Annual Report

2017-2018

CSIC
Consejo Superior de Investigaciones Científicas

UNIVERSITAS
Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

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INSTITUTO DE NEUROCIENCIAS

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The IN is located on the Mediterranean coast, in the town of Sant Joan d'Alacant, seven kilometres from the city of Alicante in its province, a region favoured by an exceptional climate throughout the year. The IN is situated in the Health Sciences Campus of the UMH giving ample opportunity for interaction with the Faculties of Medicine and Pharmacy, the University Hospital of San Juan and the Health Sciences library that are also on campus.

The IN houses over fifty 60-70 m2 laboratories for independent research groups in a building of approximately 9000 m2 distributed over four floors including a basement. Approximately 30% of the building houses common laboratory facilities with sophisticated research equipment made available for use to all IN researchers. The basement houses a modern animal house for genetically modified mice.

Salutation

The Instituto de Neurociencias (IN) is a public centre dedicated to brain research in both normal and pathological conditions. This is achieved through a multidisciplinary approach towards the study of the nervous system's structure and function at the molecular, cellular and integrative levels. The IN was founded as a Joint Centre of the UMH and CSIC in 1999. Therefore, the 2019 is the year of its 20 anniversary. First, I want to congratulate for this anniversary to all the people who have contributed and are contributing to the scientific excellence of our production of knowledge to the society. It is a great honor to be the Director of such a scientifically successful and relevant Centre.

The IN has maintained along its trajectory an increasing level of scientific publications in prestigious journals with high impact. Our groups are leaders in their respective research fields of Neuroscience. Moreover, the high degree of competitive funding of IN researchers, thanks to their scientific talent and quality of national and international projects, allows us to maintain technologically advanced services and research support units. Finally, the accreditation as a "Severo Ochoa Center of Excellence" (since July 2014), and the renewal of this accreditation in 2018 until 2022 continues to allow us to undertake new initiatives and recruit talented researchers. All this is thanks to the efforts of the staff of the Institute that, with their scientific, technical and administrative competence, allow reaching the levels of excellence for which we are recognized.

The good track laid out by Carlos Belmonte and Juan Lerma in both stimulating quality research, and considering scientific excellence as the main criterion for the incorpora-

Salvador Martínez Pérez : Director

tion of new researchers, has led our center to achieve high levels of scientific international leadership. With the new additions and the development of the professional careers of the IN members, the talent of our researchers represents its outstanding value. Adequate development also depends on the good work and the professionalism of our research support and administrative staff, which make the experimental work and the economic resources of researchers more efficient.

On the other hand, we maintain a stable proportion of approximately 60% of women and 40% of men, with about 12% of our personnel coming from other countries. We have the compromise to actively try to recruit foreign personnel, which demonstrates our vocation to be an international center of scientific excellence in neuroscience. Similarly in the educational aspect, the International Masters in Neuroscience of the IN and the UMH is partially coordinated with the Masters of Developmental Neurobiology of the Pasteur Institute and the University Paris VI (Pierre et Marie Curie), teaching 3 ECTS Exchange Credits. This has led to an important increase in the visibility and internationalization of our Master's students.

Fulfilling the mission of IN to generate basic knowledge on the brain and its mechanisms, in the last two years the IN has made a number of relevant findings, a selection of which is highlighted in the specific section of this report.

In terms of productivity, in the last two years the IN has reached a stability point, both in the number of articles (290-295) and in the average impact factor (6.2-7.1) of the journals in which these are published. The IN has also been the subject of a series of relevant actions. Several members of the IN have achieved significant recognition of their research work, congratulations to all. With this, the IN and its members continue to strengthen their national and international presence.

IN groups have continued to look for funding strategies to sort the financing crisis of science in Spain, which still threatens the most fundamental structures of our Institute. The successful participation of several researchers in the calls for proposals of the European Research Council and other Horizon 2020 programs is the natural way out of the Spanish crisis. The sustained effort to incorporate to the IN the most advanced technology allows our researchers to carry out state-of-the-art experiments and to be at the leading edge in its research fields, maintaining competitiveness with our European or American colleagues.

Sustained effort to incorporate to the IN the most advanced technology allows our researchers to carry out state-of-the-art experiments

The initiative of the Generalitat Valenciana Government (GVA) to create a Valencian Agency for Innovation (AVI) to stimulate translation of research results to the industry and society and creating a Department for Innovation (UCIE) in the IN, represents an opportunity to increase the social impact of our results in economy agents, and the welfare of citizens.

The IN has continued to collaborate with the World Brain Week through the organization of various outreach events and open days. This has allowed visiting the Institute to more than 2500 people, with live radio and television broadcasts by UMH and RNE.

We want to emphasize that the intimate knowledge of the brain will have significant consequences in the construction of the society of the future. Therefore, Neuroscience is called to modify human attitudes and habits towards higher levels of well-being and adaptation to the new circumstances that humanity will face in the future. In this task, I would like to thank once again all those who, through their commitment and effort, in one or other role throughout our history, have contributed to the IN mission by placing it at its outstanding scientific level, and thank the institutions to which we belong, CSIC and UMH, for their continuous support to our research activity.

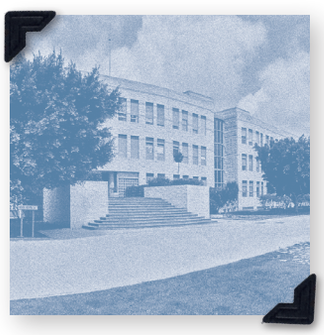
University of Alicante
group of researchers dedicated to studing the structure & function of the nervous system

1985

A bit of history

1990

University Insitute
formally recognised at the University of Alicante



In 1990 the Valencian Government formally recognised the Instituto de Neurociencias at the Universidad de Alicante 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 Ph.D. Programme was created to train young scientists in the field of neuroscience.

Five years later the Institute became an "Associated Unit" of the Instituto Cajal del Consejo Superior de Investigaciones Científicas (CSIC), which moved two of its research groups to 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.

The IN was formally created as a Joint Centre of the UMH and CSIC in 1999. Since then the IN has integrated tenured scientific staff from the CSIC and UMH, and hosted young researchers through the Ramon y Cajal, Severo Ochoa and GVA-GenT Research Programmes. In 2001 the UMH initiated the construction of a new building dedicated to house the IN, and this was completed with additional funding from the Health Department of the Valencian Government. Furniture and laboratory equipment was provided by the CSIC. Researchers finally 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.

Asociated Unit
of the Instituto Cajal CSIC

1995

1996

University Miguel Hernández
transferred to the newly created University Miguel Hernández of Elche

Joint Centre
UMH and CSIC

1999

2001

Construction
starts of of new building starts

Inauguration
by Her Royal Majesty

2005

2004

Occupation
of the new building

2019

20 Years
UMH & CSIC

The Future

In 2005 the IN implemented its first strategic plan, which shaped the Institute during five years. In 2010 the second Strategic Plan was elaborated in 2009 at the request of CSIC, outlining the guidelines for consolidation of the IN, with the clear goal of becoming a center of excellence in the european research area. The 3rd Action Plan, started in 2014, reaffirmed the IN's pursuit of excellence, and its intention to strengthen and specify some of lines of research aimed at studying the nervous system. We moved towards multi-disciplinary approaches and strengthened research around pathologies of the nervous system. This is currently being carried out by incorporating appropriate technology and with the pursuit of partnerships with hospitals and agents of the health system. The acquisition of cutting-edge technology platforms, such as imaging techniques 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, initiated with our Master, and the interaction with technological institutes to stimulate innovation platforms, are three lines of work to drive new challenges in the Action Plan of the IN of 2018-2021.

Scientific Objectives

The conceptual priority of the IN is to develop multidisciplinary and modern technological approaches in the design of original experimental research in neuroscience.
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 behaviour. It is necessary to integrate the genetic, molecular and structural

Acquisition of cutting-edge technology platforms ... is another goal of IN.

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 setup 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.
The IN proposes to work on three basic pillars of action:

- An ambitious scientific project, based on seven research lines.
- A project of service and transfer to society: teaching and biomedical innovation.
- Corporate internationalization.

The scientific work program of the IN has impact in 3 Sustainable Development Goals of the United Nations: 1) SDG3: The whole mental health related targets 3.4 and 3.5; 2) SDG4: Access to to quality early development (4.2), and Build and upgrade educational facilities that are child, disability and gender sensitive(4.A). 3) SDG5: Promote gender equality (5.C).
In relation to Scientific Areas of CSIC, the work plan of IN groups is mainly related to LIFE, although some groups have also identified links with SOCIETY.

Scientific Project

In the IN, multidisciplinary and modern technological approaches have as conceptual priority to design original experimental paradigms aiming to develop ambitious research programs in Neuroscience. Research lines (RL) in the IN define these programs and represent transversal collaborative platforms where IN groups perform their specific work integrated into one or more RL.
The Strategic Research Plan of the IN (IN-SRP) represents a coherent project, which objective is to increasing knowledge about normal brain function and the biological roots of brain diseases, to improve prevention, diagnostics, therapies and prognosis. The decision organs of the IN are compromised to improve the specific and general work conditions in the IN technological platforms (IN-TP) and laboratories, to ensure the accomplishment of the programmed collective and individual research plans.
The IN-research 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 behaviour. 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.

IN-SRP research lines

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.
The strategic support to the development of IN-SRP will be allocated inside IN-TPs and Departments. The scientific programs of research lines will be distributed according to the groups research programs, as platforms of joining interest, to stimulate multidisciplinary approaches, development of new experimental paradigms and highly competitive collaborations.

Project Of Service And Innovation

In order to encourage research applied to productive activity, the Agencia Valenciana de Innovación (AVI) supports the creation in the IN an Innovation and Technology Transfer Office (UCIE) with the specific aim of identifying and nurturing knowledge transfer. This unit becomes the link between what the IN investigates and the potential transfer of research results into innovative products. Three structures: research institutions, technological institutes and companies, under the supervision of the AVI, are the ones that identify the social challenges to be overcome and the means to address them without detracting resources of the research centers.
The IN is a center dedicated to the study of brain development and function, our contributions to the scientific knowledge have the potential of methodologically improve the clinical management of neurological and psychiatric patients. The discovery of biomarkers of brain functional maturation and environmentally-sensitive processes is an important challenge to monitor brain function and improve learning in childhood, as well as the prevention of fragility in old age.

Teaching Project

The IN is also a teaching institution that wants to spread excellence in academic and technical education in neuroscience. This training is aimed at the formation of new generations of neuroscientists through its international doctoral program in Neurosciences, declared of excellence by the Ministry of Education. Moreover, we organize an International Master in Neurosciences. This Master has 60 ECTS credits distributed in different subjects and is taught by professors of the CSIC and the UMH. It is carried out in collaboration with the Master of Neurobiology of Development of the Pasteur Institute and the University Paris VI (Pierre et Marie Curie), giving 3 ECTS Credits of exchange.

Corporative Internationalization

The IN intends to establish alliances and agreements of close collaboration with other prestigious international institutes that allow interchange of researchers, achieve a critical mass of international leadership and access to complementary technologies.

What we do

One of the greatest challenges facing today's science and society is to understand the brain and the biological basis for human behavior, including functions as diverse as movement control, language, sensations, emotions or consciousness. The promotion of adequate educational programs in relation to brain maturation and the increasing requirement for resilience to compensate brain fragility during life, together with psychiatric and neurodegenerative illnesses, represent a growing health problem and an important social burden in developed western countries. Unfortunately there is still relatively little known about the possibility to improve brain function and the causes of these illnesses, and for this reason there is an increasing interest on the study of the nervous system.

The IN is a publicly funded centre dedicated to brain research in both normal and pathological conditions. 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. The Institute is organised in three research Departments: Developmental Neurobiology, Cellular and Systems Neurobiology and Molecular Neurobiology and Neuropathology. Each Department is formed by scientists that share general research interests and technical approaches.

There is a second level of organization based on research lines. These constitute a horizontal organisation 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 IN undertakes an important training activity through its International PhD Programme in Neuroscience, which has been awarded with a mention as "Programme of Excellence" by the Ministry of Education. It also strives to be a centre of reference in terms of both national and international collaborations between clinical and basic research groups from a wide range of disciplines.

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

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 offered in several courses 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 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 significant increase in personnel has been in both young and senior researchers, several of them of recognized international prestige. The IN currently has 36 tenured researchers (21 CSIC and 15 UMH), 7 non-tenure scientists, 229 doctoral and postdoctoral researchers and 80 technical and administrative staff (See graphic IN in Numbers: Personnel).

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 generated during the preceding period and in 2015-2018 place the IN as one of the highest-ranking research centres in Spain, competitive at the European level (See graphic Impact Factors and Budget growth).

We have an external Scientific Advisory Board (SAB) that evaluates our scientific production and advises on the research activity and strategies of the Institute. SAB members are: Claudio Sterm, Ranulfo Romo, María Blasco, Magdalena Götz and and Michael Häusser.

A right-handed signalling pathway drives heart looping in vertebrates.
Ocaña OH, Coskun H, Minguillón C, Murawala P, Tanaka EM, Galceran J, Muñoz-Chápuli R, Nieto MA. (2017)

Nature 549 (7670): 86-90

In this work, the authors have been able to demonstrate that there are certain genes that are expressed more on the right side of the embryo and that this leads to a greater migration of cells to the heart from this side. The incorrect functioning of these genes can cause cardiac malformations, as the authors have been able to show in models of zebrafish, chicken and mouse. Demonstrating that this mechanism is conserved in vertebrates and will help to better understand the congenital defects derived from the alteration of cardiac laterality in humans.

Prenatal thalamic waves regulate cortical area size prior to sensory processing.
Moreno-Juan V, Filipchuk A, Antón-Bolaños N, Mezzera C, Gezelius H, Andrés B, Rodríguez-Malmierca L, Susín R, Schaad O, Iwasato T, Schüle R, Rutlin M, Nelson S, Ducret S, Valdeolmillos M, Rijli FM, López-Bendito G. (2017)

Nat Commun 8:14172

In this study, the authors demonstrate the existence of a subcortical mechanism that regulates the size of cortical areas in mouse models. This mechanism is mediated by spontaneous calcium waves that propagate between the sensory nuclei of the thalamus and reach the cortex, thus providing a means of communication between the different sensory systems. These findings reveal that calcium waves in the thalamus of the embryo can regulate the extent of sensory territories in the cerebral cortex even before they begin to process sensory information.

Increased Grik4 Gene Dosage Causes Imbalanced Circuit Output and Human Disease-Related Behaviors.
Vineet Arora, Valeria Pecoraro, M. Isabel Aller, Celia Román, Ana V. Paternain, Juan Lerma. (2018)

Cell Reports 23, 3827–3838.

It is believed that altered glutamatergic neurotransmission contributes to mental disorders and neurodegenerative diseases. The GRIK4 gene encodes a high affinity kainate receptor subunit of essentially unknown function. De novo duplication of the locus 11q23.3-q24.1 has been detected in cases of autism and other disorders. A slight gain in Grik4 increases synaptic transmission, causing a persistent imbalance in the inhibitory and exciting activity and disturbing the circuits responsible for the main outputs of the amygdala.

Scientific Milestones

2017-2018

Regulation of Cerebral Cortex Folding by Controlling Neuronal Migration via FLRT Adhesion Molecules.

Del Toro D, Ruff T, Cederfjaell E, Villalba A, Seyit-Bremer G, Borrell V, Klein R. (2017)

Cell 169(4): 621-35

The folding of the mammalian cerebral cortex into sulci and gyri is thought to be favored by the amplification of basal progenitor cells and their tangential migration. Here, we provide a molecular mechanism for the role of migration in this process by showing that changes in intercellular adhesion of migrating cortical neurons result in cortical folding.

Evolution of cortical neurogenesis in amniotes controlled by Robo signaling levels.

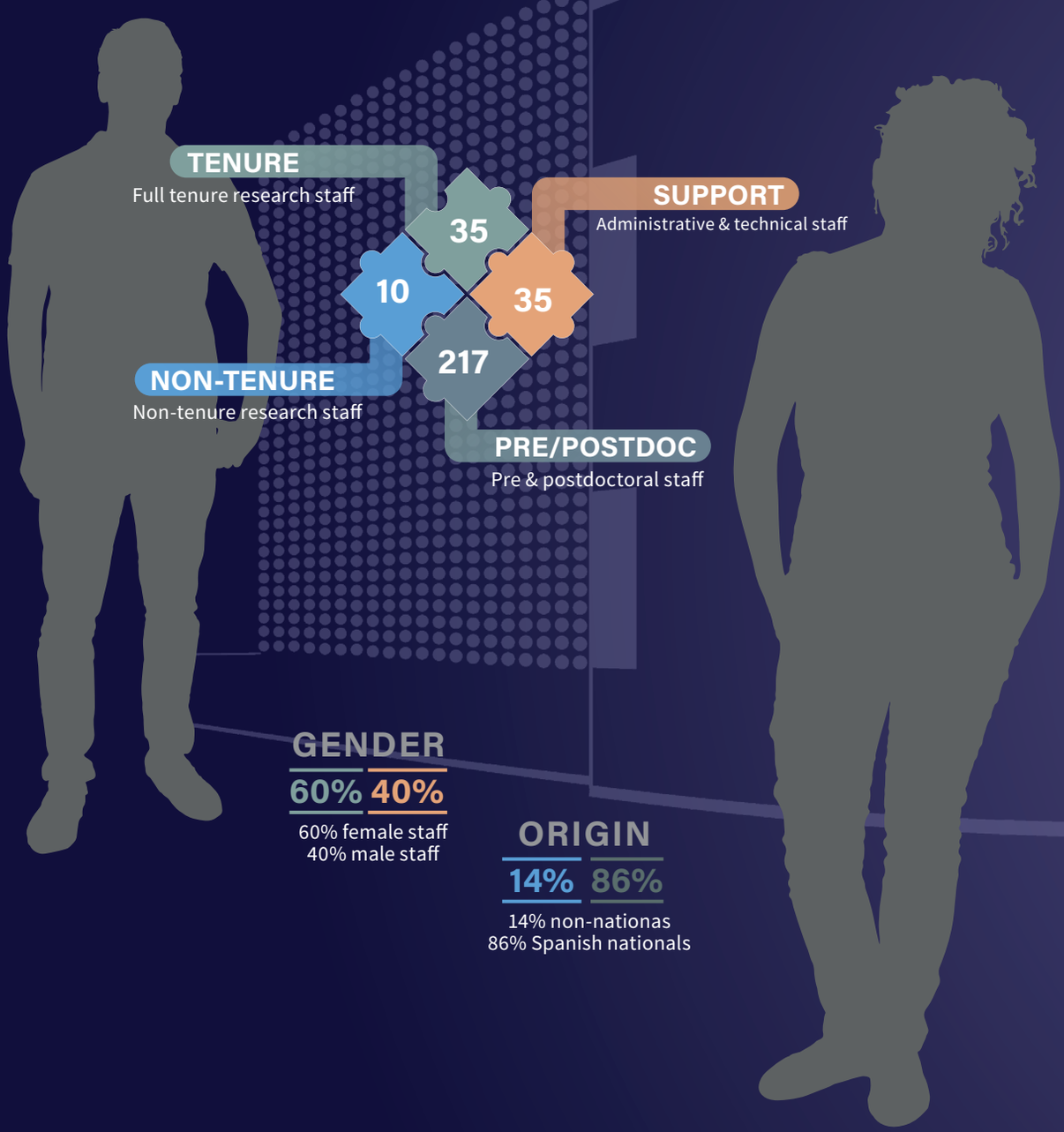
A. Cárdenas, A. Villalba, C. De Juan Romero, E. Picó E, C. Kyrousi, A.C. Tzika, M. Tessier-Lavigne, L. Ma, M. Drukker, S. Cappello, V. Borrell. (2018)

Cell 174(3):590-606.

The size of the cerebral cortex differs dramatically between reptiles, birds and mammals due to differences in neuron production during development. Gain and loss of function experiments in mouse, chicken and snake embryos, and human brain organoids demonstrate that high and low Dll1 signaling levels by Jag1 / 2 are necessary and sufficient to induce direct neurogenesis. Our study identifies the modulation of activity levels of conserved signaling pathways as a primary mechanism for the expansion and increased complexity of the mammalian neocortex during the evolution of amniotes.

The Institute in Numbers

PERSONNEL



TENURE
Full tenure research staff

35

SUPPORT
Administrative & technical staff

10

35

217

NON-TENURE
Non-tenure research staff

PRE/POSTDOC
Pre & postdoctoral staff

GENDER

60% 40%

60% female staff
40% male staff

ORIGIN

14% 86%

14% non-nationas
86% Spanish nationals

EVOLUTION OF PRODUCTIVITY INDEXES

In the period 2016 to 2018

Citations

1948

Publications in the same period

Impact

7.0

Mean IF

Publications

234

Web of Science

ANNUAL BUDGET

3.1 M€

Ordinary Budget

0.1 M€

Other

7.8 M€

Staff

1 M€

Investment

Research Units

Cellular & Systems Neurobiology

Research groups in the Cellular and Systems Neurobiology Unit are concerned with the study of integrative processes in the nervous system, combining molecular, electrophysiological, brain imaging and behavioral tools in a variety of animal models (C. elegans, 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.

Developmental Neurobiology

The Developmental Neurobiology Unit consists of ten research groups devoted to study the development of the nervous system both in vertebrate (mouse, chicken and fish) and invertebrate (*Drosophila*) embryos. Our main research lines include pattern formation, growth control, cell migration, neurogenesis, axonal guidance and synaptogenesis. We undertake genetic, cellular, molecular and experimental embryology approaches.

Molecular Neurobiology and Neuropathology

The Molecular Neurobiology Unit carries out research aimed to understand essential functions of the nervous system using primarily molecular approaches. Towards this end, we use biochemistry, pharmacology, molecular biology and molecular genetics techniques (frequently combined with non molecular techniques such as electrophysiology or behaviour). We investigate a wide variety of biological processes, from structure and function of neuroreceptors and ion channels, to the regulation of neurosecretion, axonal myelination, signal transduction and activity-driven gene expression. We are also interested in the molecular bases of a number of pathologies of the nervous system, such as Alzheimer and Huntington diseases, addiction and neuropathic pain.

| Subbasal arbustos

Research Lines

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.

Research Groups

20 **Transcriptional and epigeneticmechanisms of neuronal plasticityand its disorders**
Angel Barco (CSIC)

24 **Neurogenesis & cortical expansion**
Víctor Borrell (CSIC)

26 **Molecular control of axonal myelination**
Hugo Cabedo (UMH)

28 **Plasticity of brain networks**
Santiago Canals (CSIC)

31 **Signaling networks underlyingasymmetric cell division**
Ana Carmena (CSIC)

32 **Cellular & conductual neuroscience**
Carmen de Felipe (UMH)

35 **Mechanisms of growth control & cancer in *Drosophila***
María Domínguez (CSIC)

38 **Ocular Neurobiology**
Juana Gallar (UMH)
Mª Carmen Acosta (UMH)

40 **Physiology of the cerebral cortex**
Emilio Geijo (UMH)

42 **Mechanotransduction in mammals**
Ana Gomis (CSIC)

44 **Molecular mechanisms of neurosecretion**
Luis M. Gutiérrez (UMH)
Salvador Viniegra (UMH)
Manuel Criado (UMH)

46 **Behavior of Organisms**
Alex Gomez-Marin (CSIC)

48 **Development & Assembly of Bilateral Neural Circuits**
Eloísa Herrera (CSIC)

50 **Synaptic Neuromodulation**
Sandra Jurado Sánchez (CSIC)

53 **Synaptic physiology**
Juan Lerma (CSIC)

57 **Cellular Plasticity and Neuropathology**
José P. López-Atalaya (CSIC)

58 **Development, Plasticity and Regeneration of Thalamocortical Circuits**
Guillermina López-Bendito (CSIC)

60 **Translational neuropsychopharmacology of neurological & psychiatric diseases**
Jorge Manzanares (UMH)

62 **Neural Circuits of Social Behaviour**
Cristina Márquez Vega (UMH)

64 **Visual Neuroscience Laboratory**
Luis M. Martínez (CSIC)

66 **Experimental Embryology**
Salvador Martínez (UMH)
Constantino Sotelo (UMH)
Eduardo de Puelles (UMH)
Diego Echevarría (UMH)

68 **Mechanisms orchestrating the control of organ size and neurogenesis**
Javier Morante (CSIC)
Luis García-Alonso (CSIC)

71 **Cell movements in development & disease**
M. Angela Nieto (CSIC)
Berta L. Sanchez-Laorden (CSIC)

74 **Development and refinement of neural circuits**
Isabel Pérez Otaño (CSIC)

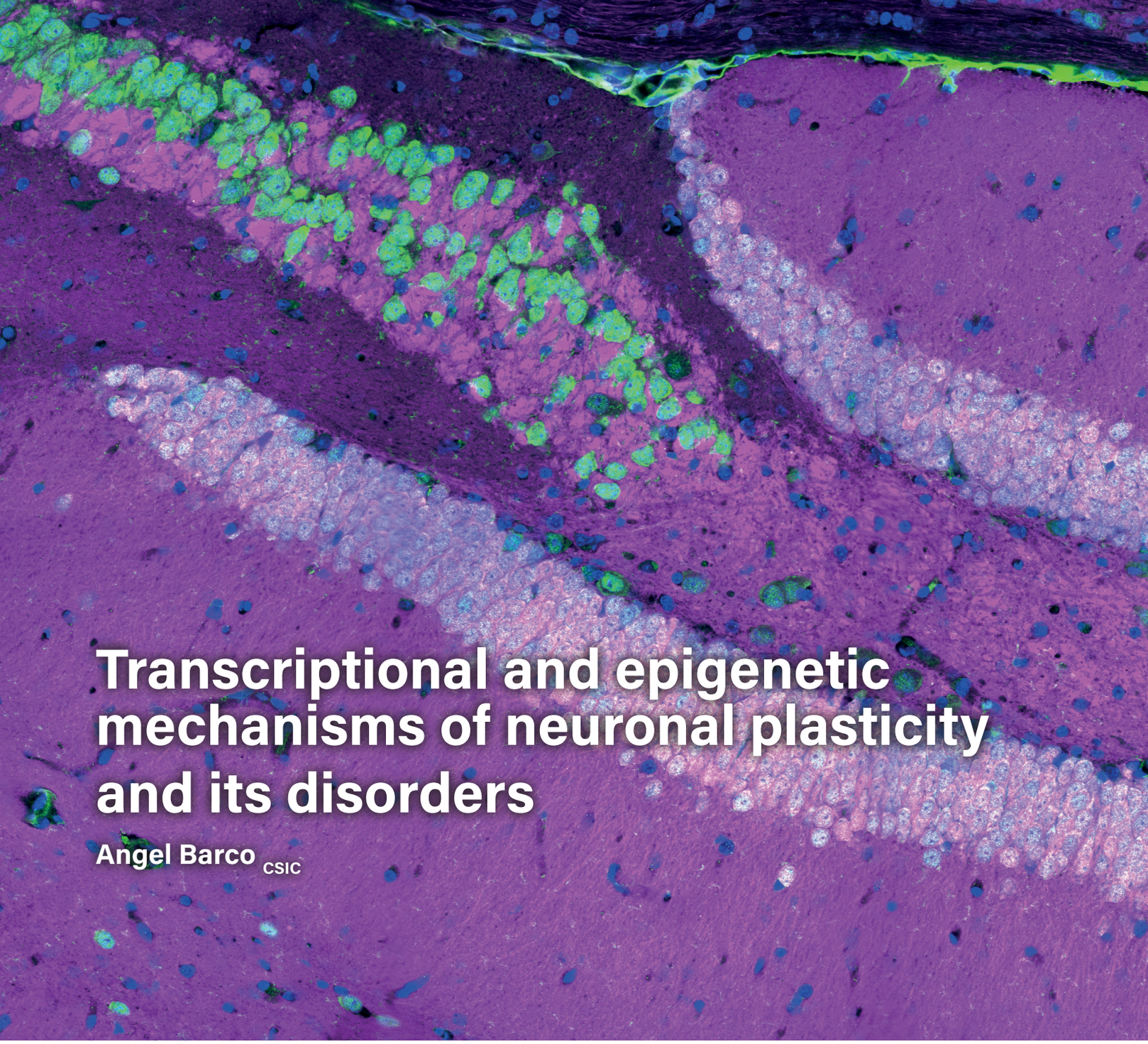
76 **Sensory-motor processing by subcortical areas**
Ramón Reig García (CSIC)

79 **Altered molecular mechanism in Alzheimer's disease & dementia**
Javier Sáez Valero (UMH)

80 **Molecular neurogenetics**
Francisco Tejedor (CSIC)

82 **Sensory transduction and nociception**
Félix Viana (CSIC)
Carlos Belmonte (UMH)

84 **Molecular and cellular physiology of synaptic transmission**
John F. Wesseling (CSIC)



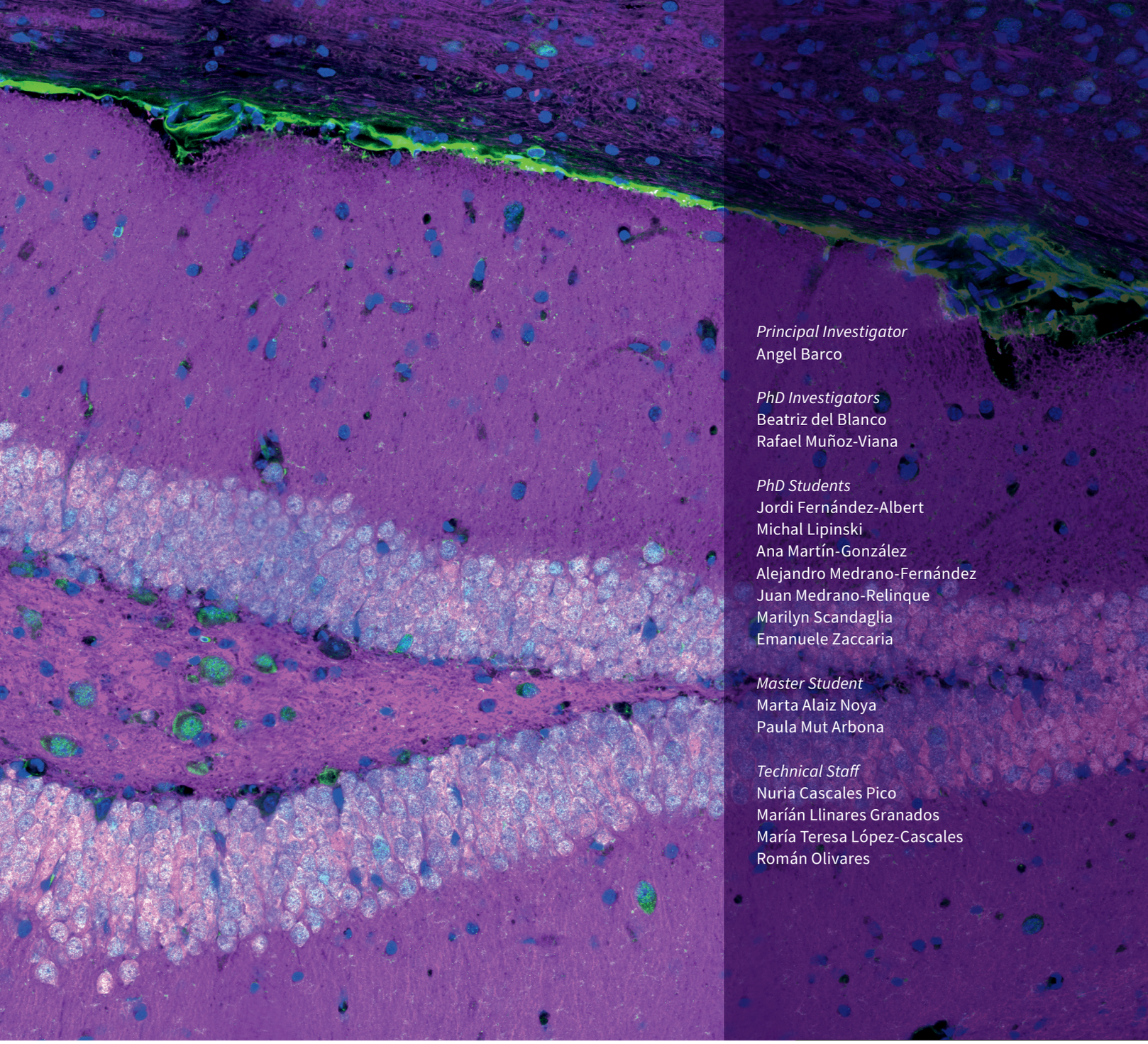
Transcriptional and epigenetic mechanisms of neuronal plasticity and its disorders

Angel Barco CSIC

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, 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 and 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,



Principal Investigator
Angel Barco

PhD Investigators
Beatriz del Blanco
Rafael Muñoz-Viana

PhD Students
Jordi Fernández-Albert
Michal Lipinski
Ana Martín-González
Alejandro Medrano-Fernández
Juan Medrano-Relinque
Marilyn Scandaglia
Emanuele Zaccaria

Master Student
Marta Alaiz Noya
Paula Mut Arbona

Technical Staff
Nuria Cascales Pico
Marián Llinares Granados
María Teresa López-Cascales
Román Olivares

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 SRF 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 DNA methylation and histone acetylation and methylation, to the pathoetiology of different neurological conditions associated with cognitive impairments and autism originated by mutations in 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 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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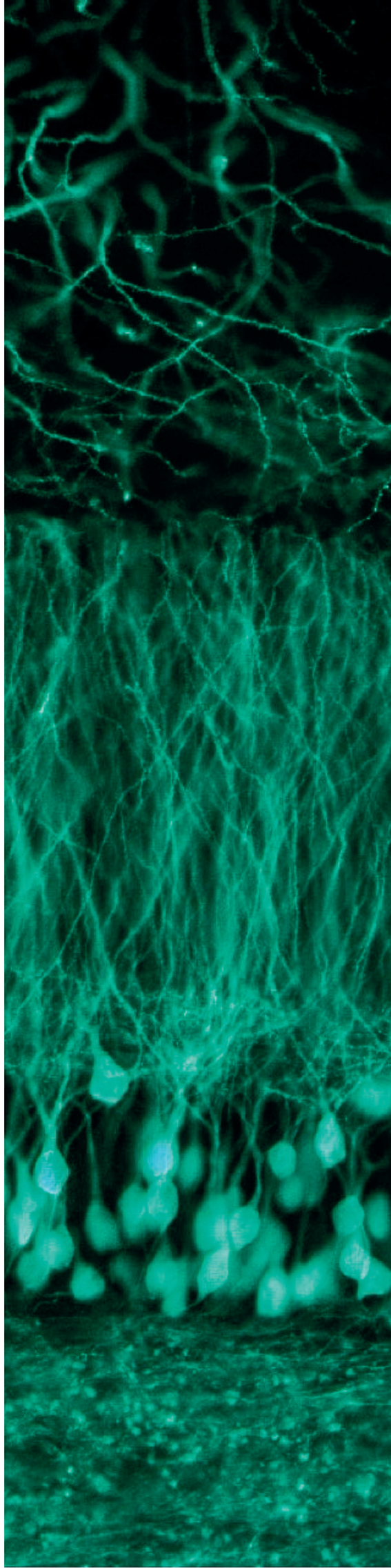

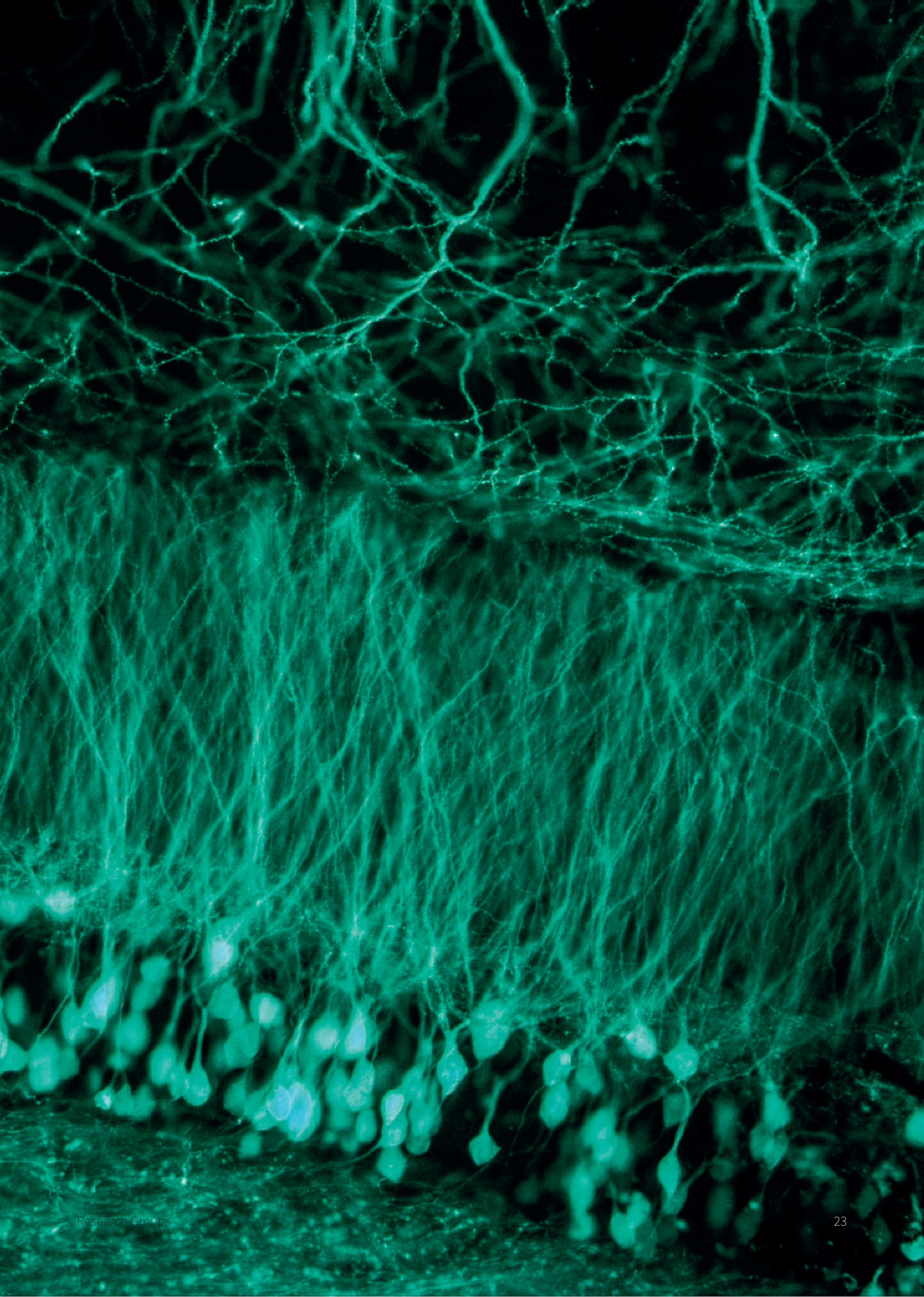

Neurogenesis & cortical expansion

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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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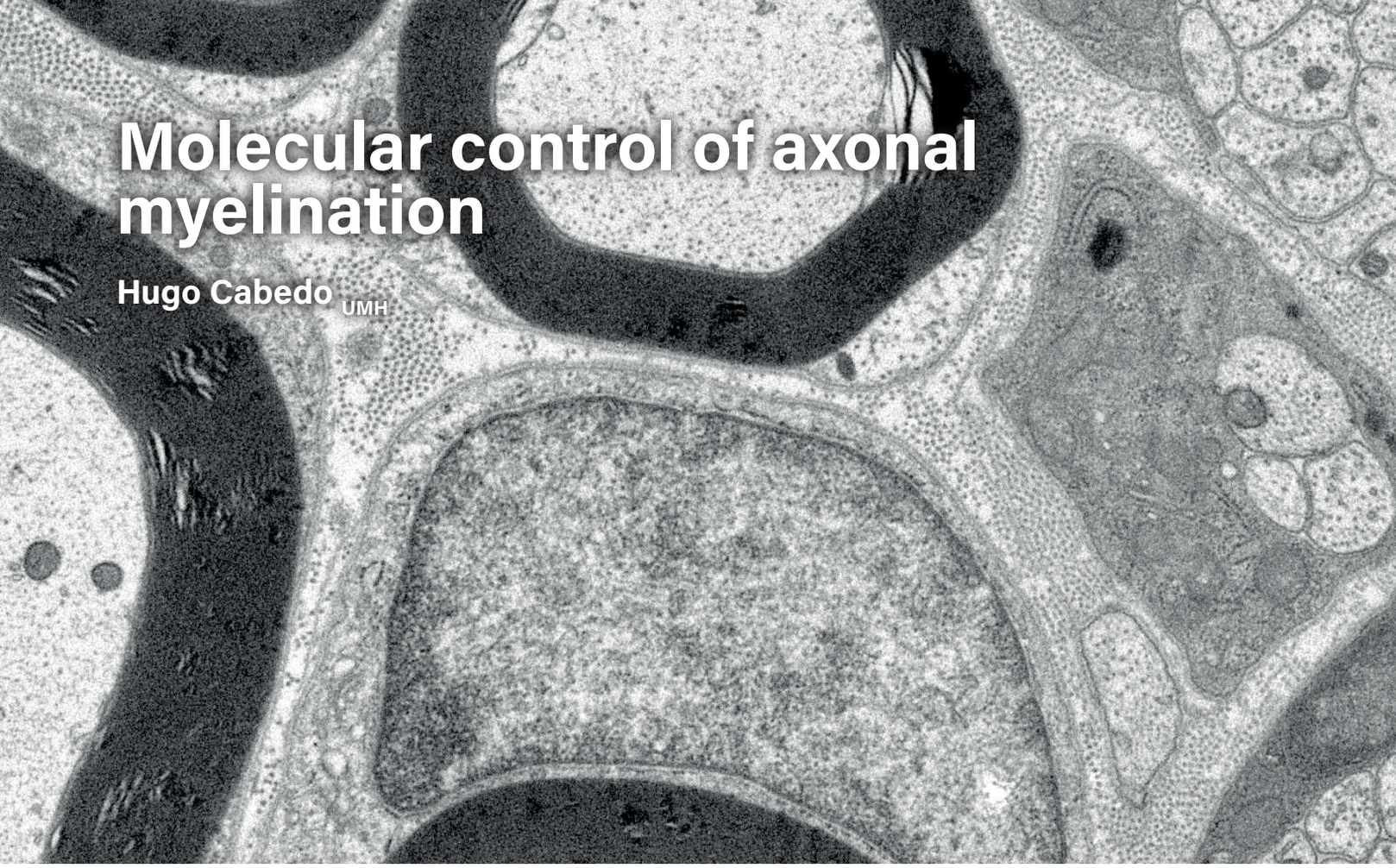

Molecular control of axonal myelination

Hugo Cabedo UMH

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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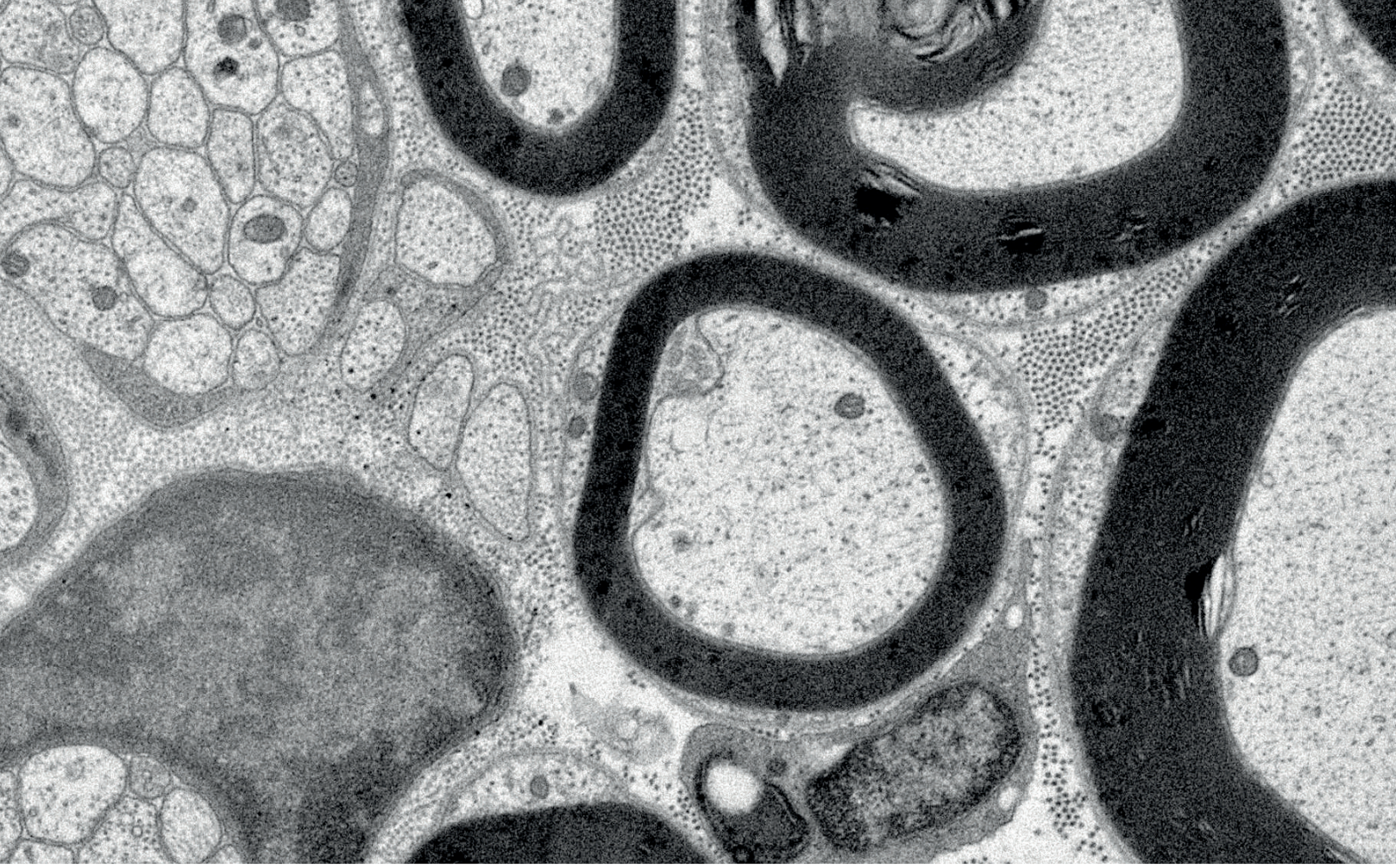

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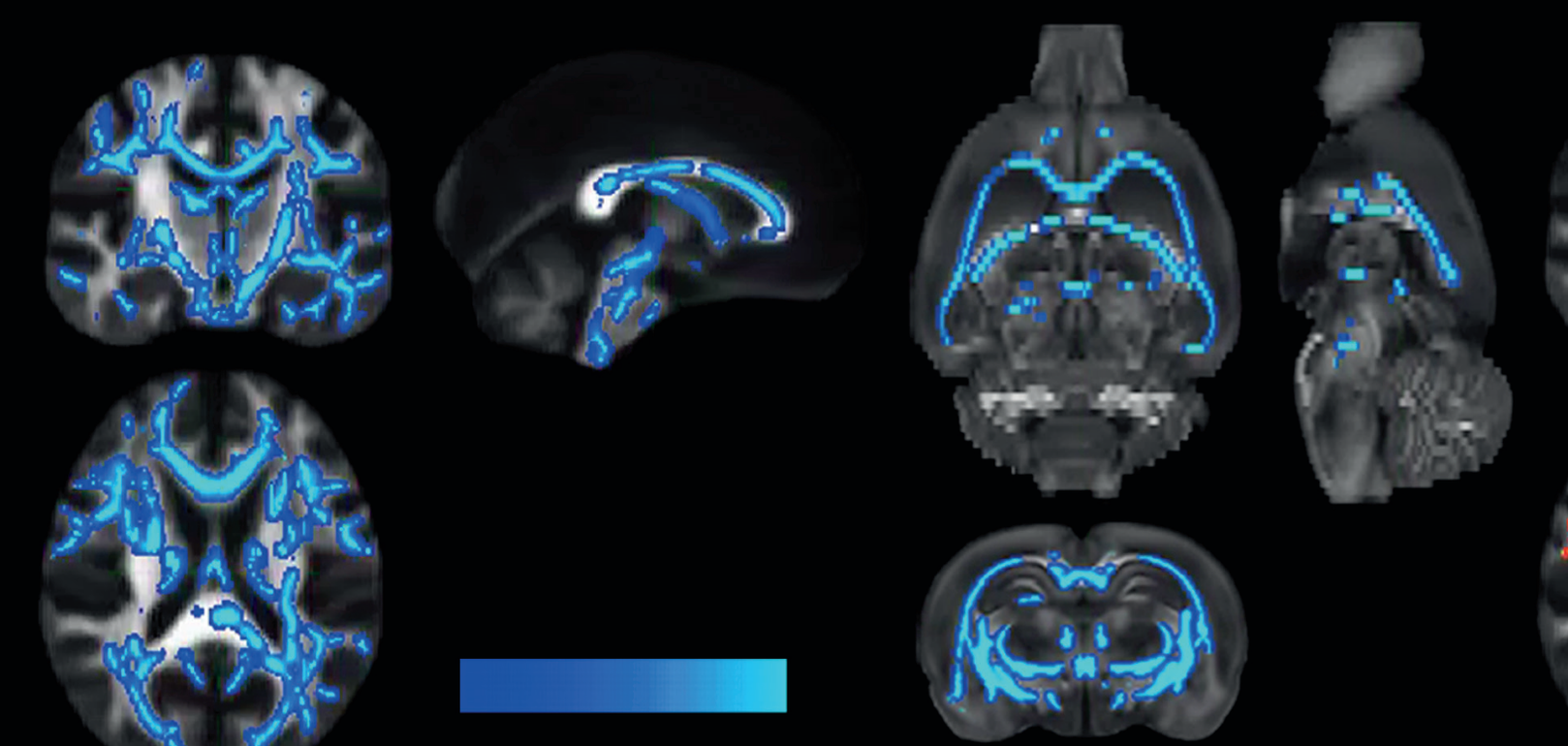

Plasticity of brain networks

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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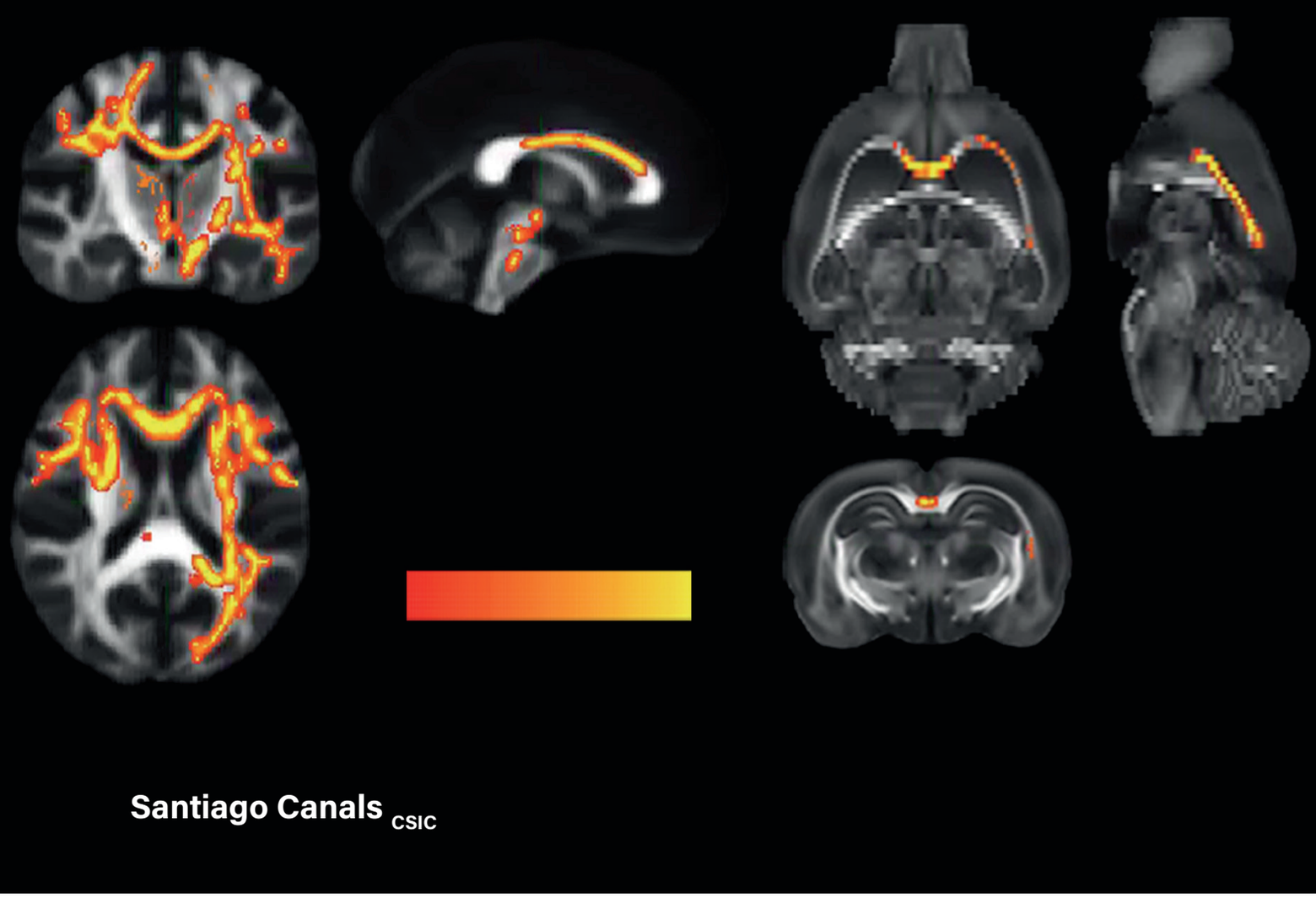

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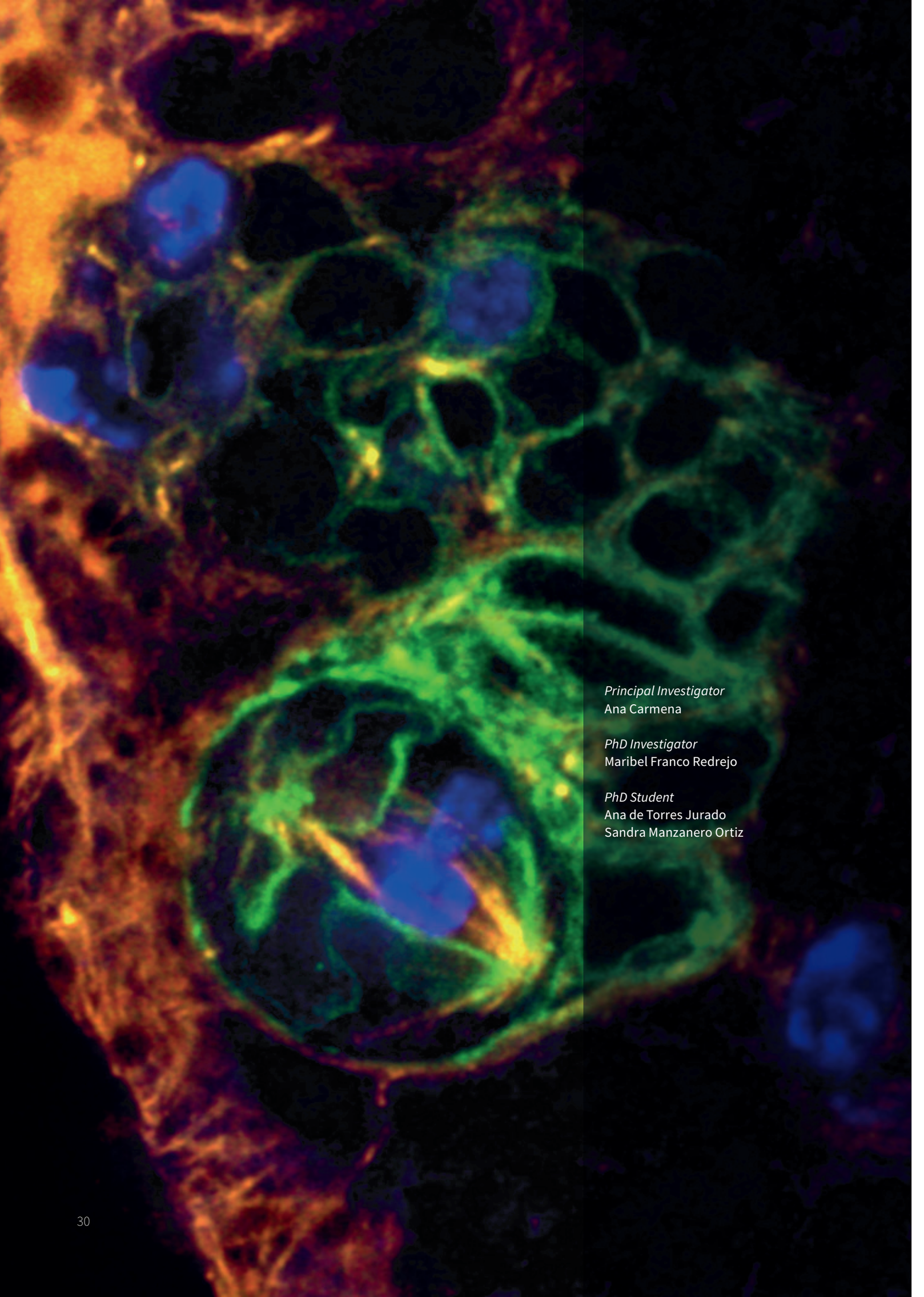

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Signaling networks underlying asymmetric cell division

Ana Carmena CSIC

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

- Which 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".
- Which are 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.
- Which are the connections between failures in the process of asymmetric cell division and tumorigenesis? Our model system are the type II neuroblasts of the *Drosophila* larval brain

The Approach: Today it has become apparent that signal transduction pathways are not mere linear cascades. Conversely, they are organized into complex signaling networks. 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 are excellent candidates as hubs of cross-talk between signaling pathways. Hence, we analyze the function of PDZ proteins, including the protein Canoe/Afadin/AF-6, as signal integrators within signaling networks during asymmetric cell division. We achieve our research integrating Genetic, Cell Biology, Biochemistry, Molecular Biology and Proteomic techniques.

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Cellular & conductual neuroscience

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The role of substance P in pain, tolerance and dependence mechanisms to opiates. We study the role of SP in tolerance effects, reward and drugs of abuse dependence, using KO animals for the NK1 gene. We investigate the molecular and behavioural effects of morphine, comparing to cocaine and amphetamine, which also induce addiction and analgesia, and the morphological localization of the areas of the brain involved. We analyse the possible association and / or dissociation of neural basis which mediate the diverse effects of morphine: analgesia, reward, tolerance, dependence, motor behaviour, withdrawal signs. Besides, we study the neural basis involved in relapse and compulsive drug self-administration behaviour.

Stress is a precipitating factor in causing relapse into drug taking in man and drug self-administration in animals. However, stress responses can be attenuated by substance P receptor antagonist or by genetic disruption of the substance P receptor. Therefore, drugs that antagonize the actions of substance P may be powerful new tools in both the treatment of opiate drugs addiction and the prevention of relapse into drug taking. Development of cell therapy in the treatment of neurodegenerative disorders: Alzheimer and Parkinson diseases.

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Mechanisms of growth control & cancer in Drosophila

María Domínguez CSIC

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 neurons 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 signalling 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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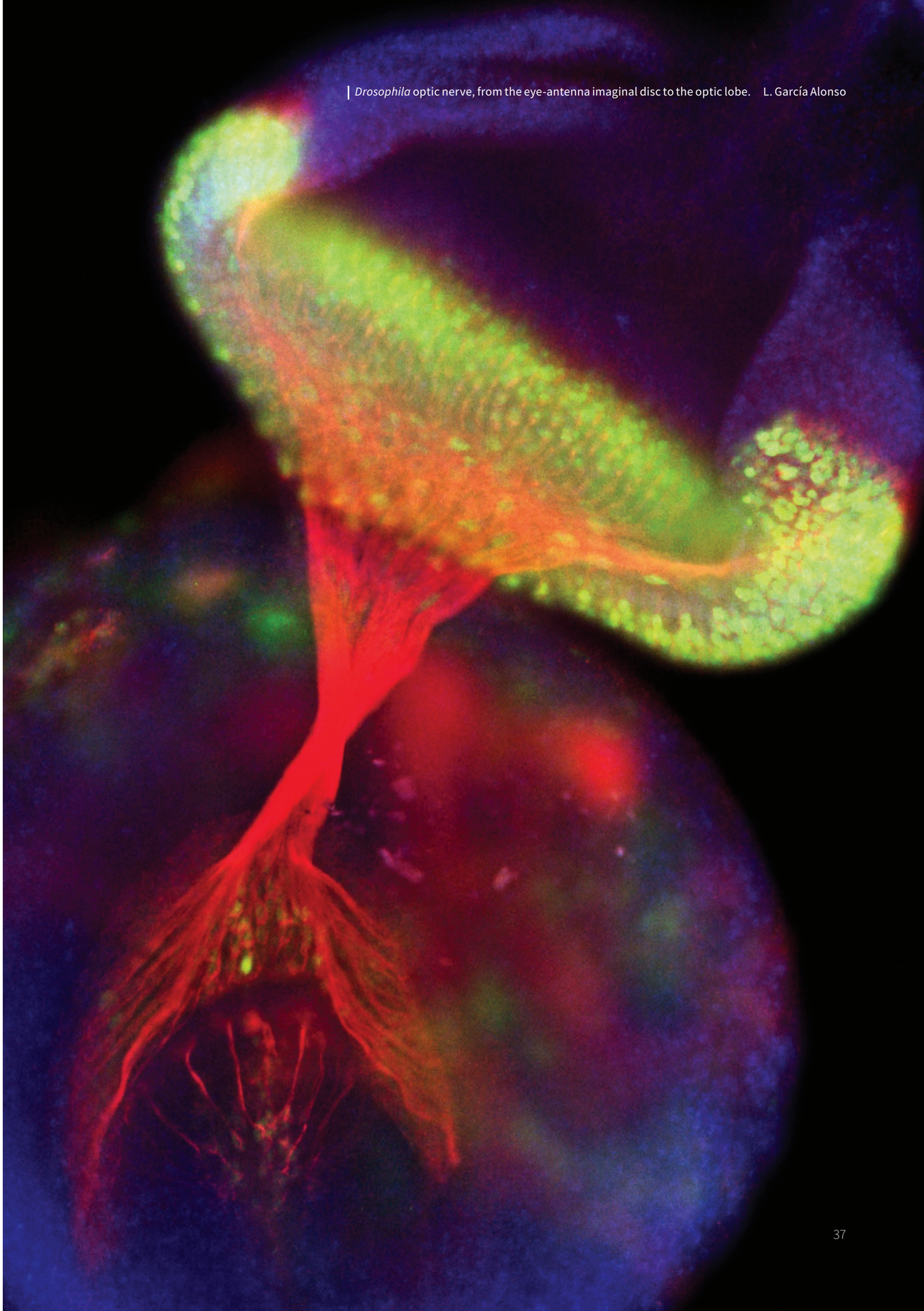

Drosophila optic nerve, from the eye-antenna imaginal disc to the optic lobe. L. García Alonso

Ocular Neurobiology

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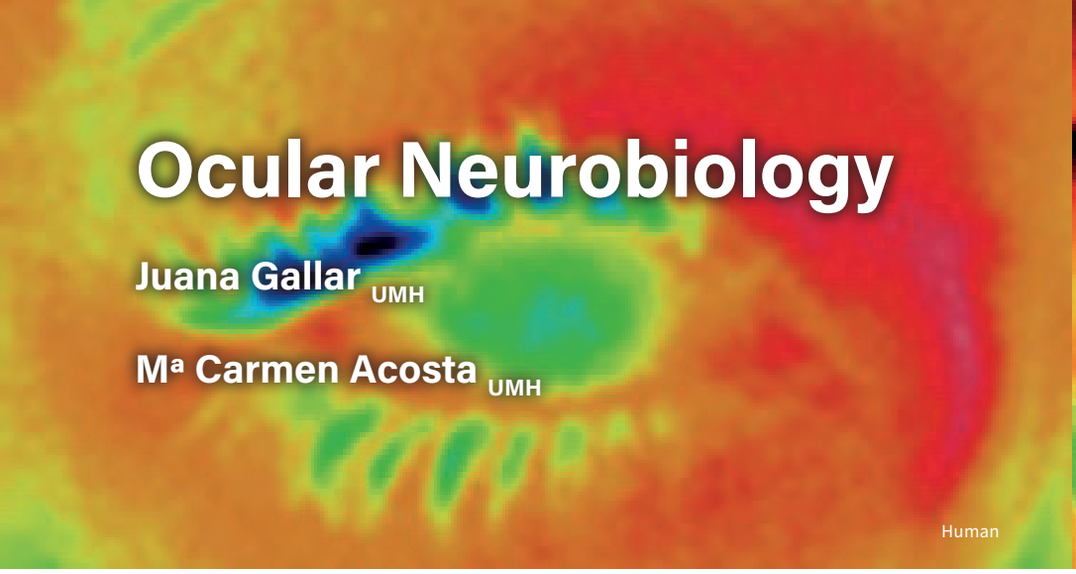

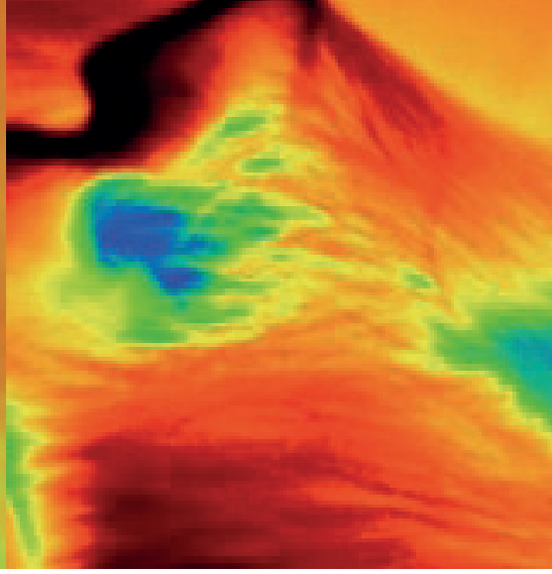

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The main interest of the Ocular Neurobiology Group (ONG) is to study the functional activity of sensory nerves from the ocular surface, responsible for the genesis of sensations evoked by stimulation of ocular tissues as well as for the trophic maintenance and correct moisturizing of the ocular surface. Using both, electrophysiological (recording nerve activity of sensory receptors in nerve endings and axons, as well as extracellular recording of trigeminal ganglion neurons) and morphological techniques (studying corneal nerve morphology in fixed and living tissue), and psychophysical studies (analyzing the characteristics of the sensations evoked by selective stimulation of the ocular surface), the ONG investigates the functional characteristics of the primary sensory neurons 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.

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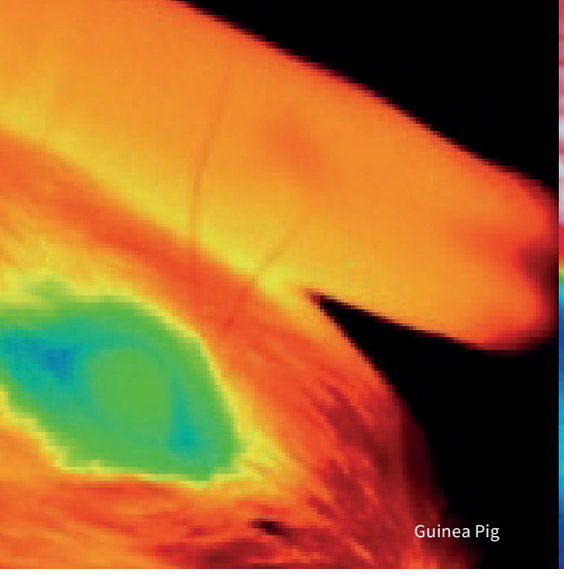

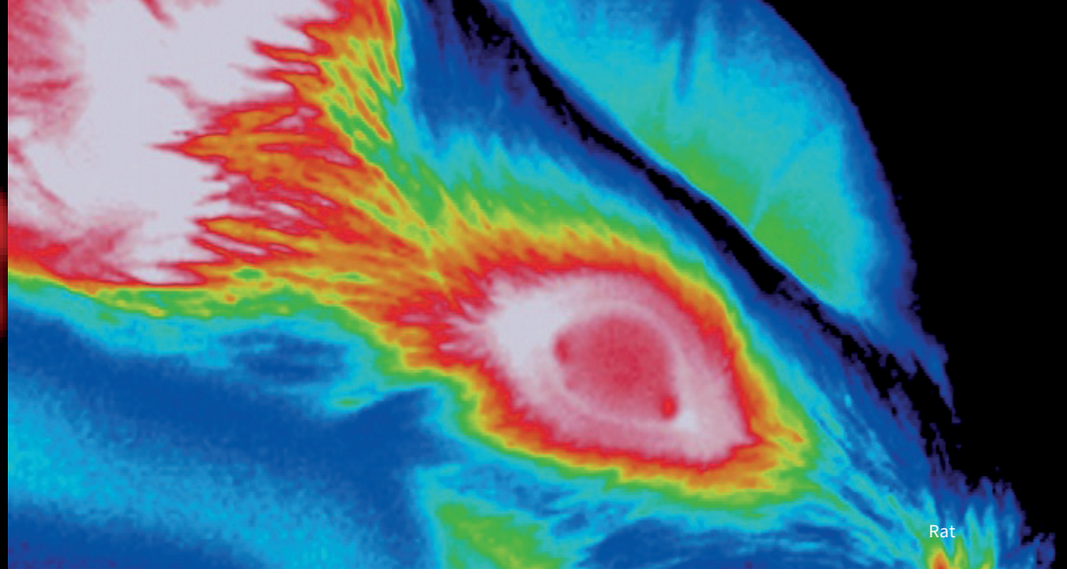

At the present time, the ONG studies the neural mechanisms responsible for the regulation of ocular surface wetness, studying the molecular and cellular mechanisms underlying sensory transduction, and the role of trigeminal sensory input in the reflex regulation of tear production and blinking, as well as their changes with ageing.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 correct moisturizing of the ocular surface. Using both, electrophysiological (recording nerve activity of sensory receptors in nerve endings and axons, as well as extracellular recording of trigeminal ganglion neurons) and morphological techniques (studying corneal nerve morphology in fixed and living tissue), and psychophysical studies (analyzing the characteristics of the sensations evoked by selective stimulation of the ocular surface), the ONG investigates the functional characteristics of the primary sensory neurons innervating the anterior surface of the eye with particular attention to those neurons participating in ocular sensations of eye dryness, discomfort and pain.

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Physiology of the cerebral cortex

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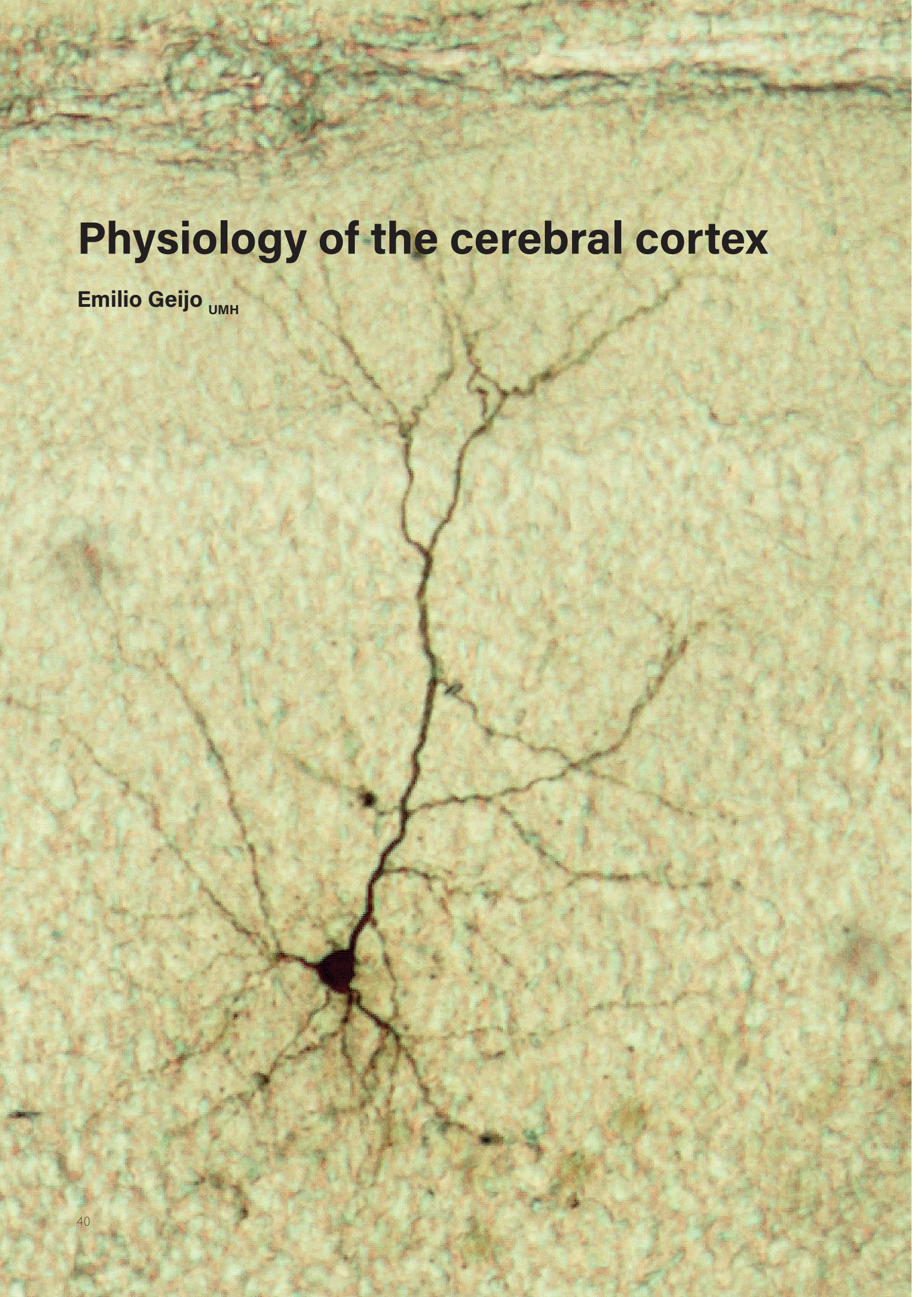

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Our group is interested in the study of the basic physiological mechanisms of the cortical local microcircuits, in particular of the prefrontal cortex and the anterior cingulated cortex; These cortical areas are implicated in cognitive functions and 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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Mechanotransduction in mammals

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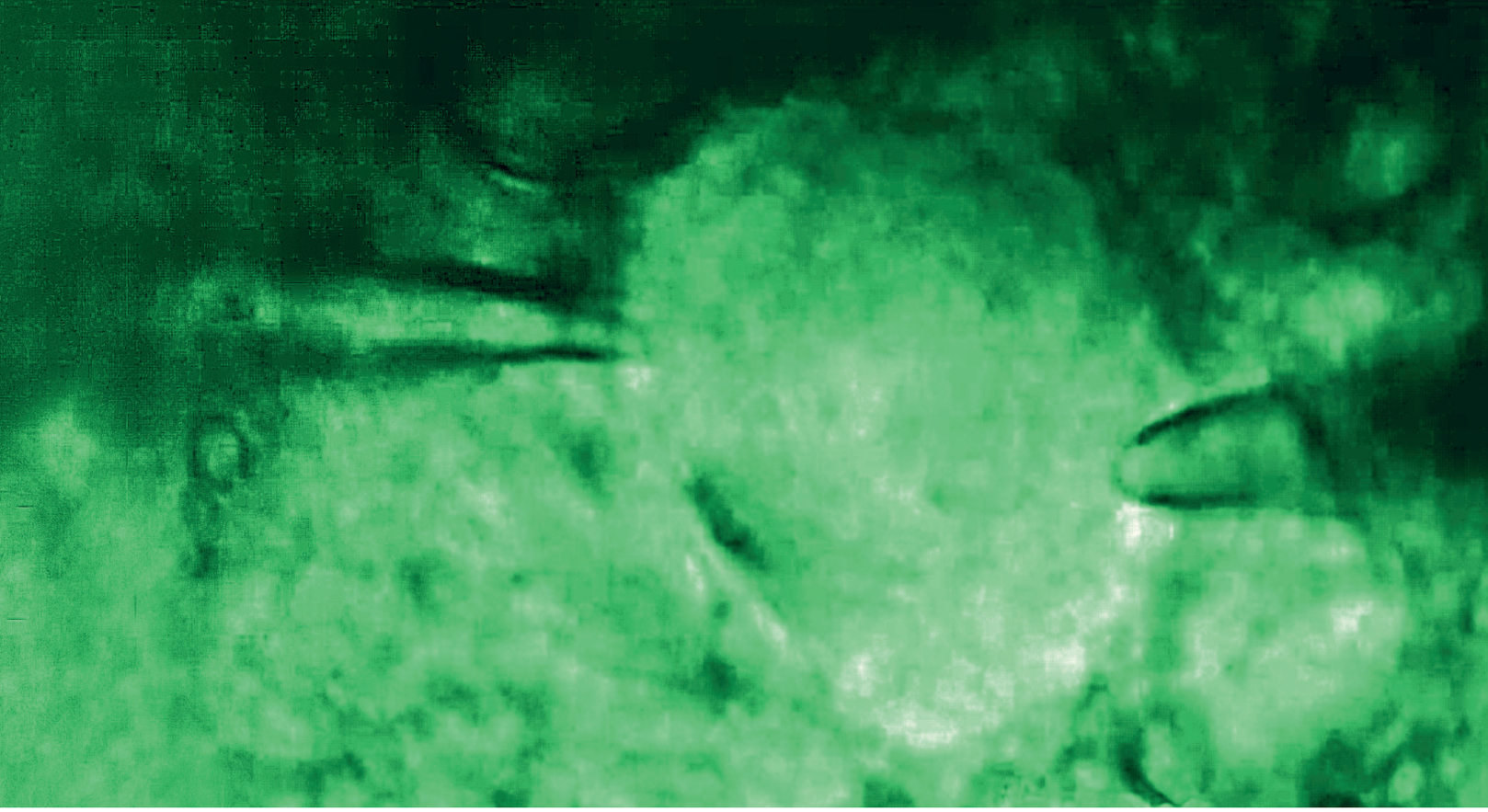
Sensory receptors are cells specialized in sensing diverse physical and chemical stimuli. Their performance has been shaped by millions of years of evolutionary pressure.

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 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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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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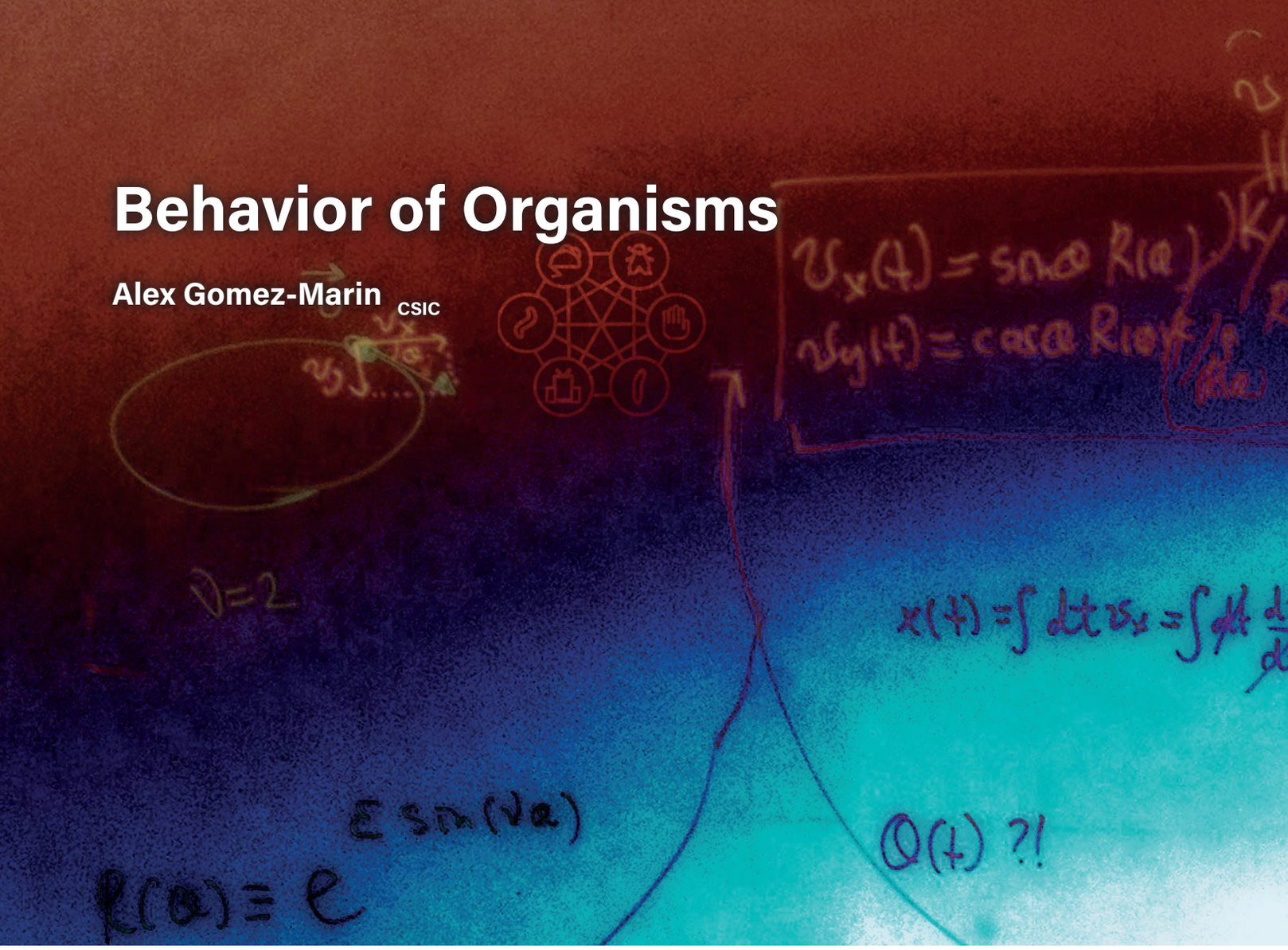
Behavior of Organisms

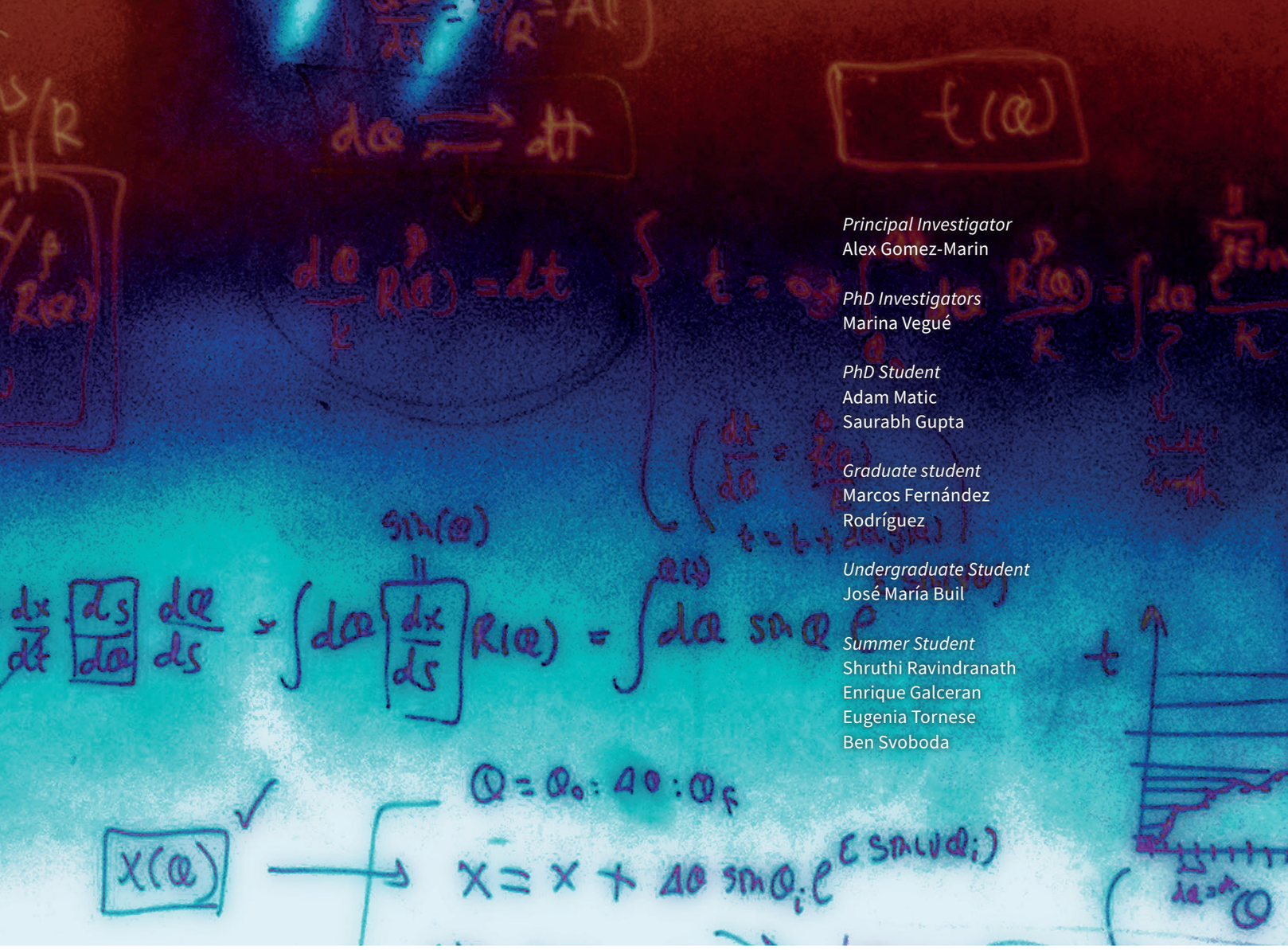
Alex Gomez-Marin CSIC



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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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 one 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. Then, we also analyze to what extent our discoveries in the visual system apply to the development of other circuits in the CNS.

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Synaptic Neuromodulation

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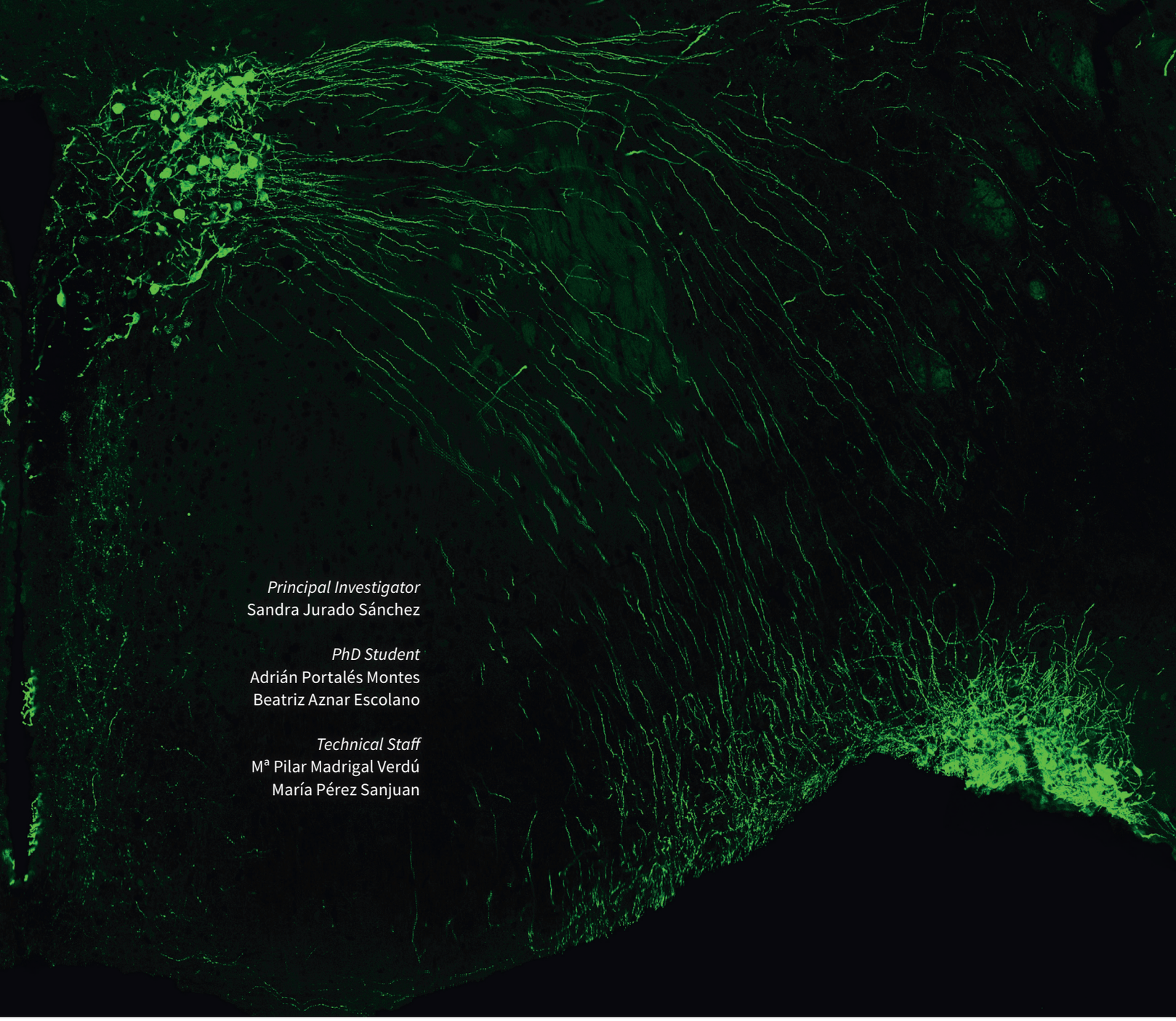
After the intensive refinement process that occurs during the developmental stages, the mature brain retains the ability of undergoing rapid adaptations in response to external stimuli by the means of a cellular phenomenon known as synaptic plasticity. Our goal is to understand how synaptic plasticity 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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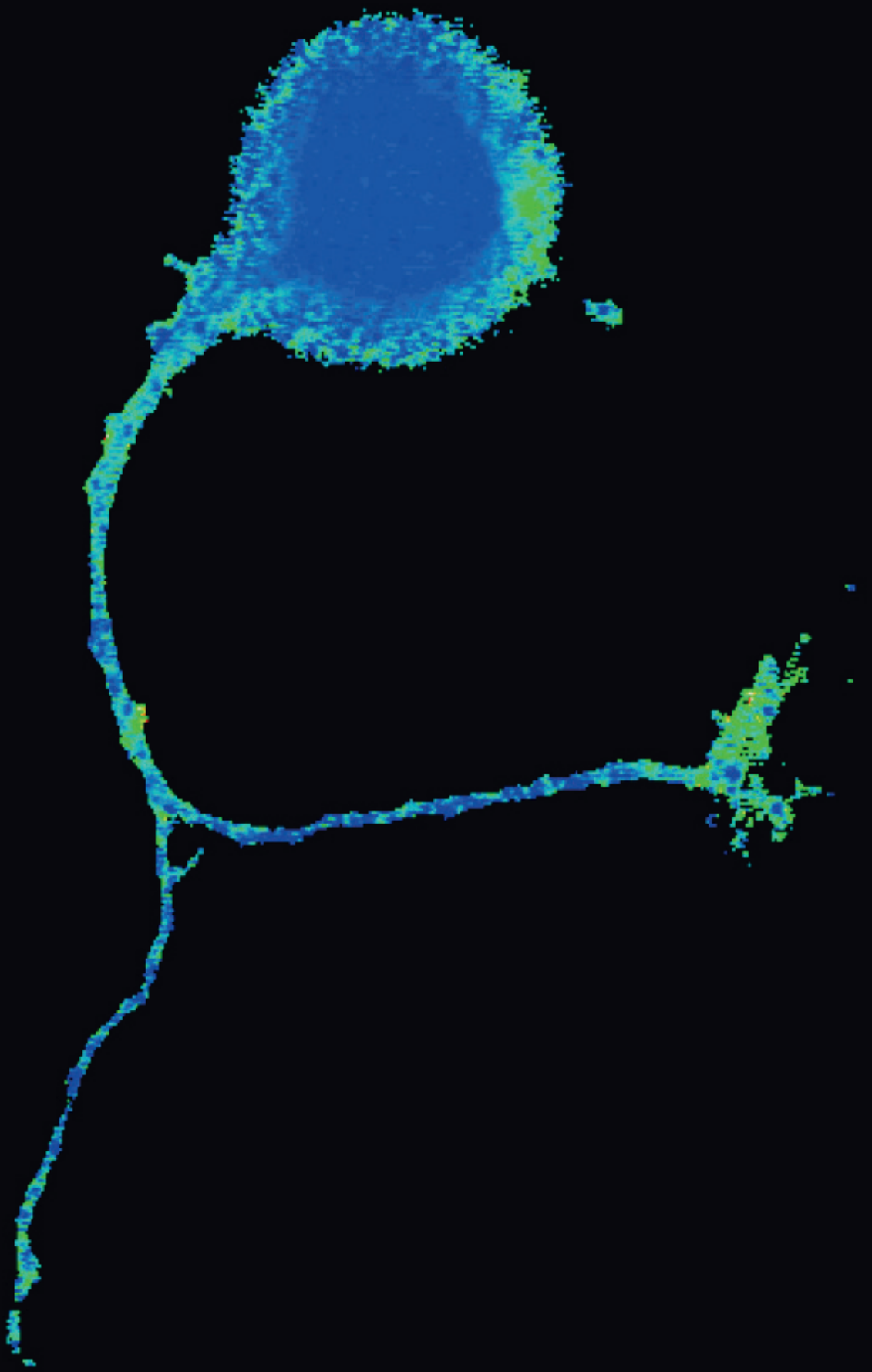

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Synaptic physiology

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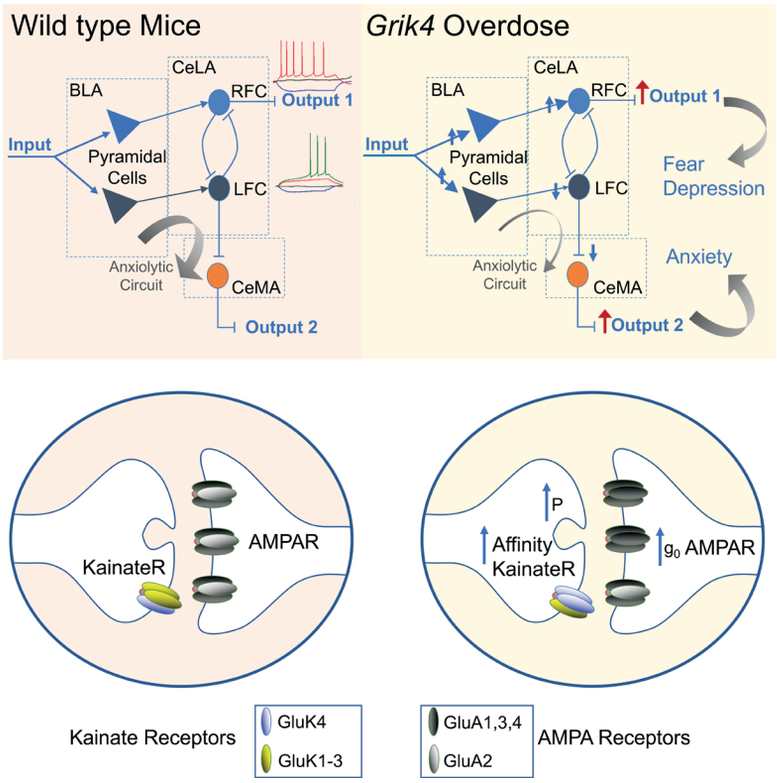
Neurons communicate with each other by means of releasing neuroactive substances that activate specific proteins situated at the postsynaptic membrane. This is a finely regulated process on which the correct performance of our brain depends, which is to say ourselves. One of the current goals of modern 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 provided the tool by which these receptors could be further studied, the drug 2-3-benzodiazepine, GYKI 53655, whicWWh allows its pharmacological isolation. Indeed, 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 in cultured neurons and brain slices and described their fundamental role in controlling neuronal tissue excitability and epileptogenesis. We have 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. Taken together, our data has helped to understand why KAR activation is proconvulsive and pointed them as targets for new treatments of epileptic disease.

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 of the receptor that positively 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. Together, these data indicate that a single gene variation in the glutamatergic system results in behavioural symptomatology consistent with autism spectrum disorders as well as in alterations in synaptic function in regions involved in social activity.



An increase in Grik4 gene dose enhances the efficiency of synaptic transmission, causing a persistent circuit disequilibrium that alters the main amygdala outputs. This may account for the behavioral abnormalities observed in disorders like autism and schizophrenia.

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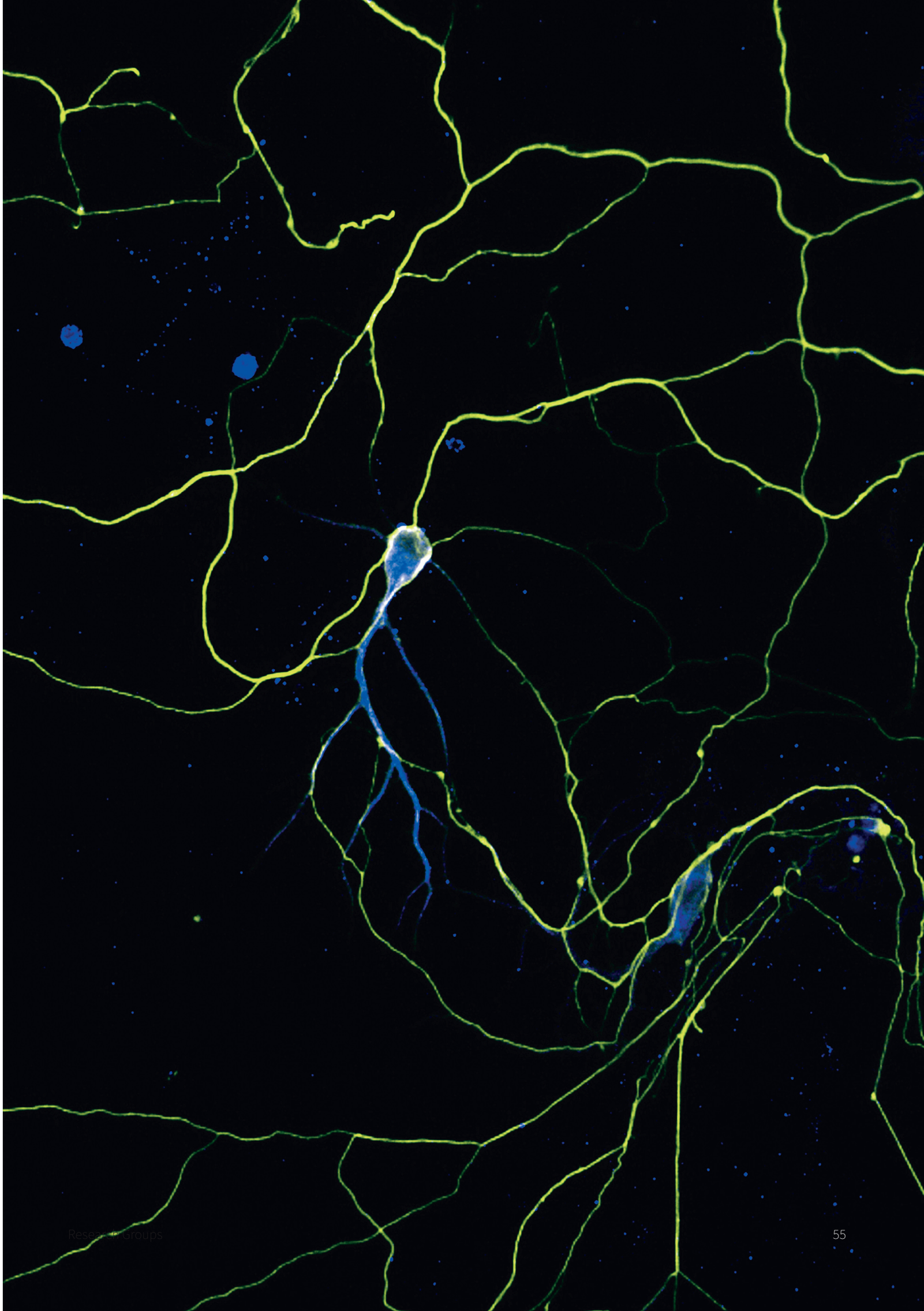

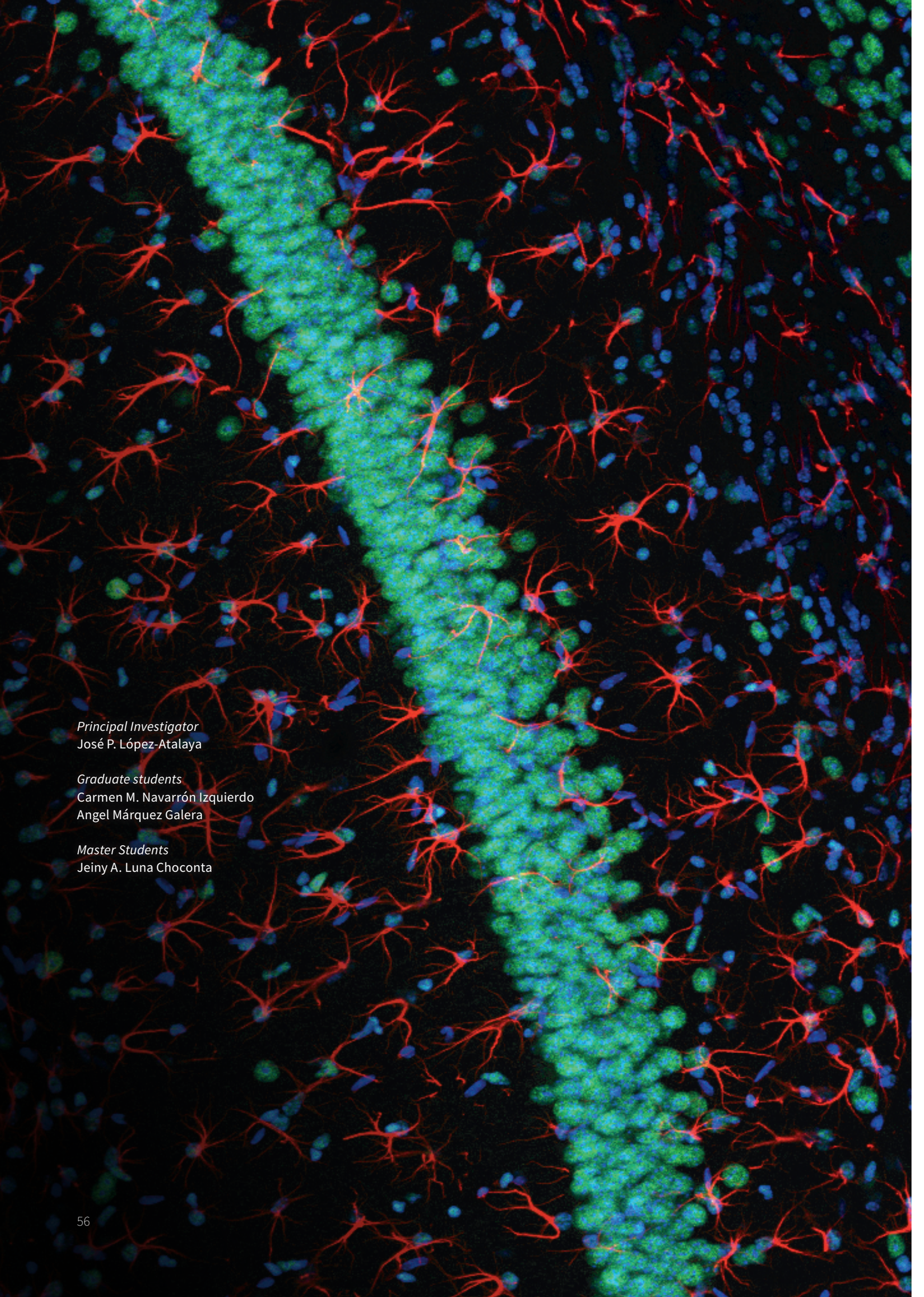

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Cellular Plasticity and Neuropathology

José P. López-Atalaya CSIC

Our research focuses on cellular plasticity of microglia and brain macrophages. The ability of a cell to adopt an alternative fate when exposed to different conditions is now emerging as an important process in normal physiology and in disease conditions, such as ageing and neurodegenerative diseases.

In the brain, glial cells play fundamental roles in neuronal physiology including regulation of neurotransmission and synapse formation and maintenance. In addition, neuroglia constitutes the intrinsic brain defense system. Stroke, trauma, infection or chronic neurodegeneration trigger a pronounced glial response. This dual role is associated to a profound phenotypic switch from "basal" to "reactive". Critically, microglia and other macrophages of the brain, and astrocytes must orchestrate complex genetic programs in response to a variety of stimuli that dictate the induction of alternations in their phenotype to serve the appropriate functions. We are interested in the identification of the mechanisms underlying phenotypic and functional plasticity of microglia and brain macrophages. We have particular interest in elucidating the molecular mechanisms underlying the transition between cell states and maintenance of cell identity. To study these mechanisms, we combine mouse genetics, genomics and standard histological, cellular and molecular biology methods.

The long-term goal of our research is to elucidate how gene regulatory interactions control cellular state and identity. We use neuroglia cells to elucidate the boundaries of epigenome and transcriptome plasticity in differentiated cells. Our research may provide direct mechanistic links to neuroinflammatory processes in brain aging and neurodegenerative diseases.

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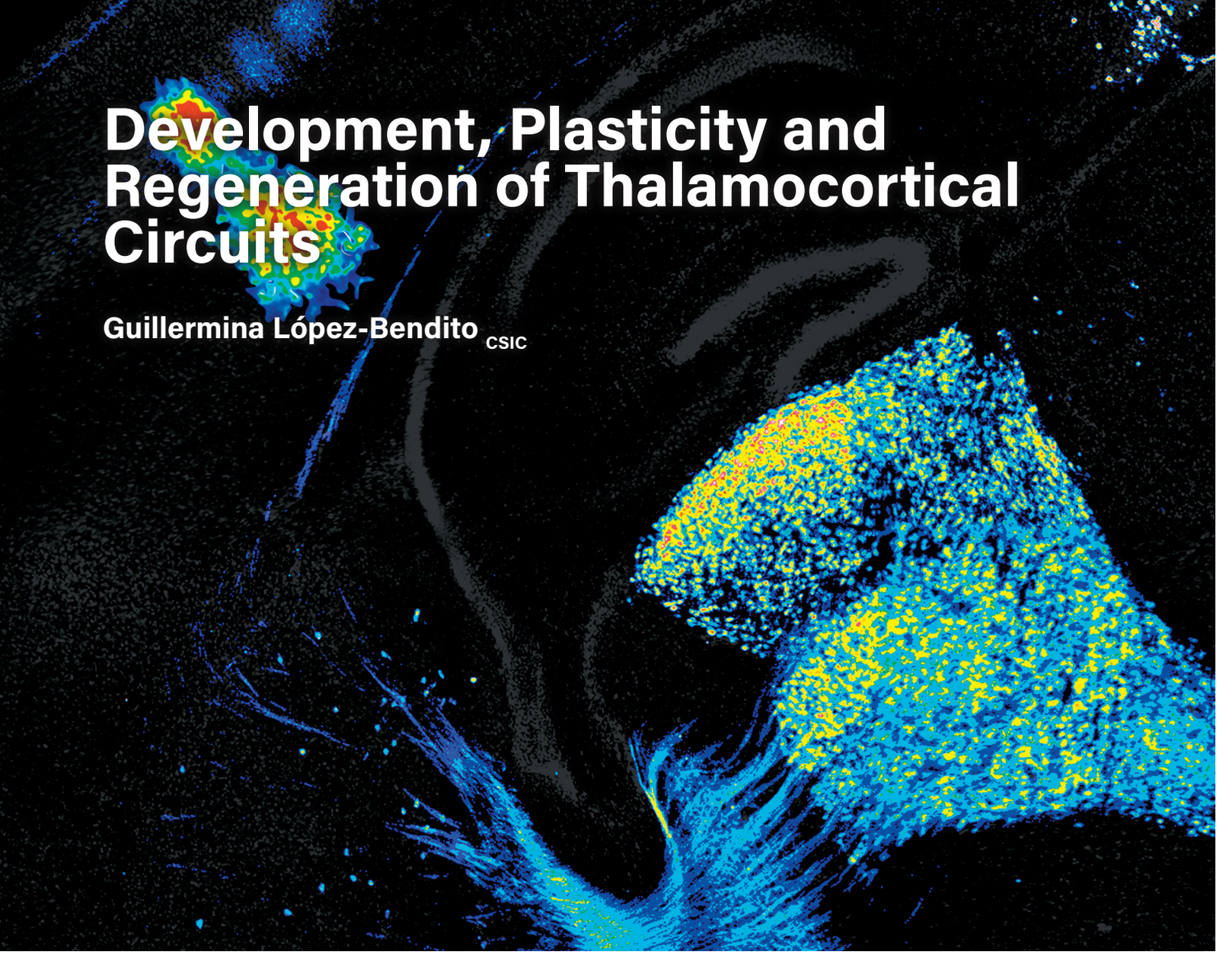
Development, Plasticity and Regeneration of Thalamocortical Circuits

Guillermina López-Bendito CSIC



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 new animal model for determining the role of thalamocortical input in cortical specification and plasticity.

Within these projects we are using several experimental programmes, these include: optical 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 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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Translational neuropsychopharmacology of neurological & 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 behaviour, 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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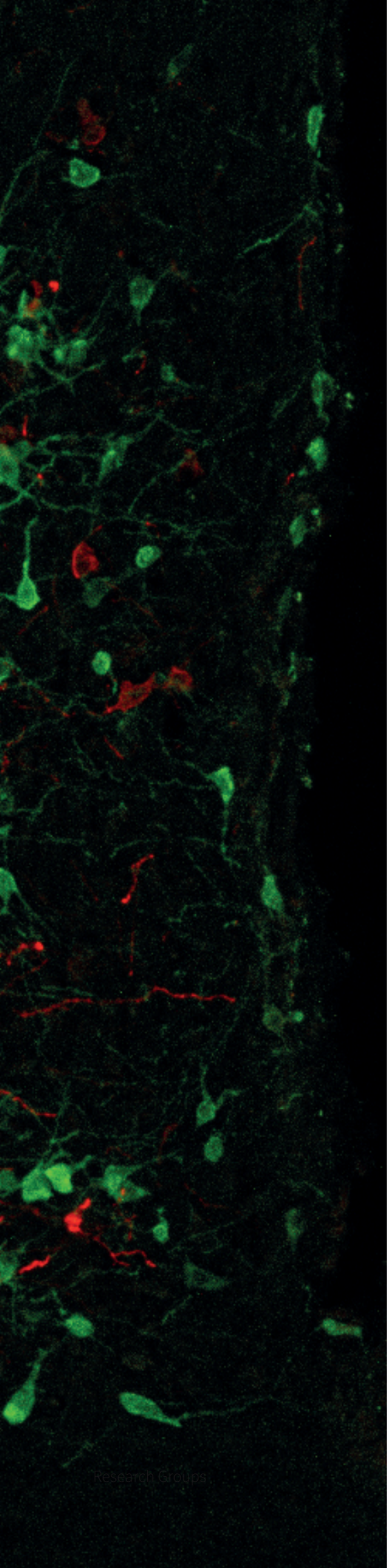
Neural Circuits of Social Behaviour

Cristina Márquez Vega UMH



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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 have recently demonstrated that Norway rats display prosocial behaviours in food foraging context, providing food to conspecifics, and identified the proximal mechanisms at the level of behaviour (Marquez et al, Current Biology, 2015). 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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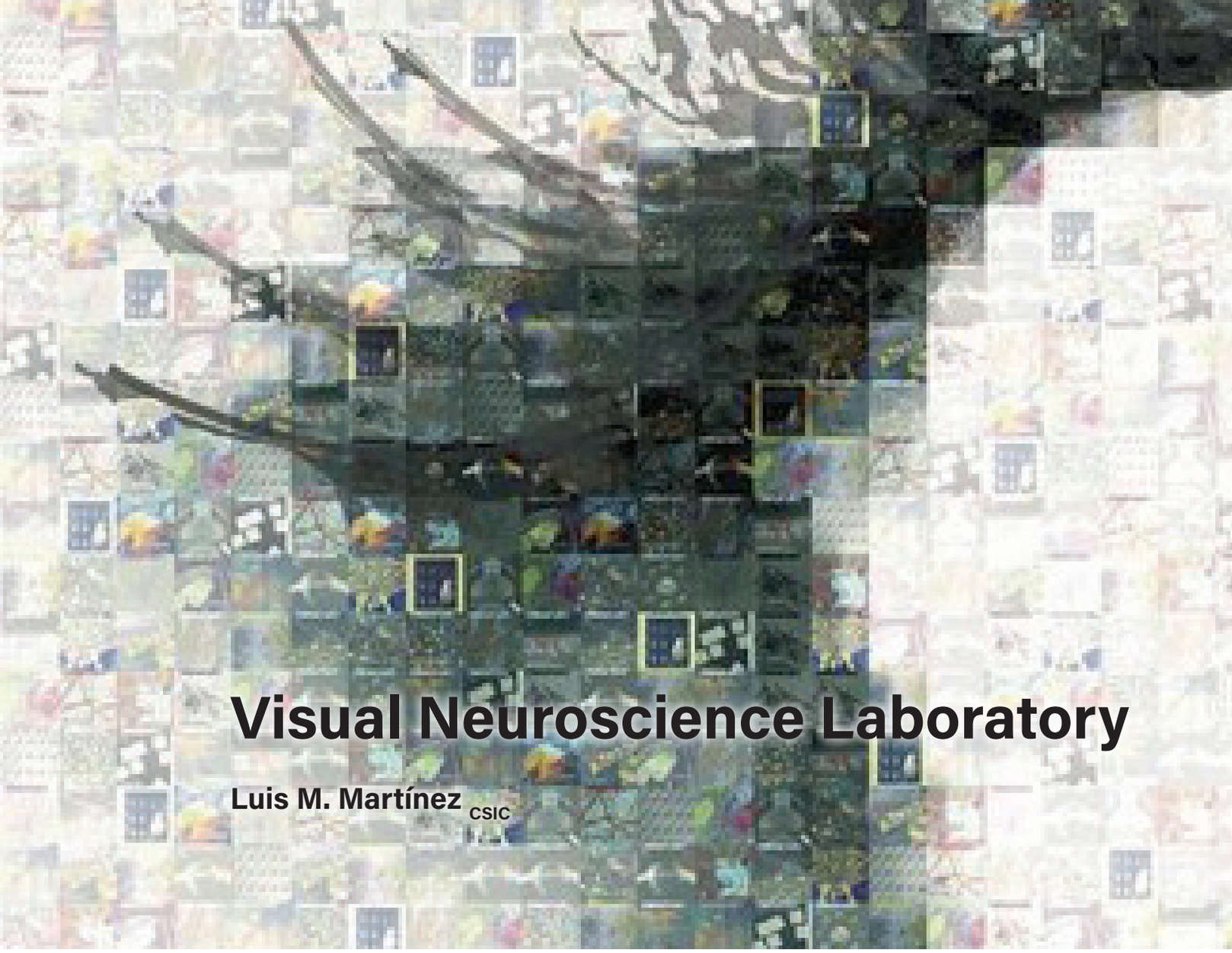

Visual Neuroscience Laboratory

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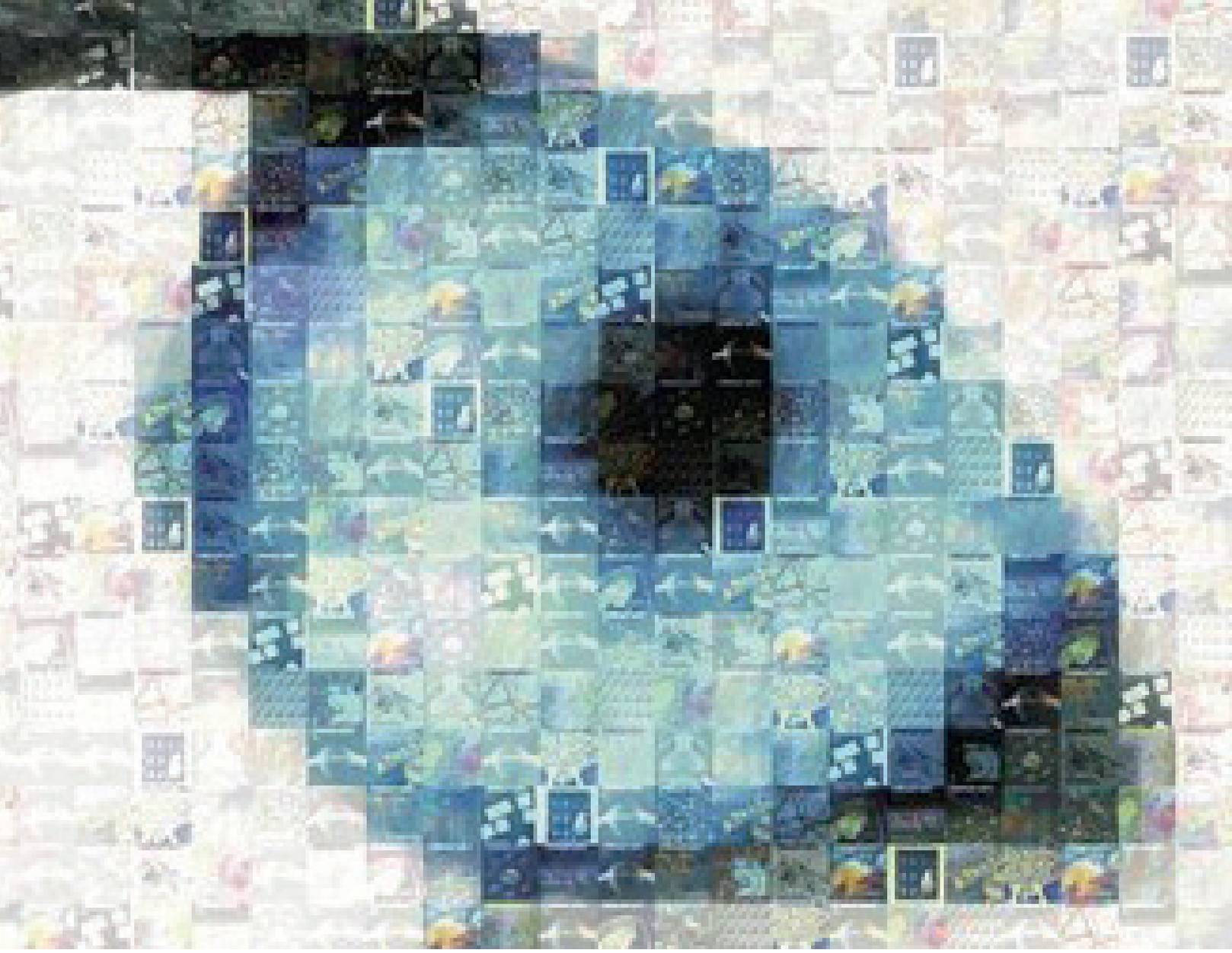
We, like many other mammals, are essentially visual animals. Thus the visual system of our brains must achieve a daunting task: it creates, in real time, an internal representation of the external world that it is used by other parts of the brain to guide our behavior. But, how do we actually see? How 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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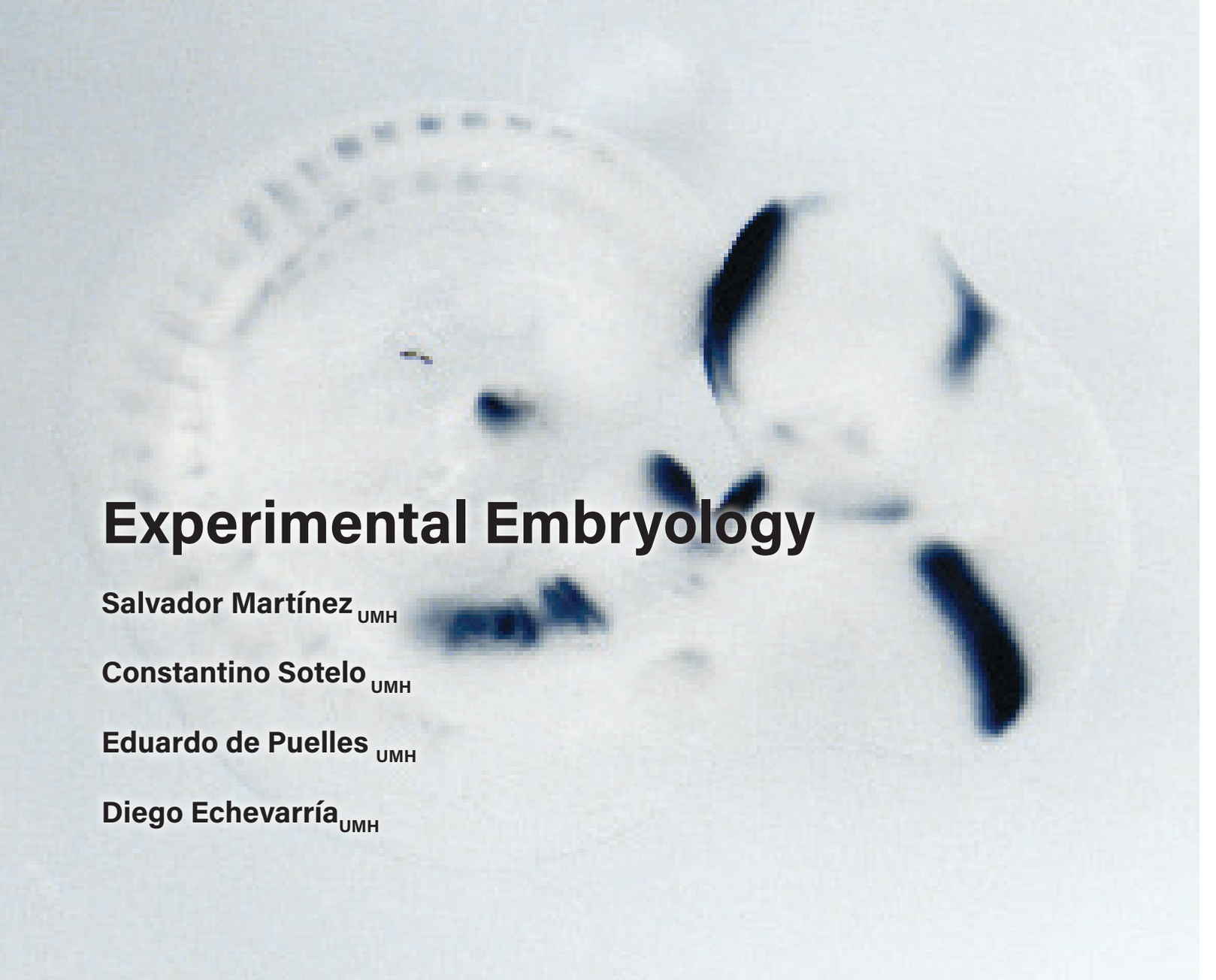

Experimental Embryology

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Diego Echevarría UMH

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.brain-map.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

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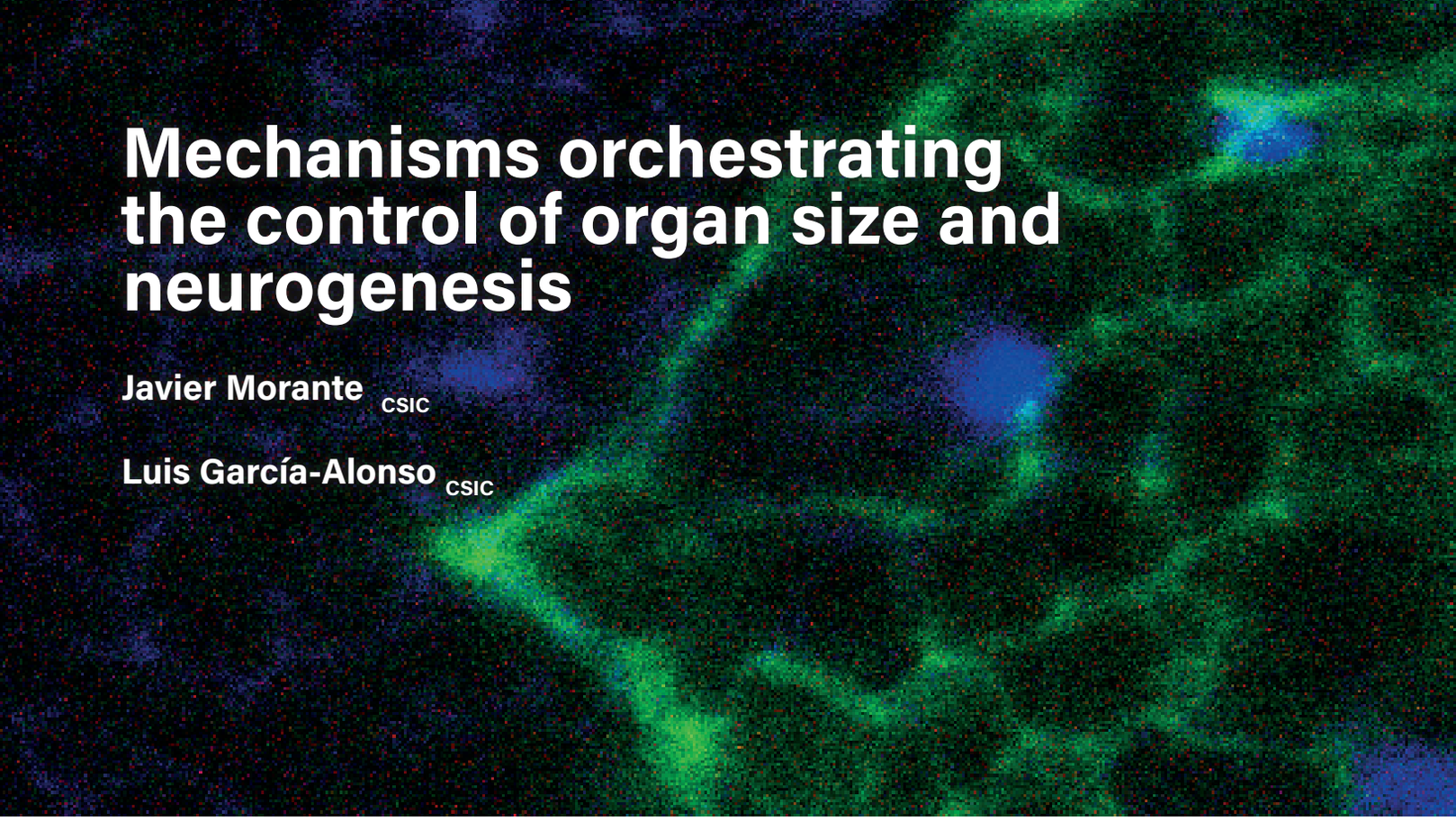
neuropathologies as well as Down syndrome. Related to this research line we are analysing the genetic alteration associated to functional psychosis (squizophrenia and bipolar disorder), particularly genes related to alteration in cortical architectural development.

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.



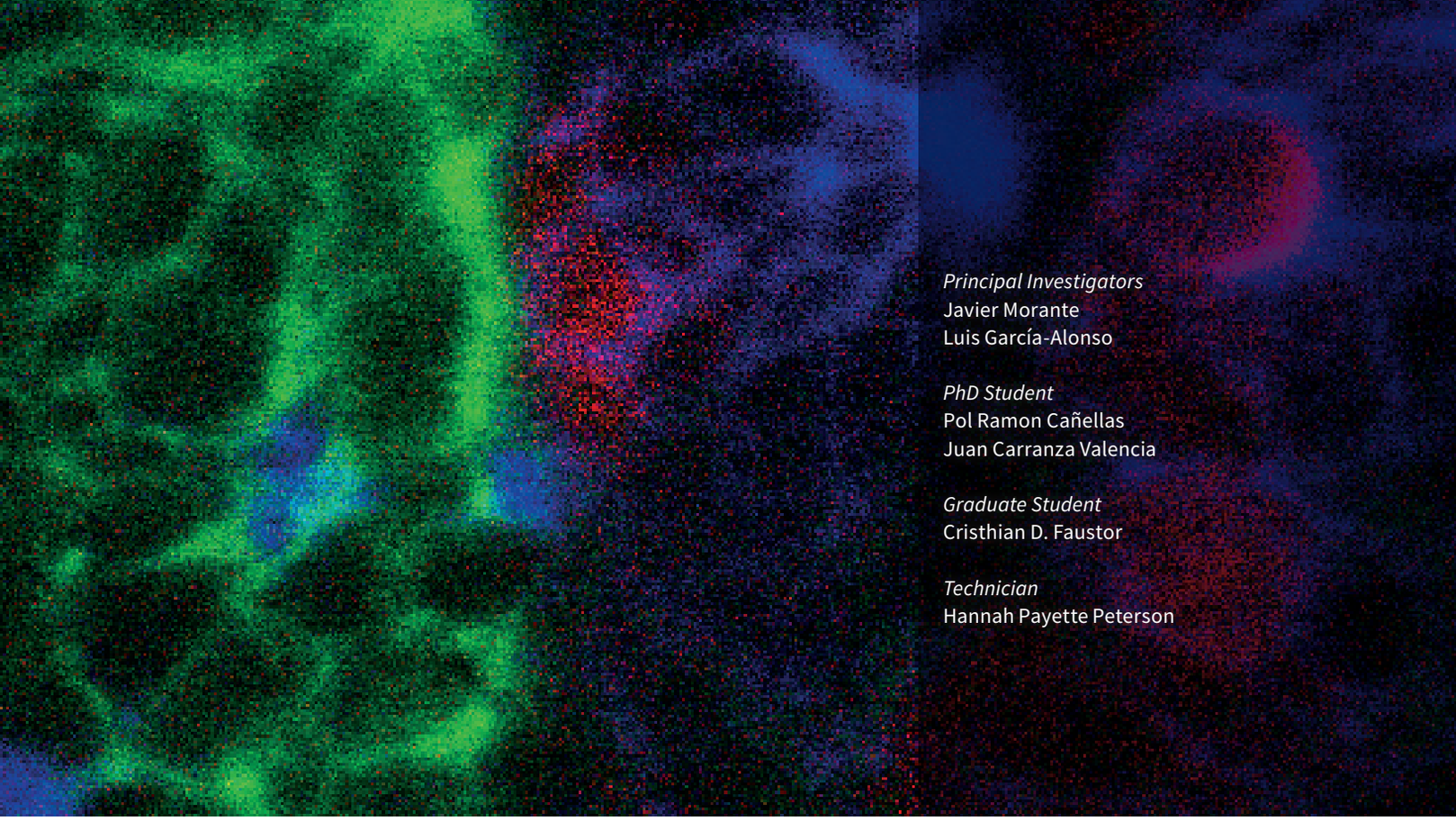
Mechanisms orchestrating the control of organ size and neurogenesis

Javier Morante CSIC

Luis García-Alonso CSIC

Number of neurons and network architecture determines the function of the Nervous System. During embryonic development, proliferation of precursors and differentiation of neurons is tightly controlled to attain a species-specific organ size, and billions of functional neural connections are formed with exquisite precision and fidelity. This process is driven by the genetic program and established in three steps: growth and neurogenesis, to generate an organ with a characteristic size and pattern; stereotyped guidance and synaptogenesis of each axon and dendrite with specific target cells; and plasticity and remodeling of synaptic connections to adapt to particular environments. Every one of these steps is critically controlled by multiple cell communication mechanisms at the local and systemic levels. L1- and NCAM-type immunoglobulins control local cell communication mechanisms involving erbB and FGFR signaling during cell proliferation, neurogenesis, axon guidance and synapse development. We study these mechanisms using *Drosophila melanogaster* as animal model. We have proposed that these molecules function as expression-level growth switches to first promote and then terminate local growth according to their expression levels (http://biorxiv.org/cgi/content/short/356196v2).

Important early events in neurogenesis are proving elusive and difficult to define. One example is the events that underlie the specification of neural stem cells, both in terms of number and cell types, which is a consequence of the processes controlling neuroepithelial cell proliferation and the transition of their progeny into neural stem cells. We have characterized a *Drosophila* glial niche that regulates early neurogenesis and that is defined by the expression and activity of the conserved microRNA, miR-8 (miR-200 in humans). This work (Morante et al., 2013) has outlined a new paradigm to explain early neurogenesis in the fly brain that could also apply to vertebrates. Hence, our research has two main goals: 1) to define the intrinsic cues responsible for balancing neuroepithelial self-renewal against the switch towards neuroepithelial-neural stem cell specification in flies and vertebrates; and 2) to define the interplay of extrinsic signals that govern these processes. We employ a combined approach in which genome-wide transcriptomic analysis of neuroepithelial cells and cells in the transition zone, or of glia and neuroepithelial cells, will help to identify candidate cues in the intrinsic and extrinsic controls underlying the earliest steps in neurogenesis, respectively. In parallel, we use genetic screenings using transgenic RNAi and gene overexpression under the control of specific cell-type promoters to functionally validate genes and establish in vivo how gene alterations impinge on neuroepithelial cell behavior to neural stem cell specification. Furthermore, we will investigate whether similar mechanisms operate in embryonic vertebrates during early neurogenesis. Thus, defining the pathways and interplay of intrinsic and niche-derived cues in earliest events of neurogenesis will pave the way to better understand stem cell-based neurodevelopmental diseases and brain tumors.



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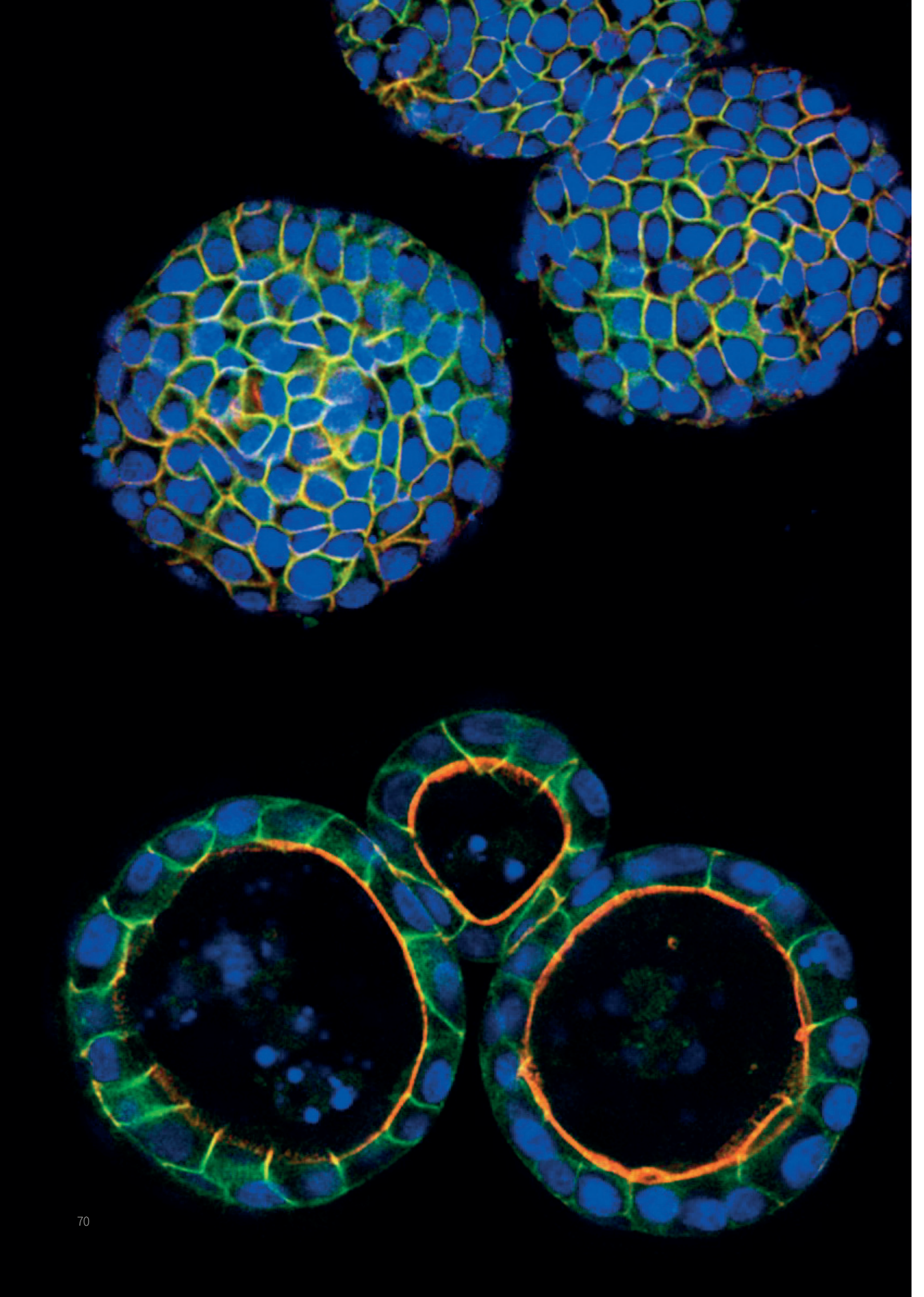
#Equal contribution. *Corresponding authors.



Cell movements in development & disease

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Our main interest is the study of cell movements and plasticity in development 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 this function associated with massive cell movements. In the last almost 20 years we have extended our studies to biomedical research, as we found that pathological activation of these factors in the adult leads to several prominent pathologies. As such, an aberrant activation of the EMT programme in tumours leads to the acquisition of invasive and migratory properties.

The invasive and survival properties of cells that undergo EMT provide a selective advantage to disseminate to distant territories both during embryonic development and during cancer progression, allowing cells to form different tissues and organs or distant metastases, respectively. Interestingly, metastasis is the cause of the vast majority of cancer-associated deaths, but the underlying mechanisms remain poorly understood. The invasion and dissemination steps during carcinoma progression have been associated with EMT, which as mentioned above, endows cells with invasive abilities and also with the stem cell-like properties required to initiate the formation of a secondary tumour. However, we have shown that while EMT is important for the acquisition of motility and invasive properties in cancer cells, its abrogation is required for these migratory cancer cells to colonize distant organs and to grow in their progress towards established metastases. This also has an impact on the design of therapeutic strategies in cancer, as inhibiting EMT (and therefore, motility) when cells have already disseminated from the primary tumour will indeed favour metastasis formation.

In non-transformed cells, we have reported that the reactivation of a partial EMT is sufficient and required for the development of fibrosis and importantly, that established renal fibrosis can be reversed by therapeutic treatment with EMT inhibitors. The latter opens new avenues in anti-fibrotic therapies. We are currently investigating putative additional inhibitors and their mechanism of action. The pathological aspect of the EMT-TFs, and in particular of Snail, is also conserved in the bone, as we have found that an excessive Snail function leads to the development of achondroplasia (the most common form of dwarfism in humans) and osteomalacia (bone demineralization in the adult). Following the same rationale as that applied to our studies in fibrosis, we are now trying to devise putative therapeutic strategies to promote the growth of the long bones.

Although pathologists did not initially consider the EMT, widely accepted by developmental biologists, relevant for cancer progression or organ fibrosis the EMT is now a leading research field in cancer and nephrology (discussed in Nieto, Science, 2013, Nieto et al., Cell 2016; Brabletz et al., Nat Rev Cancer 2018).

Going back to fundamental processes at early development, and again following cell adhesion, plasticity and cell movements, we have shown that the interplay between different transcription factors defines embryonic territories at gastrulation and neurulation, and more recently, the mechanism that drives heart looping. A left/right asymmetric EMT induces differential cell movements towards the midline, more prominent from the right, driving the leftward displacement of the posterior pole of the heart and with that, its normal positioning.

In sum, we have helped to characterize the EMT as a very dynamic and reversible process lying at the core of cell plasticity in embryonic development and pathological situations.

As such, we are now characterizing the EMTs induced by different EMT-TFs and their impact in the metastatic process particularly in breast cancer. We are developing mouse models to follow cancer cell movements from the primary tumour to the metastatic foci *in vivo* and in unveiling the signals that promote downregulation of EMT-TFs and metastatic colonization. We have recently extended our studies to melanoma, the most deadly form of skin cancer. Melanoma arises from highly motile neural crest progenitors that colonize the body during development. We are investigating the contribution of EMT inducers to melanoma plasticity, the hallmark of melanoma cells responsible for its high aggressiveness, and the microenvironmental factors that regulate melanoma dissemination and colonization to form metastases, particularly in the brain. Finally, we have found that transcription factors phylogenetically related to the EMT-TFs Snail genes, are activated in the adult neurogenic niche and we are developing *in vitro* and *in vivo* models to understand their function. In our studies we combine mouse, chick and zebrafish as experimental models for loss or gain and function analyses together with cultured cells and samples from patients with the associated pathologies.

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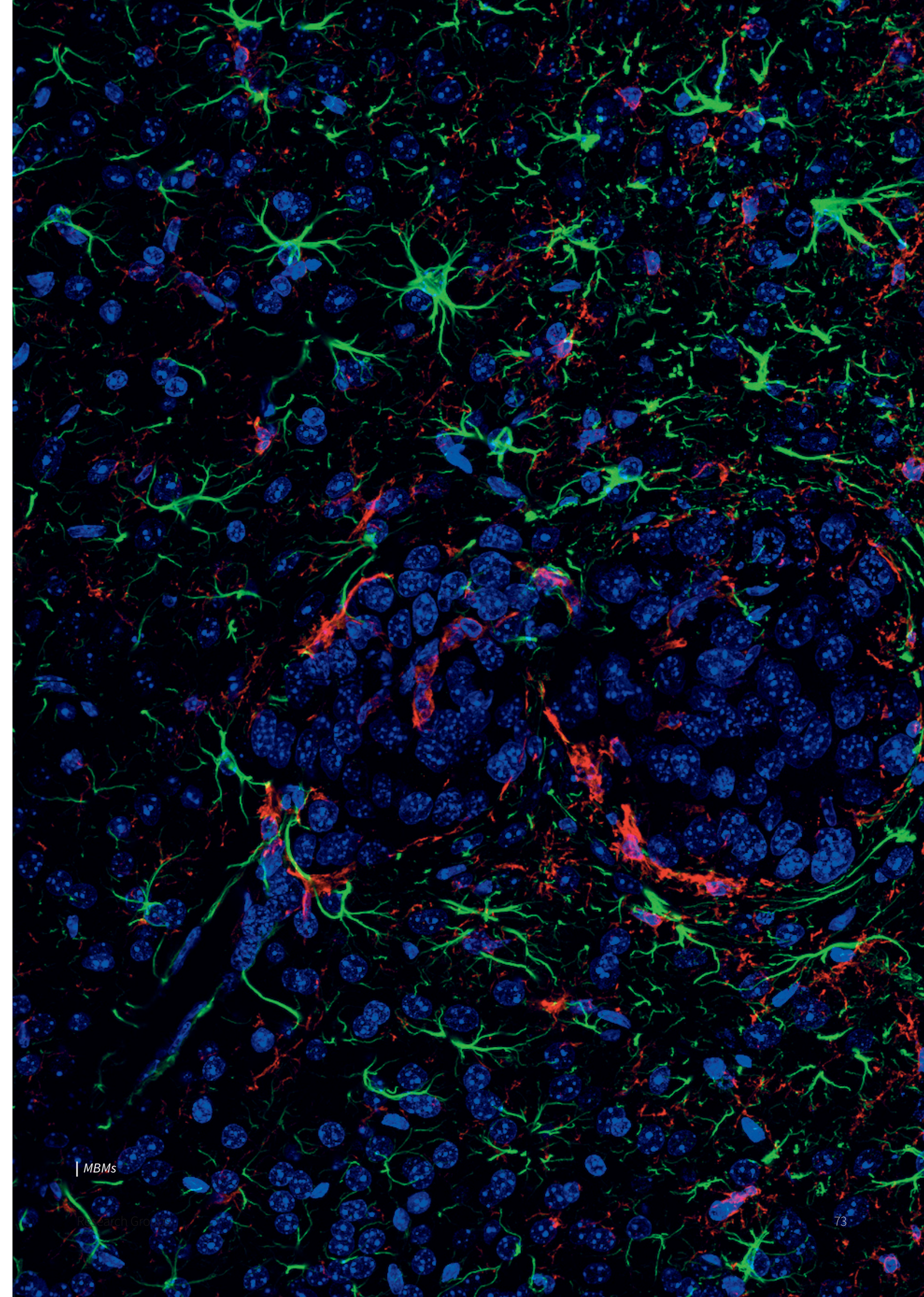
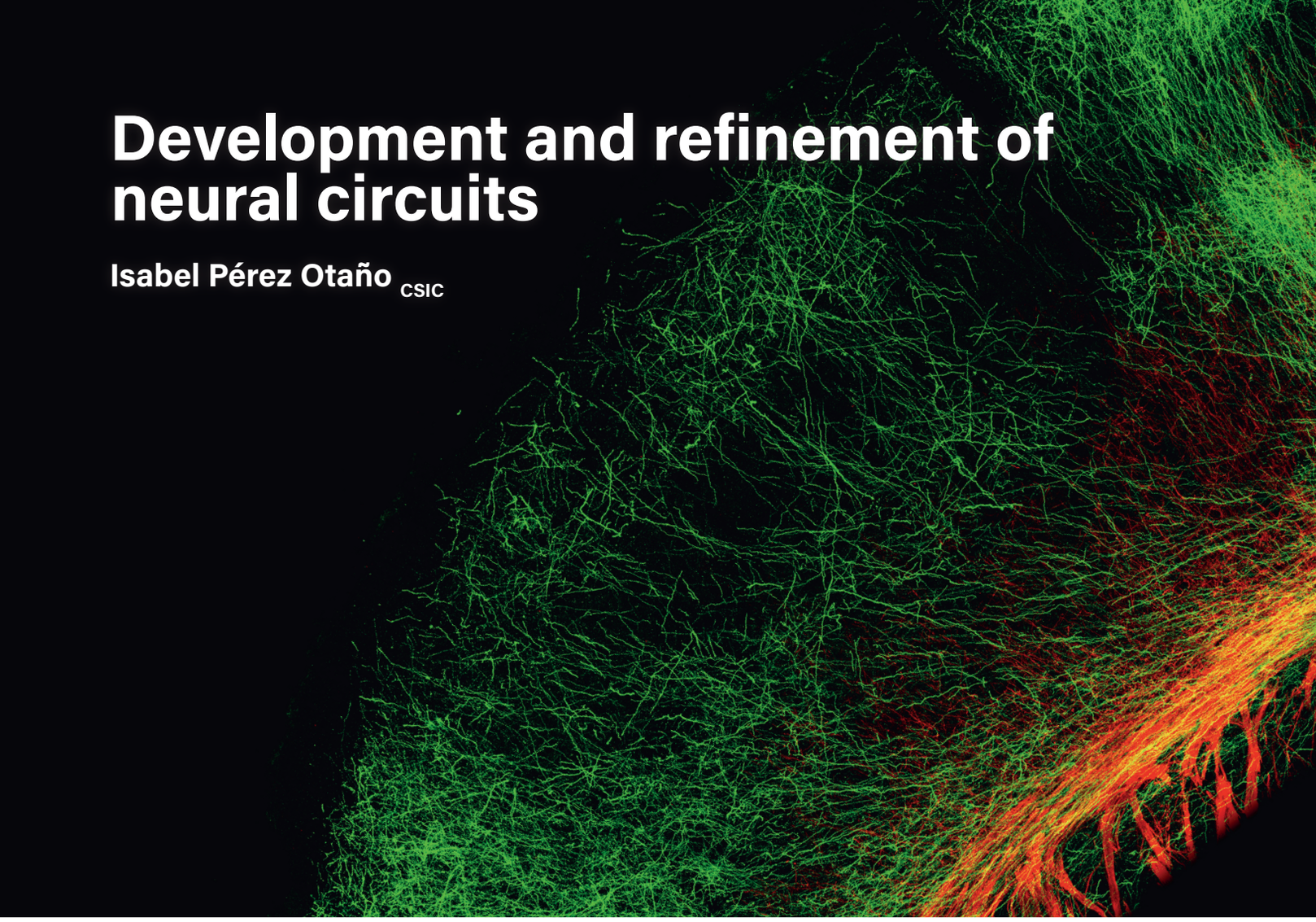


MBMs

Development and refinement of neural circuits

Isabel Pérez Otaño CSIC



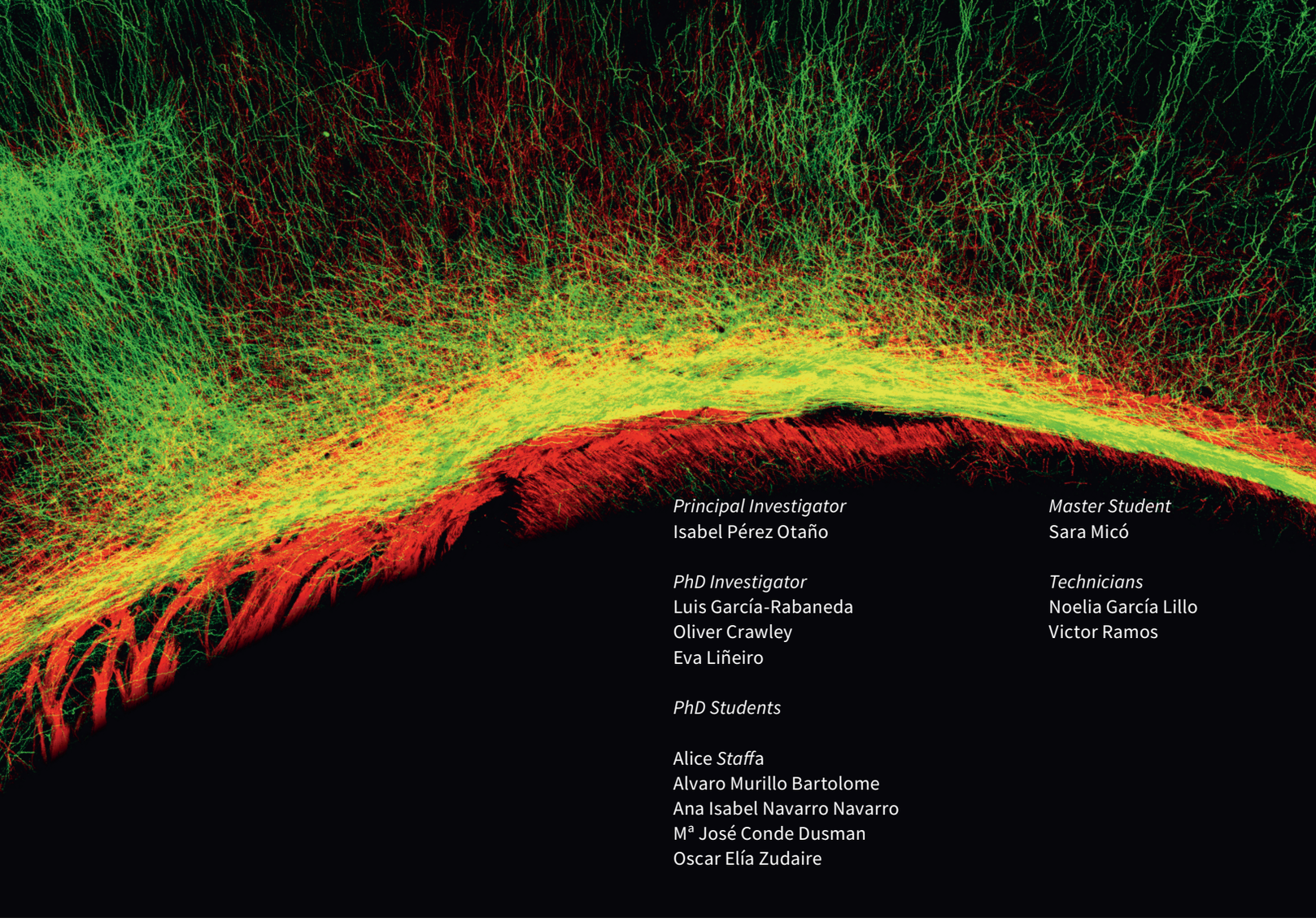
A fundamental question in neuroscience is how neuronal circuits are refined by environmental cues. Circuit refinements involve maturation of selected synaptic connections and elimination ("pruning") of others, and are most prominent during critical periods—a stage of postnatal brain development when 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 receptor 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 postsynptic 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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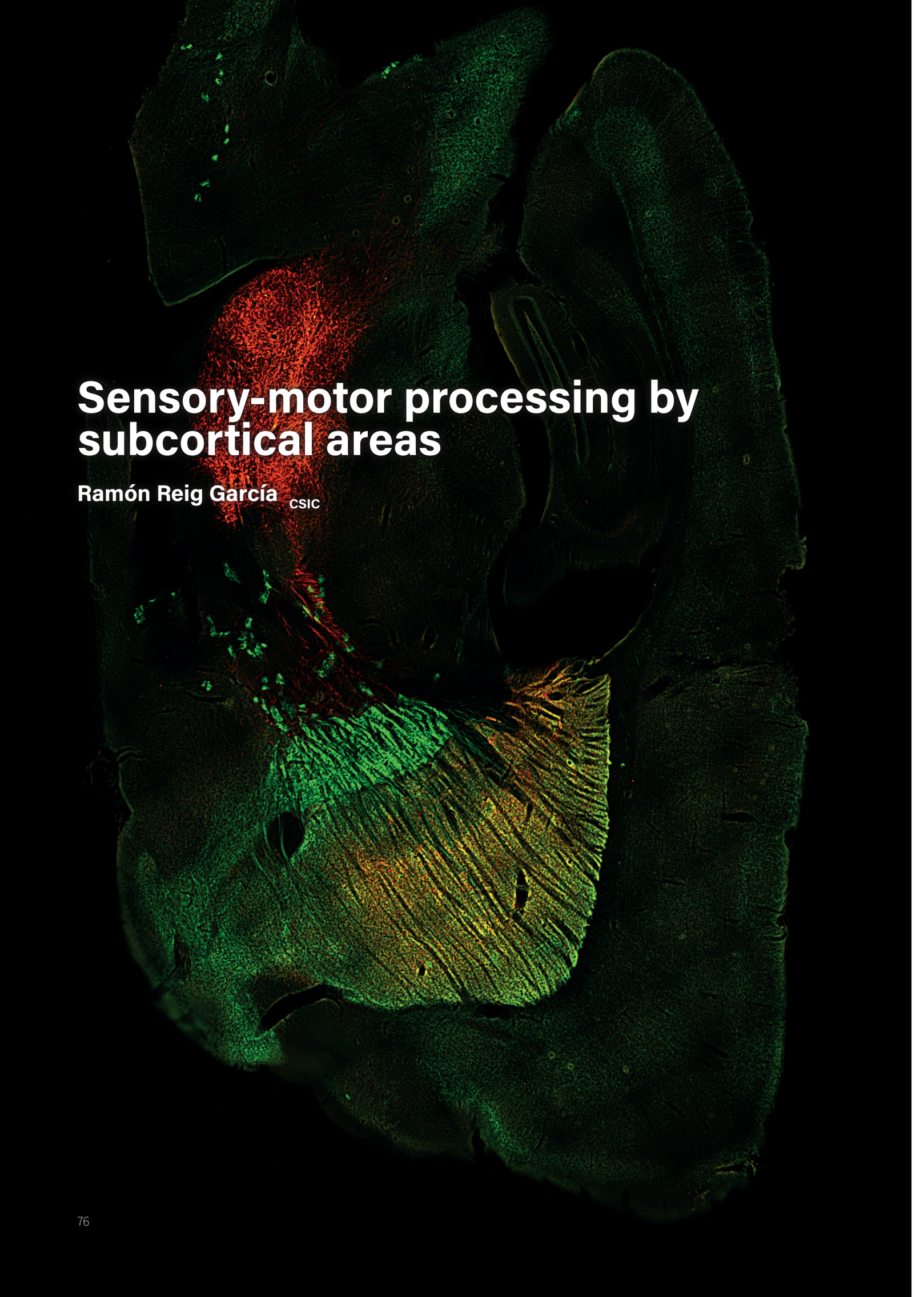

Sensory-motor processing by subcortical areas

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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 (Chl) interneurons that modulate the activity of the MSNs.

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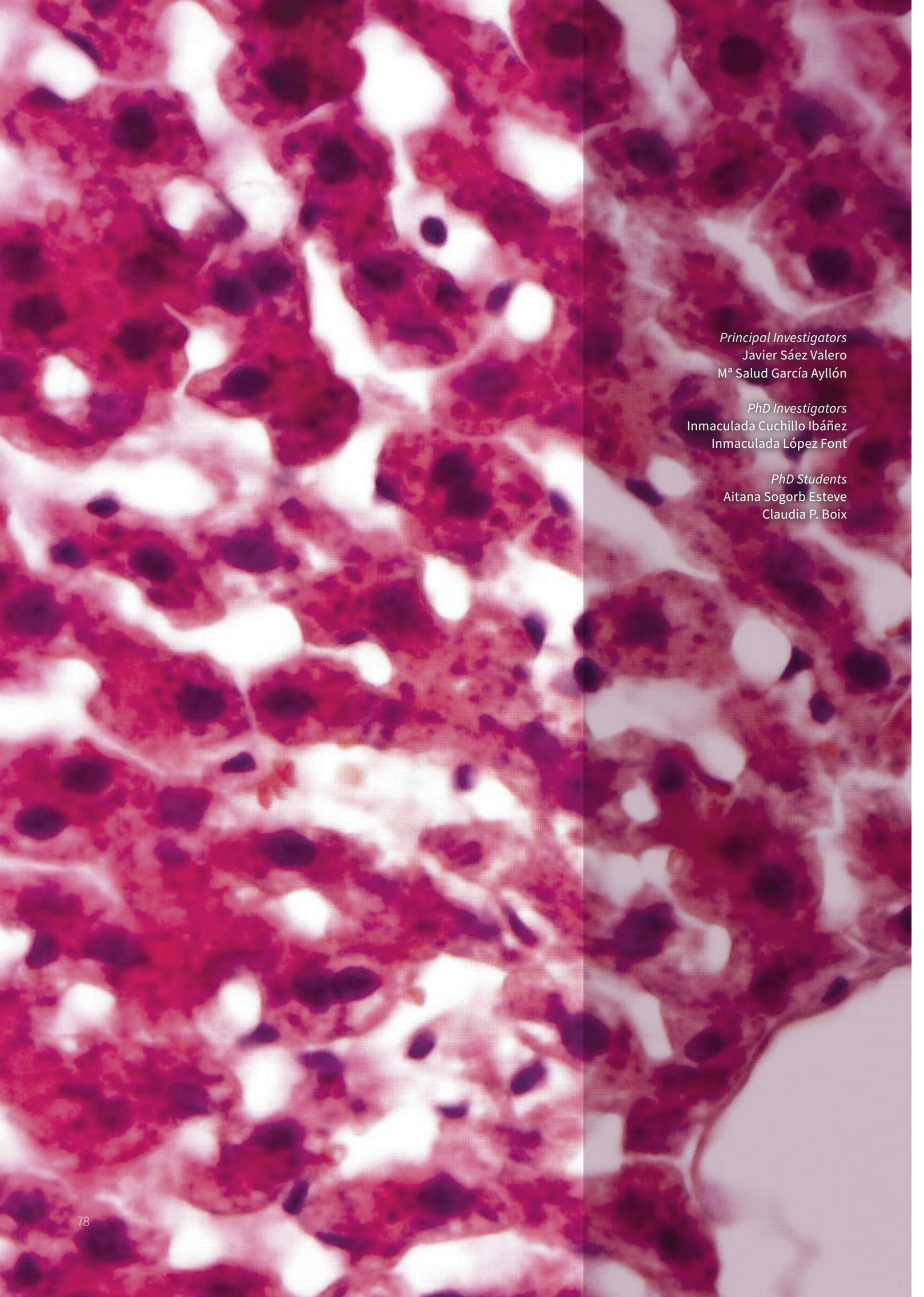

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Altered molecular mechanism in Alzheimer's disease & dementia

Javier Sáez Valero UMH

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.

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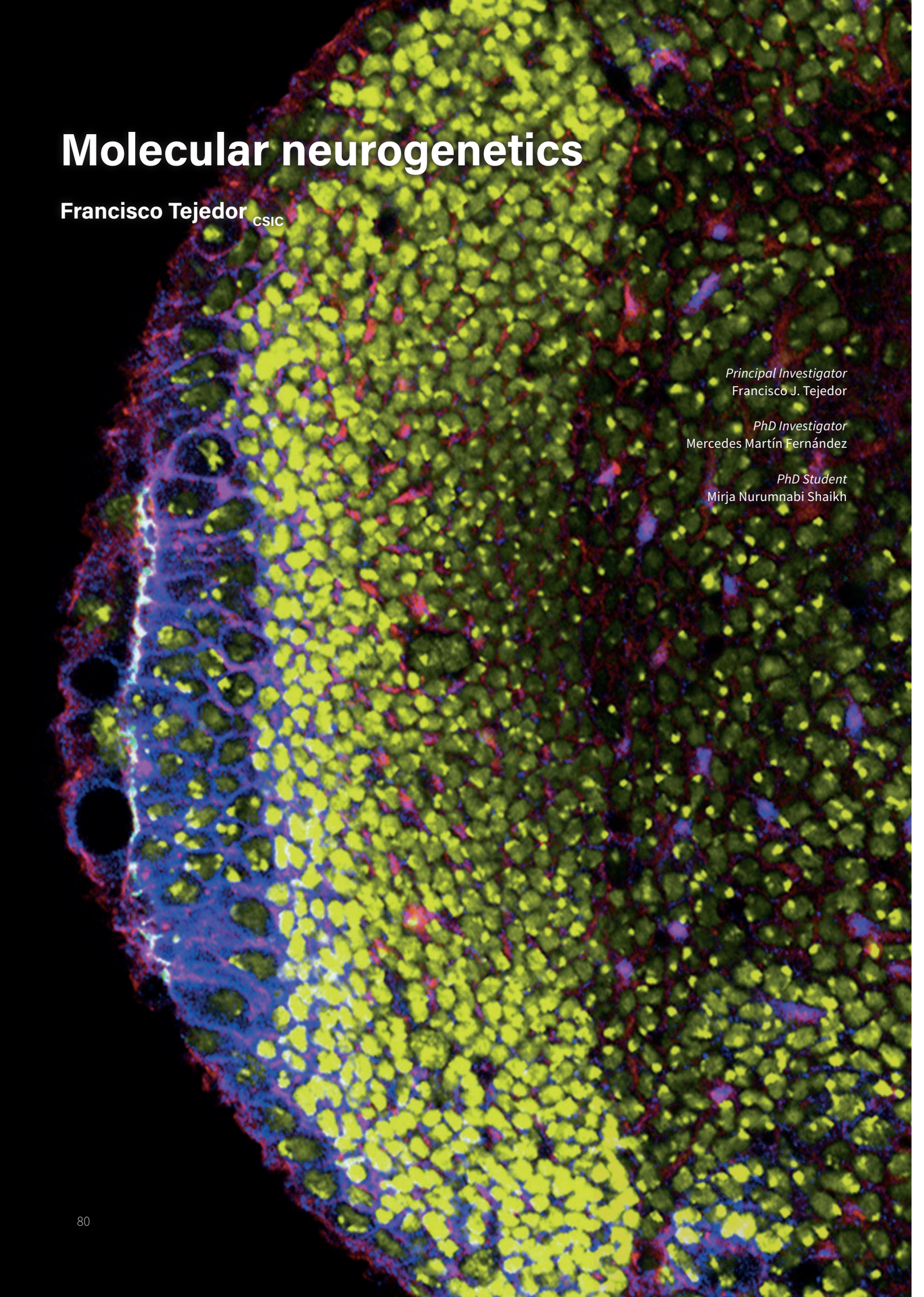
Molecular neurogenetics

Francisco Tejedor CSIC



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PhD Student
Mirja Nurumnabi Shaikh

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, happloinsuficiency 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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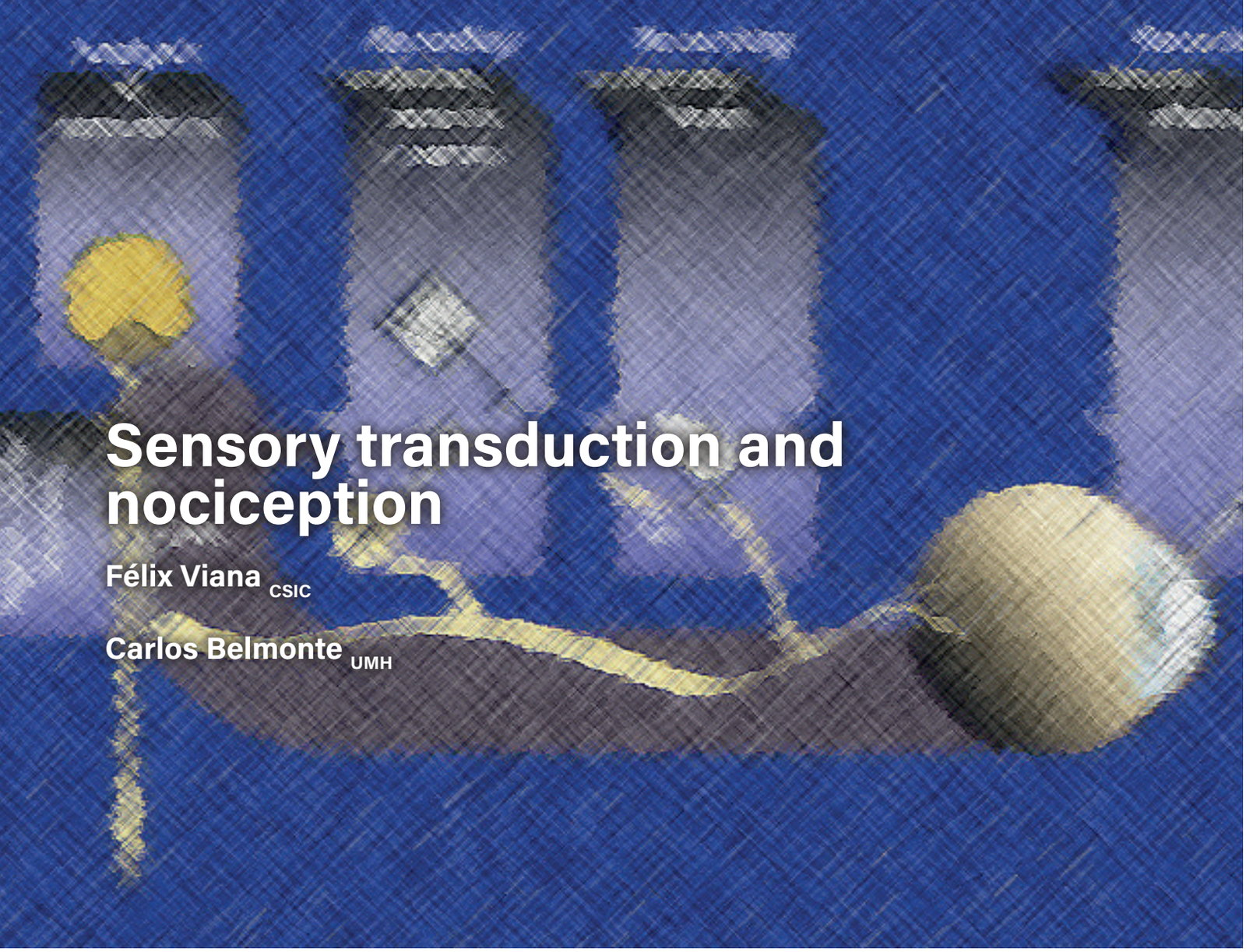

Sensory transduction and nociception

Félix Viana CSIC

Carlos Belmonte UMH

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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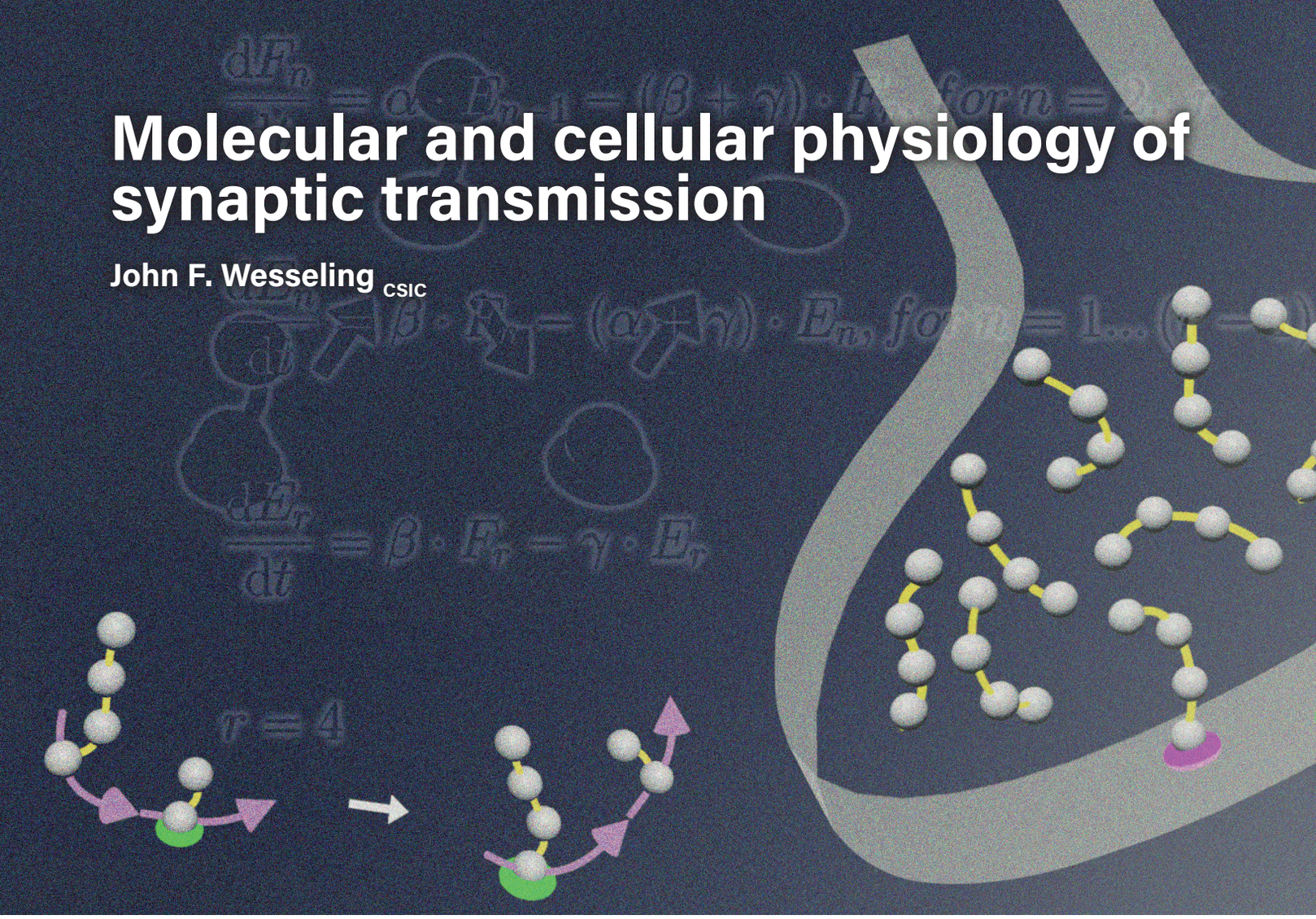
Molecular and cellular physiology of synaptic transmission

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.

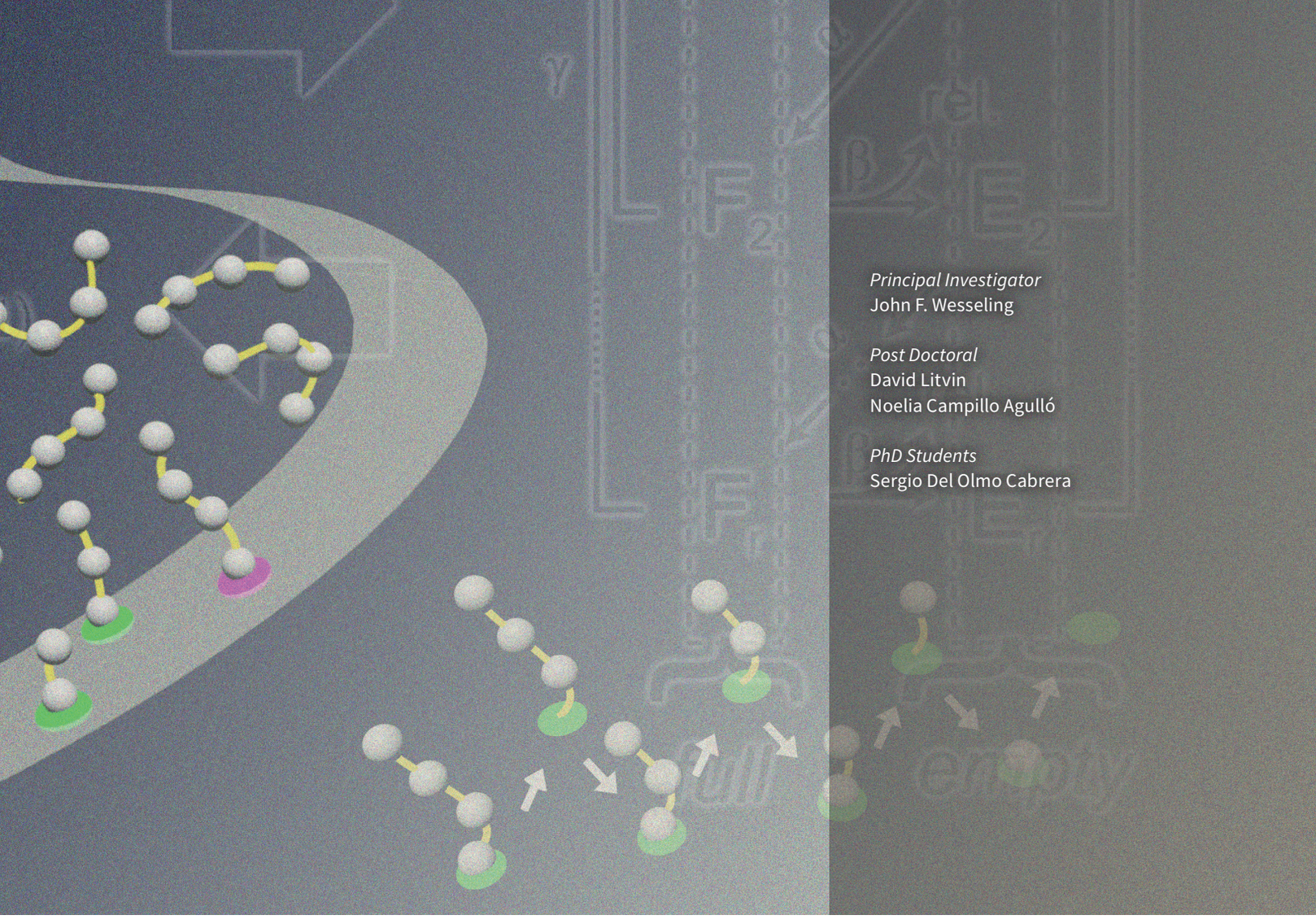
We began by developing assays for each of the rate-limiting steps in synaptic vesicle trafficking at a variety of central synapses using electrophysiological and optical imaging techniques. The assays allowed us to study each step in isolation and to ask how the underlying mechanisms interact with each 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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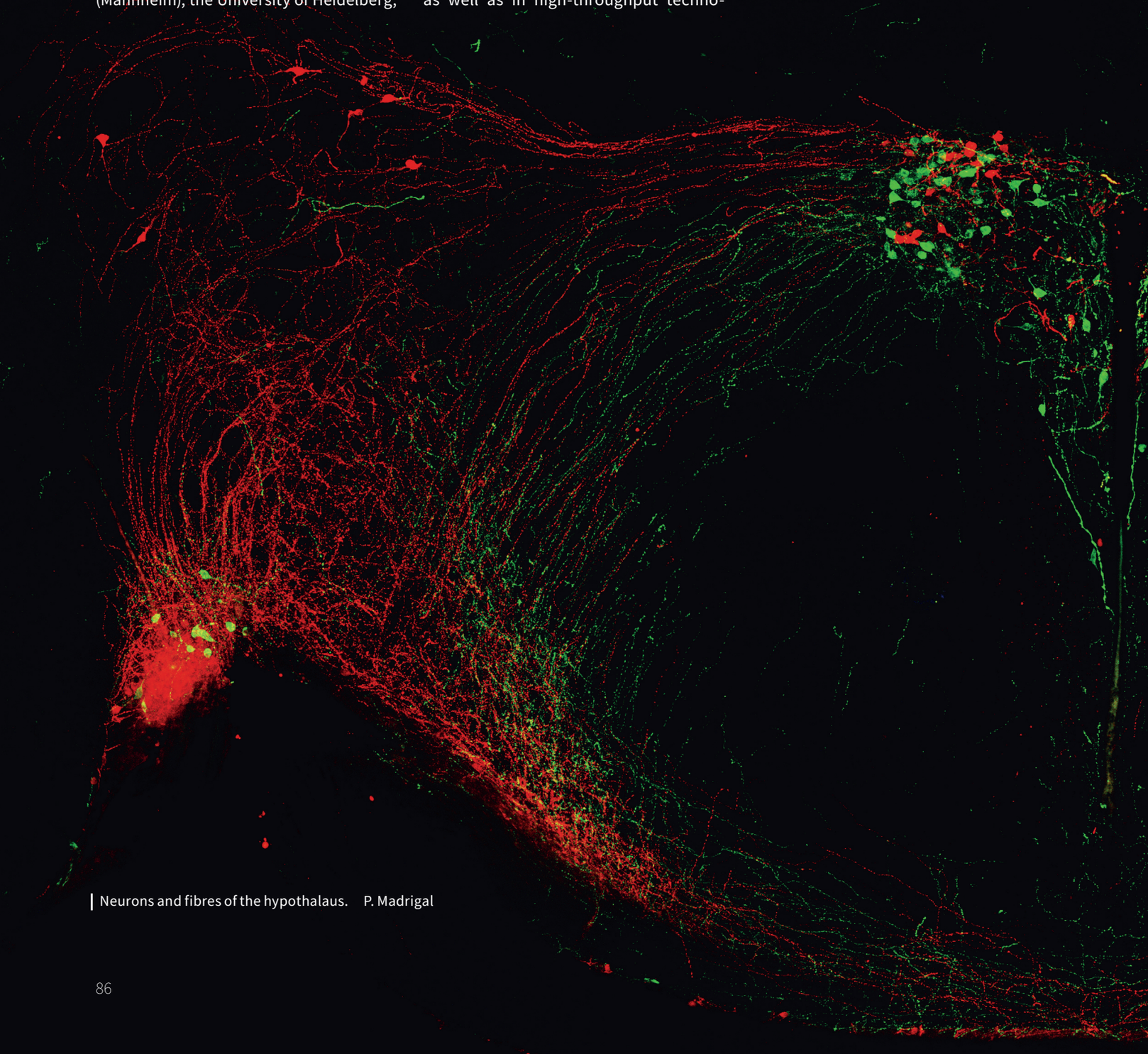
Collaborations & Agreements

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 Neurobiology 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.



Neurons and fibres of the hypothalaus. P. Madrigal

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

Agencia Valenciana de Innovación (AVI-GVA)

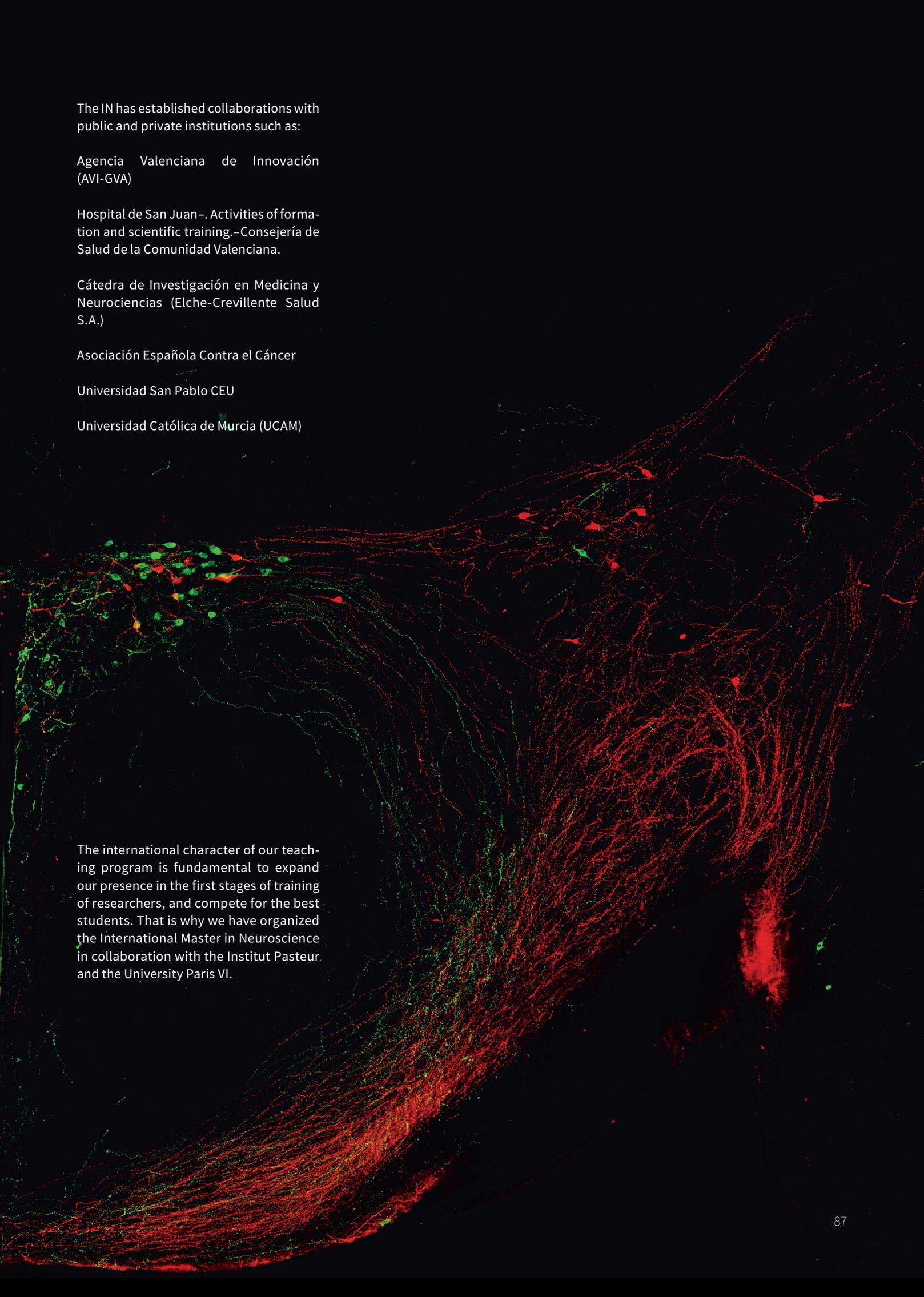
Hospital de San Juan–. Activities of formation and scientific training.–Consejería de Salud de la Comunidad Valenciana.

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)



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.

Remedios Caro Almela Prize

Dr Alain Chedotal, 2017

The jury of the 8th Edition of the "Remedios Caro Almela" Prize in Developmental Neurobiology met on June 19th of 2017 and was integrated by Silvia Arber, previous RCA awardee; Salvador Martínez, Director of the Instituto de Neurociencias; Luis Puelles, from University of Murcia; David Wilkinson, from the MRC in London; and the previous Remedios Caro Almela Chairman, Constantino Sotelo. The jury unanimously decided to award the prize "Remedios Caro Almela in Development Neurobiology" to Professor Alain Chedotal, Directeur de Recherche INSERM (DR1) and coordinator of the Department of Development at INSERM U968 (Vision Institute, Paris, France), for his contributions to understanding the development of neuronal networks in the vertebrate brain, with a specific interest in the molecular mechanisms controlling neuronal migration and axon guidance.

Alain Chedotal mostly studied three models: the cerebellum, the retina and commissural neurons. During the last 10 years, the lab of Dr. Chedotal has focused on newly discovered axon guidance molecules: netrins, semaphorins, RGMs and Slits, all of which are phylogenetically conserved and expressed in many cell types whitin and outside the nervous system. He has also contributed to the discovery of receptors for some of these proteins (neuropilin-2, A2b, L1 and neogenin). Most of his research is conducted in vivo using a variety of mouse models. Recently, his lab has developed new novel molecular and imaging techniques to study the cellular mechanisms regulating cell-cell interactions during myelination, angiogenesis and ocular vaso-proliferative diseases; he has also helped to develop technique to observe living organisms by a combination of immunolabeling, 3D microscopy and tissue clearing.

His work has received unanimous international recognition, being in recent years invited lecturer in major World Congresses dedicated to the study of the development of the nervous system. The jury highlighted the novelty and quality of his contributions and the high productivity of his research group.

Professor Chedotal was born in Nantes, in 1967. He studied Biology at the Ecole Normale Superieur (Lyon), and received his doctorate at the Pierre et Marie Curie University, Paris. After several years of postdoctoral stay at Berkeley University, he joined the INSERM in 1997.

Alain Chedotal is a member of several editorial boards of scientific journals (Dev. Growth and Diff., Frontiers Mol Neurosci., J. Neurosci., etc) and has received numerous awards and distinctions, including Young Investigator Award of Neurochemy Eur Soc (2001), Schlumberger Foundation Award (2002), Prix Recherche de l'INSERM (2017).

In 2019, in coincidence with the 20 Anniversary of IN, the 9th Edition of the "Remedios Caro Almela" Prize in Developmental Neurobiology will be selected.

Research Professorship in Neurobiology

The Remedios Caro Almela Chair of Developmental Neurobiology was created in the year 2000 as a result of a philanthropic initiative by Fernando Martínez Ramos and his family, to honor the memory of his deceased wife Remedios Caro Almela. She graduated in Philosophy at the University of Murcia, majoring in Art History. The funding that the Martínez-Caro family provides to this Chair seeks to keep alive the memory of their beloved mother and wife Remedios Caro Almela. The Chair was established at the Institute of Neurosciences with the aim of promoting research of the nervous system in its molecular, cellular and organ levels, both in normal and pathological conditions, with a focus on the study of nervous system development. In 2012 it was changed to the "Remedios Caro Almela Chair in Neurobiology".

Since its creation and until his retirement in 2012, Professor Constantino Sotelo was the Chairman, developing an excellent job for more that 10 years.

In 2013, Professor Richard Morris was appointed as the new Chairman. Professor of Neurosciences of the University of Edinburgh and fellow of the Royal Society, Richard Morris has made countless contributions to the neurobiology of learning and memory, by applying concepts and techniques that enable the development of new therapies for Alzheimer's disease. Some of his major scientific achievements include the development of the water maze, known as Morris Water Maze, now used world-wide; the discovery of the role of NMDA receptors in learning and memory; the development of the hypothesis of synaptic labelling and capture; discoveries about the neurobiology of previous knowledge (schema), etc.

Since 2006, the Remedios Caro Almela Chair sponsors an international prize in Developmental Neurobiology as part of the Chair's activities, consisting of an unrestricted award of 20.000€.

Richard Morris & Constantino Sotelo

This Prize has been so far awarded to some of Europe's best young neuroscientists: Barry Dickson (2006), François Guillemot (2007), Rüdiguer Klein (2008), Steve Wilson (2009), Christine Holt (2011), Magdalena Götz (2013), Silvia Arber (2015) and Alain Chedotal (2017).

Dr Barry J. Dickson
2006

Dr François Guillermot
2007

Dr Rűdiger Klein
2008

Dr Stephen Wilson
2009

Dr Christine Holt
2011

Dr Magdalena Götz
2013

Dr Silvia Arber
2015

Services and Facilities

Cell Imaging.
The unit has: 2-photon microscopes; upright and inverted confocal microscopes with multiple laser lines, both supplemented with electrophysiological equipment; microscopes equipped with a super-resolution STORM module; light-sheet technology and CLARITY-dedicated equipment; TIRF imaging. Neurolucida and other image quantification and analysis systems (Imaris 3D and 4D software)·

Functional Magnetic Resonance Imaging Unit.
The IN's fMRI unit has a 7T magnet suitable for a range of experimental animals, equipped with ultra-high performance gradients for high-resolution functional experiments and micro-MRI in embryos (spatial resolution below 50 microns). Detailed longitudinal studies are possible using diffusion tensor imaging (DTI), tractography, volumetry, morphometry, perfusion, manganese-enhanced MRI (MEMRI) and blood-oxygenation level dependent (BOLD) signal fMRI.

Cellular Analysis Service & the Genomic Analysis Unit.
This unit analyze neuron diversity by single-cell or ultra-low material genomic approaches. The unit haS an ultrasonicator for microvolumes, microcapillary based electrophoresis, a 10x genomic microfluidics station, and two Fluorescence Assisted Cell Sorting (FACS) stations.

Organotypic & Cell Culture.
Facilities dedicated to the maintenance and use of immortalized cell lines, primary cell cultures and organotypic brain slice cultures. A BSL2 facility is available to prepare viruses and other biohazardous vectors. The unit is fully equipped with electroporators for slice and whole brain transfection, microinjectors for cell transplantation, an ultrasound microscope for in utero manipulations, and computer-assisted phase contrast and epifluorescence microscopes for microdissection of live reporter-tagged tissues.

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*.

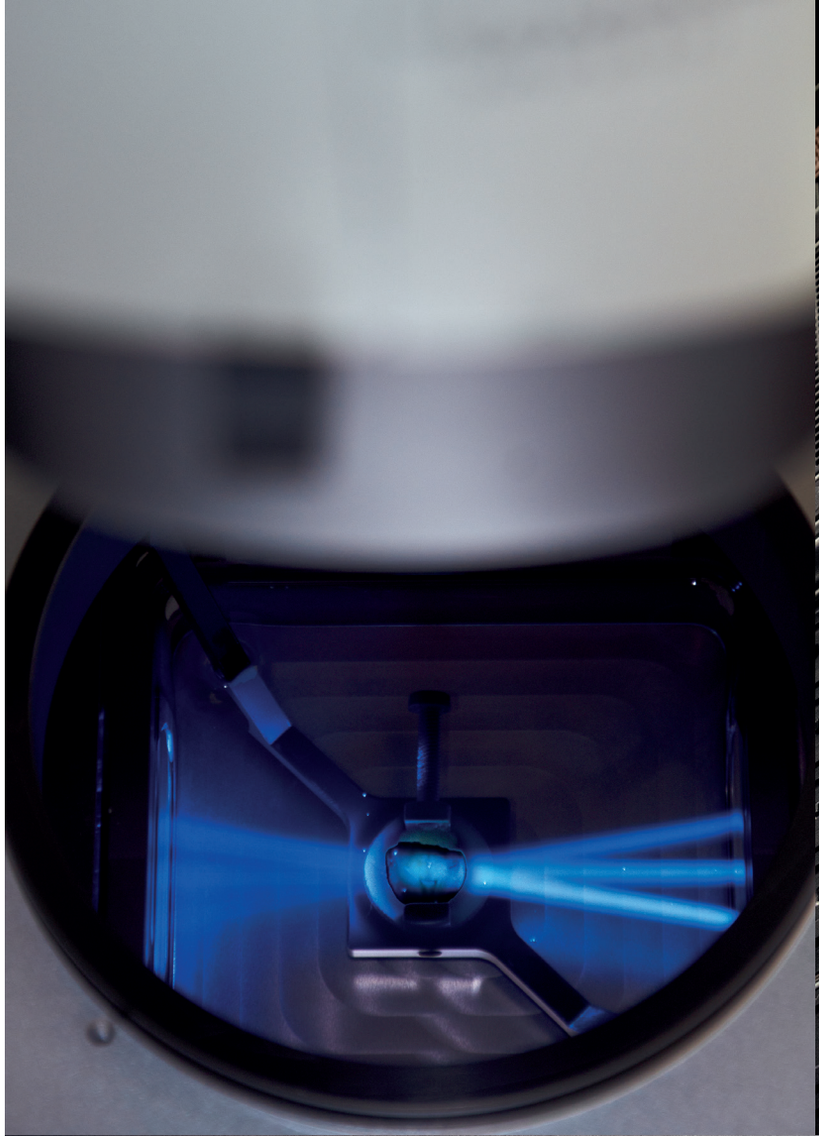
Behavioural Phenotyping Facility.
The SPF animal house also hosts a facility (8 rooms) with state-of-the-art equipment for behavioural analysis of small rodents, including different types of arenas and mazes, a Morris water maze, fear and operant conditioning boxes, 24-h monitoring equipment, etc.

Purchasing & Stockroom.
Central purchasing of laboratory supplies and equipment is a critical issue that produces relevant savings

Illustration & Photography.
The service is fully equipped to undertake all types of illustration, graphic design and photographic work.

Scientific Unit of Innovation (UCIE).
The objective is to innovate by transferring the research results of IN research lines and groups. This unit represents a paradigmatic change in and attempt to transfer scientific results to society, identifying the need to establish a solid bridge between basic research and the companies.

Electronics Workshop
The electronic unit provides services to adapt and create instruments and experimental devices according to the specific needs of IN groups. It has precision machinery for the prototype manufacturing and is intimately related to the innovation unity (UCIE).



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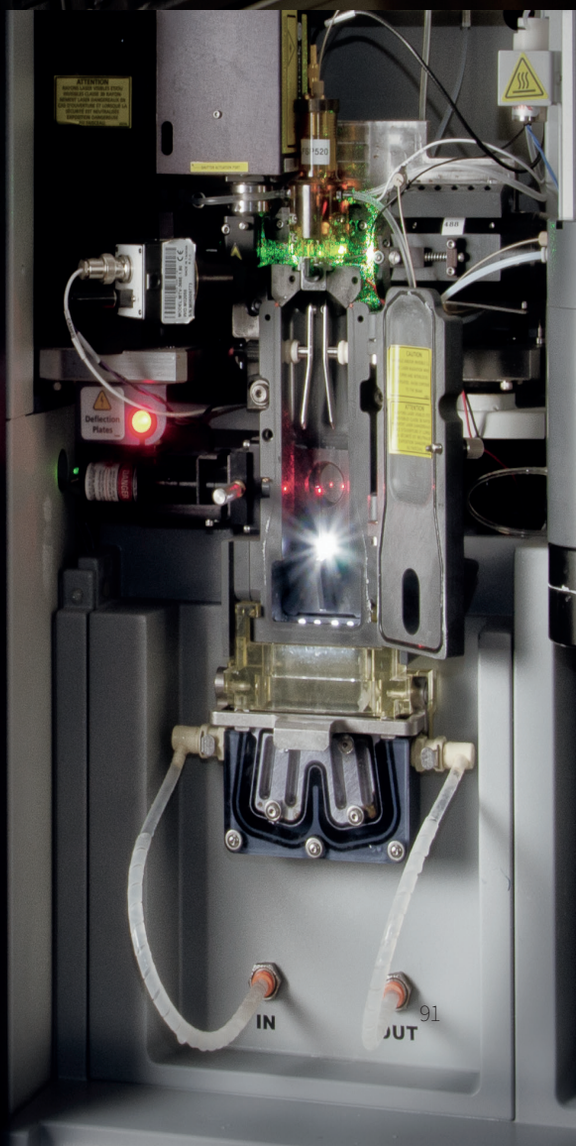
IN
OUT

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Mª Teresa García Hedo

Administration
Mª Luz Arce Fernández
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 Romero García
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Rosa Mª Sánchez Cayuela
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Maintenance
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Electronic Workshop
Víctor Rodríguez Milán

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Scientific Illustration
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Cell Culture
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Rebeca Ortiz Méndez
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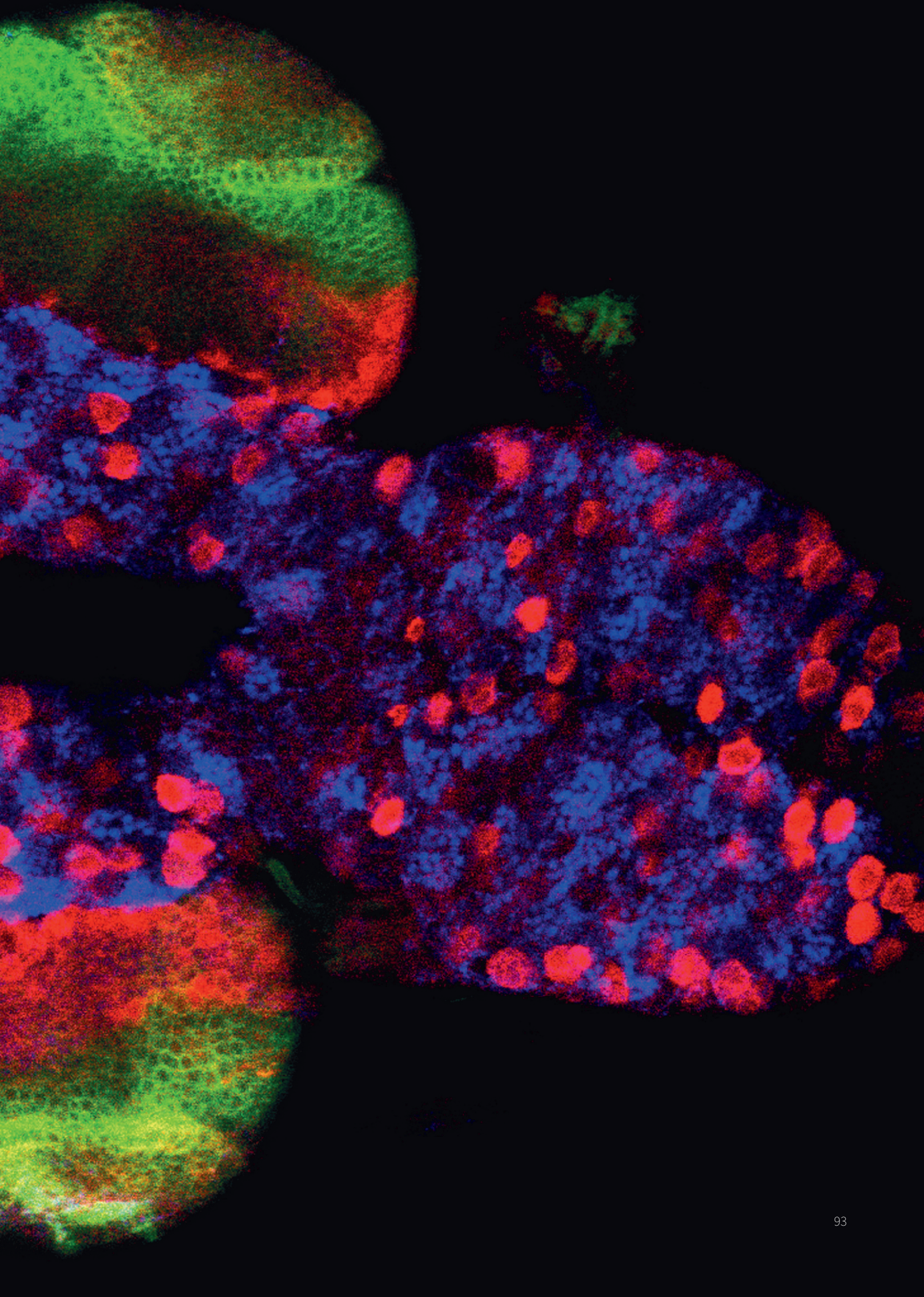
Jéssica Valdivia García

***Drosophila* Service**
Noelia García Lillo
Alicia Sánchez Rincón

Zebrafish Facility
Diana Abad Bataller
Sandra Moreno Valverde

Drosophila larva CNM. A. Carmena



Master & PhD Program

Master in Neurosciences: from the bench to the bedside.

Official Master of the UMH.

The Master is organized to be the first step of a career in Neuroscience research for those graduate students with a particular interest in this field. The obtaining of this Master qualifies for the Access to doctorate programs, both the Doctorate program in Neurosciences of the Institute and other programs in other Universities.

The Master in Neuroscience 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 20, so the selection criteria tend to be restrictive. For access to the master's degree, the academic record and the degree made by the student as well as their previous experience in laboratories (including IN laboratories) are valued. In the current year (2017-18) there are 17 students enrolled.

The Master is taught in English. It covers one academic year (60 ECTS credits) and is made up of the following subjects:

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).

Internacionalización del Master

During the last academic year a series of activities have been implemented to internationalize the Master and to improve its quality and competitiveness. Funding has been obtained from the "Severo Ochoa" Program of the Neurosciences Institute for 5 grants for foreign students, which has allowed the incorporation of 5 students from Mexico, Colombia, Macedonia, Slovenia, and Egypt to the Master. For the next academic year (2018-19) there are two grants from the Carolina Foundation for the incorporation of a student from a Spanish-American country. In addition, since the 2016-17 academic year, a student exchange program has been set up with the Pasterur Institute in Paris.

The Master in Neurosciences is part of the ***Network of European Neuroscience Schools (NENS)*** and was re-accredited by the AVAP during the 2015-16 academic year.

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.

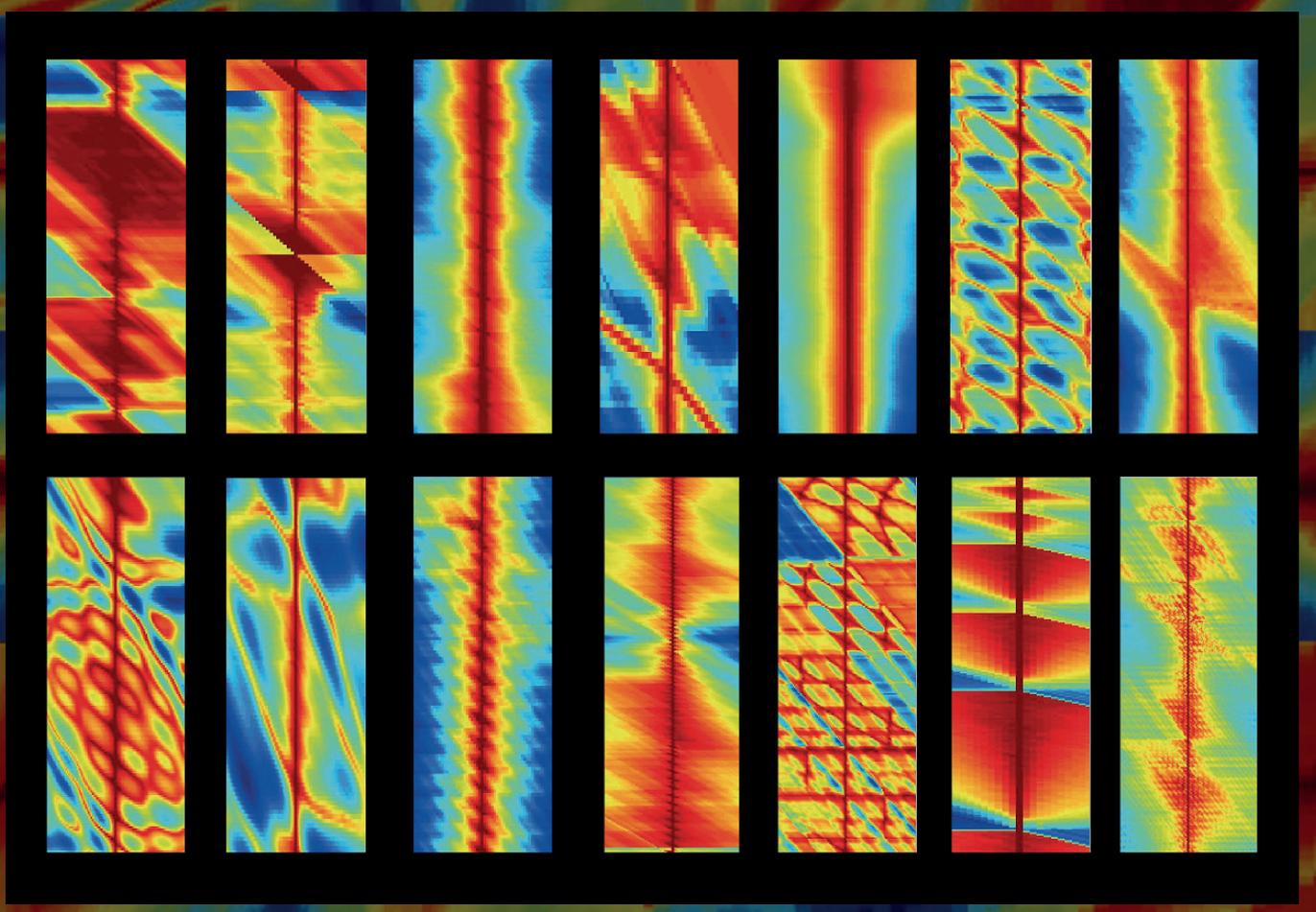
The program offers a variety of Training activities like:

- 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.

Quality accreditation of the program:

The criteria of quality for the Thesis are to present a "European thesis" format, in which the student accredited a minimum of 3 months stay in a laboratory outside of Spain. Also the thesis can be presented by articles. In this case the requirement is a published (or formally accepted) article in the first quartile in which the student is first author. The same article cannot be used to endorse two theses, even if the first authorship is shared.

The PhD program in neuroscience is a member of the ***Network of European Neuroscience Schools (NENS).*** The PhD program in Neurosciences has renewed every year the ***Award of Excellence*** from the Spanish Ministry of Education.



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2018

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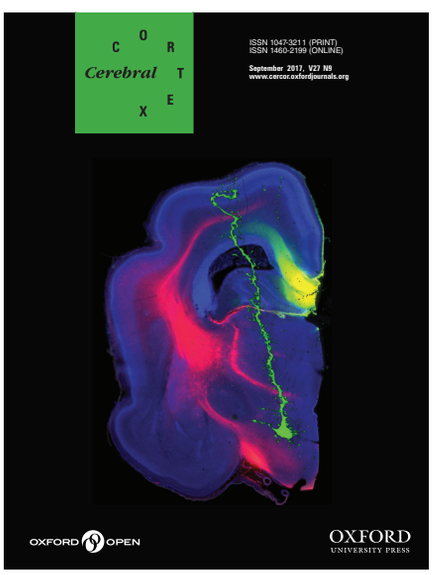

Seminars

2018

Dr Angelika Lampert University Hospital RWTH Aachen, Aachen, Germany **Sodium channels and pain: about structure, mutations and the importance of the cellular background.**

Dr Anne Eichmann Cardiovascular Research Center and the Department of Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, USA **Guidance of vascular patterning in development and disease**

Dr Carlos Parras L'institut du Cerveau et de la Moelle Epinière, Paris, France **Regulation of neonatal brain progenitor's genetic programs by chromatin remodelers: a focus on CHD7 and CHD8 remodelers in oligodendrocyte precursor cells.**

Dr Carol Mason Columbia University, New York, USA **Wiring the embryonic eye to the brain for binocular vision .**

Dr Cedric Maurange IBDM, Marseille, France **Regulation of neural progenitor hierarchy during development and tumorigenesis**

Dr Charles Ffrench-Constant MRC Center for Regenerative Medicine, The University of Edinburgh **Smart wiring in the brain - innate and adaptive myelination.**

Dr Christian Lüscher University of Geneva, Geneva, Switzerland **A circuit model of drug addiction.**

Dr David Wilkinson The Francis Crick Institute, London, UK **Borders and communities in hindbrain segmentation.**

Dr Enrique Martin Blanco Instituto de Biología Molecular de Barcelona-CSIC, Barcelona **The JNK signaling links the CNS architectural balance to motor coordination in the *Drosophila* embryo.**

Dr Ernst Bamberg Max Planck Institute of Biophysics, Frankfurt, Germany **Rhodopsin based Optogenetics:Basics,Applications, Chances**

Dr Gaia Novarino IST Austria, Klosterneuburg, Austria **Neurodevelopmental disorders: from molecular mechanisms to novel treatments**

Dr Gerhard Christofori University of Basel, Basel, Switzerland **Transcriptional and functional dissection of EMT and cell plasticity in breast cancer**

Dr Gonçalo Castelo-Branco Karolinska Institutet, Stockholm, Sweden **Transcriptional and epigenetic states of oligodendrocyte lineage cells in development and disease: insights from single cell RNA-Seq**

Dr Helmut Kessels Netherlands Institute for Neuroscience, Amsterdam, The Netherlands **Creating and retrieving memories through AMPA-receptor plasticity**

Dr Henrik Zetterberg Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden **Update on fluid biomarkers for neurodegenerative diseases**

Dr Jeremy Henley University of Bristol, Bristol, UK **Why kainate receptors are important - Mechanisms and consequences of kainate receptor regulation**

Dr Juan Carlos Arevalo Universidad de Salamanca, España **NGF/TrkA axis in pain: relevance for the identification of potential therapeutic targets**

Dr Juan Carlos Saez Pontificia Universidad Católica de Chile, Santiago, Chile **Role of glial hemichannels in neuroinflammation.**

Dr Matthijs Verhage CNCR, VU University Amsterdam and VU University Medical Center, Amsterdam, The Netherlands. **Trafficking and fusion of secretory vesicles in human and rodent CNS neurons.**

Dr Miguel Maravall University of Sussex, Brighton, UK **Deconstructing tactile sequence recognition.**

Dr Mireille Montcouquiol Universite de Bordeaux Segalen, Bordeaux, France **The core PCP protein vangl2 is critical for motility of neurons & structural plasticity**

Dr Nael Nadif Kasri Radboud University Medical Centre, Nijmegen, The Netherlands **Exciting cells on-a-chip: relevance for neurodevelopmental disorders**

Dr Natalia Rodríguez Muela Centro de Investigaciones Biológicas, CSIC, Madrid **Utilizing stem cells to model motor neuron diseases.**

Dr Nuria Flames Instituto de Biomedicina de Valencia (IBV-CSIC) , Valencia **Transcriptional regulatory logic of serotonergic specification**

Dr Ofer Yizhar Weizmann Institute of Science, Rehovot, Israel **Optogenetic dissection of prefrontal circuits for cognitive control and social behavior.**

Dr Reza Dana Harvard Medical School **Regulation of Ocular Surface Immune Homeostasis in Health and Disease.**

Dr Sebastian Jessberger Brain Research Institute, University of Zurich, Zurich, Switzerland. **Molecular and cellular mechanisms regulating neural stem cell activity**

Dr Sonia Garel Ecole Normale Supérieure, Paris (France) **Microglia and prenatal inflammation in early cortical wiring**

Dr Tim Petros Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA **Mechanisms regulating the differentiation and maturation of distinct interneuron subtypes**

Dr Tom Otis UCL, London, Uk **Cerebellar circuit mechanisms of normal movement & ataxia**

Dr Verónica Martínez-Cerdeño MIND Institute, University of California, Davis **Anatomy of Autism.**

2017

Dr Abdel El Manira Karolinska Institutet, Stockholm, Sweden **Modular microcircuits controlling the versatility of motor actions**

Dr Alessandro Treves SISSA-Cognitive Neuroscience, Trieste, Italy **Shattering the crystal of entorhinal cortex restores memory in grid cells**

Dr Alex Bishtock Hebrew University of Jerusalem **Coloring Pain: Multispectral Mapping and Activity-Dependent Silencing of Primary Afferents as a Tool to Reveal Distinct Pain and Itch Sensory Lines**

Dr Angel Cedazo-Minguez Karolinska Institutet, Stockholm, Sweden **Cholesterol-based targets in neurodegenerative disorders**

Dr Antonio G. García Universidad Autónoma de Madrid (UAM) **Ceremonia de Entrega de la Medalla de Plata del IN. "40 Years Around the Chromaffin Cell"**

Dr Ashwin Woodhoo CICc bioGUNE **Molecular and cellular control of Schwann cell plasticity in nerve injury, demyelinating neuropathies and tumours of the PNS**

Dr Christoph Kellendonk Columbia University Medical Center, New York, NY, USA **Using human brain imaging studies as a guide to model cognitive and negative symptoms in mice**

Dr Claude Desplan NYU, Department of Biology, New York, USA **Generation of neural diversity in the visual system**

Dr David Lyon University of California, Irvine, USA **Novel viral based strategies for cell-type specific optogentic manipulation in visual cortex**

Dr David Robbe Institut de Neurobiologie de la méditerranée, Marseille, France **The striatum contribution to action monitoring and control**

Dr Denis Jabaudon University of Geneve **Dynamic control of neuronal identity in the developing neocortex**

Dr Elisabeth B. Binder Max Planck Institute of Psychiatry, Munich, Germany **Molecular mechanisms of gene x environment interactions: implications for psychiatric disorders**

Dr Frederic Meunier Queensland Brain Institute, The University of Queensland, Australia **Tracking Munc18 uncovers an unsuspected link with Synucleinopathies**

Dr Greg Longmore Washington University Medical School, St Louis, USA **Tumor-Stromal Interactions Regulating Cancer Metastasis**

Dr Gul Dolen The Johns Hopkins University, Baltimore, USA **Social reward: basic mechanisms and therapeutic opportunities**

Dr Gustavo Deco Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona **CANCELLED ** Novel concept of intrinsic ignition characterises the broadness of communication underlying different brain states**

Dr Heiko Luhmann Institute for Physiology, Univ. Mainz, Germany **Early cortical activity - more than an epiphenomenon!**

Dr Iñigo Romero Arandia Universitat Pompeu Fabra, Barcelona **Reading out neural populations: Shared variability, global fluctuations and information processing.**

Dr Javier Orlandi Department of Physics and Astronomy, University of Calgary, Canada **Inferring structural and functional neuronal networks from calcium imaging recordings**

Dr Jens Hjerling-Leffler Karolinska Institutet, Stockholm, Sweden **Single-Cell Transcriptomics in the Study of the Brain**

Dr Joaquin Piriz IFIBIO-Houssay, Buenos Aires, Argentina **Papel de la Habénula Lateral en la Persistencia Temporal de las Memorias Aversivas.**

Dr Jose Antonio López Universidad de Alcala, Madrid **Analysis of spike trains in superficial dorsal horn neurons: many questions & a few answers.**

Dr Jose María Delgado Universidad Pablo de Olavide - UPO, Sevilla **When and where learning is taking place: neuronal & synaptic changes in activity during the acquisition of associative learning tasks.**

Dr Juan Alvaro Gallego Centre for Robotics and Automation, CSIC & Department of Physiology, Northwestern University **How does the brain control movement? A view from the neural manifold**

Dr Juan Manuel Encinas Achucarro Basque Center for Neuroscience, Zamudio, Bizkaia **Reactive Neural Stem Cells in the Hippocampus**

Dr Marcos Malumbres CNIO, Madrid **Mitotic entry and exit: implications in disease and therapy**

Dr Nicola S. Clayton , Dr Clive Wilkins Department of Experimental Psychology. Cambridge, UK **Memory as the product of forethought**

Dr Norbert Perrimon HHMI-Harvard University, Cambridge, USA **The intricate world of interorgan communication**

Dr Peter Reeh Institute of Physiology and Pathophysiology, Erlangen, Germany **The Janus head of TRPA1 in pain and analgesia**

Dr Richard L. Huganir Brain Science Institute, The Johns Hopkins University School of Medicine, Baltimore, USA **Receptors, Synapses and Memory**

Dr Sam Pleasure UCSF, San Francisco, USA **Regulation of neocortical progenitor cell fate by Shh signaling**

Dr Setsuko Sahara King's College London, London, UK **Control of cortical size and neuronal number**

Dr Steffen Wolff Center for Brain Science, Harvard University, Cambridge, USA **Motor skill learning and execution in a distributed brain network**

Dr Stephan Herlitze Ruhr-Universität Bochum, Germany **Optogenetic control of GPCR pathways in mouse brain.**

Dr Tara Spires-Jones University of Edinburgh, Scotland **Synaptic contributors to Alzheimer's disease**

Dr Tomas Marques Institut de Biologia Evolutiva - UPF/CSIC, Barcelona **Genetic diversity of humans and great apes and their impact on the evolution of epigenetic divergence**

Dr Vania Broccoli San Raffaele Scientific Institute, Milan, Italy **Human iPSC-based modelling of Parkinson's disease and new treatments based on CRISPR/Cas9 gene editing and novel AAV serotype variants**

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

2018

Dr Andrés Parra Instituto de Neurociencias **¿Cómo te ayuda tu cerebro a memorizar el temario?**

Dr Francisco Navarrete Rueda Instituto de Neurociencias **¿Cómo afectan las drogas a nuestro cerebro?**

Dr Inmaculada Cuchillo Instituto de Neurociencias **¿Por qué no hemos curado el Alzheimer aún?**

Dr Javier Sáez Valero Instituto de Neurociencias **Avanzando en la Búsqueda de Herramientas Bioquímicas para el Diagnóstico de la Enfermedad de Alzheimer.**

Dr Salvador Sala Pla Instituto de Neurociencias **Modelos matemáticos en neurociencias**

2017

Dr Alejandro Gómez Marín Instituto de Neurociencias **La mosca y tú.**

Dr Berta López Sánchez-Laorden Instituto de Neurociencias **¿Cómo se desarrolla y regula el cáncer de piel?**

Dr Eduardo De Puelles Instituto de Neurociencias **¿Cómo se conectan los componentes neuronales que regulan nuestro sistema emocional?**

Dr Elvira de la Peña Instituto de Neurociencias **¿Duele, duele!!.. o no?**

Gonzalo Moreno del Val Instituto de Neurociencias **La importancia de las técnicas de reproducción asistida en el ratón**

Dr José P. López-Atalaya Instituto de Neurociencias **"¿Cómo se produce la inflamación del cerebro?"**

Pilar Quijada Responsable de comunicación - Programa Severo Ochoa - Instituto de Neurociencias **¿Por qué dar visibilidad a mi investigación?**

Dr Ramón Reig Instituto de Neurociencias **"¿Cómo la información sensorial controla las respuestas motoras?".**

Dr Sandra Jurado Instituto de Neurociencias **Los secretos de la memoria**

PhD Tesis

2018

Virginia Fernández Martínez.
Role of Mirnas In Early Brain Development.

Adrián Viudez Martínez.
Potencial Utilidad Terapéutica del Cannabidiol en el Trastorno por Uso del Alcohol

Sergio Juárez Carreño.
The Neuroendocrine Control of Animal Size, Body Proportion & Symmetry.

Yolanda Gimenez Molina.
Functional architecture and dynamics of the F-actin cytoskeleton in neurosecretion.

José María Caramés Tejedor.
Hilar Parvalbumin Interneurons Control Functional Connectivity Associated to Spatial Memory Encoding.

Javier Abarca Olivas.
:La Visión 3D-estereoscópica en el Aprendizaje de la Neuroanatomía Quirúrgica

Aitana Sogorb Esteve.
"Secretases as Potential Biomarkers and Therapeutic Target for Alzheimer's Disease

Verónica Moreno Juan.
Thalamic Control of Cortical Plasticity Following Input Deprivation

Marilyn Scandaglia.
"Role of Lysine Demethylase 5C in Neurodevelopment and Intellectual Disability

2017

Gloria Fernández García.
Embryonic Origin of Adult Stem Cells in Ventral Hippocampus. Role and Interaction Between SHH and EMX2.

Eduardo Domínguez Sala.
Estudio experimental de las propiedades funcionales de la corteza cerebral de un modelo animal de Lisencefalia: el ratón Lis1/sLis1

Valeria Pecoraro.
Synaptic Effects of Gluk4 Subunit Overexpression

Patricia Andreo Lillo.
Hallazgos Clínicos en Pacientes Neuropediátricos con Mutaciones en la Región Crítica de la Lisencefalia

Emilia Favuzzi.
Cell-type Specific Programs Regulate the Assembly and Dynamics of Cortical Circuits.

Antonio Jesús Hinojosa García.
Specific Molecular Mechanisms Differentiating Gabaergic from Glutamatergic Synaptogenesis

Hakan Coskun
PRRX1 Factor Controls Organ Positioning in Vertebrates

Shaikh Mirja Nurunnabi.
Novel Functions of Minibrain in the Regulation of Cell Cycle, Neuronal Differentiation & Asymmetric Division in *Drosophila*

Geraud Chauvin.
Implication of retinal EphA4 in refinement of collicular visual maps

20th Anniversary of the IN

Milestones in 20 years of the Instituto de Neurociencias

Universitary Institute: the IN is created in 1990 by initiative of professors of the Faculty of Medicine in the University of Alicante headed by Carlos Belmonte as Universitary Institute. The Neurosciences Institute was created by the interest of these professors in sharing equipment and promoting neuroscience in Spain. A pioneering vision that has demonstrated a successful approach by the importance of Neuroscience as a frontier of knowledge to respond to the most important challenge of current science: understanding the human brain.

Joint Research Center: in 1999 the IN becomes a Joint Center of the UMH and the CSIC; with the construction of the own building, which was inaugurated in September 2005 by S.M. Queen Sofia. With the creation of the Joint Center, consolidated and prestigious groups of the CSIC are incorporated into the IN. The IN becomes an attractive research center at the international level, which will include excellent young researchers, most of them returning from very successful post-doctoral stays and with Ramón y Cajal contracts.

Strategic plans: the strategic action plans of the IN develop and promote a collaborative research model. They began in 2005 with the first strategic plan, they have been based on the development of research lines that encourage collaboration among researchers from the different units of the IN. This allows the sharing of scientific interests, with multidisciplinary approaches and the creation of synergies to attract resources. This is coupled with an exemplary model in the recruitment of scientists, based on scientific excellence and foresight, and the design of research support platforms.

Corporate scientific competitiveness: the IN is presented in a corporate way to obtain prestigious research projects, such as the Consolider project (INGENIO program), obtained in 2007, which promote the development of platforms with adequate resources and increase scientific leadership of IN researchers, despite the economic crisis with its destructive impact on the investment and scientific development of our country. The success of this model is reflected in obtaining the accreditation of the IN as Center of Excellence “Severo Ochoa” in 2014, and its re-accreditation in 2018 to 2022.

Success in attracting talent and technology: successive corporate projects have allowed the development of a policy aimed at increasing scientific excellence, the result of which is the recruitment of young researchers with interest in the research lines and strategic plans of the IN , with potential to become leaders in different aspects of neuroscience. Likewise, competitive funds have been obtained to incorporate cutting-edge technology into the IN’s technical support platforms for research. The most illustrative result is the obtaining of 5 Projects of the European Research Council (ERC), which are highly competitive and internationally prestigious.

1999 - 2019

20 AÑOS

INSTITUTO DE NEUROCIENCIAS

UNIVERSITAS Miguel Hernández

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