynamics in in vivo and in vitro models.

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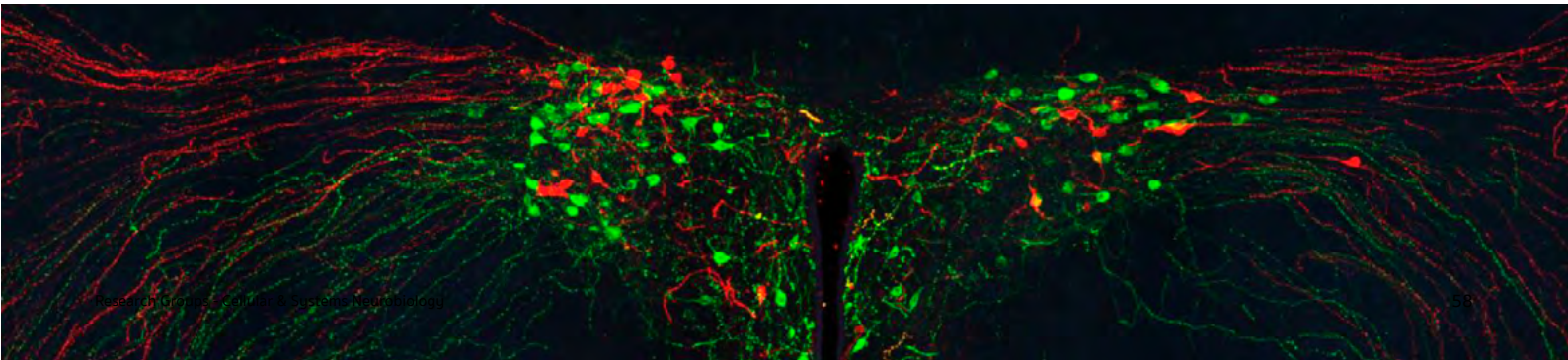

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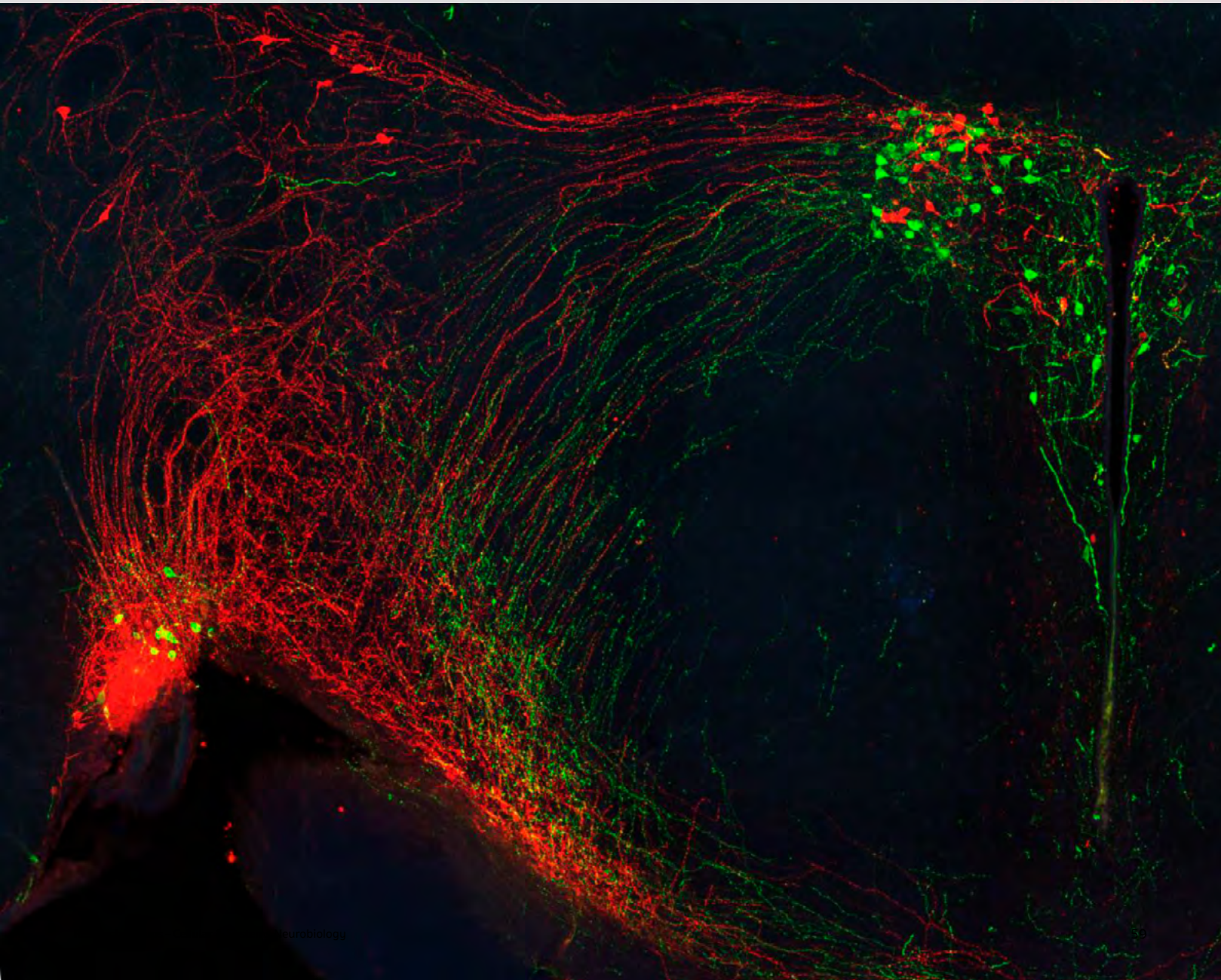

Synaptic physiology

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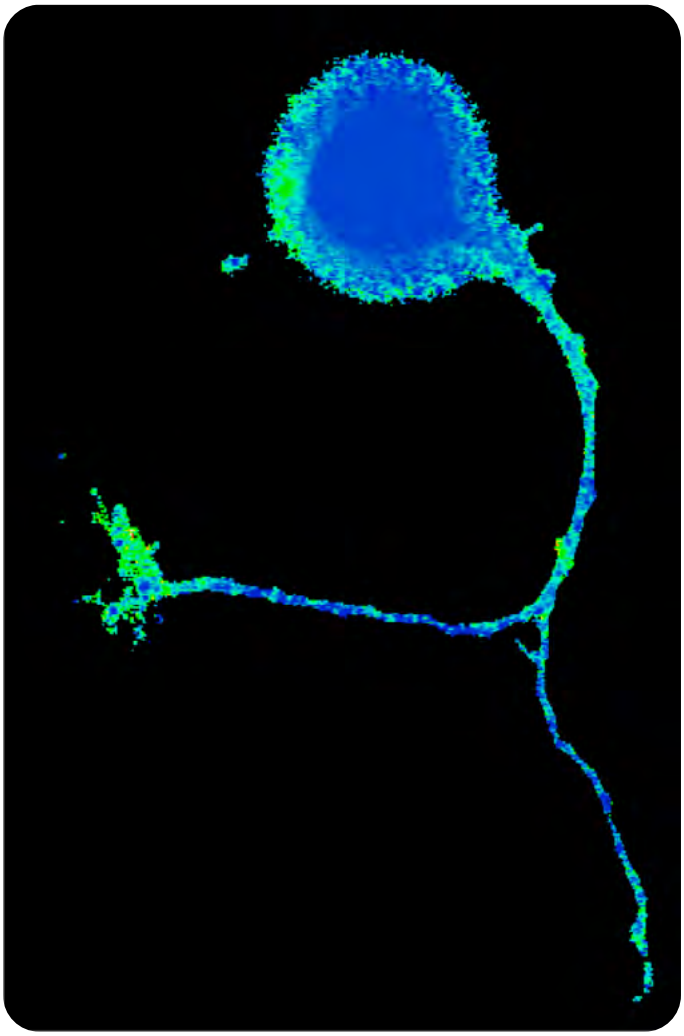
Neurons communicate with each other by means of releasing neuroactive substances that activate specific proteins situated at the postsynaptic membrane. This is a finely regulated process on which the correct performance of our brain depends, which is to say ourselves. One of the current goals of modern Neuroscience is to identify the "synaptic proteome" and to characterize the role played by each protein in the process of synaptic transmission. One important part of the synaptic proteome is the synaptic receptors, proteins in charge of transducing the chemical message into electrical and/or metabolic activities. Our group has been working on the structure and the function of glutamate receptors, the most important signalling system in the brain since it mediates more than 90% of the excitatory neurotransmission. To this end we have implemented molecular and electrophysiological approaches.

In the frame of defining the molecular structures mediating neuronal communication, we described for the first time the existence in central neurons of another type of functional glutamate receptors, the kainate receptor (KAR). We have demonstrated that KAR proteins form functional receptor channels in hippocampal neurons and also identifed the tool by which these receptors could be further studied, the drug 2-3-benzodiazepine, GYKI 53655, which allows its pharmacological isolation.This finding paved the way for progress in the field. Since then, we and other groups have addressed specific questions on the functional role of KARs. We have characterized these receptors and described their fundamental role in controlling neuronal tissue excitability and epileptogenesis. We have also demonstrated that these receptors have a dual mechanism for signalling: in addition to their expected capability of acting as ion channels, they trigger a second messenger-mediated cascade, involving a G-protein. This and subsequent work put forward the new concept that ion channel-forming receptors are also able to signal through a G-protein, opening new vistas on the mechanisms by which glutamate receptors of the ionotropic type work.

The idea that KARs activate a G-protein has encouraged us to study interacting proteins that may influence their correct targeting and their signalling capacities. Therefore, one the main objectives of the lab has been to identify and to evaluate the role of interacting proteins in the signalling properties of KARs using a number of model systems. Using proteomic techniques, including two-dimensional gels and mass spectrometry analysis, we have identified a set of over 20 proteins that take part of the "interactome" of these receptors and analysed the impact of some of them on the roles of kainate receptors likely play have in neuronal physiology. Among the identified proteins are SNAP25, which we have shown plays a key and

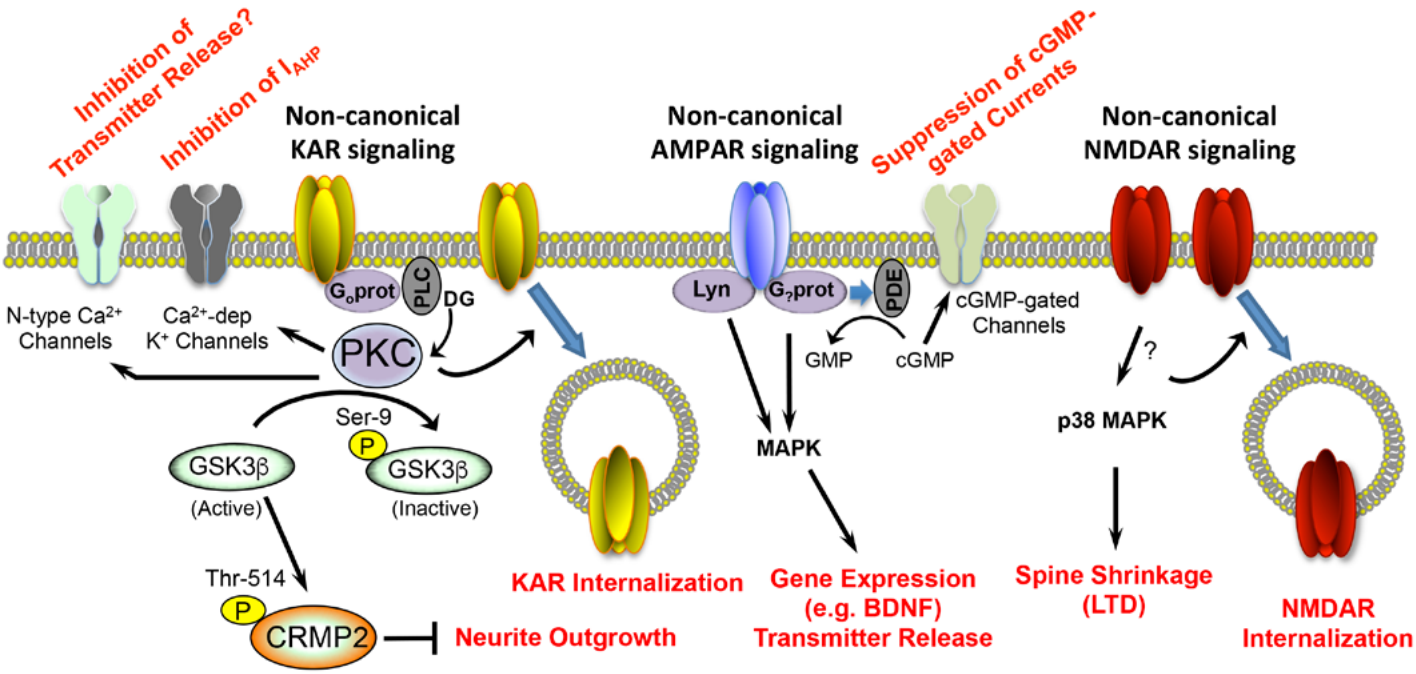


unexpected role in endocytosis of these receptors from the synaptic membrane. Indeed, it is responsible for a type of long-term synaptic plasticity of the kainate receptor-mediated synaptic component. Also, CRMP2 and CRMP4 were also identified as interactors of GluK5. Indeed KARs influence neuronal maturation and neuritic proliferation through these proteins in a bidirectional manner. We have also identified the subunit GluK1 that interacts with a Go protein, and that is most likely responsible for non-canonical signaling of these receptors. The regulation of receptors by all these proteins provides innovative strategies to finely influence its function and may constitute targets for

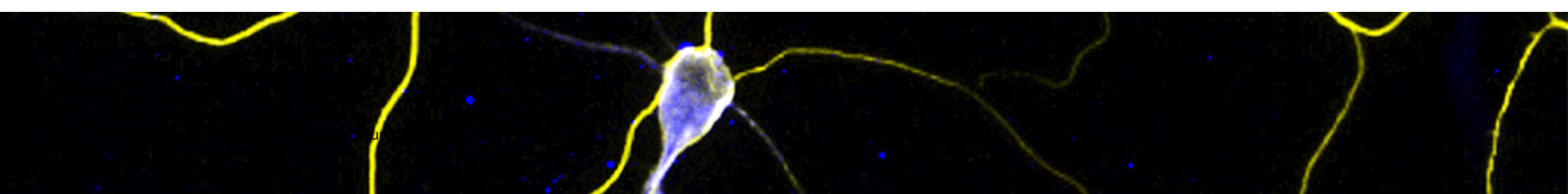
development of new active drugs in problems of excitability, such as epilepsy.

These are salient properties of KARs but their role in both physiology and pathology is still limited. 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. The understanding of brain diseases requires the definition of the molecular, synaptic and cellular disruptions underpinning the behavioural features that define the disease. For this reason, 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 normalization strategy of the gene dose, we identified that triplication of the KAR encoding gene GRIK1 is the cause of spatial memory impairment observed in Down syndrome. Indeed, normalization of Grik1 dosage in Ts2Cje mice specifically restored spatial memory and reversed the 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.

All together, these data indicate that a single gene variation in the glutamatergic system results in behavioural symptomatology consistent with autism spectrum disorders and Down syndrome which concomitantly run with alterations in synaptic function in regions involved in social activity and spatial memory.



Non-canonical Signaling of iGluRs Controls Multiple Aspects of Neuronal Function. KARs, AMPARs, and NMDARs exert a significant part of their roles through the activation of metabotropic pathways



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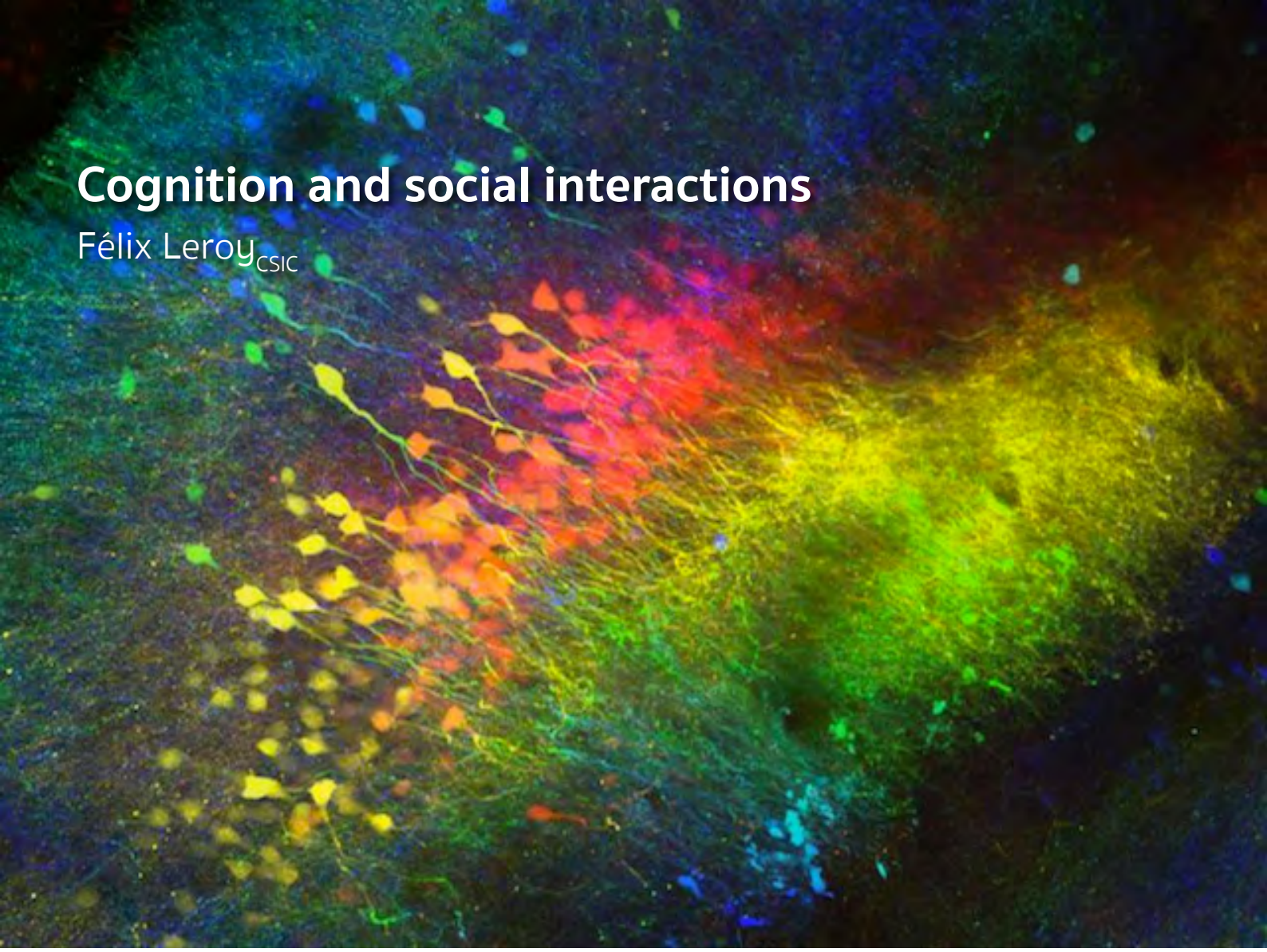
Cognition and social interactions

Félix Leroy CSIC



Research interests: Our research focuses on determining cellular- and circuit-based mechanisms by which higher-order brain regions such as the hippocampus and prefrontal cortex relay cognitive information to the hypothalamus in order to modulate innate motivated behaviors (sociability, aggression, mating). As alterations in higher brain regions contribute to neuropsychiatric diseases associated with disordered social behaviors, insight into both the normal and abnormal functions of these circuits is of critical importance. In addition, I am investigating how neuronal plasticity rules, mostly described ex vivo in brain slices, can support learning-related behaviors in vivo.

Techniques: immunohistochemistry, in situ hybridization, viral tracing of neural circuits, patch-clamp in acute slices with optogenetic, fiber-photometry, miniature endoscopes, opto- and chemogenetic in freely behaving animals. Behavioral assays of social interactions.

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Neural circuits of social behaviour

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Social interactions shape the way we perceive, feel and learn about the world, and despite its importance for social species, we still know very little about how the brain computes social information. Our lab is interested in understanding the mechanisms of how social behaviour shapes our brain, and for this, we focus on cooperative social interactions in rodents. We were pioneers in the demonstration that Norway rats display prosocial behaviours in food foraging context, providing food to conspecifics, and identified the proximal mechanisms at the level of behaviour. Current and future projects aim to identify the neural circuits responsible for this fascinating social decision-making, using a combination of behavioural, anatomical, pharmacological, imaging and optogenetic tools in rodents.

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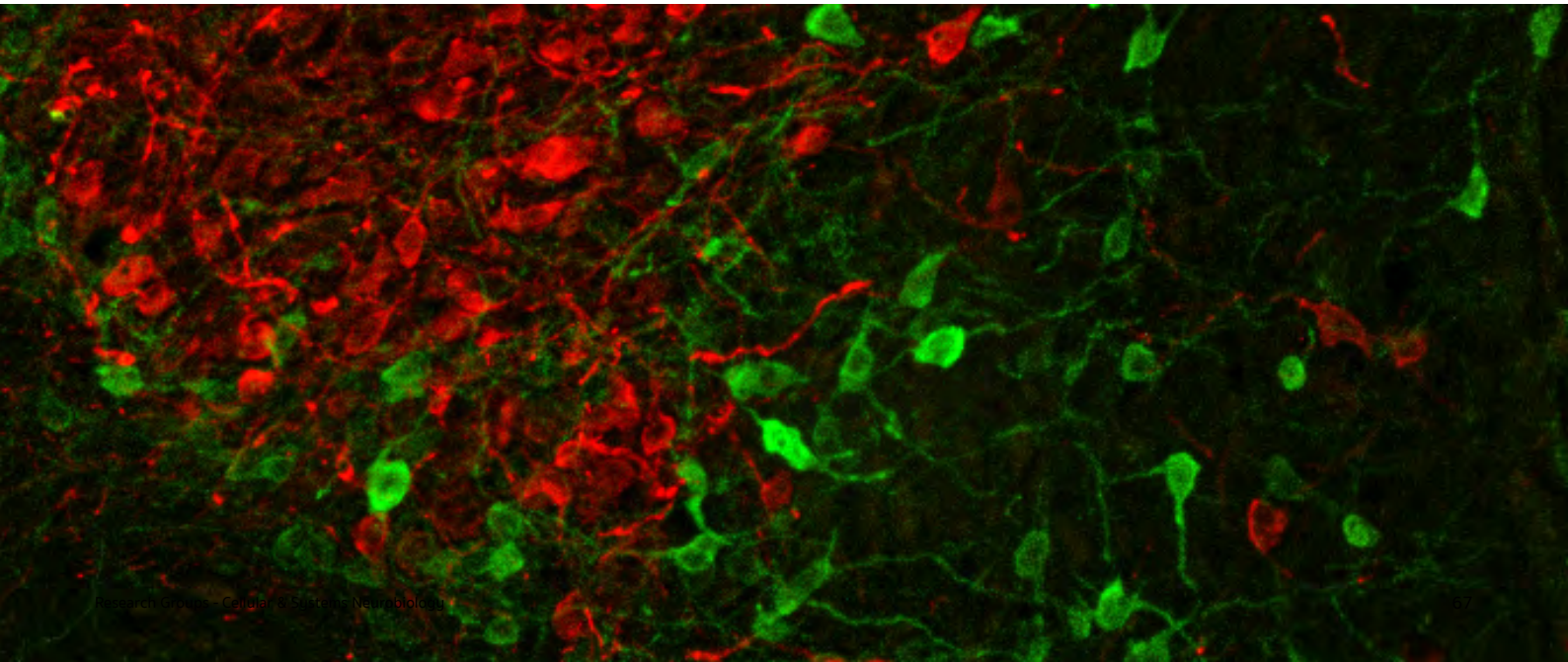

Visual neuroscience laboratory

Luis M. Martínez$_{CSIC}$

We, like many other mammals, are essentially visual animals. Thus the visual system of our brains must achieve a daunting task: it creates, in real time, an internal representation of the external world that it is used by other parts of the brain to guide our behavior. But, how do we actually see? How does this neural system accomplish the job? A parsimonious explanation proposes that visual information is analyzed in a series of sequential steps starting in the retina and continuing along the multiple visual cortical areas. As a result, the information captured by the approximately 105 million of photoreceptors in the back of each eye is continuously rearranged in a complex combination of points and lines of different orientations and curvatures that are defined by differences in local contrast, color, relative timing, depth, movement, etc. Ultimately, by mechanisms that remain largely unknown, these elementary features of the image are integrated into the perception (our "vision") of each individual object in the visual scene.

In our lab, we want to understand the synaptic mechanisms and neural circuits that underlie the earliest stages of visual processing and perception. Our main goal is to determine the synaptic structure of the thalamocortical microcircuit at a functional level, which currently represents one of the most fascinating challenges of systems neuroscience. In addition, since vision is the most accessible and best understood of our senses, our results directly inform theoretical models (both conceptual and computational) that are proposed to explain the functional organization of the cerebral cortex and thalamus in general. Finally, a better understanding of the visual system is essential to develop prosthesis that will eventually restore vision to the blind and, on a shorter time scale, to design more efficient tools for the rapidly growing field of object recognition.

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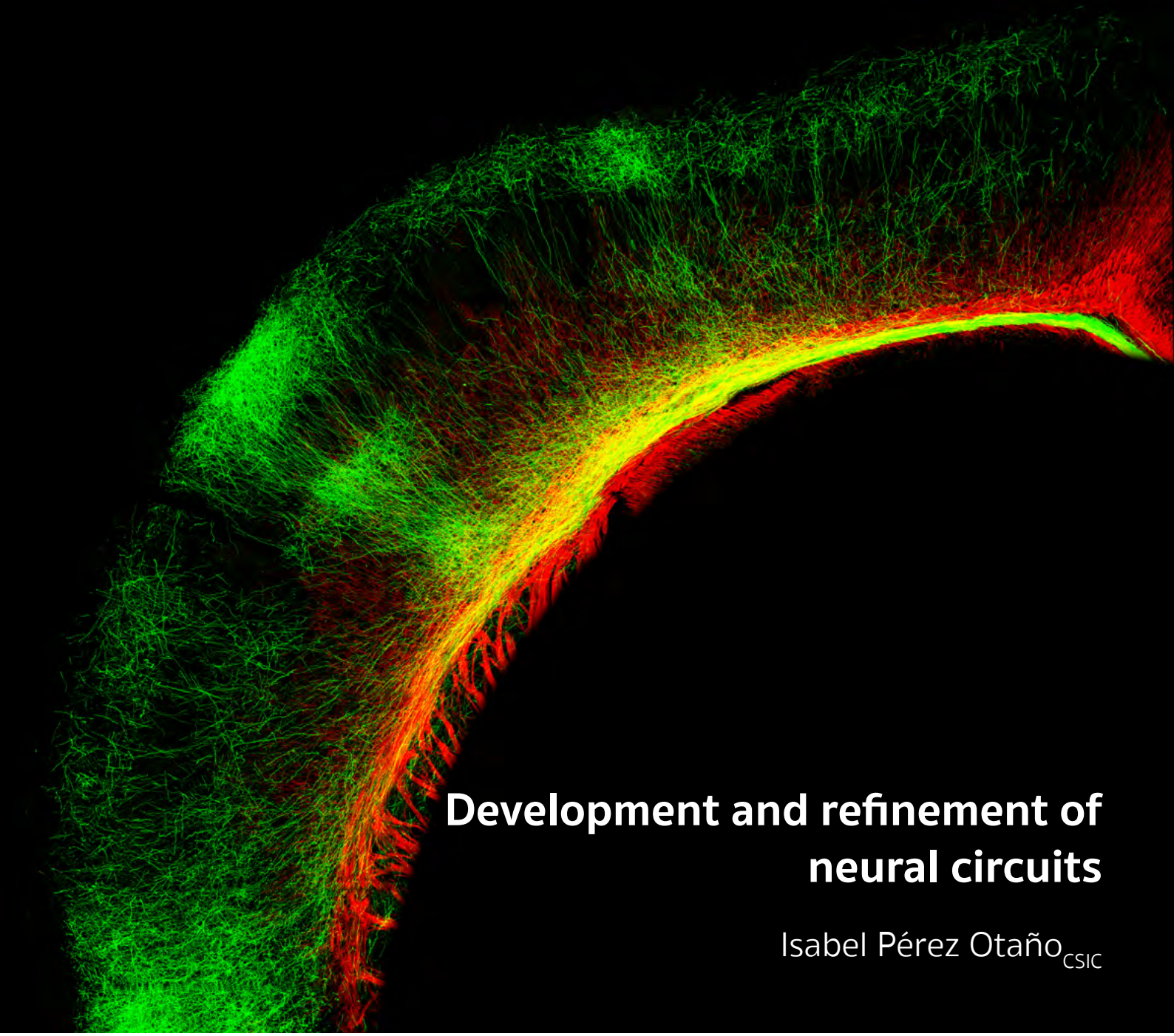

Development and refinement of neural circuits

Isabel Pérez Otaño CSIC

A fundamental question in neuroscience is how neuronal circuits are refined by environmental cues. Circuit refinements involve maturation of selected synaptic connections and elimination ("pruning") of others, and are most prominent during critical periods—a stage of postnatal brain development when synapses have a high potential for undergoing plasticity. This malleability allows early experience to modify the architecture of neural circuits, providing a foundation for future learning. Perhaps more importantly, it shapes (often permanently) the cognitive, social and emotional abilities of an individual so it can adapt to the environment at hand. Critical periods are of medical relevance as well because some types of experience-dependent wiring no longer occur after they end, or when the proteins and genes supporting this wiring work incorrectly.

Our work focuses on two major aspects. First, what are the basic mechanisms that control the development, refinement, and homeostasis of neural circuits? Second, what goes wrong in disorders of brain development, cognition or memory?

In the past 10 years, we have defined the biological functions of a new class of NMDA-type glutamate receptors that contain GluN3A subunits and are typically expressed during the critical period in many brain regions and cell types. They have crucial roles in preventing premature or disordered synapse stabilization and maturation and in targeting non-used synapses for pruning. Later, GluN3A-containing NMDA recep-

tor expression is largely down-regulated via a combination of mechanisms. Prolonging or switching back GluN3A expression in adult brains reactivates a juvenile state of enhanced pruning and underlies circuit rearrangements that underlie the pathophysiology of Huntington's disease (HD) and cocaine addiction.

Current projects investigate:

- Cell biology mechanisms underlying synapse pruning at pre- and postynptic levels.
- Impact of early synaptic remodeling on the emergence of cognitive and emotional capabilities.
- Discovery and targeting of disease mechanisms: Failure to maintain the balance between synapse maturation and pruning is at the root of neurodegenerative and neuropsychiatric disorders, leading to impaired connectivity and circuit dysfunctions. We have shown that adult reactivation of GluN3A expression is at the basis of Huntington´s disease and are currently exploring its involvement in alcohol abuse and other forms of addiction. Work in the lab is also directed to develop pharmacological/gene therapies to block GluN3A function or expression, and test whether they promote recovery of function.

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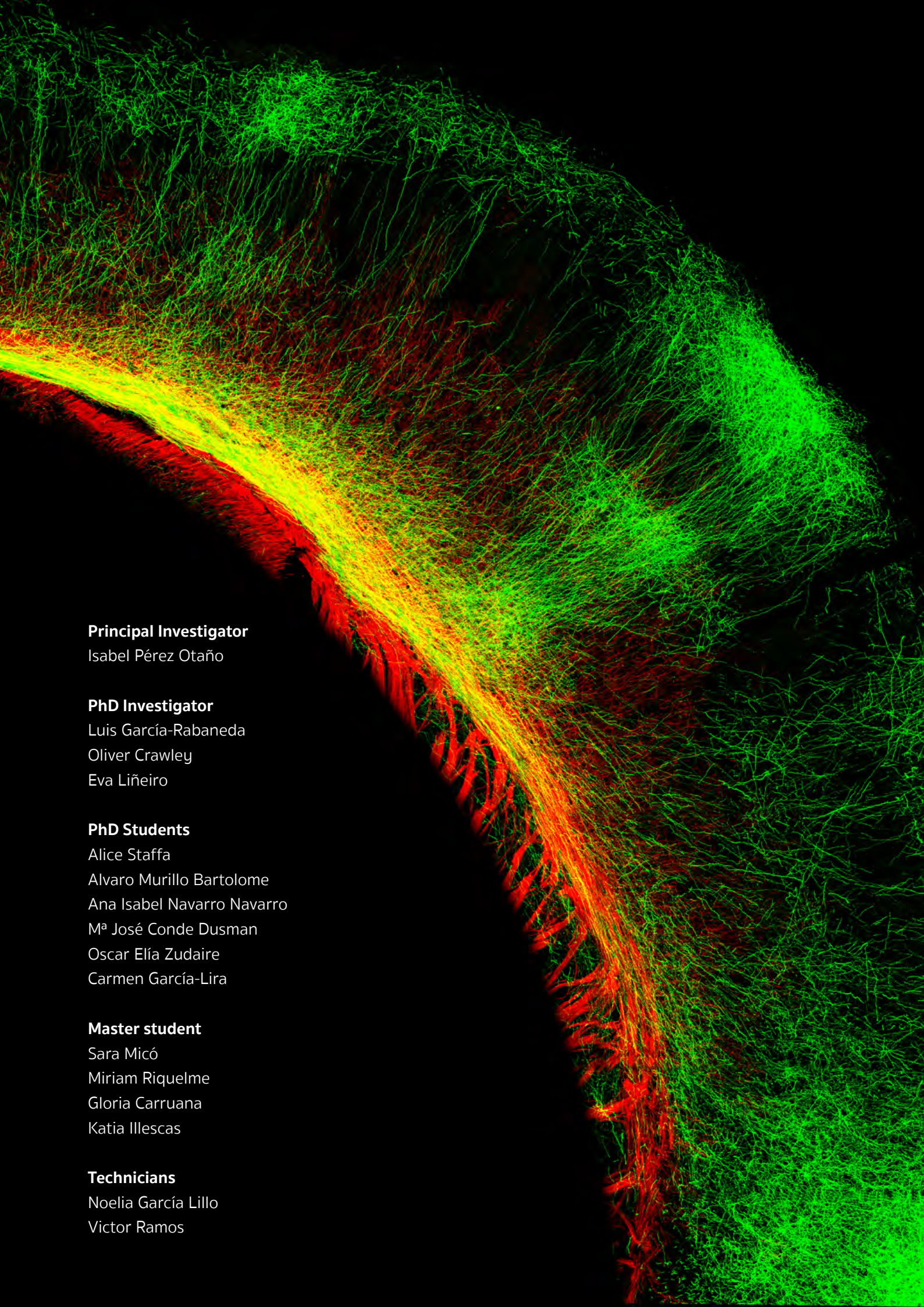

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Sensory-motor processing by subcortical areas

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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 compound by 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. The 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 compound by different types of GABAergic (FSI, SOM+/NPY/NOS+, CR+, TH+...) and cholinergic (ChI) 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 the 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.

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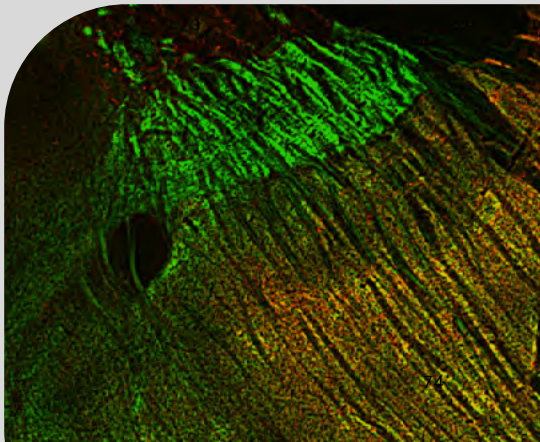
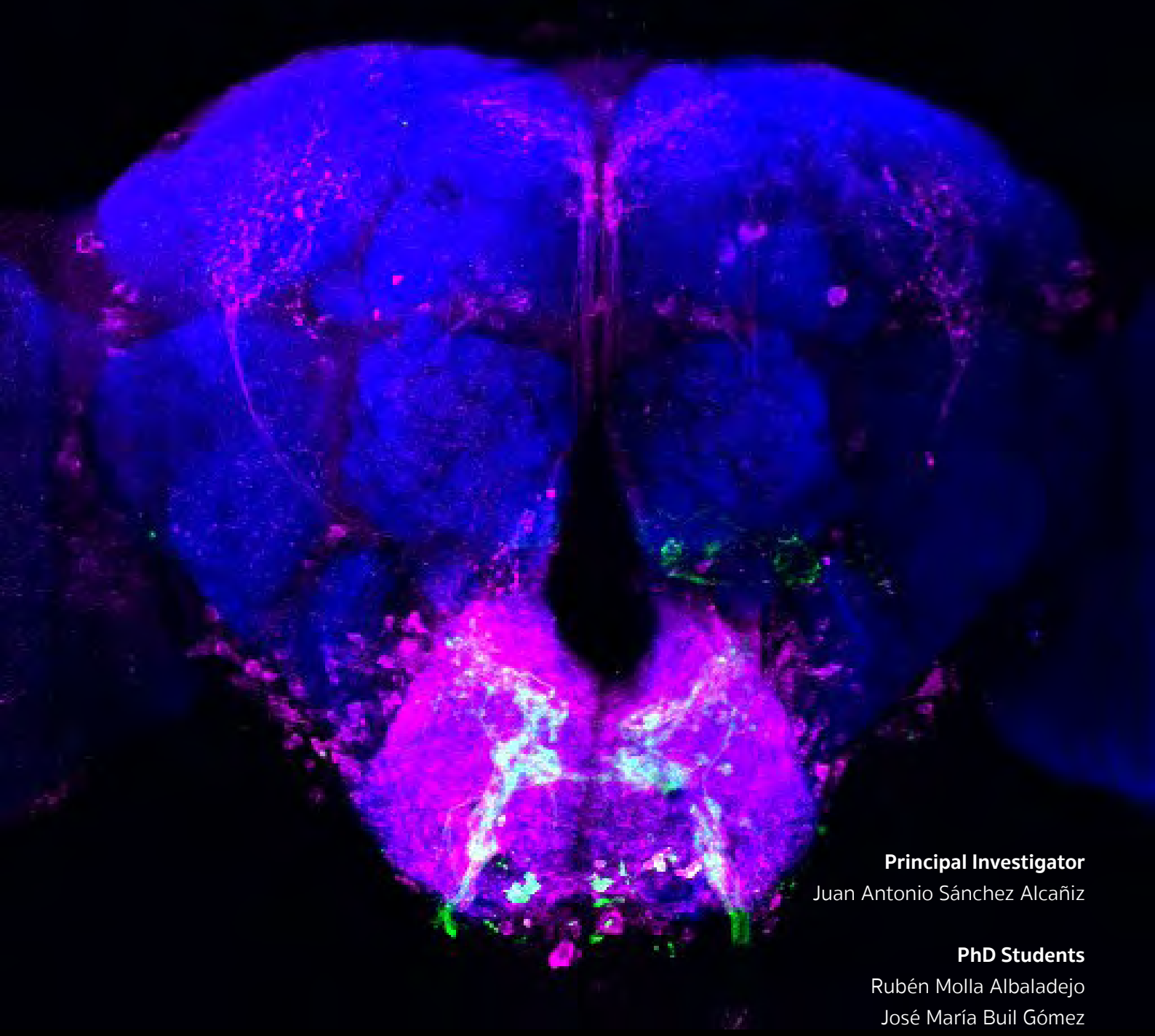


Neurogenetic basis of behavior

Juan Antonio Sánchez Alcañiz$_{CSIC}$



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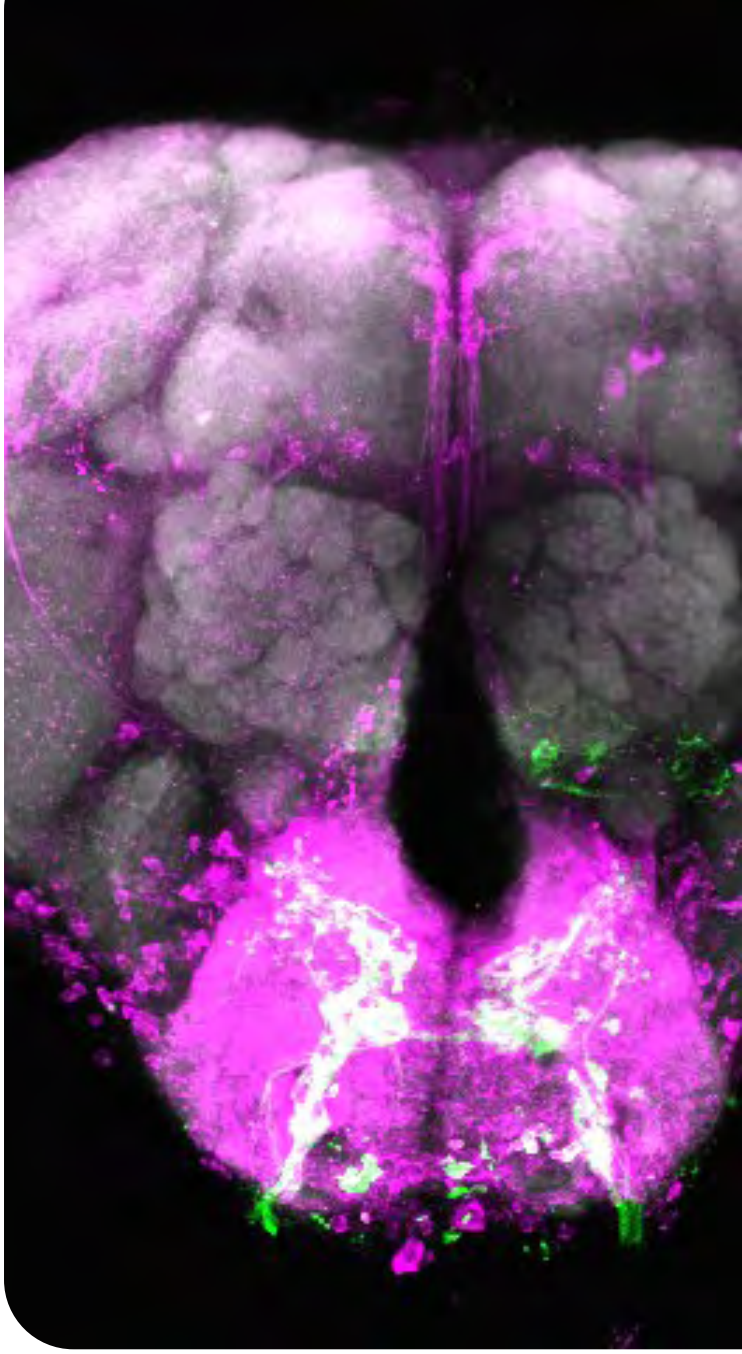
Animal survival depends on the proper interpretation of environmental information. Through evolution animals have developed an exquisite array of sensory organs that can collect large amounts of different environmental cues. This information is sent to the central brain where it is processed and integrated with previous experiences and internal states to produce the proper behavior. In order to understand how this 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.



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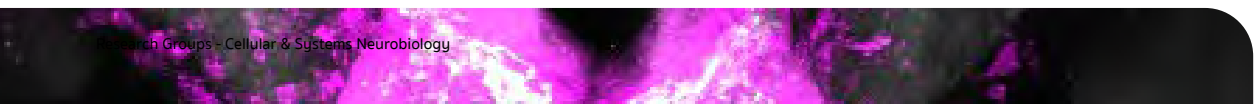

Wiring and function of somatosensory circuits

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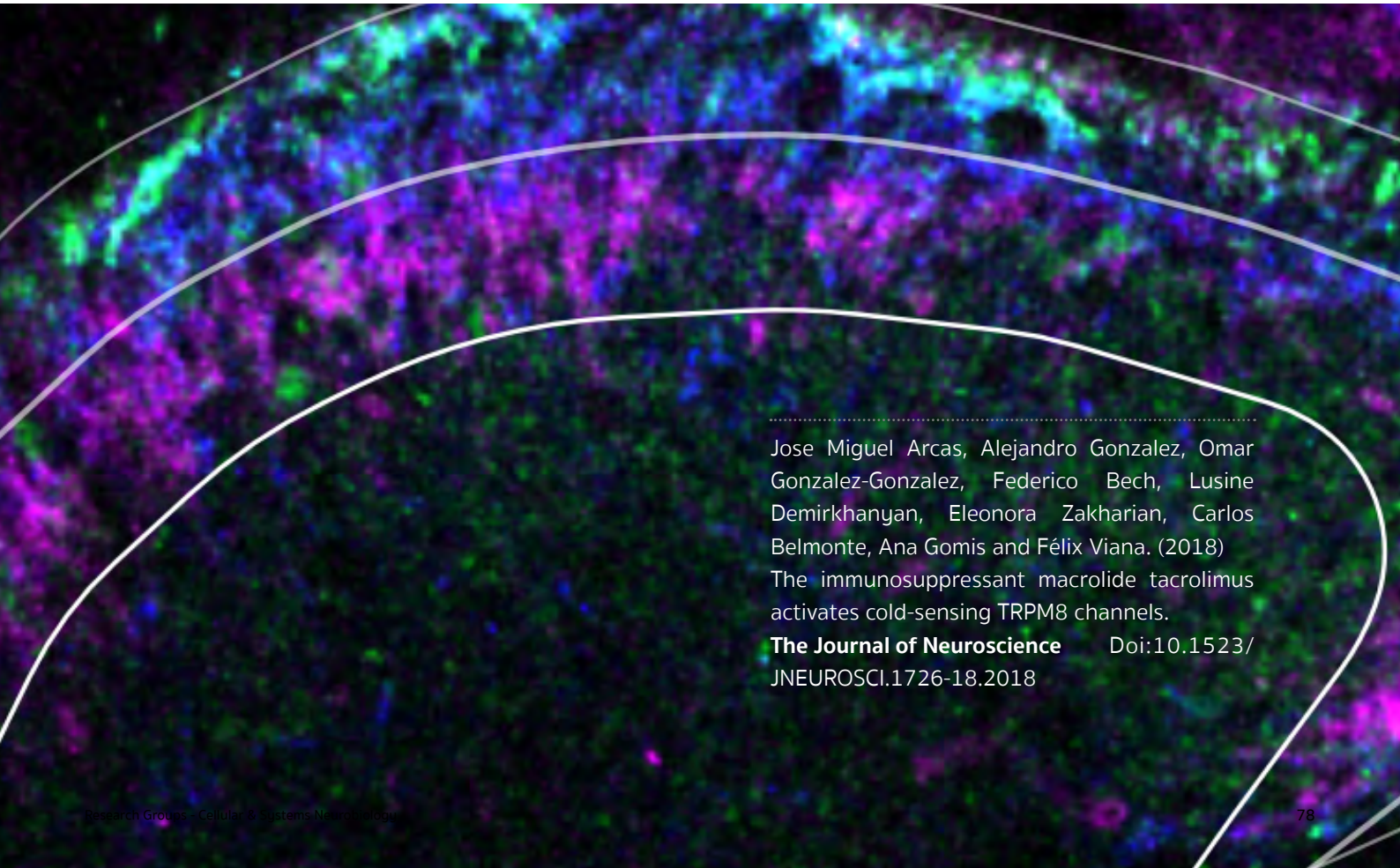
Specialized subsets of primary sensory neurons innervating different body tissues detect and transduce different environmental cues into itch, touch, temperature or pain information. When these signals eventually reach the brain, they generate the sensory percept and evoke the convenient physiological 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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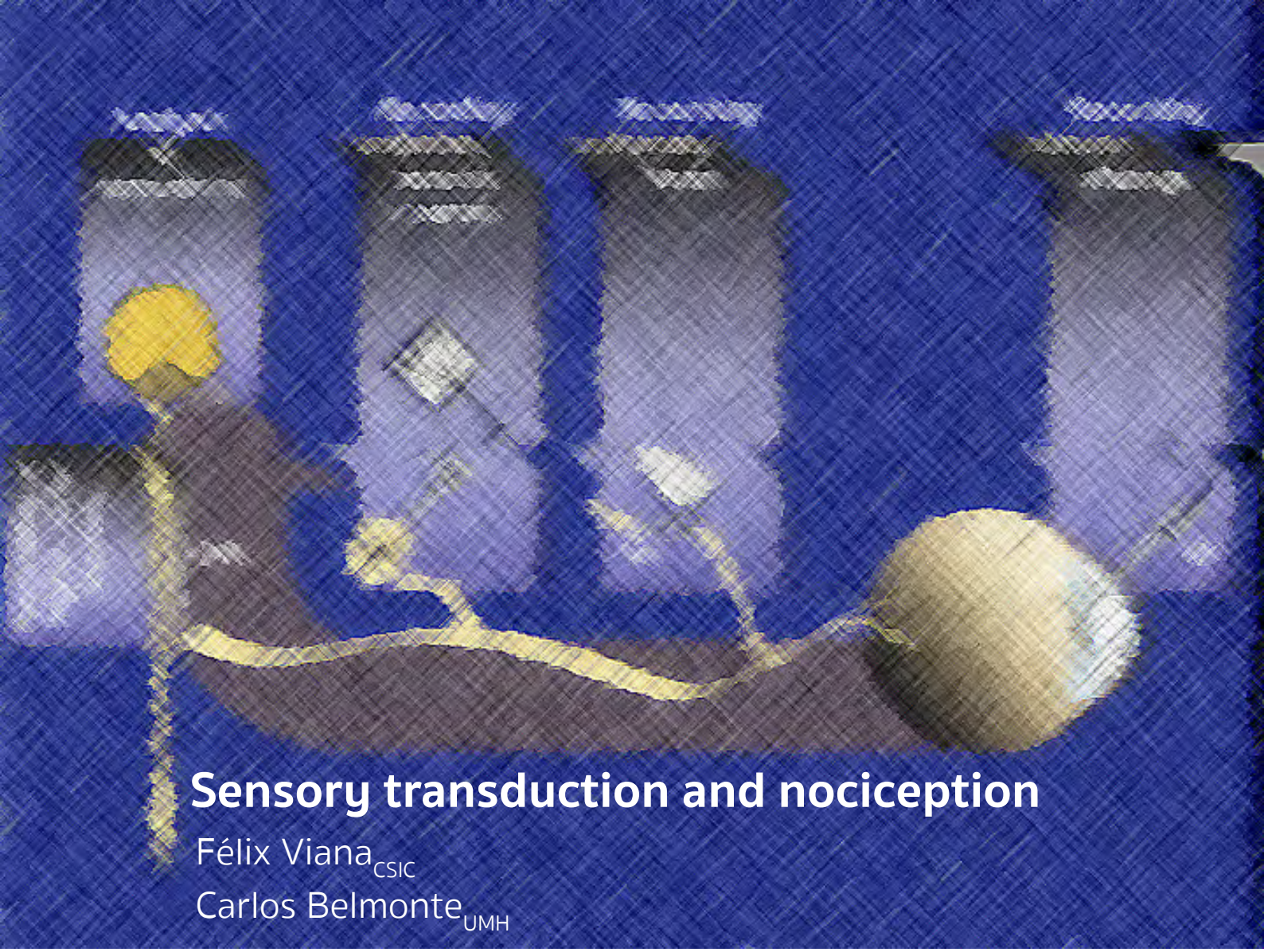

Sensory transduction and nociception

Félix Viana[CSIC]
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Mammalian somatic sensory receptors are highly specialized structures devoted to the precise detection of thermal, mechanical and chemical stimuli, both innocuous and noxious, that impinge upon the organism from the environment. They also monitor the internal state of the organism. Activation of these receptors by specific stimuli gives rise to an electrical signal proportional to the intensity and duration of the incoming stimulus. This neural message travels to the brain, eventually evoking distinct sensations.

Our research group is interested in the analysis of the cellular and molecular mechanisms that determine the activation of thermoreceptors, low- and high-threshold mechanoreceptors, as well as polymodal and silent nociceptors. We are trying to identify the cellular and molecular determinants of stimulus specificity, and the mechanisms that give rise to the different response thresholds. To this end, we use different experimental approaches, ranging from the transcriptional profiling of subpopulations of sensory neurons, optopharmacology, the molecular analysis of transduction ion channels and receptor molecules, recordings of sensory nervous activity in isolated cells and single neurons in anesthetized animals to behavioral analysis in different animal models of chronic pain.

We are examining the problem of sensory transduction at different conceptual levels. From a reductionist point of view, we are trying to establish which transduction molecules and which cellular mechanisms give rise to the preferential response to a particular stimulus and how they are modulated. In a more integrative approach, we are also trying to define the functional relationships between different transduction molecules, the ion channels involved in neuronal excitability and intracellular signal transduction pathways in sensory receptor neurons. The final goal is to obtain an integrated view of their cellular mechanisms for stimulus detection and the coding of these stimuli into a discharge of nerve impulses with a defined

temporal sequence. We are also exploring the biological significance of this sensory message in the regulation of bodily functions. The analysis includes the search for selective pharmacological agents capable of interfering with the different steps of the transduction process or their modulatory mechanisms. An additional important research line of our group involves the analysis of the short- and long-term cellular and molecular changes that occur in primary sensory neurons during pathological process such as lesions and inflammation.

Finally, we have collaborations with other national and international research groups interested in pain mechanisms and the functional study of ionic channels.

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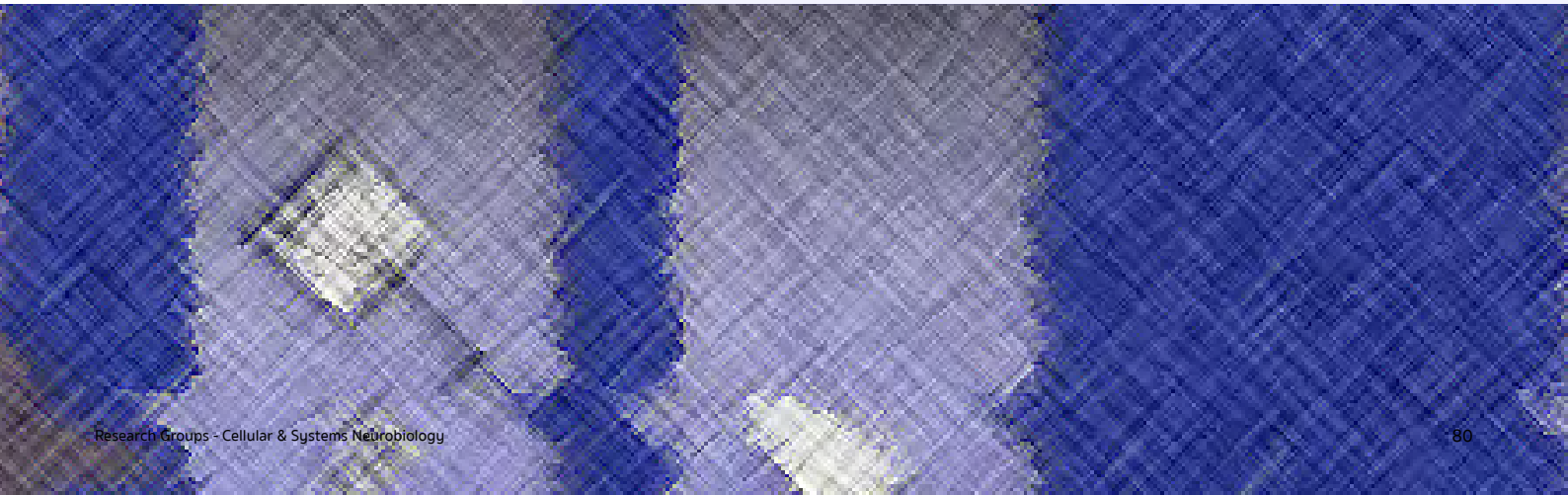

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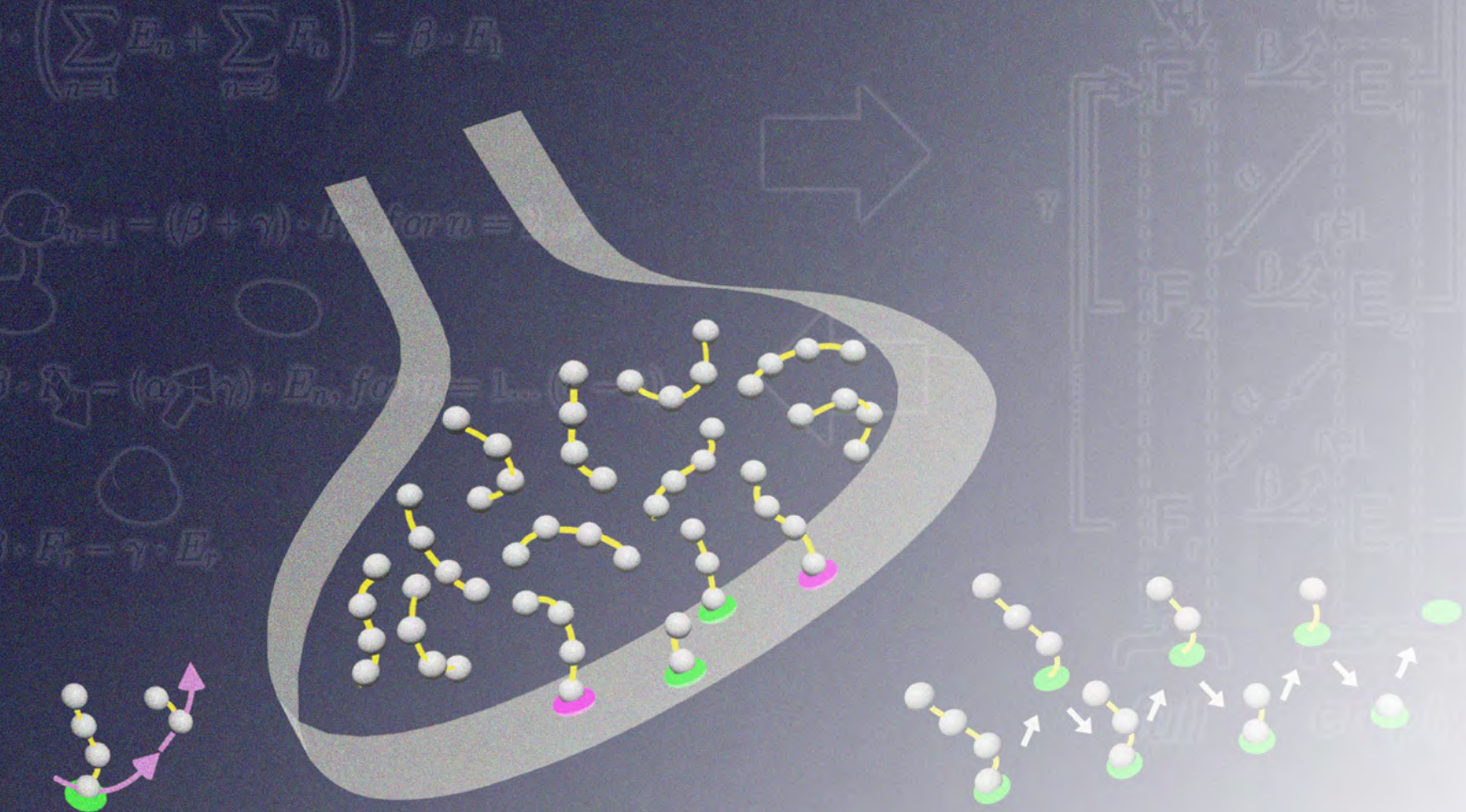

Molecular and cellular physiology of synaptic transmission

John F. Wesseling$_{CSIC}$

We are developing a new framework for understanding the history-dependent 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, or synaptic dynamics, and have a presynaptic origin. The directionality, timing, and range of the dynamic changes all vary greatly between individual synapses, suggesting that the underlying mechanisms can be modulated over development and/or as a result of learning. The idea is that the new framework will provide a comprehensive method for categorizing the variation, which 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 study each step in isolation and to ask how the underlying mechanisms interact with each other. The framework that emerged is mathematically simpler than predicted, in a way that requires re-thinking conventional views about how synaptic vesicle trafficking works. 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.

Ongoing work is attempting to:

1) Re-evaluate key pieces of evidence for alternative/competing ideas in the context of the new model.

2) Determine if the composition of the various types of frequency filtering modules within individual synapses can be regulated over the long-term by activity-dependent stimulation protocols that have already been shown to control synaptic strength in the contexts of learning and memory and development.

3) Combine the assays developed to isolate rate-limiting steps in vesicle trafficking with molecular biology techniques to determine the function of classes of presynaptic proteins. Current work is focused on the four members of the synaptophysin family.

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Ángel Barco CSIC

Transcriptional & epigenetic mechanisms of neuronal plasticity and its disorders

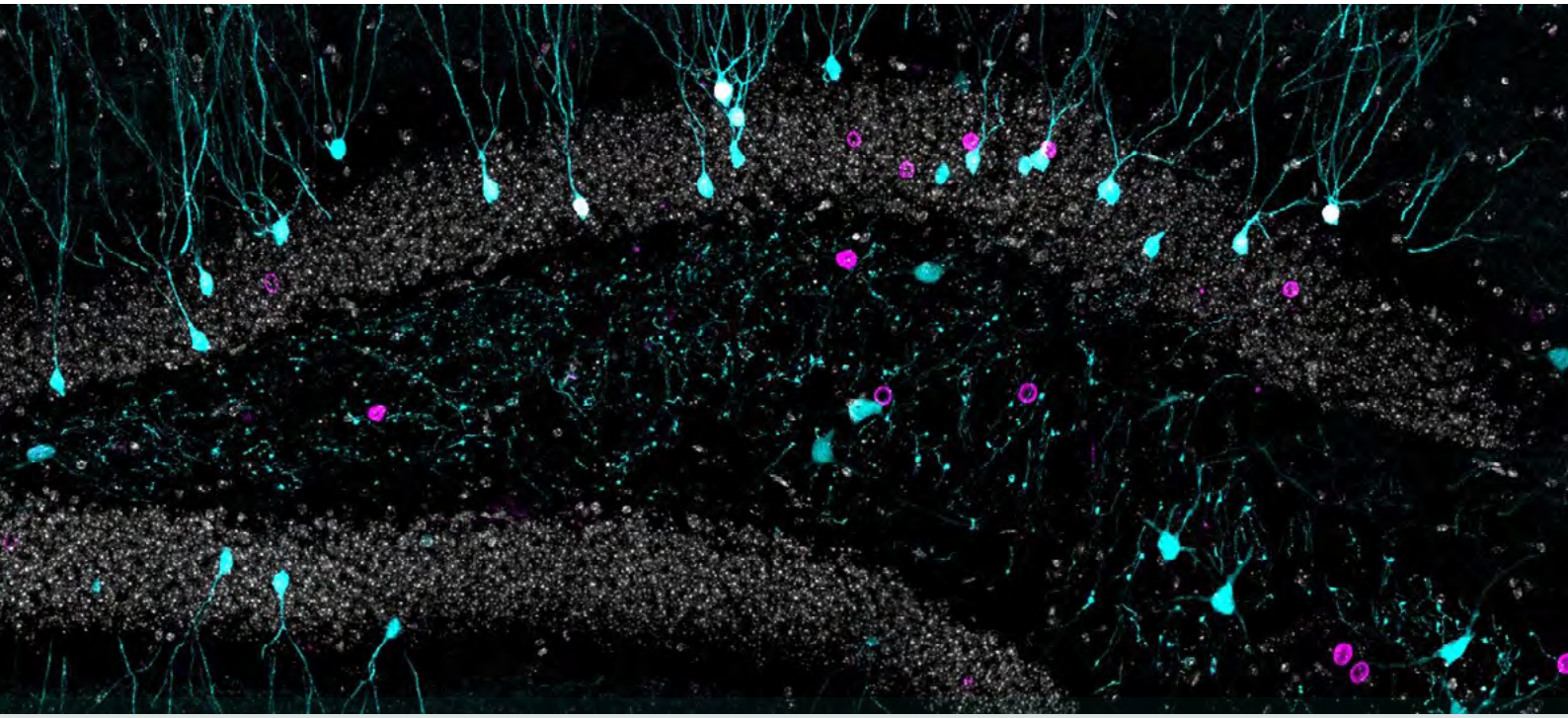
Our research focuses on molecular mechanisms that regulate neuronal gene expression and underlie learning and memory, and other long-lasting modifications of the animal's behavior. We also aim to determine how the malfunction of epigenetic mechanisms leads to different pathological situations in the 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. From the methodological point of view, we are particularly interested in the application of genomic profiling techniques based on next generation sequencing (NGS) and epigenetic editing approaches in the nervous system.

We currently work on two main lines of research:

- Interplay of transcriptional avand epigenetic mechanisms in activity-dependent transcription: Activity-driven transcription and epigenetic remodeling are both integral part of the neuronal response to stimulation. Moreover, epigenetic mechanisms have been postulated as an appropriate molecular substrate for enduring changes of animal's behavior, including learning and memory. Therefore, unveiling the interplay between these mechanisms and neuroplasticity will provide fundamental insight into brain function. 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 this process. We are also interested in determining the role of the covalent modifications of the chromatin in neuroplasticity. In these projects we prefer to use genome-wide approaches instead of single-gene studies. With these experiments, we 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 and Claes-Jensen X-linked intellectual disability caused by mutations in the gene encoding the lysine demethylases KDM5C. Towards this end, we generate and characterize cellular and mouse models for these conditions, explore the molecular causes of the disease using the novel epigenome analysis techniques, and tackle new therapies.



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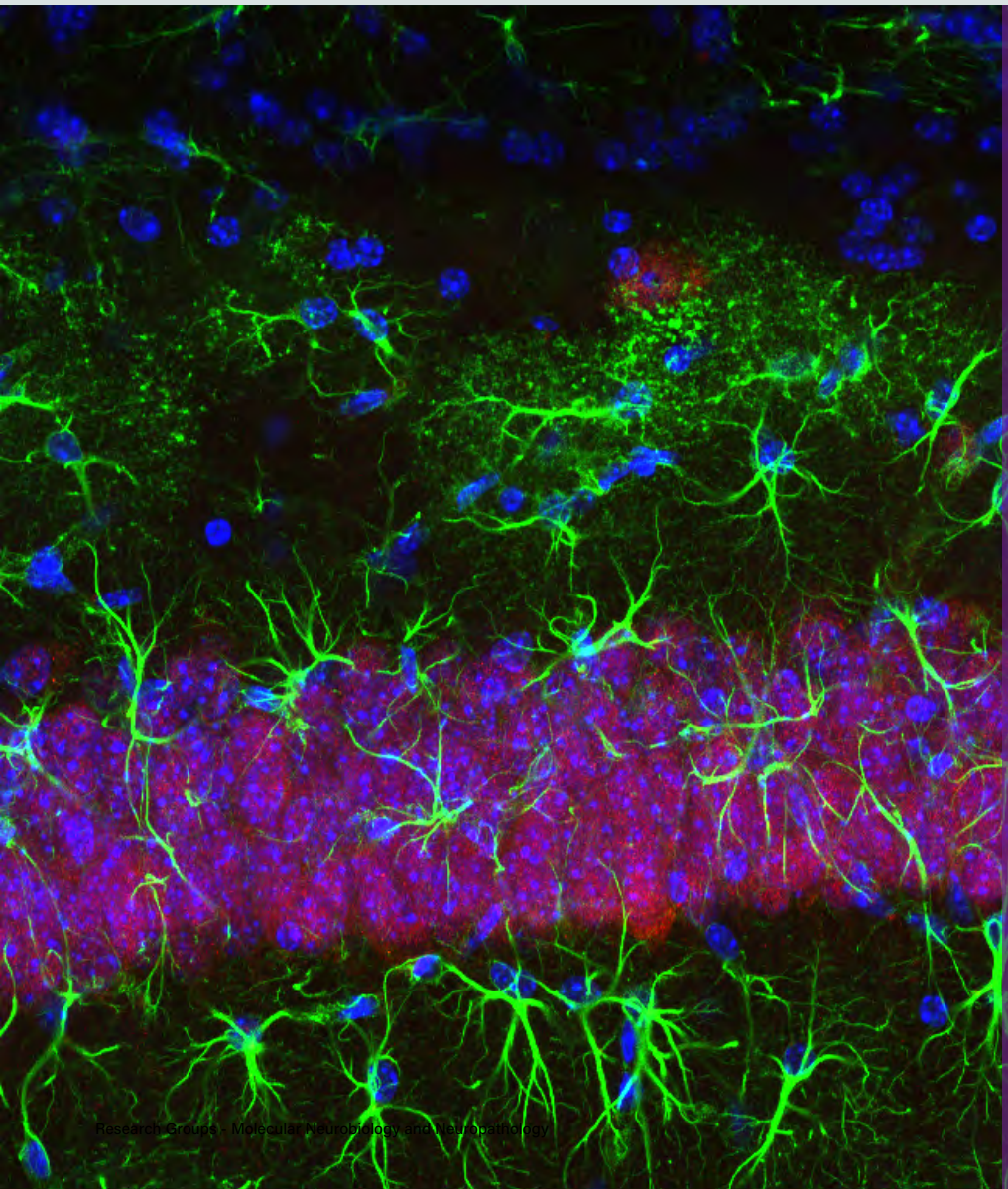

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Molecular control of axonal myelination

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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 squid) decreases 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. Recently it has been established that the decision whether or not an axon is “myelinated” as well as the thickness of the myelin sheath depends on the axonal levels of a particular type of protein of the family of “neuregulins”.

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 or Canavan disease 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 us Next-Generation Sequencing of patient’s DNA and genetic modification of mice using both conventional and the CRISPR/CAS9 technology.

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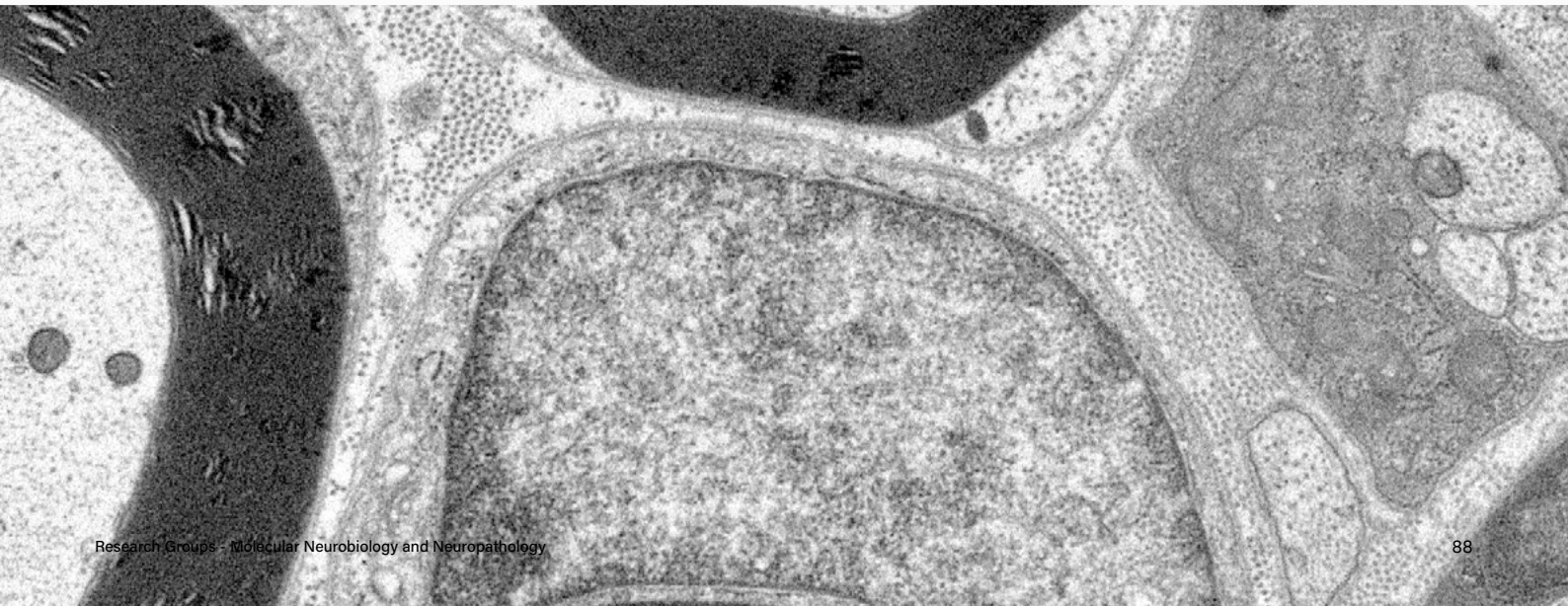

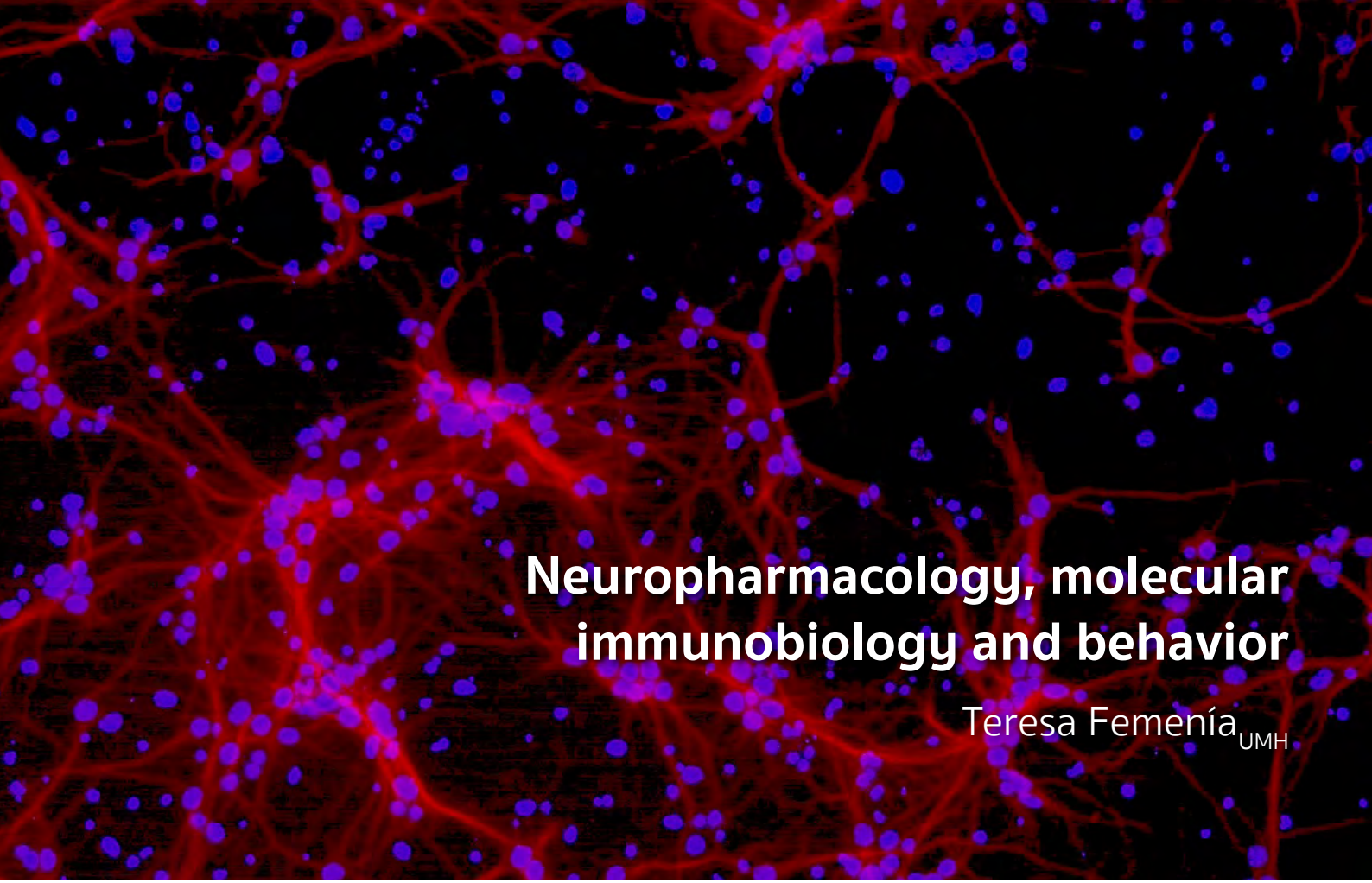

Neuropharmacology, molecular immunobiology and behavior

Teresa Femenía UMH

Our recently established 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 and 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.

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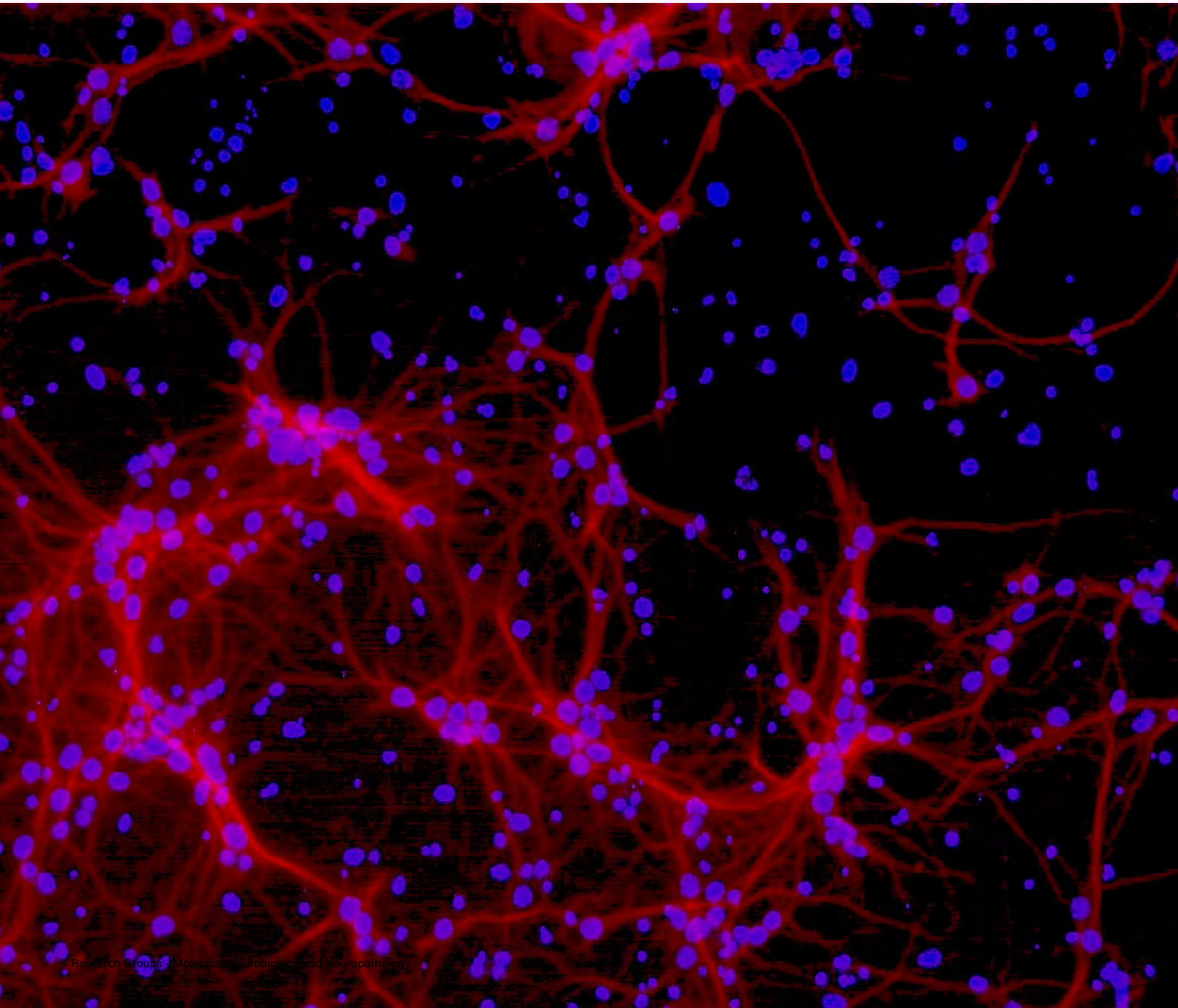

Molecular mechanisms of neurosecretion

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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 recently, the line of research on the role of nicotinic receptors in the neurosecretory systems coordinated by Dr. Criado.

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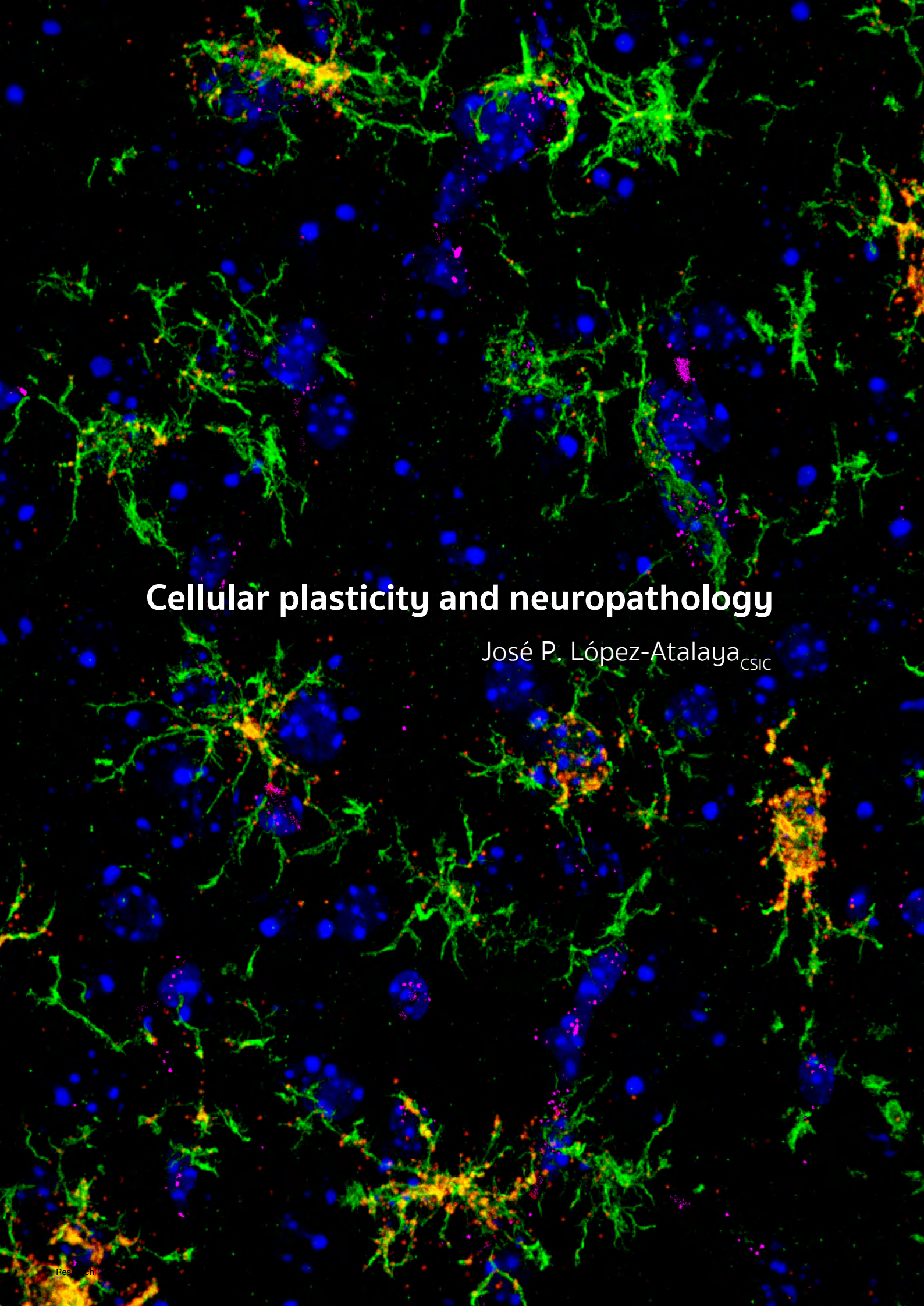


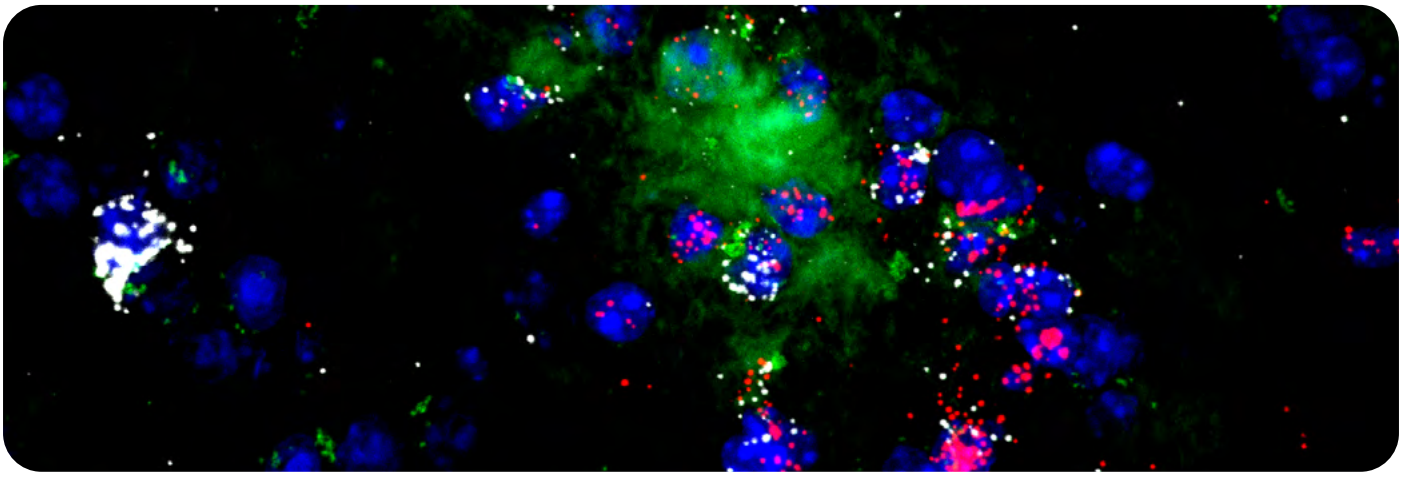
Cellular plasticity and neuropathology

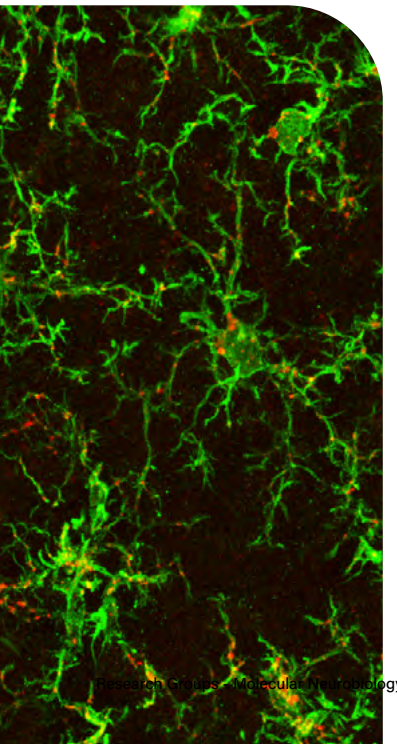
José P. López-Atalaya$_{CSIC}$

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.





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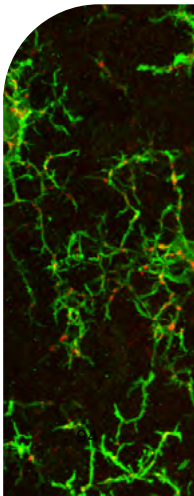

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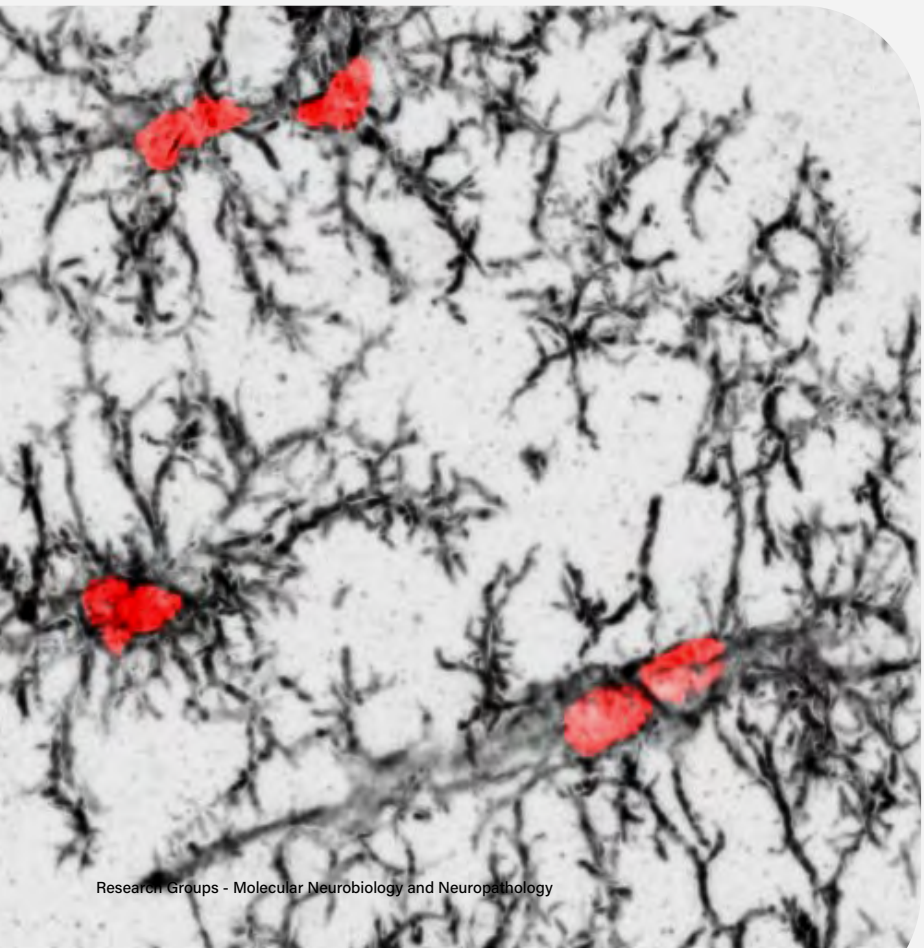

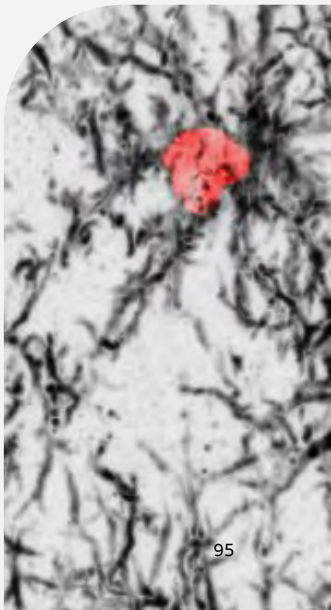

Translational neuropsychopharmacology of neurological and psychiatric diseases

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Research lines of our laboratory are focused on the identification of genes and proteins implicated in the occurrence and development of psychiatric (anxiety, depression, substance use, post-traumatic stress, etc.) and neurological (Parkinson´s disease, Alzheimer´s disease, etc.) disorders, which can be relevant for the discovery of new therapeutic targets to improve its pharmacological management.

For that purpose, we employ validated animal models of the psychiatric and neurological disorders that we want to study. These animal models must be able to reproduce, at least in part, certain behavioural traits and/or neurobiological features of the illnesses that they are simulating. Thus, the objective is to enhance the translational capacity of animal modelization that allows for applying the results to the patient.

The improvement of our knowledge about the alterations implicated in the aetiology and the development of different psychiatric and neurological disorders is one of our main goals, closely related with the discovery of more effective and safer pharmacological approaches. In the last years, we are focused on the role of the endocannabinoid system in the regulation of different brain functions and its potential pharmacotherapeutic exploitation. To this aim, we are very interested in the behavioural and neurochemical effects of genetic or pharmacological manipulation of the endocannabinoid system, employing transgenic animal models or cannabinoid compounds, respectively.

In our studies, we design and perform experiments to evaluate behavioral features related with emotional (anxiety, depression, stress, etc.) and cognitive (prepulse inhibition, memory impairment, etc.) alterations, and with the reinforcing and motivational effects of drugs of abuse (alcohol, cocaine, etc.). Furthermore, to evaluate the neurochemical changes that could be related with avv, we analyse gene expression of key targets by real time PCR or in situ hybridization experiments, as well as protein expression by immunohistochemistry or Western Blot techniques.

Laboratory members have a long-lasting and continuous relationship with several groups of psychiatrists and neurologists. This fact has significantly contributed to establish a reciprocal bridge of information between preclinical and clinical research, which has been reflected in several joint publications. Our objective is to maintain and to strengthen this type of collaborative strategies aimed to encourage translational research and finally improve the quality of life of psychiatric and neurological patients.

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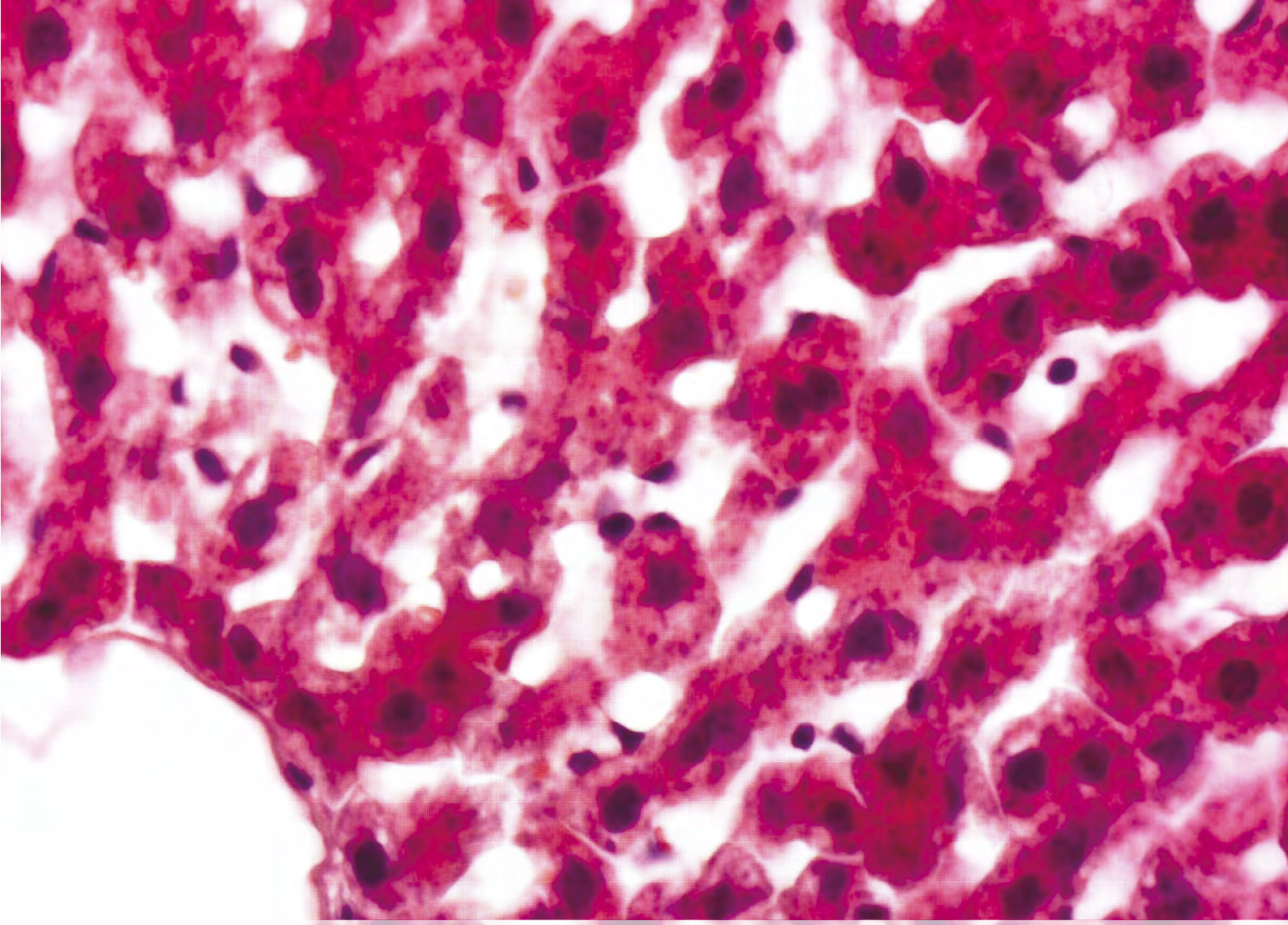

Altered molecular mechanism in Alzheimer's disease & dementia

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Our research line at the IN is focus in Alzheimer's disease (AD), but with interest also in other neurodegenerative disorder. The translational benefits of our research lie in the fact that we not only aim to clarify the pathological mechanisms behind these diseases, but also to define potential diagnostic tools and/or processes with therapeutic relevance. Our group is also member of CIBERNED (an ISC-III Center for Networked Biomedical Research focused in neurodegenerative diseases).

In recent years, we have been involved in studying how β-amyloid influences the expression of acetylcholinesterase (AChE, a key enzyme of the cholinergic system). In addition, we have described for the first time a direct association between presenilin 1 (PS1, a key enzyme in the proteolytic processing of amyloid protein precursor) and AChE, which may be relevant for the pathological progress of dementia and the design of therapeutic strategies.

We are pioneers in describing an altered expression and glycosylation patterns of the glycoprotein Reelin in AD. Reelin is a signaling protein that modulates synaptic function and plasticity in the mature brain, thereby favouring memory formation. Our effort is to demonstrate a novel mechanism by which β-amyloid regulates Reelin expression, thereby influencing its signaling cascade that ultimately controls tau phosphorylation.

Furthermore, we evaluate the diagnostic potential and methodological approaches for analysis of particular glycoforms of proteins, which improve sensitivity and specificity of the biomarkers. We also develop assays to identify secretase-related proteins, related with β-amyloid metabolism, in the cerebrospinal fluid. We also collaborate in the BiomarkADPD project (a JPND initiative of the UE) and the Society for CSF analysis and clinical neurochemistry in the validation and standardization of CSF biomarkers. We have recently initiated a research line focused in the study of the SARS-CoV-2 receptor in human cells, the ACE2 protein, as a read-out of the infection and prognostic biomarker.

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Functional epi-genomics of aging and Alzheimer's disease

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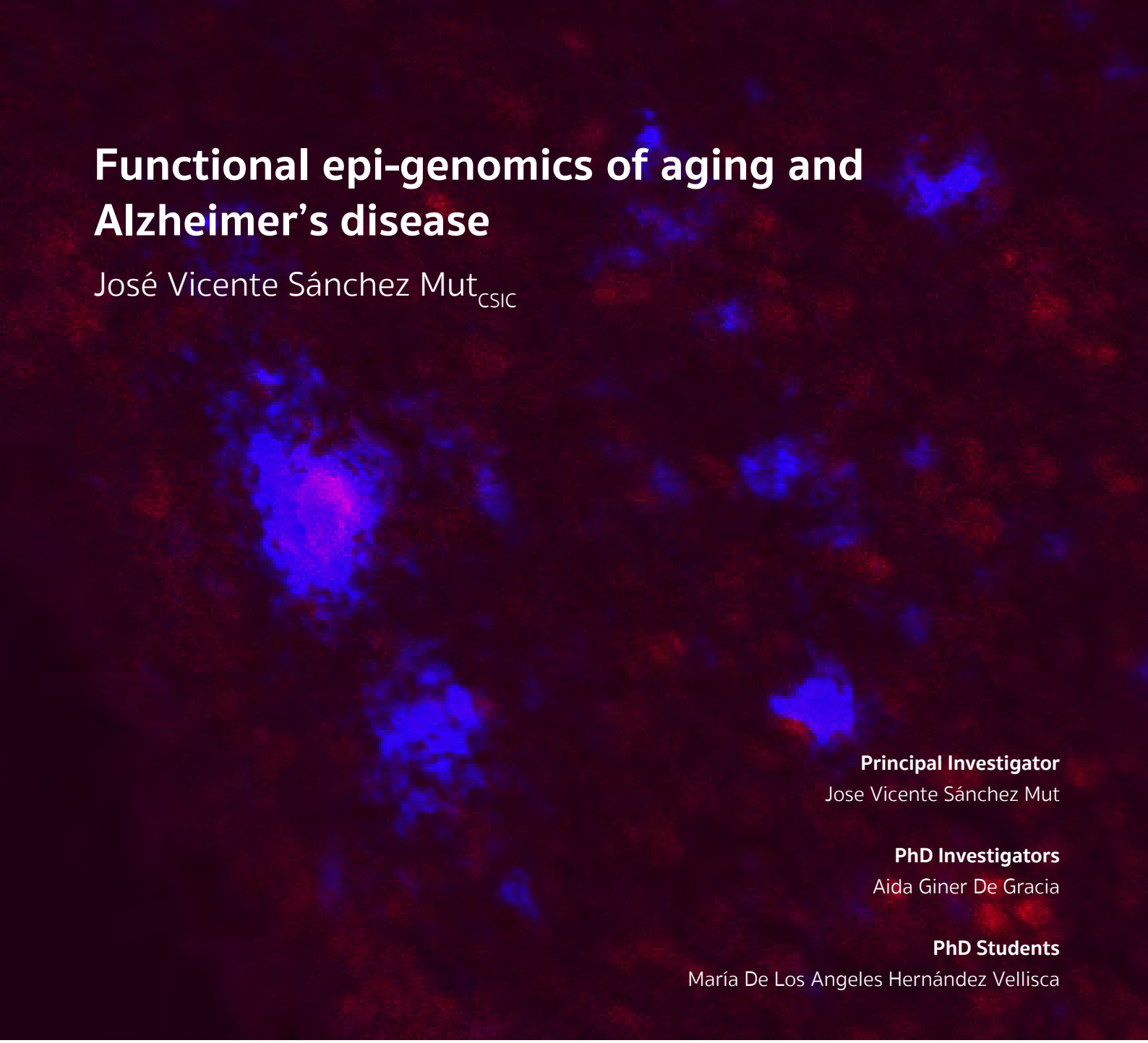

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PhD Investigators
Aida Giner De Gracia

PhD Students
María De Los Angeles Hernández Vellisca

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.

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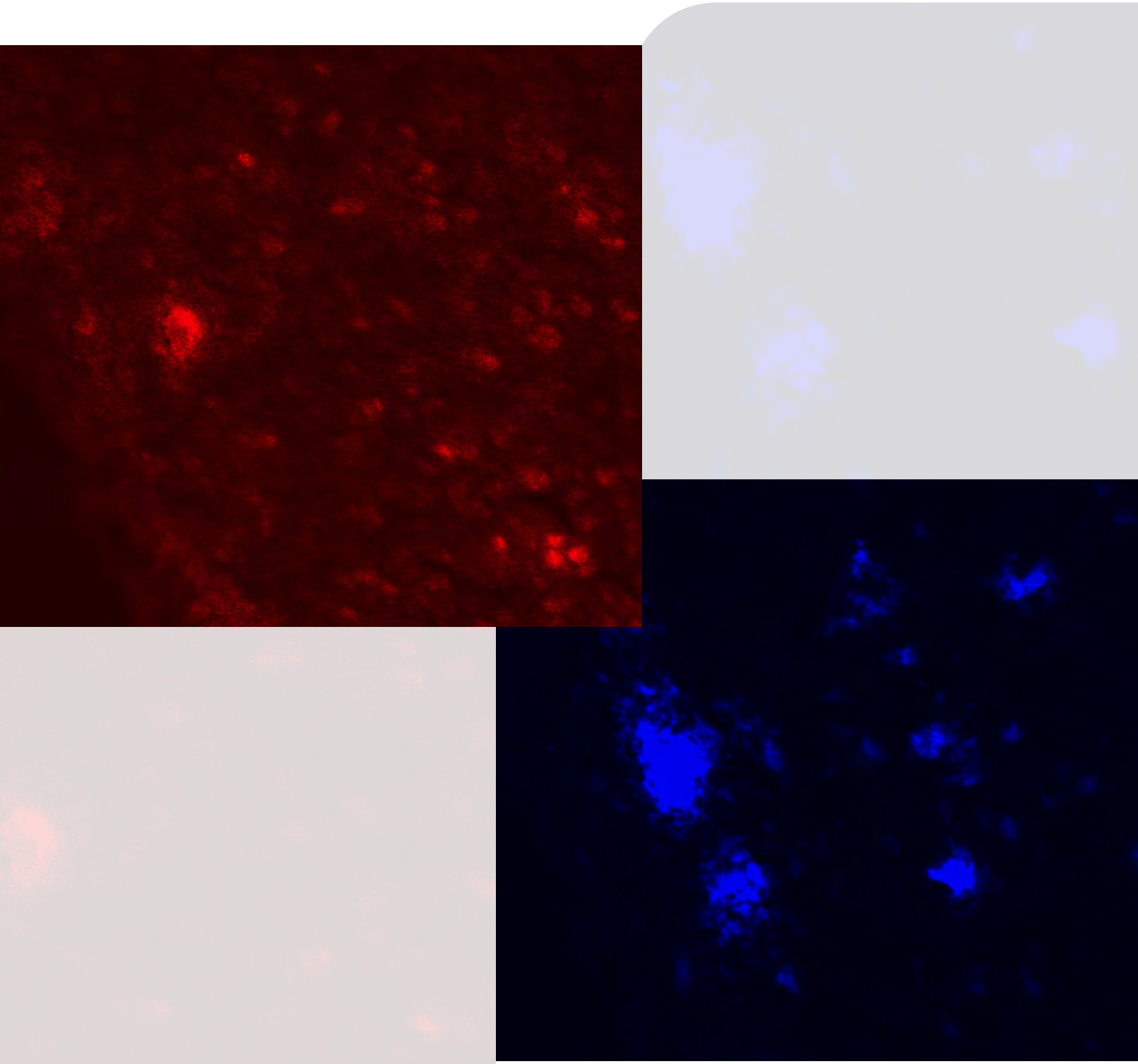

Servicies & Facilities, including Administration & Service Staff

M. Fuentes Ramos

Imaging Facility

The Instituto de Neurociencias (IN) Imaging Facility is a platform for microscopy and image 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 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.

Staff

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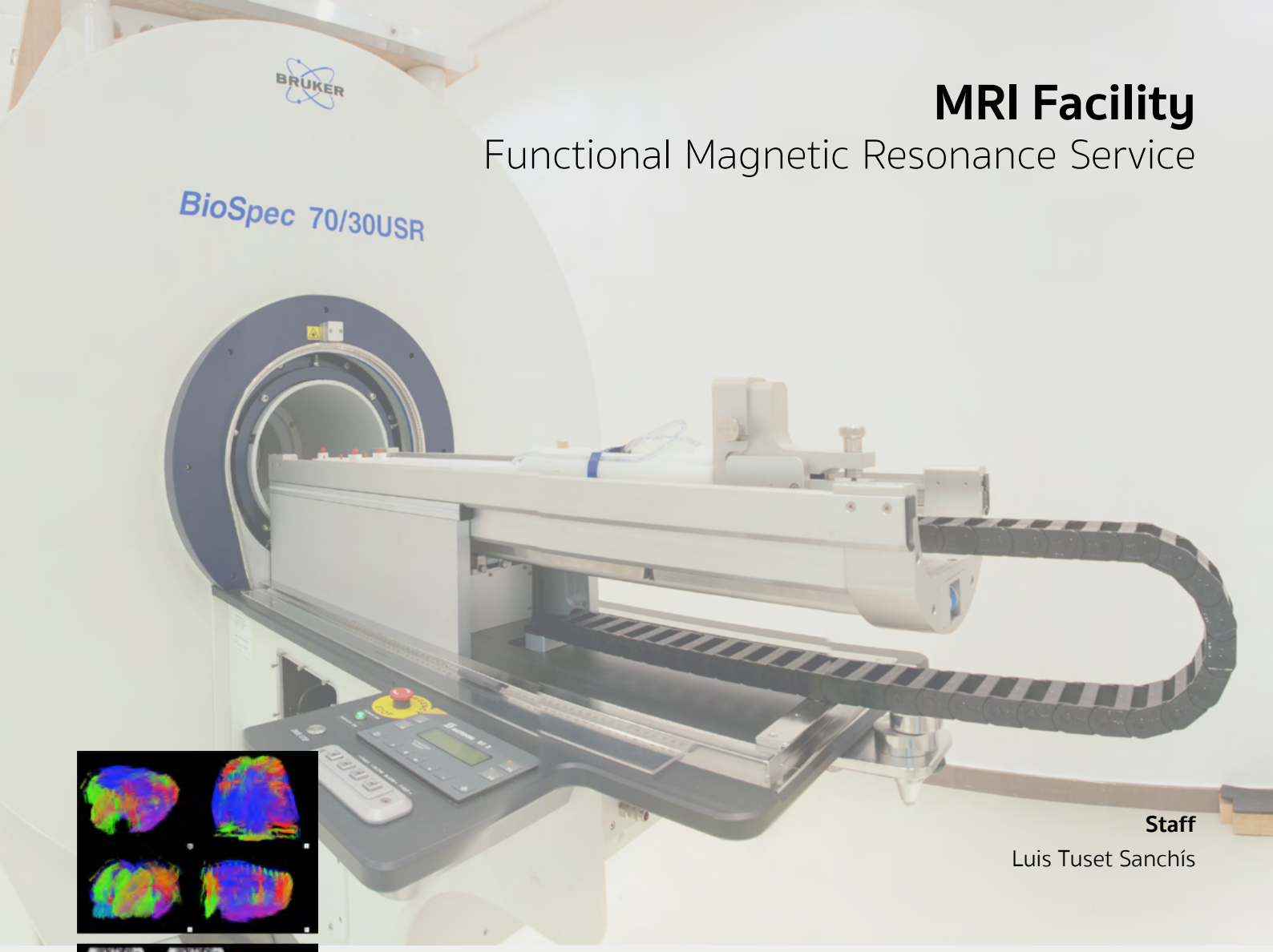
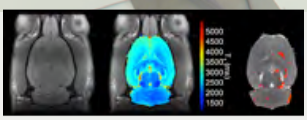
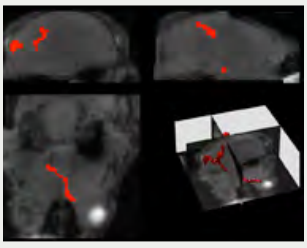
Verona Villar Cerviño

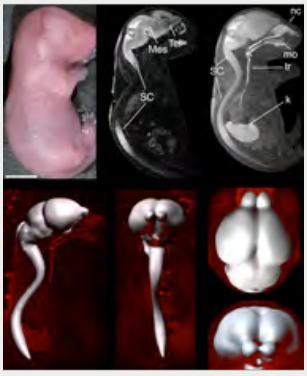
MRI Facility

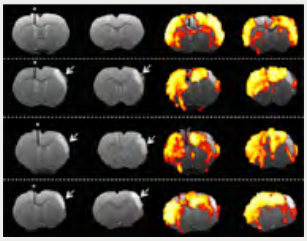
Functional Magnetic Resonance Service











Staff

Luis Tuset Sanchís

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.

Animal Housing Facility

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.

3F Facility (Fish, Frog & Fly)

The IN also has core facilities for Zebrafish, Xenopus frogs and Drosophila.

Animal Research Facility

Behavioural Phenotyping Facility

The SPF animal house also hosts a facility (8 rooms) with state-of-the-art equipment for behavioural analysis of small rodents, including different types of arenas and mazes, a Morris water maze, fear and operant conditioning boxes, 24-h monitoring equipment, etc.

Wieland Brendel

Veterinary Staff

Tomás García Robles
Gonzalo Moreno del Val

Animal House

Mª Carmen Checa Lara
Jénifer Gómez Gabaldón
Verónica Jiménez Villar
Estefanía López Ronda
Ana Lorena Marín Sánchez
Erika Moyano Soler
Patricia Muñoz Robledano
Mª Carmen Navarro García
Rebeca Ortiz Méndez
Raúl Pardo Mérida
Mª Ángeles Soler Ripoll

Drosophila Service

Laura Mira Valdelvira
Irene Oliveira Ávalos

Zebrafish Facility

Cristina Minaya Ramírez
Alba Olmos Franco

Genotyping

Mª Trinidad Gil García
Eva Mª Sabater Sánchez

Omics Facility

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, dis-aggregated living tissues, cell cultures and cellular organelles can be analyzed.

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

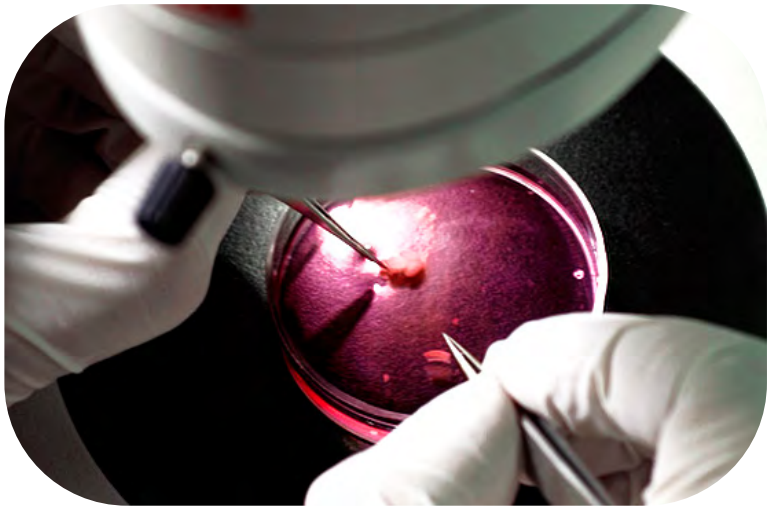
Staff

Antonio Javier Caler Escribano

Cell Culture Facilities

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.



Staff
Sara Carratalá Gosálbez
Rosa García Velasco

SHARE Service

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.

Staff
Víctor Javier Rodríguez Milán

SHARE
Scientific Hardware & Electronics Service

Administration & Service Staff

Manager
Mª Teresa García Hedo

Administration
Mª Jesús Arencibia Rojas
Helena Campos Martín
Mª Auxiliadora Casanova Javaloyes
Alicia Ferri Coballes
Virtudes García Hernández
Eva García Raigal
Ana María López Martínez
Sonia Martín Rodríguez
Virtudes Monasor Gómez
Isabel Ortega Castillo
Javier Paniagua Paniagua
Isabel Romero García
Ruth Rubio Sánchez
José Sánchez Ardila
Rosa Mª Sánchez Cayuela
Mª José Soria Pedrera
Beatriz Yunta Arce

Maintenance
Jesús Campos Roldán

Computing
Mª Isabel Sánchez Febrero

Radioactivity Control
Emilio Gutiérrez Flores

Audiovisual, Photography and Illustration
Sergio Javaloy Ballestero

Glassware & Autoclaving
Trinidad Guillén Carrillo

D. Echevarría Aza

Research Highlights 2019/20

Piezo2 Mediates Low-Threshold Mechanically Evoked Pain in the Cornea.

Fernández-Trillo et al. **The Journal of Neuroscience 2020**
URL: http://in.umh-csic.es/destacada102.aspx

A Zic2-regulated switch in a noncanonical Wnt/Beta-catenin pathway is essential for the formation of bilateral circuits.

Morenilla-Palao et al. **Science Advances 2020**
URL: http://in.umh-csic.es/destacada101.aspx

Repression of Irs2 by let7 miRNAs is essential for homeostasis of the telencephalic neuroepithelium.

Fernández et al. **EMBO J 2020**
URL: http://in.umh-csic.es/destacada100.aspx

Different theta frameworks coexist in the rat hippocampus and are coordinated during memory-guided and novelty tasks.

López-Madrona et al. **eLife 2020**
URL: http://in.umh-csic.es/destacada99.aspx

Chronic alcohol consumption alters extracellular space geometry and transmitter diffusion in the brain.

De Santis et al. **Science Advances 2020**
URL: http://in.umh-csic.es/destacada98.aspx

KAT3-dependent acetylation maintains neuronal identity in the adult mouse brain.

Lipinski et al. **Nature Communications 2020**
URL: http://in.umh-csic.es/destacada97.aspx

A gene regulatory network to control EMT programs in development and disease.

Fazilaty et al. **Nature Communications 2019**
URL: http://in.umh-csic.es/destacada96.aspx

Unbalanced dendritic inhibition of CA1 neurons drives spatial-memory deficits in the Ts2Cje Down syndrome model.

Valbuena et al. **Nature Communications 2019**
URL: http://in.umh-csic.es/destacada95.aspx

MicroRNAs Establish the Right-Handed Dominance of the Heart Laterality Pathway in Vertebrates.

Rago et al. **Developmental Cell 2019**
URL: http://in.umh-csic.es/destacada94.aspx

Immediate and deferred epigenomic signatures of in vivo neuronal activation in mouse hippocampus.

Fernandez-Albert J et al. **Nat Neurosci 2019**
URL: http://in.umh-csic.es/destacada93.aspx

Research Highlights 2019/20

The evolutionary history of Ephs and ephrins: toward multicellular organisms.

Arcas et al. **Molecular Biology and Evolution 2019**
URL: http://in.umh-csic.es/destacada93b.aspx

Elevated synaptic vesicle release probability in synaptophysin/gyrin family quadruple knockouts.

Raja MK et al. **eLife. 2019**
URL: http://in.umh-csic.es/destacada91.aspx

Ecdysone-Induced 3D Chromatin Reorganization Involves Active Enhancers Bound by Pipsqueak and Polycomb.

Gutierrez-Perez et al. **Cell Reports 2019**
URL: http://in.umh-csic.es/destacada92.aspx

Prenatal activity from thalamic neurons governs the emergence of functional cortical maps in mice.

Antón-Bolaños et al. **Science 2019**
URL: http://in.umh-csic.es/destacada90.aspx

Microstructural White Matter Alterations in Men With Alcohol Use Disorder and Rats With Excessive Alcohol Consumption During Early Abstinence.

De Santis S et al. **JAMA Psychiatry 2019**
URL: http://in.umh-csic.es/destacada89.aspx

A Retino-retinal Projection Guided by Unc5c Emerged in Species with Retinal Waves.

Murcia-Belmonte et al. **Current Biology 2019**
URL: http://in.umh-csic.es/destacada88.aspx

CBP and SRF co-regulate dendritic growth and synaptic maturation.

Blanco et al. **Cell Death & Diff. 2019**
URL: http://in.umh-csic.es/destacada87.aspx

Eph signaling controls mitotic spindle orientation and cell proliferation in neuroepithelial cells.

Franco M., Carmena A. **J Cell Biol. 2019**
URL: http://in.umh-csic.es/destacada86.aspx

The Immunosuppressant Macrolide Tacrolimus Activates Cold-Sensing TRPM8 Channels.

Arcas et al. **J Neurosci. 2019**
URL: http://in.umh-csic.es/destacada85.aspx

Scientific Meetings

IN Seminar Program

The IN runs a very successful international seminar program. Dozens of prominent scientists from all over the world visit our institute and interact with our researchers during 1 or 2 days.

Scientific Meetings

The IN researchers are very active in the organization of scientific meetings. As a result of this activity Alicante has become an essential European hub for activities in the field of neurosciences. Hundreds of PhD students, postdoctoral researchers and group leaders from all over the world visited our institute and/or the city of Alicante to participate in these events. The most prominent meetings, conferences and workshops organized in 2019 and 2020 were:

- **20th Aniversary of Instituto de Neurociencias**

Commemorative 2-day long meeting with the participation of 15 prestigious international researchers.

- **European Developmental Biology Congress**

International congress supported by the main Developmental Biology Societies in Europe that gathered hundreds of experts in this field.

- **3rd Edition of the AXON meeting on Circuits Development and Regeneration**

International meeting that gathers world leaders and promising young researchers in the field of Circuits Development and Regeneration.

- **Neuroscience meets 3D Genome Biology**

Workshop that combined talks by leaders in the field of genome biology and 3D chromatin architecture with a hands-on training mini-course on Single Cell ATAC-seq .

- **XVI & XVII Christmas Meetings**

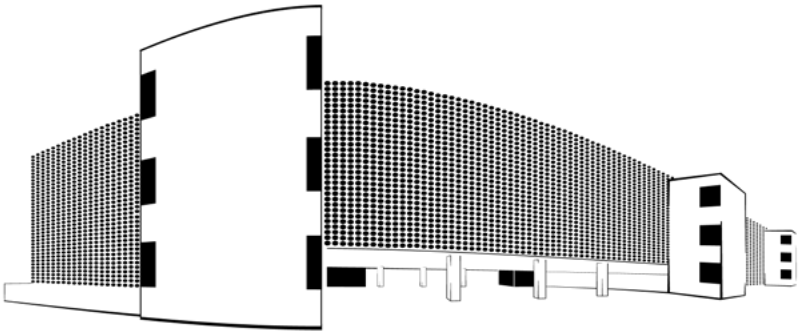
Annual meetings organized by the IN every year in which young researchers working abroad interested in knowing, and possible joining, the IN get to know our staff and facilities. During the meeting there is a poster session in which young IN researchers present the investigations carried out in the current year.

See Annex for complete list.

Master & PhD Program

Master in Neurosciencies: from the bench to the bedside.

Official Master of the UMH



The International Master in Neurosciences: from the bench to the bedside organized to be the first step of a career in Neuroscience research for those graduate students with a particular interest in this field. The Master is open to graduates in biology, biochemistry, medicine, psychology, biotechnology, veterinary medicine or other related degrees, as well as graduates in fields not directly related to biology (such as physics, mathematics and computers) interested in Neuroscience. The number of places in the Master is limited to only 20 applicants that are selected based on their academic record and their previous experience in laboratories. The Master is taught in English and covers one academic year (60 ECTS credits). It qualifies for the Access to doctorate programs, both the Doctorate program in Neurosciences of the Institute and other programs in other Universities.

Internationalization

The "Severo Ochoa" Program of the IN provides 5 grants for foreign Master students. The support of the Carolina Foundation further supports the incorporation of international student from South and Central America. In addition, the Master in Neurosciences is part of the **Network of European Neuroscience Schools** (NENS) and a student exchange program has been set up with the Pasteur Institute in Paris.

The following subjects are covered:

Mandatory subjects:

- Advances in genetic analysis and embriology in animal models for the study of the nervous system (6 ECTS)
- Organization and cellular components of the nervous system (6 ECTS).
- Advances in neuronal communication: from the cellular level to the whole animal (6 ECTS)
- Processing of informations in the central nervous system: synaptic transmission, plasticity and sensory processing (6 ECTS).
- Animal facilities and tools in neuroscience (3 ECTS).
- Functional imaging analysis (3 ECTS).
- Neuropathology (3 ECTS).
- New therapies (3 ECTS).
- Neuroscience today (4,5 ECTS).

Optative subjects (the student must choose one):

- Developmental biology: from neurogenesis to circuit formation (4,5 ECTS).
- From ionic channels to sensory processing: a functional approach. (4,5 ECTS).

Master Research Project:

- Original laboratory research work (15 ECTS).

Master & PhD Program

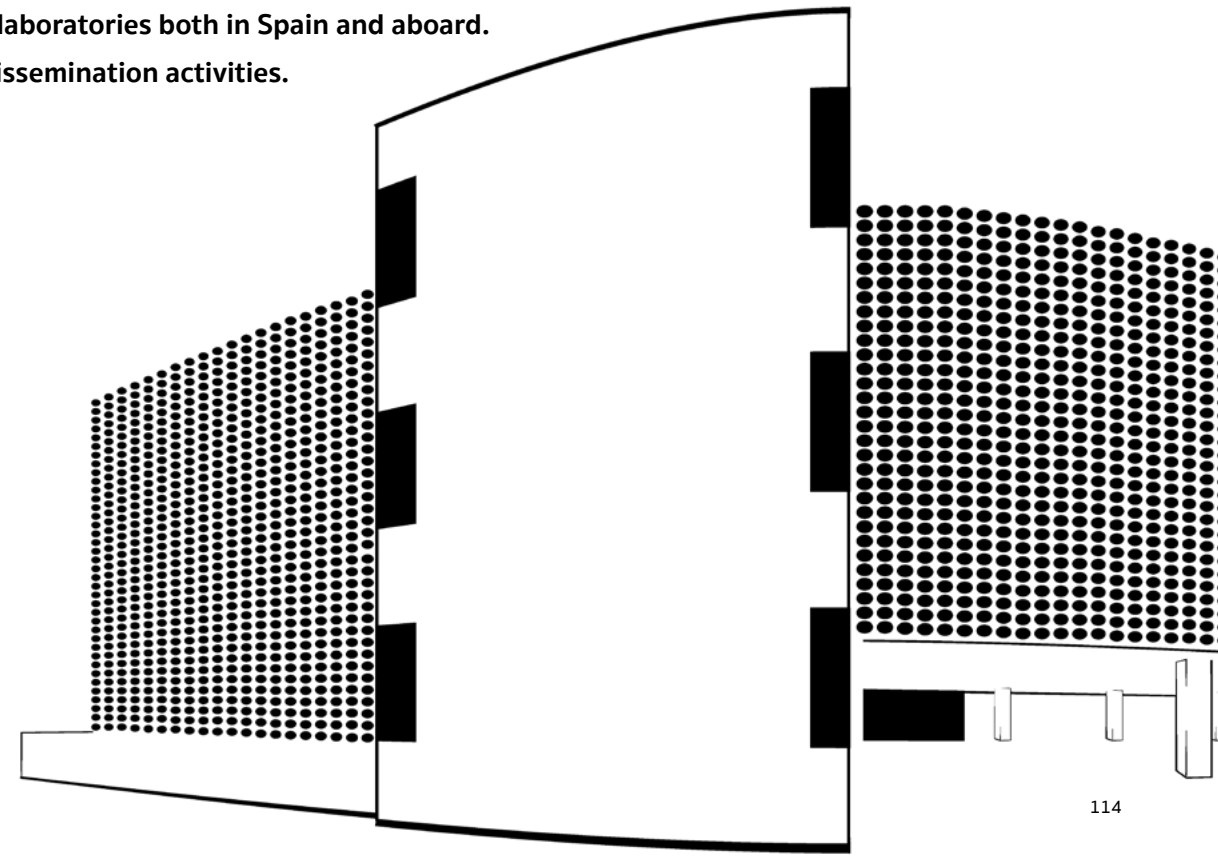
PhD program (RD 99/2011)

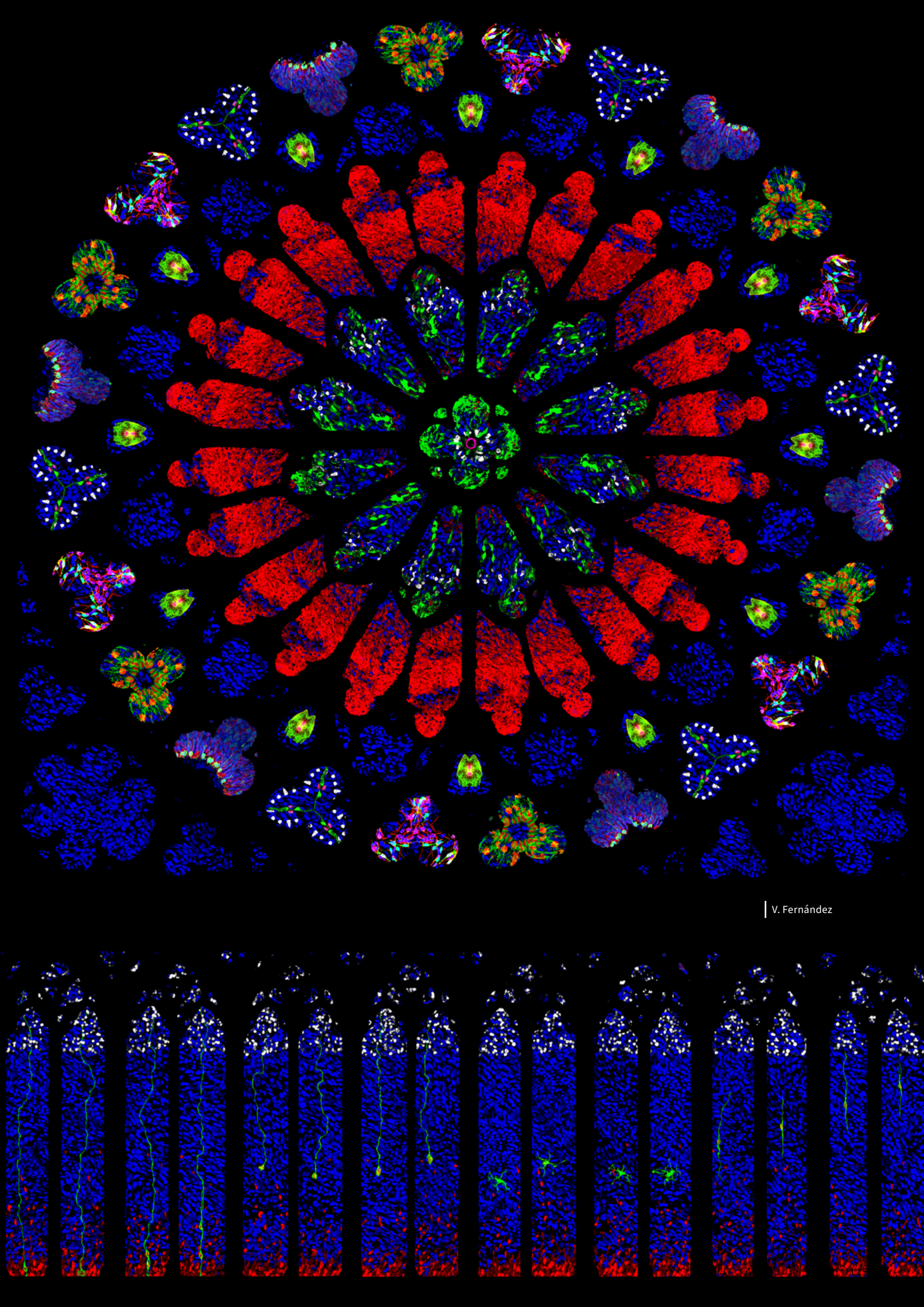
The program is designed to stimulate the initiative and abilities of the students, helping to orient the development of their scientific careers. The PhD program in Neurosciences has been always a vehicle for the internationalization of the Institute in which a mean of 30% of the students come from abroad.

The PhD in Neuroscience welcomes graduates in biology, biochemistry, medicine, psychology, biotechnology, veterinary medicine, as well as students from non-biology fields (like physics, maths and computer science) interested in neuroscience. Students with a degree within the European Higher Education Area with a minimum of 300 ECTS are eligible. Typically, students have 60 ECTS Master Degree, preferably in Neuroscience. The university degree should qualify for the start of a PhD thesis in the student's home country. Non-European university degrees should be equivalent to a European MSc. According to the current law, students require a total of 300 ECTS credits to be admitted. It is also necessary to have a letter from the thesis supervisor accepting the direction of the thesis. On average 20 new PhDs are admitted yearly.

The program offers a variety of Training activities like:

- **Research seminars at the Institute of Neuroscience.**
- **Presentation and discussion of the thesis project.**
- **Participation in Institutional Scientific Activities.**
- **Participation in national and international conferences.**
- **Participation in neuroscience courses.**
- **Stays in external laboratories both in Spain and aboard.**
- **Participation in dissemination activities.**





V. Fernández

Innovation

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 include the development of biomarkers for Alzheimer's disease, treatments to improve eye comfort, new drug delivery vectors for the treatment of glioblastomas, and the use of AI to improve the definition of treatments in parkinsonism, the phases of disease or mood and loneliness in the elderly.

Staff

José Manuel del Río
Virtudes García Hernández
Andrés Giner Antón
Silvia Ortín González

Outreach Activities

Brain Awareness Week 2019 - Open Days

Dates: March 11-19, 2019
Coordinator: Diego Echevarria

The conference began with a conference at the Alicante "Club Información" within the cycle "Brain and Society" with the debate "**Transfer of scientific results to solve society's problems."** This colloquium was moderated by Professor Salvador Martínez, director of the Instituto de Neurociencias and had the participation of Mr. Andrés García Reche, Executive Vice President AVI and Prof. Pablo Artal, Prof. of the University of Murcia.

During the open days, 2,900 people, aged between 5 and 90 years old, came from 66 institutions, including IES, schools, special assistance centers and centers for the elderly.

There was a great collaboration of the staff of the Neurosciences Institute (65%) in the development of the activities.

20 informative talks were given in the format of mini-talks in which researchers and specialists from the Institute of Neurosciences explain the research, methods and animal models used to carry out their studies.

Exhibition by Dr. Luis Miguel Gutiérrez

Date: November 7, 2019 to January 31, 2020.
Place: Museo Nacional de Ciencias Naturales

The professor of Biochemistry and Molecular Biology at the Miguel Hernández University (UMH) of Elche, Luis Miguel Gutiérrez, exhibited his work **"From the Universe to the Brain: Macro and Microcosmos"**. at the National Museum of Natural Sciences (MNCN) in Madrid.

Brain Awareness Week 2020 - Open days

Dates: March 9-13, 2020
Coordinator: Diego Echevarria

Brain Week 2020 (March 9-13) had a very reduced celebration due to the pandemic situation produced by COVI-19 and that following the recommendation of the Health Authorities it was decided to suspend, on Wednesday, March 11, the World Brain Week activities including Open Days.

Among the activities that could be carried out is the inauguration of the Brain Week with the Brain and Society Cycle at the Club Information, (Avenida Doctor Rico, 17, 03005 Alicante), with the assistance of the Vice-Rector for Research, Domingo Orozco, with the

round table: "**The COVID-19 coronavirus epidemic and our fears"** moderated by Salvador Martínez Pérez, professor of Human Anatomy and director of the Instituto de Neurociencias and with the participation of the speaker Prof. Rafael Tabarés Seisdedos (Professor of Psychiatry at the University de Valencia) and Prof. Ildefonso Hernández Aguado (Professor of Public Health. Miguel Hernández University of Elche).

The Open Days were held in the **Francisco Javier Balmis** building and the talks were planned to be held in the Assembly Hall of the Severo Ochoa building to accommodate as many visitors as possible.

Stay of 3 winning students of the XXXI Young Researchers Contest

Date: September 10-24, 2020

Three winning students of the XXXI Young Researchers Contest spent a 5-day stay at the IN, in the Experimental Embryology laboratory.

Visit of students from the ESTALMAT program

Date: February 22, 2020

50 young students from the **Estalmat** project (Stimulus for Mathematical Talent) visited the IN. The project is organized by the Royal Academy of Exact, Physical and Natural Sciences and has the support and funding of the CSIC and the Spanish Foundation for Science and Technology (FECyT). The young people were received by Víctor Borrell with a presentation talk about the Neurosciences Institute and later they were divided into groups to visit the Imaging, Omic and NMR services and to finish Dr. Diego Echevarría gave a talk about the Human Brain.

Press Cutting

The Instituto de Neurociencias UMH-CSIC appeared **607 times in the media** in 2019, and **546 times** in 2020. The lockdown caused by the pandemic reduced the impact on the media compared to 2019.

[Access the full report on media impacts 2019]

[Access the full report on media impacts 2020]

Meet us at the Social Networks

@NeuroAlc

1,7k Followers

+ 4k People reached

Collaborations & Alliances

There are regular collaborations between IN researchers and scientists of the most prestigious biomedical research institutions. Just to mention some of the most consolidated, we collaborate with: the Institute Pasteur and the École Normale Supérieure (París), the Institut de Génomique Fonctionelle (Montpellier), the Max-Planck-Institut für Neurobiologie (Munich), the Max-Planck-Institut für Immunbiologie und Epigenetik (Freiburg), the Helmholtz Zentrum (Munich), the Central Institute of Mental Health (Mannheim), the University of Heidelberg, the University of Mainz, the Laboratory of Ion Channel research (Leuven), the MRC Developmental NeurobiolVogy Unit (Mill Hill), the University of Edinburgh, the Harvard University (Boston), the Columbia University (New York), the Salk Institute (La Jolla), the University of Buenos Aires, and the University of Hong Kong.

The participation of the IN researchers is fostered in European Networks of Excellence, Integrated Projects and International Training Networks (ITNs) as well as in high-throughput technological platforms, to facilitate mobility with partner labs. The "Remedios Caro Almela" prize, supported by private funds, is awarded by the IN (http://in.umh.es/remedios-caro-almela.aspx). This prominent and well-regarded international prize has been consistently sought by leading Europe-based neuroscientists, has reliably identified some of the very top leaders in European developmental neuroscience, and has succeeded in bringing attention to the Institute.

The IN has established collaborations with public and private institutions such as:

- Agencia Valenciana de Innovación (AVI-GVA)
- Hospital de San Juan. Activities of formation and scientific training. Consejería de Salud de la Comunidad Valenciana.
- Cátedra de Investigación en Medicina y Neurociencias (Elche-Crevillente Salud S.A.)
- Asociación Española Contra el Cáncer
- Universidad San Pablo CEU
- Universidad Católica de Murcia (UCAM)
- Universidad Cardenal Herrera CEU

The international character of our teaching program is fundamental to expand our presence in the first stages of training of researchers, and compete for the best students. That is why we have organized the International Master in Neuroscience in collaboration with the Institut Pasteur and the University Paris VI.

SOMMa and “Severo Ochoa” acreditation of Excellence

The IN, a Severo Ochoa Center of Excellence

The Institute of Neurosciences renewed its accreditation as a Severo Ochoa Center of Excellence in 2018, which was first awarded in 2014. This accreditation seeks to boost Spanish science by recognizing cutting-edge research centers, and by further supporting them to enhance their impact, international scientific leadership, and competitiveness. Successful proponents hold the Excellence award for a period of 5 years and receive an additional budget of 1 million Euros per year during the four first years. Currently, 28 centers hold the ‘Severo Ochoa’ Centers of Excellence accreditation. In addition, 22 units hold the ‘María de Maeztu’ Units of Excellence accreditation aimed to smaller institutions. They cover a wide breadth of scientific disciplines, from life sciences and medicine, mathematics, chemistry, physics, engineering, to humanities and social sciences.

Together, this 50 centers and units constitute **SOMMa: The “Severo Ochoa” Centres and “María de Maeztu” Units of Excellence Alliance**. Such initiative aims to strengthen excellence at institutional- and unit-level to originate and maintain stimulating, creative, and cutting-edge environments. The ultimate goal of this scientific ecosystem is to attract and nurture scientific talent and promote ground-breaking research, following principles of excellence, integrity, external peer-review, competitiveness, and international cooperation.

EXCELENCIA
SEVERO
OCHOA

Chair of Neurobiology

Remedios Caro Almela

Richard Morris & Constantino Sotelo

The **Chair "Prof. Remedios Caro Almela"** was established in 2000 as a tribute of Fernando Martínez Ramos to his wife, Dª. Remedios Caro Almela, a dedicated teacher and science lover. Fernando Martínez Ramos and his family launched the Chair in collaboration with the University Miguel Hernández (UMH) and the Institute of Neuroscience (IN) to support and promote the research in Neurosciences. During the last two decades the Chair has distinguished two outstanding European researchers with strong ties to Alicante and the IN. The Chair has contributed enormously to the visibility and promotion of the IN as a reference center in Neurosciences at the national and international levels through the sponsorship of various actions, such as the "Remedios Caro Almela" Prize for Research in Developmental Neurobiology, activities for dissemination of science and travel grants for students to attend international scientific meetings.

Professor Constantino Sotelo (2000-2012) Professor at the CNRS in France and Director of Unit 106 INSERM, Hospital de la Salpetriere, Paris.

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

Professor Richard Morris (2013-present) 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.

Remedios Caro Almela Prize

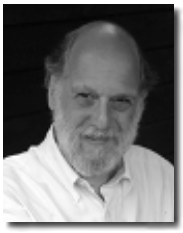
Dr. Óscar Marín, 2019

The jury of the "Remedios Caro Almela Prize" awarded the IX Prize to Professor Oscar Marín, Director of the Center for Studies on Developmental Disorders of the Nervous System at the King College London.

Prof. Marín was awarded for his work on the principles that govern the organization of cortical neuronal circuits. In particular, the mechanisms that control migration, the final acquisition of the neuronal phenotype and the connectivity of cortical interneurons. He has studied the balance between excitation and inhibition, a balance that during the critical period of development is crucial for the formation of those circuits responsible for cortical function. The breakdown of this dynamic balance leads to the appearance of functional abnormalities of the cerebral cortex. His work is essential to begin to understand the causes of some psychiatric disorders and, eventually, allow the development of a therapy that allows not only treating the symptoms but also treating the neurobiological causes of some mental disorders.

Prof. Marín obtained his doctorate in Neuroscience at the Universidad Complutense de Madrid, followed by a postdoctoral stay at the University of California, San Francisco. He was a CSIC research professor at the Institute of Neurosciences in Alicante before joining the King College in 2014. He was one of the founding members of the Scientific Council of the European Research Council, where he served from 2005 to 2010. Currently, he is a Welcome Trust researcher, second-time recipient of an ERC Advanced Grant and member of the Board of Reviewing Editors for Science magazine. Among other distinctions he has also received the EURYI European Young Researcher Award (2004), the Banco Sabadell Award for Biomedical Research (2008), the Rey Jaime I Award for Basic Research (2011), the FENS-EJN Award (2012) and the Roger de Spoelberch Prix (2014).

IN Scientific Advisory Board 2016-2020



Prof. Claudio Stern (Chair)
UCL Research Department of Cell and Developmental Biology
London, UK

Claudio Stern has been elected Fellow of the Royal Society, Academy of Medical Sciences, Academia Europaea, Institute of Biology and of the Latin-American Academy of Sciences and member of EMBO. In 2006 he was awarded the prestigious Waddington Medal from the British Society for Developmental Biology. He was also president of the International Society for Developmental Biology 2009-2013.

Prof. María Blasco
Spanish National Cancer Research Centre - CNIO
Madrid, ES

María Blasco joined the CNIO as Director of the Molecular Oncology Programme and Leader of the Telomeres and Telomerase Group. In 2005 she was also assigned as Vice-Director of Basic Research and in 2011 she was appointed as CNIO Director. She has received the Josef Steiner Cancer Research, Rey Jaime I, Körber European Science, Alberto Sols and Fundación Lilly Preclinical Research, Awards; the Spanish National "Santiago Ramón y Cajal" Research Award in Biology and the EMBO Gold Medal, and has served on its Council since 2008.

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

Michael Häusser has made fundamental contributions to our understanding of how the complex dendritic structures of nerve cells contribute to the functional computations that occur in the mammalian brain. He has achieved this by the introduction and exploitation of advanced techniques, coupled with careful quantitative analysis and modelling of the experimental results. He was also elected Fellow of the Academy of Medical Sciences in 2012, and Fellow of the Royal Society in 2015.

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

Magdalena Götz is the Director of the Institute for Stem Cell Research at the Helmholtz Center and Professor at the Ludwig-Maximilians-University in Munich, Germany. Her developmental work in neurogenesis has identified radial glial cells as the source of neurons in the developing brain. She was elected member of Academia Europaea (2006), EMBO (2006), and the Leopoldina Academy (2008), and external member of the Max-Planck-Society (2013).

Prof. Ranulfo Romo
Institute of Cellular Physiology, National Autonomous University of Mexico (UNAM)
México DF, MX

Ranulfo Romo has received the Demuth Prize in Neuroscience (1990), the National Prize in Sciences and Arts from the Mexican government (2000), the Prize in Basic Medical Sciences from the Academy of Sciences for the Developing World (2002), and the Ranwell Caputto prize from the Argentinean Society of Neuroscience (2009). He is a member of the Mexican Academy of Sciences, and a foreign associate of the U.S. National Academy of Sciences.

Other Activities

Project for the Expansion of International Diffusion of the Instituto de Neurociencias in Non-Community Countries of Europe - Belarus:

3-month internship in Belarus of 12 Occupational Therapy students

Date: 1/11/2018 - 30/03/2019

Coordinator: Diego Echevarria

Visit of the President of the Generalitat Valenciana, Ximo Puig, to the facilities of the Institute of Neurosciences:

The president of the Generalitat Valenciana, Ximo Puig, visited the facilities of the Instituto de Neurociencias. The rector of the UMH, Jesús Pastor Ciurana accompanied Mr. Puig during the tour. The visit was also attended by the mayor of Sant Joan d'Alacant, Jaime Joaquín Albero Gabriel, the director of the Institute of Neurosciences, Salvador Martínez and the vice director of the Institute, Víctor Borrell.

During the tour, they had a meeting with the researchers Prof. Carlos Belmonte and Dr. Juan Lerma, as well as with the directors of the three research units of the Institute of Neurosciences, the researchers Prof. Javier Sáez, Dr. Santiago Canals and Dra Maria Domínguez. They have also visited three laboratories of the Institute, equipped with funds from the Generalitat: the Microscopy, Omic and Magnetic Resonance Service.

Date: February 12, 2019

Visit of Pedro Duque, Minister of Science, Innovation and Universities, to the Instituto de Neurociencias:

D. Pedro Duque, Minister of Science, Innovation and Universities, has visited the Institute of Neurosciences. Pedro Duque has learned about the latest generation functional magnetic resonance imaging and platforms, as well as meeting with the principal investigators from the different laboratories.

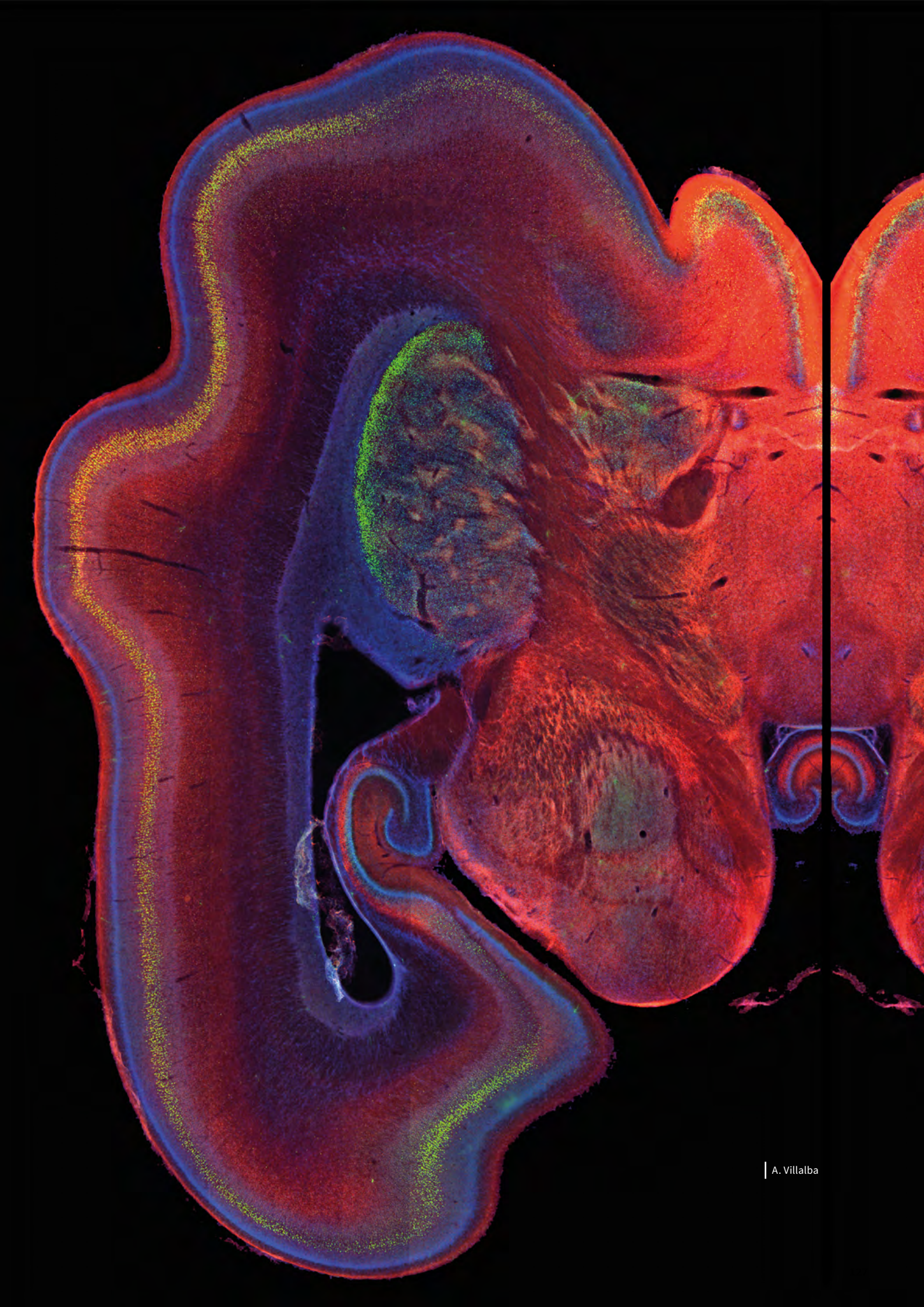
The visit was accompanied by, among others, the director of the center Dr. Salvador Martínez, the rector of the Miguel Hernández University, Jesús Tadeo Pastor Ciurana, the CSIC delegate in the Valencian Community, José Pío Beltrán and Jaime Albero, the mayor of Sant Joan.

Date: April 15, 2019

Visit of Prof. Avram Hershko, Nobel Prize in Chemistry 2004:

Researcher Avram Hershko, 2004 Nobel Prize Winner in Chemistry with researchers Aaron Ciechanover and Irwin Rose for the discovery of ubiquitin-mediated protein degradation. Dr. Hershko visited the facilities of the Instituto de Neurociencias. During the visit he held meetings with the management of the Institute and the units.

Date: June 3, 2019



A. Villalba

2020, a year marked by the pandemic

The year 2020 has been a different, complicated and atrocious year. A year in which we have gone through numerous difficulties in the field of healthcare and we had to adapt to new procedures and ways of working.

Although it has been a really hard year, the Institute of Neurosciences has not stopped in its efforts to advance in the understanding of the brain and the diseases of the nervous system. In addition, we helped in everything we could to combat the COVID-19 pandemic.

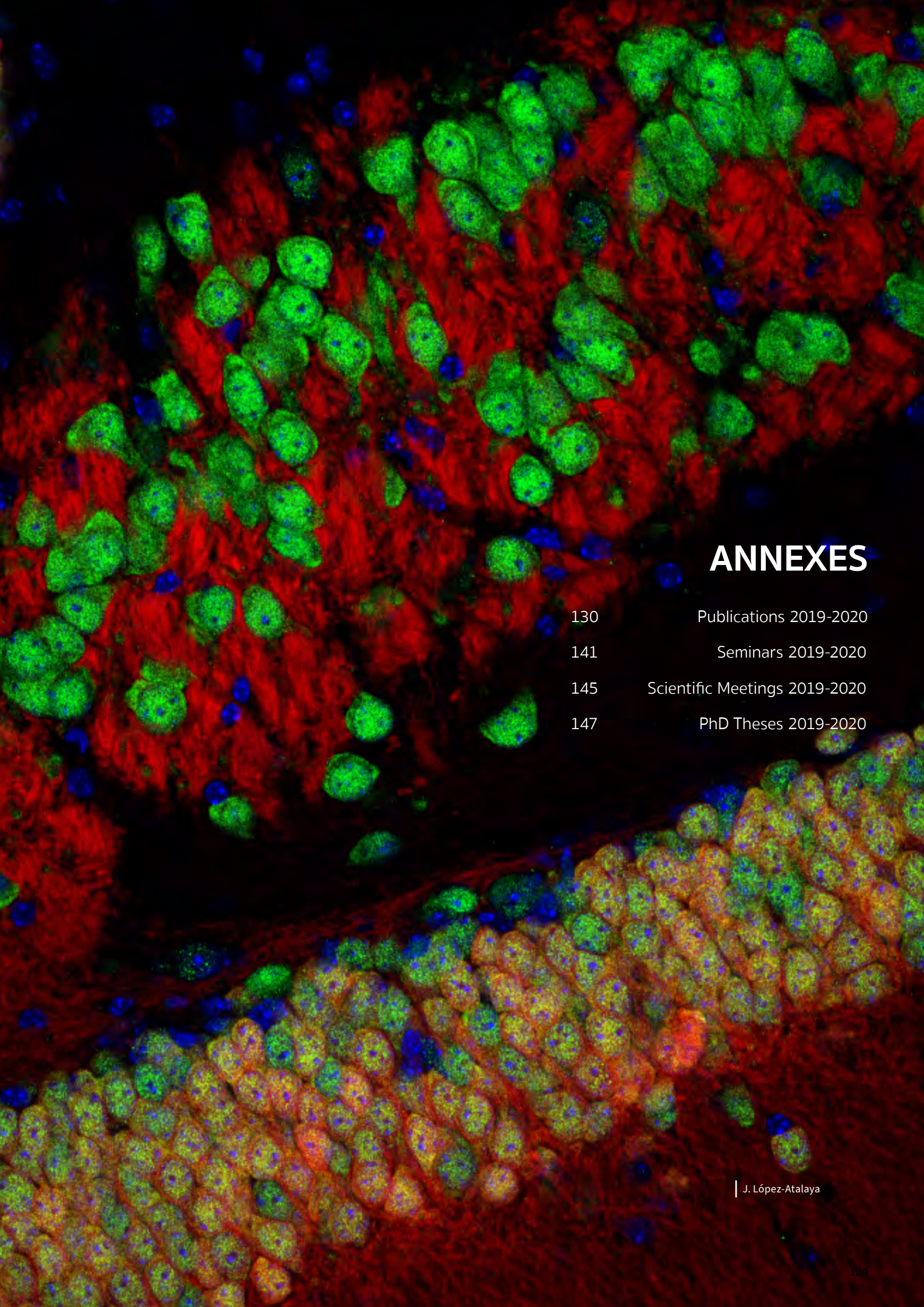
When Spain entered a State of Alarm and most of our workers had to telework and stay at home, the IN began a solidarity initiative together with "**Psychologists without Borders - Alicante**" to sterilize masks, in collaboration which the Civil Guard, and the Local and National Police, taking advantage of our autoclaves. To do this, groups of IN researchers and technicians were organized to pack and sterilize thousands of masks that were distribute to health workers. Overall, more than 75,000 masks were sterilized.

The IN staff also participated in the "**Coronavirus-makers"** initiative, in which the 3D printing collective of San Juan de Alicante and San Vicente del Raspeig, including two colleagues from the IN, began to manufacture ears protectors that were jointly distributed with the masks. These colleagues manufactured more than 1,600 ears protectors using the IN printers transferred to their homes. They also made 632 visors, 45 protective glasses and several connectors for respirators and collaborated in the UMH Patronage Project creating 460 glasses. Once it was possible to return to work, we began to create material for the protection of IN researchers and to date 40 protective visors, 308 individual eye protectors for microscopes, 72 protective goggles and 872 ear protectors for the rubbers have been made.

The IN together with the UMH processed the permits to be able to carry out diagnostic tests against SARS-CoV-2 in our new higher security culture facilities (NCB2) with the anticipation of being able to collaborate if the hospital services became saturated. Fortunately, this reinforcement in diagnostic tests was not finally necessary.

The IN in collaboration with the UMH also processed the permits to be able to carry out diagnostic tests against SARS-CoV-2 in a new high biological security facility (NCB2), although our services were not ultimately required.

Finally, some of our researchers have been or are working directly on research projects related to COVID-19. This is the case of Prof. Salvador Martínez who has participated in clinical trials with Defibrotide, an endothelial anti-inflammatory drug, in severe COVID-19 patients and in a cell therapy trial with allogeneic mesenchymal cells. Furthermore, the group of Prof. Javier Sáez started a line of research on determining the levels of circulating ACE2, the receptor that SARS-CoV-2 uses to infect patients with COVID-19. The team collaborates with the COVID-19 group at the Hospital de Alicante-ISABIAL and with basic groups that develop vaccines at CNB (CSIC) to assess the usefulness of circulating ACE2 as a prognostic marker in patients and follow-up in clinical trials.



ANNEXES

J. López-Atalaya

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2020

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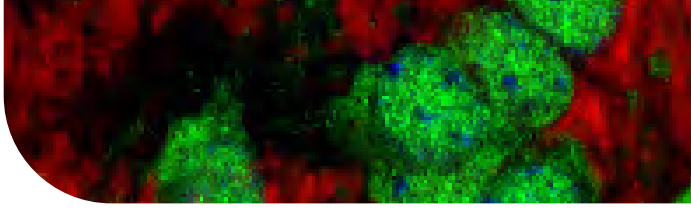

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Capítulos de libro

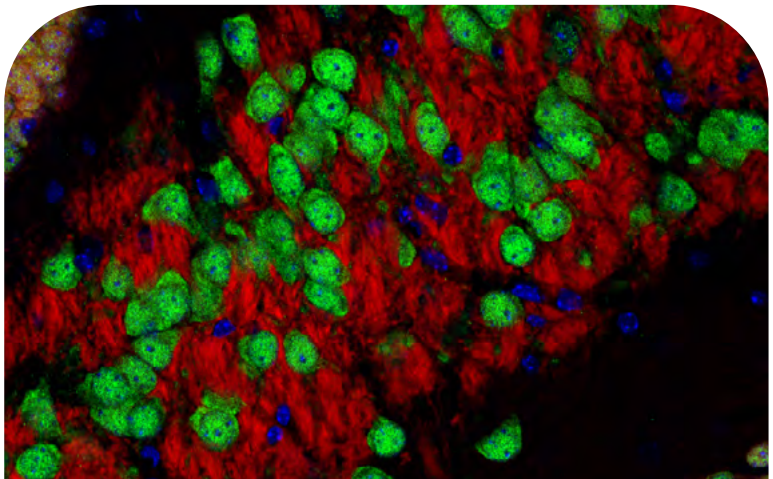
TRPC channels: Methods and Protocols, Methods in Molecular Biology: Characterization of TRPC Channels in a Heterologous System Using Calcium Imaging and the Patch-Clamp Technique pag: 83-97 **Springer Ed.** Elvira de la Peña; Ana Gomis

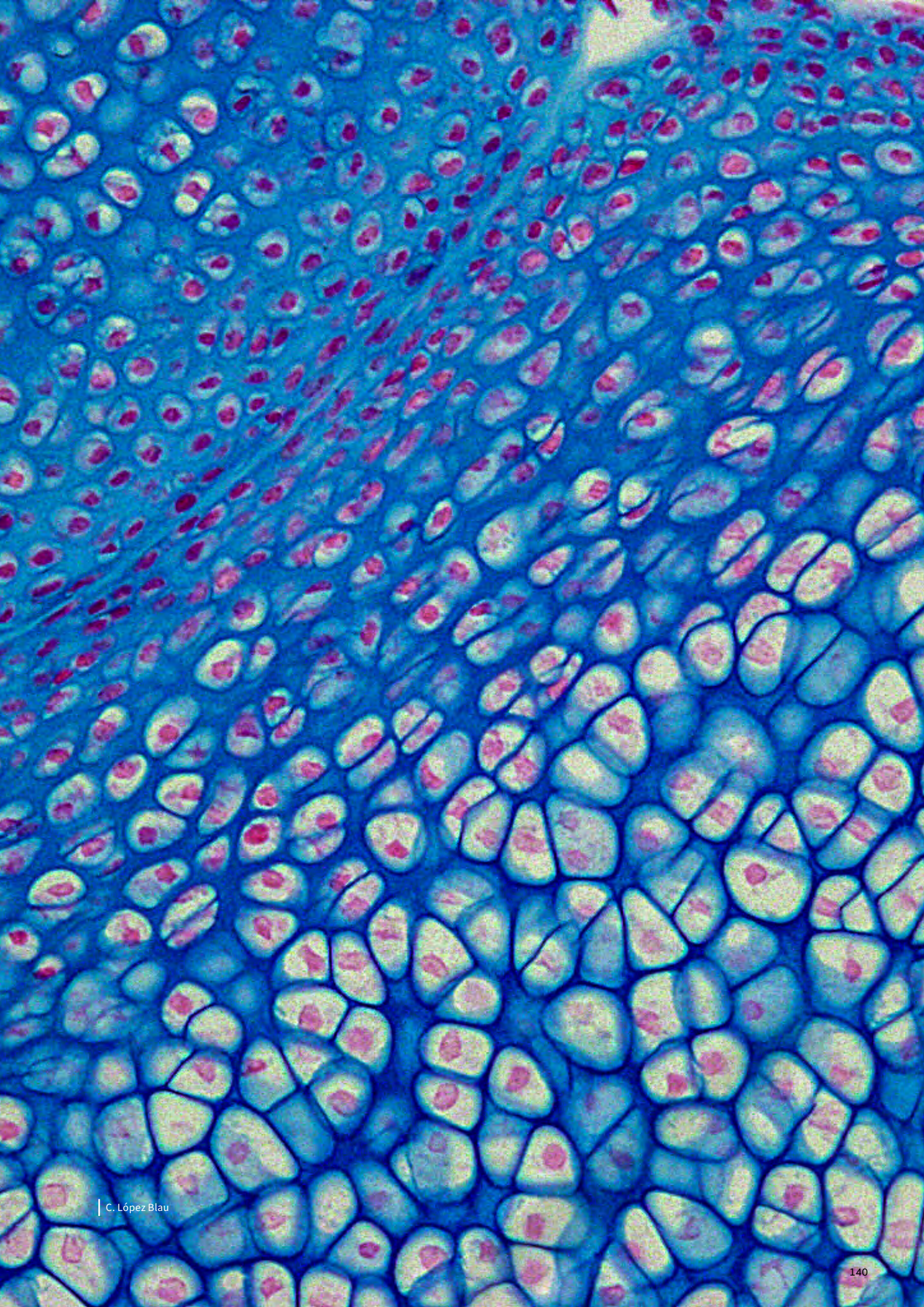
SNAREs. Methods in Molecular Biology book series (MIMB, volume 1860): Studies of the Secretory Machinery Dynamics by Total Internal Reflection Fluorescence Microscopy in Bovine Adrenal Chromaffin Cells. Chapter 25. pag:379-389 **Humana Press / Springer** Ed. Villanueva J; Gimenez-Molina Y; Gutiérrez LM

The Drosophila Model in Cancer: Using Drosophila Models and Tools to Understand the Mechanisms of Novel Human Cancer Driver Gene Function pag:15-35 **Springer Ed.** Villegas SN; Ferres-Marco MD; Dominguez M

Libro

The chick brain in sterotaxic coordinates and alternate stains. https://www.elsevier.com/books/ISBN/9780128160404 **Academic Press / Elsevier Ed.** Margarita Martinez de la Torre; George Paxino; Charles Watson; Salvador Martinez;Luis Puelles





C. López Blau

Seminars

2020

Dr. Maria Antonietta Tosches Columbia University, New York, USA **The evolutionary origins of cortical cell types.**

Dr. Simone Di Giovanni Imperial College London, London, UK **Axonal regenerative signalling affecting the epigenetic environment.**

Dr. Maurizio Mattia Instituto Superiore di Sanità, Rome, Italy **The multiscale nonlinear dynamics underlying slow-wave activity**

Dr. Luis Escudero Universidad de Sevilla, SevillaQuantitative **Biology to capture how tissues are organized (and name new shapes)**

Dr. Andreas Lüthi Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland. **Dynamic encoding of behavioral states in amygdala circuits**

Dr. Paul Heppenstall SISSA (International School for Advanced Studies), Trieste, Italy **Ligand Mediated Targeting of Primary Afferent Subtypes**

Dr. Rosa Cossart INMED, INSERM U901, Aix-Marseille Université, Marseille, France. **How development scaffolds internal hippocampal dynamics.**

Dra. Elena Gracheva Yale University, New Haven, USA **Molecular adaptation to the unique lifestyle in mammalian hibernators.**

Dr. Fumio Matsuzaki RIKEN Center for Developmental Biology, Kobe , Japan **Temporal patterning in the gyrencephalic brain organization; integration of single cell transcriptomes between ferrets and humans**

Dr. Hugo Bellen HHMI and Baylor College of Medicine, Houston, USA **Lipids and the demise of neurons: from rare to common diseases.**

Dr. Xavier Gasull Institut de Neurociències, Universitat de Barcelona, Barcelona **Regulation of pain and itch sensitivity by potassium background channels.**

2019

Dr. Víctor Briz Centro de Biología Molecular Severo Ochoa, Madrid. **Protein homeostasis in synaptic plasticity. Implications for neurodevelopmental disorders.**

Dr. Meritxell Canals University of Nottingham, Nottingham, UK **GPCR signaling platforms for pain and analgesia.**

Dr. Svante Päabo Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany **A Genomic View of Human and Neandertal Uniqueness.**

Dr. Ole Kiehn University of Copenhagen, Copenhagen, Denmark **Brainstem Circuits Controlling Locomotion.**

Dr. José Obeso Hospital Universitario HM Puerta del Sur, Mostoles, Madrid. **Neuronal vulnerability in Parkinson's disease- a human only disorder**

Dr. Manuel Irimia CRG, Barcelona **Neuronal proteome remodeling by microexons and their misregulation in autism spectrum disorder.**

Dr. Juan Lerma Instituto de Neurociencias **Submitting your work to an international journal: the peer review process & what we expect in a good paper.**

Dr. Alfonso Perez-Escudero Université Paul Sabatier, Toulouse, France **From the individual decision to the fate of a species. A case study with Caenorhabditis elegans.**

Dr. Derek Jones CUBRIC Cardiff University, Cardiff, UK **New windows on white matter architecture in vivo**

Dr. Fiona Doetsch Biozentrum, University of Basel, Basel, Switzerland **The Niche Goes Global: Long-Range Regulation of Adult Neural Stem Cells.**

Dr. Lukas Sommer University of Zurich, Zurich, Switzerland **Neural Crest Stem Cells in Development, Tissue Regeneration and Cancer**

Dr. Pierre Paoletti Ecole Normale Supérieure - PSL University, Paris, **France NMDA receptors: allosteric machines in neurotransmission.**

Dr. Ross Cagan Icahn School of Medicine at Mount Sinai, New York (USA) **Fly-to-Bedside**

Dr. Christos Delidakis IMBB, Heraklion, Crete, Greece Dissecting **Hes-centered transcriptional networks in neural stem cell maintenance and tumorigenesis in Drosophila**

Dr. Kim Rewitz University of Copenhagen, Copenhagen, Denmark **A fat-tissue oxygen sensor controls insulin secretion and growth.**

Dr. Elior Peles Weizmann Institute of Science, Rehovot, Israel **Role of Axoglial Cell adhesion molecules in myelination.**

Dr. Emily Osterweil University of Edinburgh, Edinburgh, Scotland **Cell-type specific translation profiling identifies novel disease mechanisms in mouse models of autism.**

Dr. Stefan Lechner Universität Heidelberg, Heidelberg, Germany **How do we sense pain? The molecular basis of mechanosensitivity in primary sensory neurons.**

Dr. Jonas Neher DZNE, Tubingen, Germany **Innate immune memory in the brain shapes neurological disease hallmarks.**

Dr. Moritz Helmstaedter MPI Institute for Brain Research, Frankfurt, Germany **Cerebral Cortex Connectomics.**

Dr. Daniel López Garaulet Memorial Sloan Kettering Cancer Center , New York **A post-transcriptional regulatory circuit specifies the virgin behavioral state.**

Dr. Douglas Bayliss University of Virginia, Charlottesville, USA **Properties, regulation and functions of Pannexin 1 channels.**

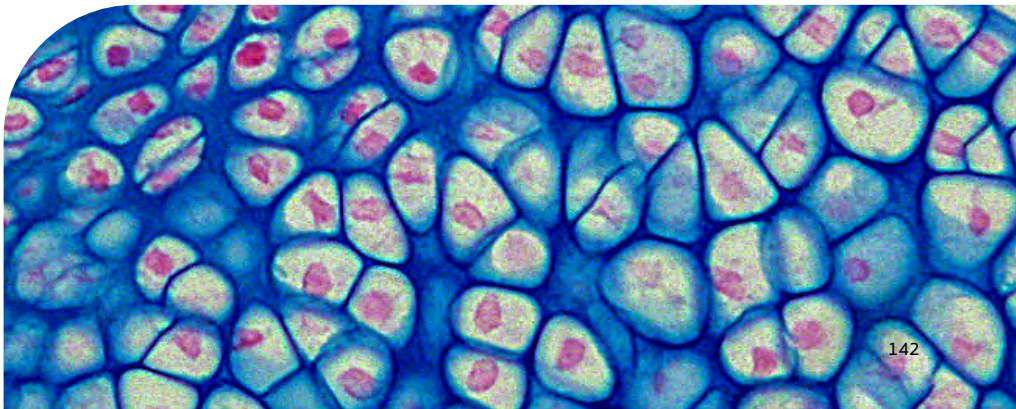
Dr. Joel Richter University of Massachusetts Medical School, Worcester, USA **The Fragile X Syndrome.**
Ieva Gailite Editor at The EMBO **Journal Behind the scenes at The EMBO Journal: the editorial process.**

Dr. Karel Talavera KULeuven, Leuven, Belgium **Relevance of agonist promiscuity among sensory TRP channels: Redundancy or wide dynamic range?**

Drs. Ana M. Soto y Carlos Sonnenschein Tufts University School of Medicine, Boston, USA **Carcinogenesis explained within the context of a theory of organisms.**

Dr. Ragnhildur Thora Karadottir Department of Veterinary Medicine, University of Cambridge, UK **Neuronal regulation of oligodendrocyte precursor fate and (re)myelination**

Dr. Pierre Marie Lledo Institut Pasteur, Paris, France **Brain plasticity: A process fueled by brain-body interactions.**



Informative Talks: ¿Quieres saber qué se hace en tu instituto?

2020

Dra. Mª Carmen Acosta Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto? - **Lágrimas y ojo seco**

Dr. Luis Miguel Gutiérrez Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto? **"Del universo al cerebro: divulgando en los límites entre la ciencia y el arte"**

2019

Dra. Beatriz del Blanco Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto? - **¿Es posible cambiar nuestra información genética?**

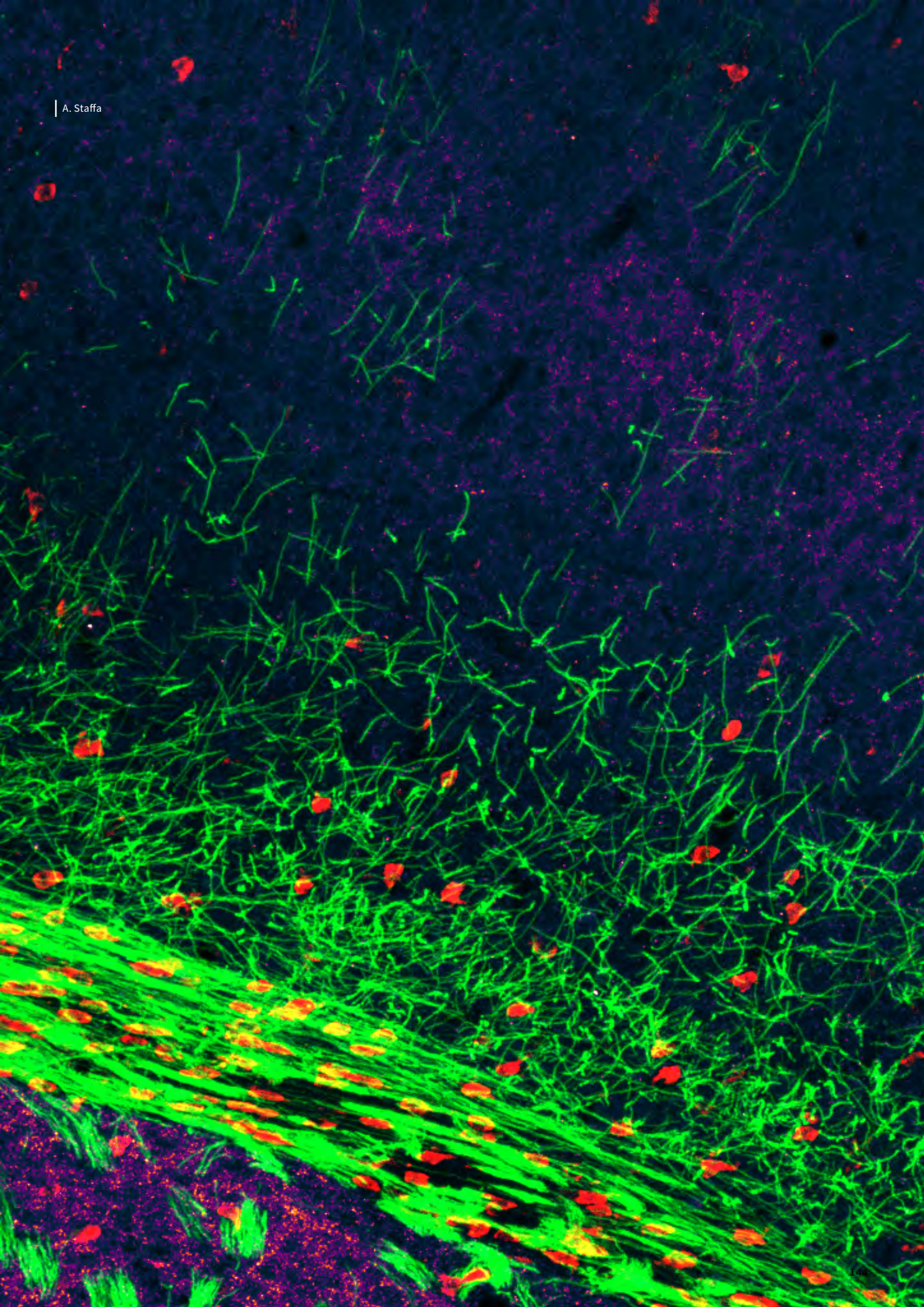
Dra. Silvia de Santis Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto?-**¿Cómo fotografiar un cerebro usando un imán?**

Dr. María Salud García-Gutiérrez Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto? - **El estudio en ratones para predecir la depresión**

Dr. Francisco Martini Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto? **El cerebro antes del cerebro**

Dr. Hugo Cabedo Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto? - **¿Se regenera el sistema nervioso?**

Dr. John Wesseling Instituto de Neurociencias Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto? - **¿Qué es la sinápsis y para qué sirve?**



A. Staffa

Scientific Meetings

IN Seminar Program

Organizers: **Javier Morente**

Date: Every Friday (disrupted during part of 2020 due to the COVID-19 pandemic) Venue: Instituto de Neurociencias

Workshop: Neuroscience meets 3D Genome Biology

Organizers: **Ángel Barco** and **José López Atalaya**

Date: 16 May de 2019 Venue: Instituto de Neurociencias

20th Aniversary of Instituto de Neurociencias

Organizer: **Víctor Borrell**

Date: 3-4 July 2019 Venue: Severo Ochoa Building, Campus de Sant Joan d'Alacant, UMH

AXON meeting: Circuits Development and Regeneration

Organizers: Alain Chedotal, **Eloisa Herrera**, Robert Hindges, Simon Hippenmeyer, Rudiger Klein, **Guillermina López Bendito**.

Date: 11-13 September 2019 Venue: Alicante

Workshop: Improving Openness in Animal Research in Spain

Organizer: **Cristina Marquez**

Date: 1 October 2019

European Developmental Biology Congress

Organizers: **Ángela Nieto, Victor Borrell**, Sergio Casas Tito, Pilar Cubas, **Joan Galcerán**, Leonor Saude, Miguel Torres

Date: 23-26 October 2019 Venue: Alicante

XVI Christmas Meeting

Organizer: **Javier Morante**

Date: 19-20 December 2019 Venue: Instituto de Neurociencias

1st IN Retreat

Organizer: **OPINA group**

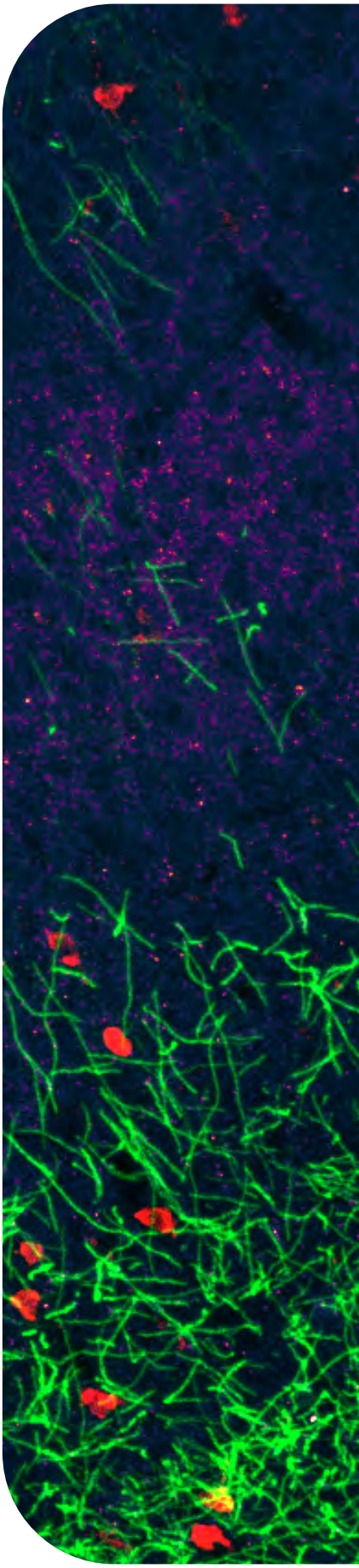
Date: 17-18 2020 Venue: Pueblo Acantilado, Campello, Alicante

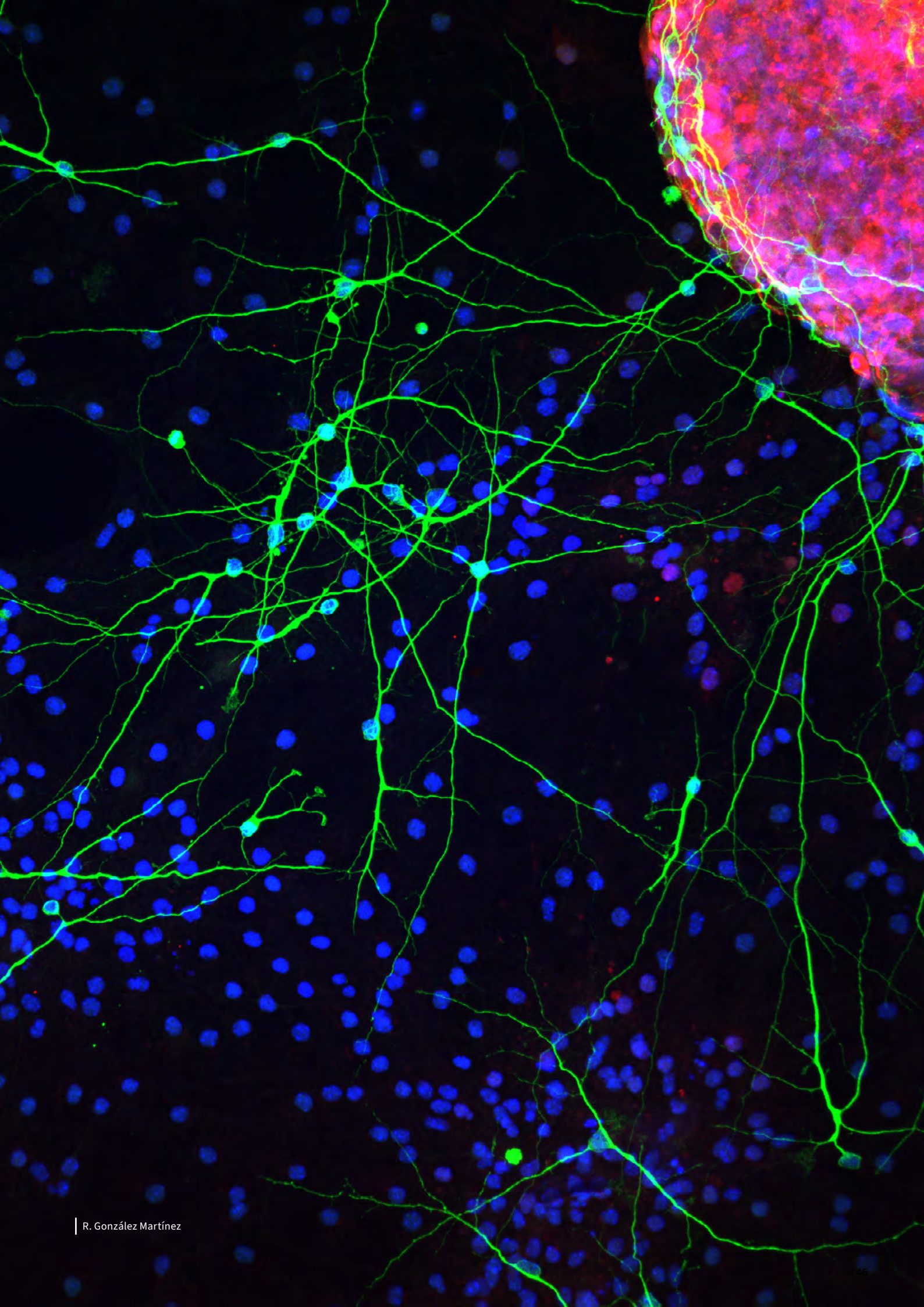
XVII Christmas Meeting

Organizer: **Javier Morante**

Date: 22 December 2020

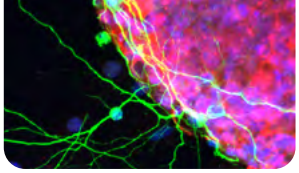
Venue: Virtual meeting organized by the Instituto de Neurociencias





R. González Martínez

PhD Theses



2020

Boix Rodríguez, Claudia Paula
Estudios de fragmentos solubles de la proteína precursora amilioide como biomarcadores en la enfermedad del Alzeimer.
Dr. Javier Sáez Valero
Dra. Inmaculada Belén López Font

Gers-Barlag, Katharina
Mechanisms of cold sensitivity in mouse vagal and trigeminal ganglio neurons: Functional and molecular characterization in healthy and neuropathic conditions.
Dr. Féix Viana de la Iglesia

Giner De Gracia, Aida
Molecular mechanisms underlying Zic2-associated holoprosencephaly.
Dra. Eloísa Herrera González de Molina

Marcotti, Aida
Modulación del canal iónico Trpa1 por la chaperona sigma 1: papel en la neuropatía periférica inducida por oxaliplatino.
Dr. Félix Viana de la Iglesia
Dra. Elvira de la Peña García

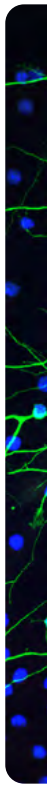
Muça, Gerald
The Role of the Zic2 Transcriptor Factor During Neural Crest Development.
Dra. Eloísa Herrera González de Molina

Negueruela, Santiago
Activity-dependent refinement of the developing visual system. A comparative study across retinal ganglion cell populations and target nuclei.
Dra. Eloísa Herrera González de Molina
Dra. Maria Cruz Morenilla Palao

Ordas Fernández, Purificación
Caracterización de líneas transgénicas murinas para el canal iónico termosensible TRPM8: Valoración funcional, expresión extraganglionar e identificación de nuevas dianas de inervación.
Dr. Félix Viana de la Iglesia

Quirce Vázquez, Susana
Actividad de los nervios sensoriales de la córnea durante la deficiencia lagrimal crónica y su modulación farmacológica.
Dra. Juana Gallar Martínez
Mª del Carmen Acosta Boj

Villalba Requena, Ana
The role of the synaptic protein SV2B in embryonic development of the cerebral cortex.
Dr. Víctor Borrell Franco



2019

Antón Bolaños, Noelia
Role of thalamic input in the development of sensory cortical maps.
Dra. Guillermina López Bendito

Aracil Marco, Adolfo
Efecto de los neuropéptidos codificados en los genes Tac1 y Calca sobre la cicatrización de lesiones experimentales del epitelio corneal.
Dra. Juana Gallar Martínez
Dr. Carlos Belmonte Martínez

Arcas Santos, Jose Miguel
The cold-activated TRPM8 channel: agonism by macrolide immunosuppressants and modultaion by Gq protein-coupled receptors signaling pathways.
Dr. Félix Viana de la Iglesia
Dra. Ana Gomis García

Arora, Vineet
The Roles of GluK4 in amygdala and associated behaviours.
Dr. Juan Lerma Gómez

Fernández Albert, Jordi
Inmediate and deferred epigenomic signatures of in vivo neuronall activation in mouse hippocampus.
Dr. Angel Barco Guerrero

Lipinski, Michal
Role of CBP and P300 in the establishment and maintance of transcriptional programs in adult excitatory neurons.
Dr. Angel Barco Guerrero
Dr. José P. López-Atalaya Martínez

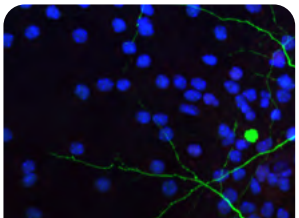
Llinares Benadero, Cristina
Genetic alterations in cortical development as a cause of epileptogenic disorders.
Dr. Víctor Borrell Franco

López Madrona, Víctor José
Gamma Oscillations Drive the Phase of Theta Waves in the Hippocampus to Enhance Directed Functional Connectivity During Memory Processes.
Dr. Santiago Canals Gamoneda

Merino Suárez, María Luisa
Métodos Alternativos para el Diagnóstico de la Enfermedad de Ojo Seco: Termografía Corneal y Determinación del Flujo de Secreción Lagrimal Refleja Mediante Estimulación Corneal con CO2.
Dra. Juana Gallar Martínez
Dr. Carlos Belmonte

Ramón Cañellas, Pol
The Role of the Neuroepithelial-glial Niche in Drosophila Larval Neurogenesis: a Transcriptomic Analysis.
Dr. Javier Morante Oria

Valbuena Alvarez, Sergio
Role of GRIK1 Triplication in Physiological and Cognitive Phenotypes in a Mouse Model of Down Syndrome.
Dr. Juan Lerma Gómez



Annual Report

2019 - 2020

INSTITUTO DE NEUROCIENCIAS

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