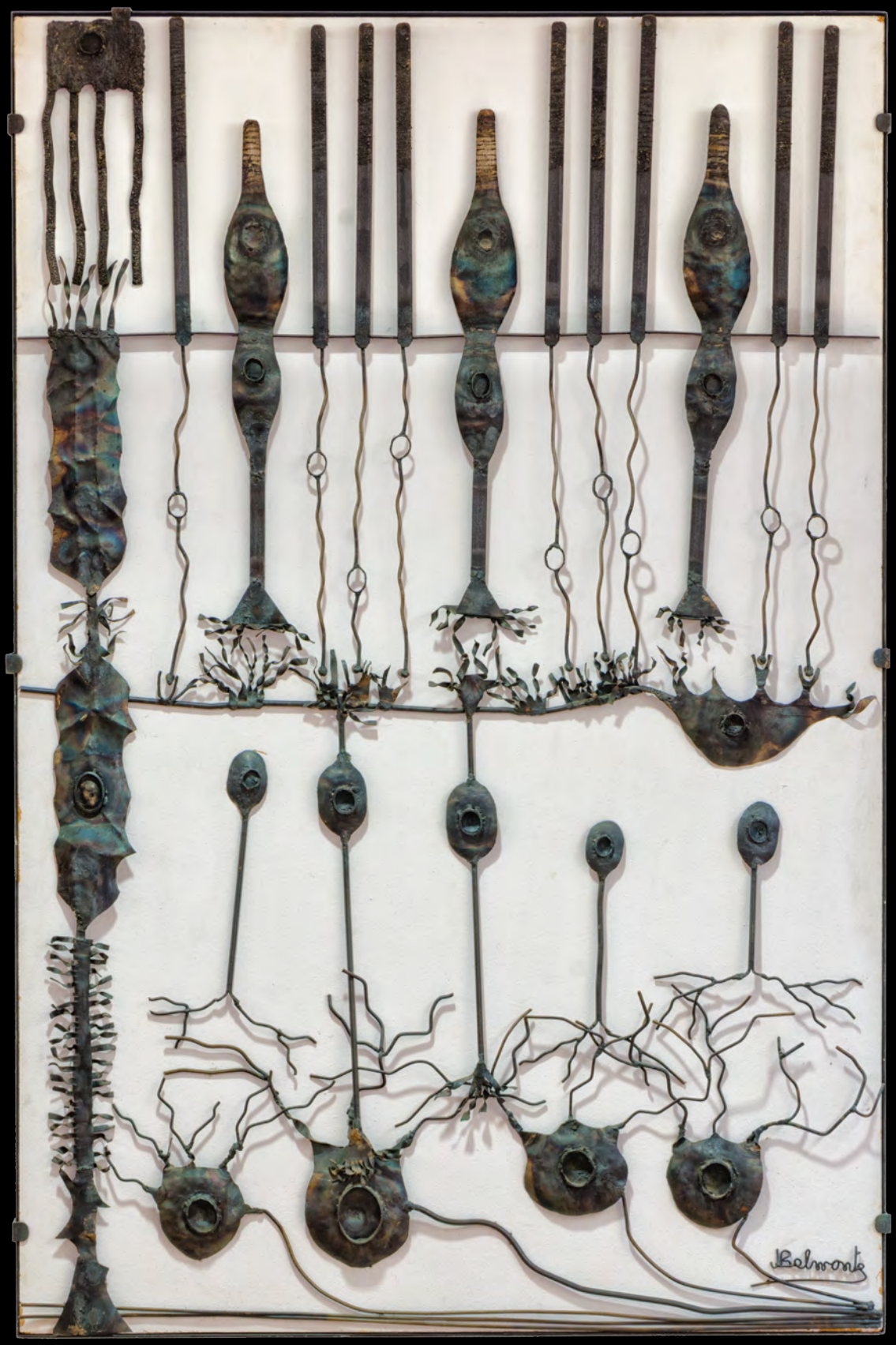
Instituto de Neurociencias UMH-CSIC

Annual Report 2021



INSTITUTO DE NEUROCIENCIAS

CSIC

UNIVERSITAS Miguel Hernández

Cover work: “La retina según Cajal”

Iron sculpture by José Belmonte González, 1986

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Saludation

Dr. Ángel Barco, Director of Institute of Neuroscience

Like for many of us, 2021 was also a transition year for the Instituto de Neurociencias (IN). We started to get out of the COVID-19 pandemic and embraced a new normality in which we were able to return to the full occupancy of the labs and in-person meetings but maintained social distance and mobility restrictions. This year also represented the end of the Strategic Plan developed by the IN between 2018 and 2021 and the preparation of a new and exciting Strategic Plan for the 2022 to 2025 period. The new plan includes the launching of eight Research Programs and several organizational changes, some of which were already initiated during 2021, that we hope will contribute to strengthen our institution, favor collaborative research, and nurture young talent. During 2021, the IN maintained its positive trajectory, increasing the number and quality of our scientific publications and attracting funding of International, European, Spanish, and Regional agencies and foundations. These achievements have been possible thanks to the excellent work and professionalism of our researchers, technicians, and administrative staff. Important challenges lay ahead, like the renewal of our accreditation as a Severo Ochoa Center of Excellence and the difficulties derived from our success in recruiting talented researchers and incorporating new technologies in competitive calls, which led us to surpass the original capacities of our building. Thanks to the quality and dedication of our personnel and the continuous support of our parental institutions, CSIC and UMH, we are confident about our capability to overcome these challenges. I would like to end this brief introduction to our scientific report for the year 2021 by thanking and congratulating all the employees of the IN for their invaluable contribution to the excellence and vitality of our institution.

Who we are

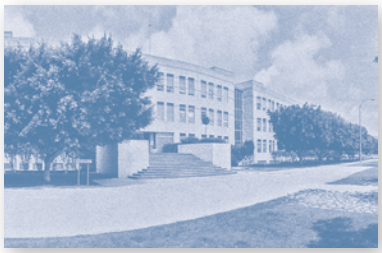
The IN, a joint center of the Spanish Research Council (CSIC) and the Universidad Miguel Hernández de Elche (UMH), is today the largest publicly funded center dedicated to brain research in Spain. More than 300 people dedicate their talent and effort to progress in our understanding of the biological basis of brain function and the mechanisms of brain disease. The IN maintains a balanced ratio between men and women, even at the highest management positions, and a high level of internationality. The accreditation as a "Severo Ochoa Center of Excellence" in 2014 and its renewal in 2018 have allowed us to develop an ambitious and multidisciplinary research program, undertake new methodological initiatives and recruit talented young researchers.

A bit of History

In 1990, the Valencian Government formally recognized the Instituto de Neurociencias (IN) at the Universidad de Alicante (UA) as a University

Institute, constituted by a group of its researchers that, since 1985, had been dedicated to the study of the structure and function of the nervous system. The members of the new Institute began to share not only their ideas but also funding and resources in order to improve their research environment. At the same time, a Ph.D. Program was created to train young scientists in the field of neuroscience. Five years later, the IN became an “Associated Unit” of the Instituto Cajal del Consejo Superior de Investigaciones Científicas (CSIC), and the first two CSIC research groups moved to the “Associated Unit” in Alicante. In 1996, the Institute along with the School of Medicine was transferred to the newly created University Miguel Hernández of Elche (UMH). During this period the Institute was physically located in the building of the School of Medicine, at the San Juan Campus site.

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



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

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

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

1999 — **Joint Centre**
UMH and CSIC

2001 — **Construction**
of the new building

2004 — **Occupation**
of the new building

2005 — **Inauguration**
by Her Royal Majesty

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

Consolider

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

EXCELENCIA SEVERO OCHOA

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

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

IN 20th Anniversary

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

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

EXCELENCIA SEVERO OCHOA

2018 Renewal of SO Distinction received by the IN

20 Years UMH & CSIC 2019

1999 - 2019

ANOS

INSTITUTO DE NEUROCIENCIAS

CSIC

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

Where we are

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

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

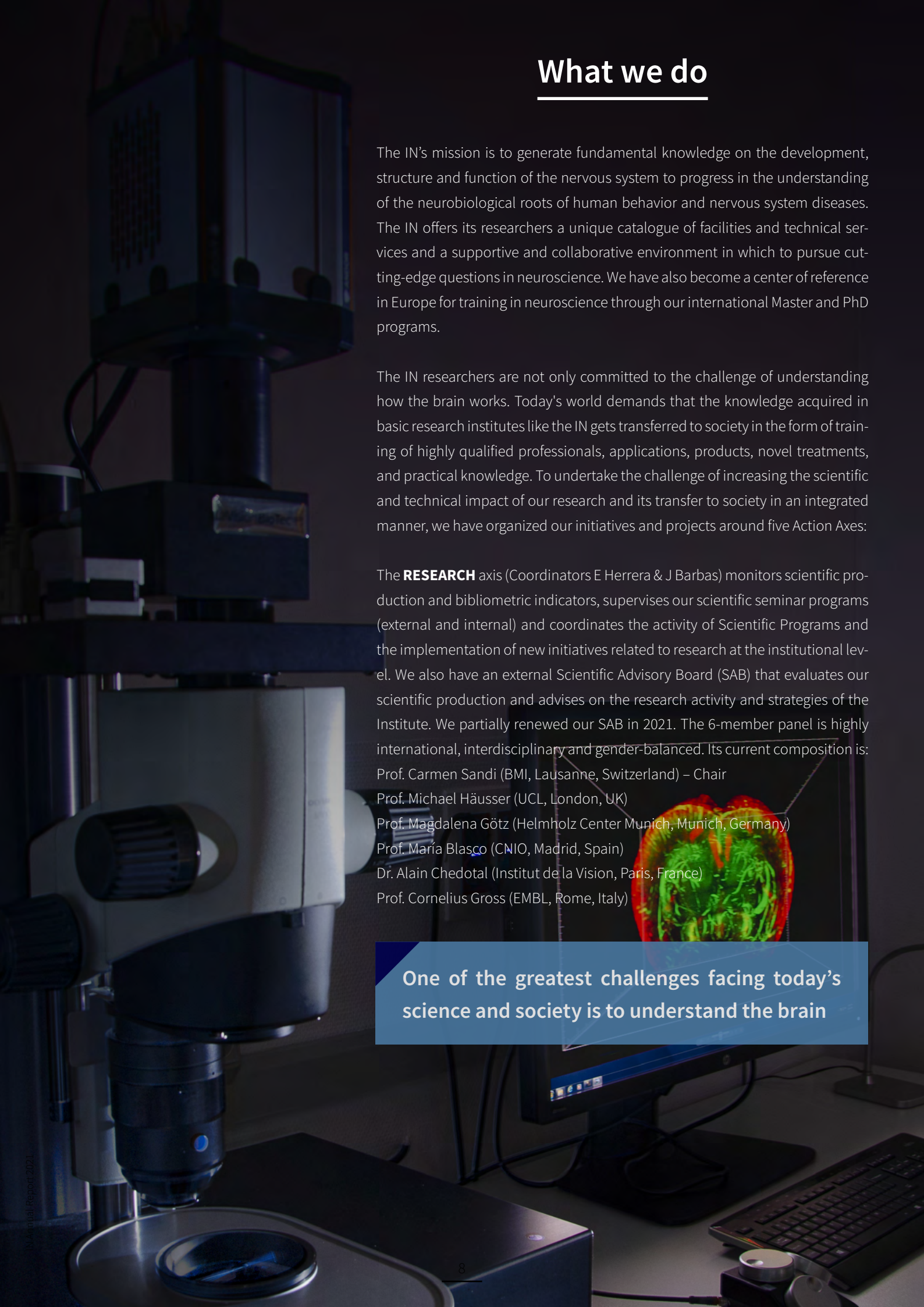
L.M. Gutiérrez

What we do

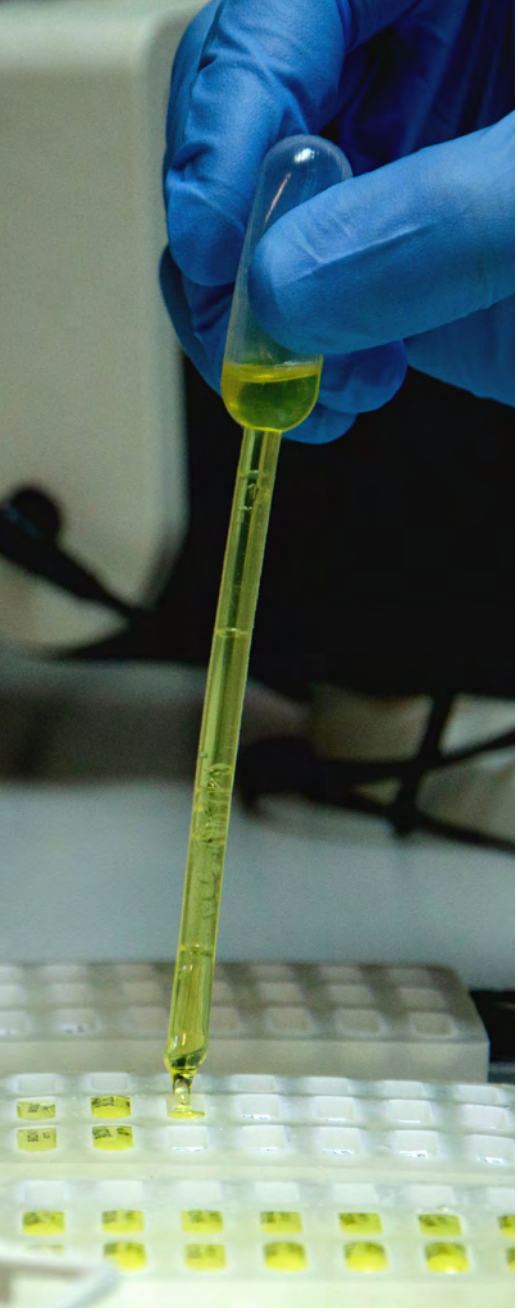
The IN's mission is to generate fundamental knowledge on the development, structure and function of the nervous system to progress in the understanding of the neurobiological roots of human behavior and nervous system diseases. The IN offers its researchers a unique catalogue of facilities and technical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

The IN researchers are not only committed to the challenge of understanding how the brain works. Today's world demands that the knowledge acquired in basic research institutes like the IN gets transferred to society in the form of training of highly qualified professionals, applications, products, novel treatments, and practical knowledge. To undertake the challenge of increasing the scientific and technical impact of our research and its transfer to society in an integrated manner, we have organized our initiatives and projects around five Action Axes:

The **RESEARCH** axis (Coordinators E Herrera & J Barbas) monitors scientific production and bibliometric indicators, supervises our scientific seminar programs (external and internal) and coordinates the activity of Scientific Programs and the implementation of new initiatives related to research at the institutional level. We also have an external Scientific Advisory Board (SAB) that evaluates our scientific production and advises on the research activity and strategies of the Institute. We partially renewed our SAB in 2021. The 6-member panel is highly international, interdisciplinary and gender-balanced. Its current composition is:
Prof. Carmen Sandi (BMI, Lausanne, Switzerland) – Chair
Prof. Michael Häusser (UCL, London, UK)
Prof. Magdalena Götz (Helmholz Center Munich, Munich, Germany)
Prof. María Blasco (CNIO, Madrid, Spain)
Dr. Alain Chedotal (Institut de la Vision, Paris, France)
Prof. Cornelius Gross (EMBL, Rome, Italy)



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



The **TRAINING** axis (Coordinators E de la Peña & E Geijo) supervises our diverse training programs. These include: (i) one-year Master in Neuroscience named "International Master in Neuroscience: from the bench to the bedside" (Director: E Geijo) that consists of both theoretical lectures and practical exercises to introduce the trainees to a variety of the methodologies used to study the nervous system; (ii) PhD Training Program in Neurosciences (Director: E de la Peña) that provides courses and research training in several areas of basic neurosciences and related disciplines (programming, statistics, etc.); (iii) leadership and career opportunity courses for postdocs, and (iv) career development and specialized courses for technical and administrative personnel. Both the Master and PhD programs are part of the international network of neuroscience schools (NENS).

The **INNOVATION** axis (Coordinators S Canals & J Gallar) seeks opportunities for the generation of exploitable intellectual property and supervises the activities of the novel Scientific Unit for Business Innovation. The office is responsible for identifying projects with direct translation potential and supports them in their transfer process. The axis also promotes innovation activities in the IN organizing seminars on different aspects (e.g., protection of intellectual property, patents, creation of spinoffs). and represents IN at innovation fairs. It bridges the gap with clinicians, pharmaceutical and biotech companies, facilitating a bidirectional exchange that establishes the most suitable conditions to drive the discovery and development of novel diagnostic and therapeutic strategies.

The **TRANSLATION** axis (Coordinators H Cabedo & S De Santis) seeks opportunities for collaboration and translation to the clinic. The axis aims to potentiate the collaboration between IN researchers and clinicians, particularly but not exclusively from local hospitals and health institutions, and patients' organizations through meetings and collaboration agreements. Our partners include the new Institute of Clinical and Biomedical Research of Alicante (ISABIAL), the Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) and different CIBERs and RICORs (networks dependent on the ISCIII, aimed at coordinating Spanish research on the most prevalent human diseases).

The **OUTREACH** axis (Coordinators V Borrell & S Jurado) coordinates actions aimed to disseminate our scientific discoveries to society, to inform and advise on science and technology matters to public and private entities and to promote scientific culture and rational thinking in our society. This axis is committed to promote the involvement of society with science through communication and educational projects (e.g., defense of animal experimentation, promotion of women in sciences) and to carry outreach activities related to neurosciences. It coordinates the activities for public awareness, such as open-doors visits, lay conferences and round tables on social implications of brain science, and monitors the presence of the IN in the media and social networks.

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

The Institute in Numbers

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

PERSONNEL

TENURE
Full tenure research staff
45

SUPPORT
Administrative & technical staff
100

NON-TENURE
Non- tenure research staff
11

POSTDOC
Postdoctoral staff
59

PREDOC
Predoctoral staff
117

GENDER

60% Female staff

40% Male staff

ORIGIN

Non-Nationals 12%

Spanish nationals 88%

PUBLICATIONS

Web of Science

93

IMPACT

Mean IF

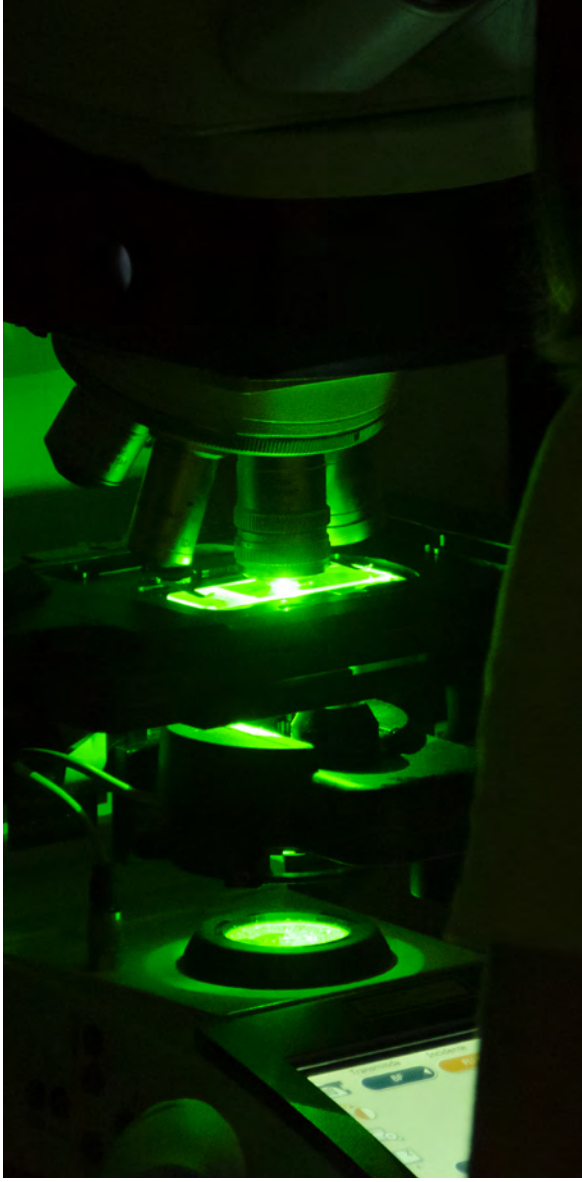
7

ACTIVE RESEARCH PROJECTS

in 2021

74

Strategic Plan and Research Lines



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

The IN wrote its first strategic plan in 2005. Since then, we have designed and implemented four 4-year strategic plans that shaped the research and growth of our Institute and enabled our positioning as a center of excellence in the European research area. The main objective of the Strategic Research Plan of the IN (IN-SRP) for the 2018-2021 period was to increase the knowledge about normal brain function and the biological roots of brain diseases, to improve prevention, diagnostics, therapies, and prognosis. The IN-SRP 2018-2021 defined a second level of organization, independent of Departments, based on seven 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.

These lines represented a multidisciplinary approach to study the molecular and cellular mechanisms underlying brain morphogenesis, synaptic establishment, and maturation in sensorial, motor, social and emotional neuronal circuits; to finally understand how combinatory function of these circuits explain perception, cognition, and behavior. The double structure of research lines and Departments promoted the interaction between IN researchers, facilitating a coherent internal discussion to update our main strategic research lines for the next years that led to the eight **Scientific Programs** (SPs) that constitute the novel IN-SRP for 2022-25. The new organization was implemented in January 2022 and will be presented in our next Scientific Report.

Research Groups

Developmental Neurobiology (Head: G. López-Bendito)

It comprises ten research groups devoted to study the development, evolution, and repair of the nervous system and to understand the developmental origin of pathologies using vertebrate and invertebrate animal models. Their objectives include the study of pattern formation, growth control and cancer, neurogenesis, cell migration, neuronal differentiation and plasticity, reprogramming, axonal guidance, circuit development and synaptogenesis. Overall, the Department comprises 84 researchers plus 20 technicians and support personnel.

R. Jiménez Castaño

Research Groups

Cellular and Systems Neurobiology (Head: S. Jurado)

The sixteen research groups in this Department study the mechanism by which the nervous system integrates information to regulate behavior combining molecular, electrophysiological, optogenetics, brain imaging and behavioral approaches in a variety of animal models and human studies. Specific topics cover 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. Overall, the Department comprises 85 researchers plus 12 technicians and support personnel.

| A. González Masa

Research Groups

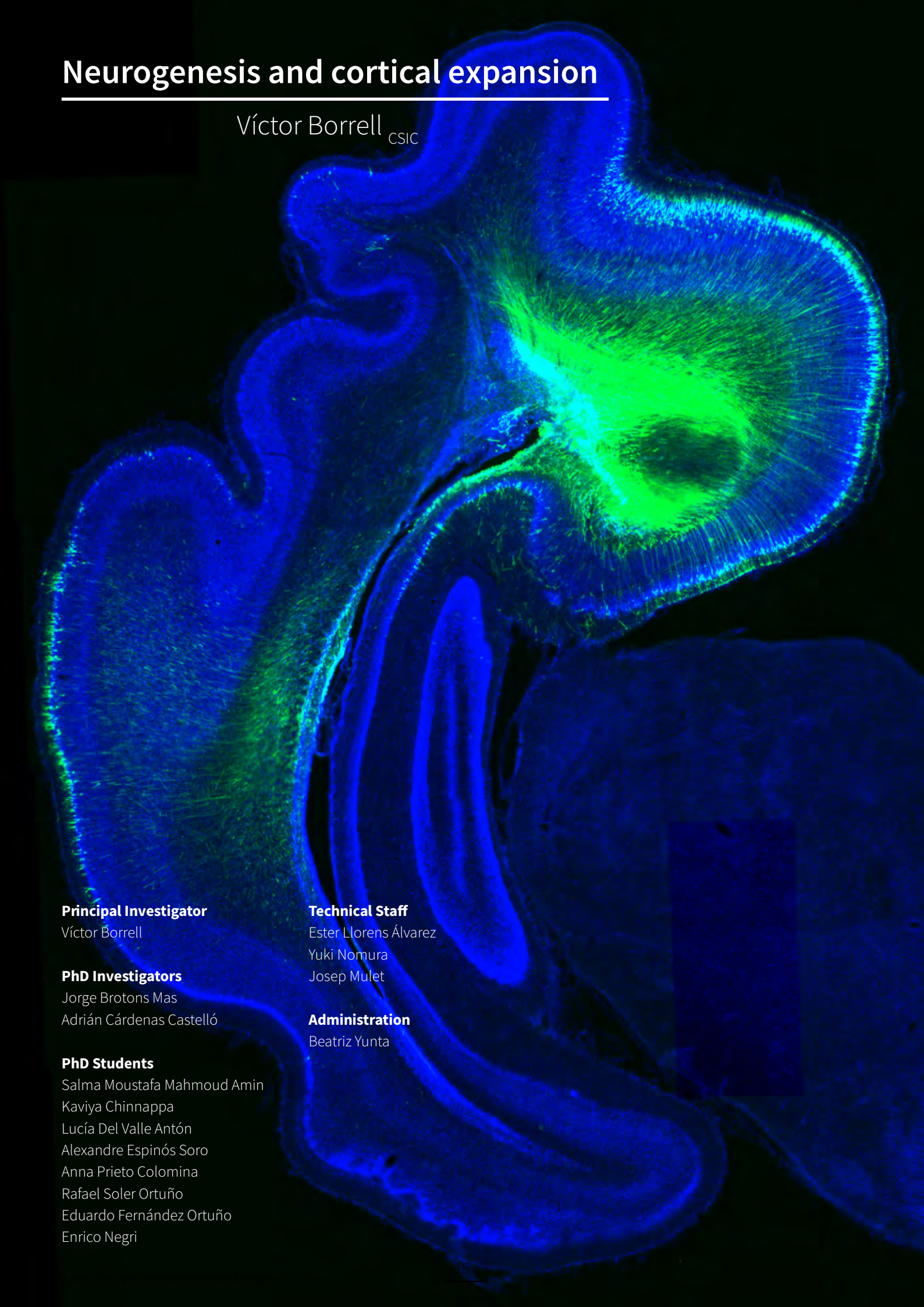
Molecular Neurobiology and Neuropathology (Head: J.P. López-Atalaya)

The eight groups in this Department investigate the biological basis of rare and prevalent psychiatric and neurological diseases using a combination of behavioral and electrophysiological analyses, cellular and molecular biology techniques, and high-throughput omics approaches. Their collective effort seeks to better understand the molecular and environmental grounds of brain malfunction to improve current therapeutic strategies for brain disorders. Overall, the Department comprises 46 researchers plus 5 technicians.

J. López-Atalaya Martínez

Neurogenesis and cortical expansion

Víctor Borrell CSIC



Principal Investigator
Víctor Borrell

PhD Investigators
Jorge Brotons Mas
Adrián Cárdenas Castelló

PhD Students
Salma Moustafa Mahmoud Amin
Kaviya Chinnappa
Lucía Del Valle Antón
Alexandre Espinós Soro
Anna Prieto Colomina
Rafael Soler Ortuño
Eduardo Fernández Ortuño
Enrico Negri

Technical Staff
Ester Llorens Álvarez
Yuki Nomura
Josep Mulet

Administration
Beatriz Yunta

Neurogenesis and cortical expansion

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

Multiple genetic mutations have been identified as the leading cause for intellectual or learning disability and intractable epilepsy in humans. These mutations are consistently linked to defects of cortical development during fetal de development, and functional studies in rodents have shown that these genes play essential roles in distinct aspects of cortical neurogenesis, neuron migration or cortical folding.

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

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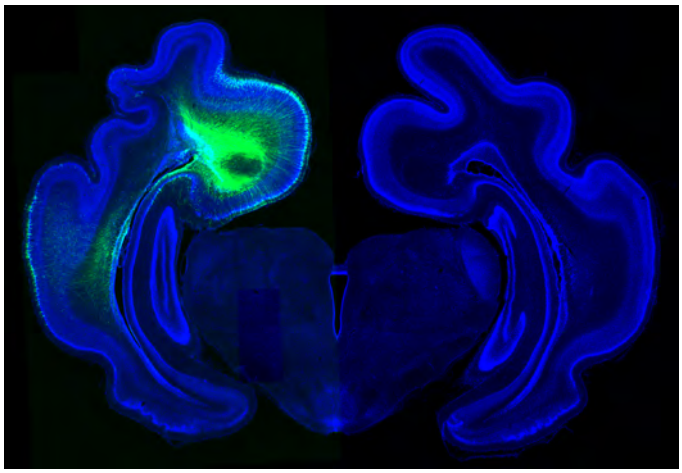
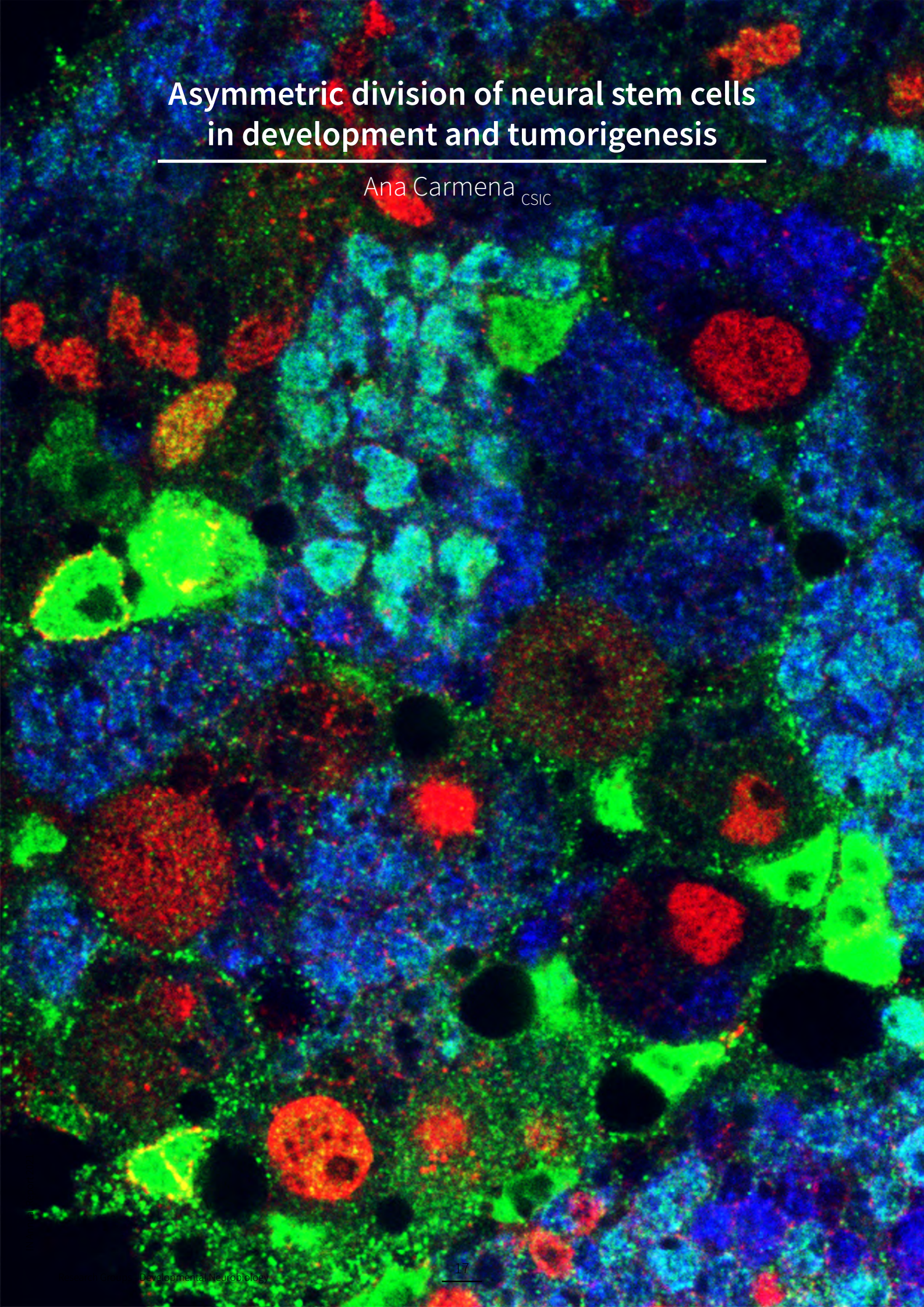
Department
Developmental Neurobiology



Visit the group website for more information

Asymmetric division of neural stem cells in development and tumorigenesis

Ana Carmena CSIC



Asymmetric division of neural stem cells in development and tumorigenesis

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

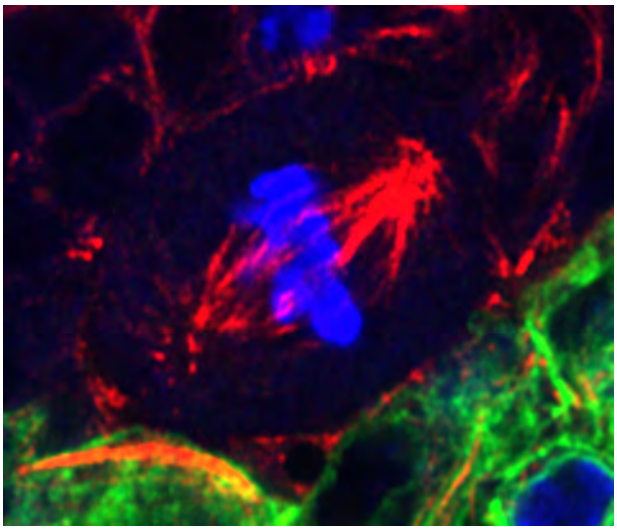
Specifically, we are interested in studying and contributing to answering three fundamental questions in the field:

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

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

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

Department
Developmental Neurobiology



Visit the group website for more information

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Eph signaling controls mitotic spindle orientation and cell proliferation in neuroepithelial cells. Franco, M and Carmena, A. (2019) **Journal of Cell Biology** doi: 10.1083/jcb.201807157

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Principal Investigator
Ana Carmena

PhD Investigator
Maribel Franco Redrejo

PhD Students
Ana de Torres Jurado
Sandra Manzanero Ortiz

Mechanisms of growth control and cancer

María Domínguez CSIC

Principal Investigator
María Domínguez Castellano

PhD Investigators
Dolors Ferrés Marcó
Diana M. Vallejo Martínez
Isabel Adrados Morán
Lucía García-López

PhD Students
Roberto Santoro
Ernesto Sáez-Carrión
Daniel Tendero López

Master Student
Lucia López Gil

Technical Staff
Esther Ballesta Illán
Laura Mira Valdelvira
María Trinidad Maciá Pérez
Alicia Estirado Bronchalo
Clara Serrano Navarro
Juan Ramón Guirado Roig

Administration
Rosa Sánchez Cayuela

Professor Colaborator
Dr. Jorge Bolivar (Universidad de Cádiz)

Mechanisms of growth control and cancer

Our research focuses on the molecular mechanisms behind high-order growth control and tumorigenesis. This research is concentrated in two areas:

Two matching sides. Animal size is remarkably constant within species despite disturbances. This constancy is most impressive when we consider how the left and right parts, like our legs or an insect's wings, growing separately during ontogeny can attain an exact match in size and shape. Bilateral asymmetry reflects the genetic and environmental stress during development, and such variation, if left uncorrected, can impact locomotion, vision, feeding, or balance. 'Fluctuating asymmetry' is a valuable index to expose factors associated with buffering size variations and some medical conditions. For example, using that index, we have found that the high-order control of growth that results in perfect bilateral symmetry resides in the nervous system and requires extensive communication between growing organs and neurons through the relaxin hormone ILP8 and its receptor Lgr3. Flies deficient in the hormone *Ilp8*, or with its receptor silenced in the nervous system, cannot maintain perfect symmetry, display more varied size, and are more vulnerable to diseases like cancer. Factors linked to fluctuating asymmetry are associated with fitness, genetic quality, and resilience.

Making inroads into cancer pathways and therapeutics. We have pioneered high-throughput unbiased genetic screens in vivo to identify combinations of genes that drive tumour initiation and metastasis. These studies have identified new links to cancer, including cooperation between epigenetic silencers of the Polycomb family (Pipsqueak) and Notch in malignant transformation, identified ligands of Notch, Serrate and JAGGED, as targets of miR-200 microRNA, or collaboration between Notch and the Pten/PI3K pathway, which have been extensively validated in other animals and human cancers. We recently reported a cost-effective, high-throughput drug screening platform using tumour-bearing flies that capture alterations found in certain human cancers. These studies have identified the FDA-approved Montelukast and Zileuton's anti-asthmatic medicines that could be repositioned to treat leukaemia. These pharmacogenetic studies have also determined that PTEN deficiency facilitates tumorigenesis via a nitric oxide (NO)-dependent inflammation that requires the production of leukotrienes derived from arachidonic acid that acts locally and systemically.

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Department
Developmental Neurobiology

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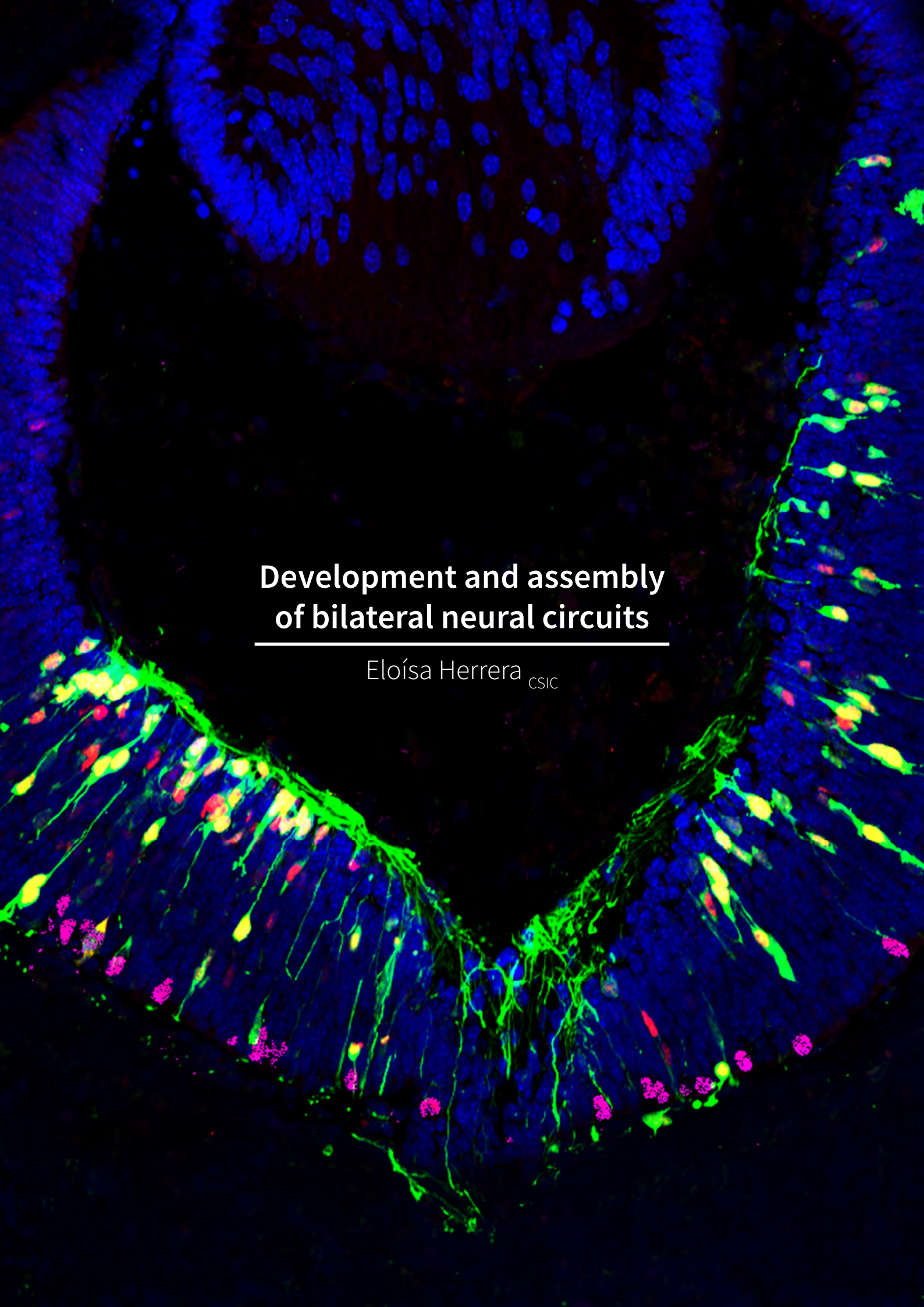
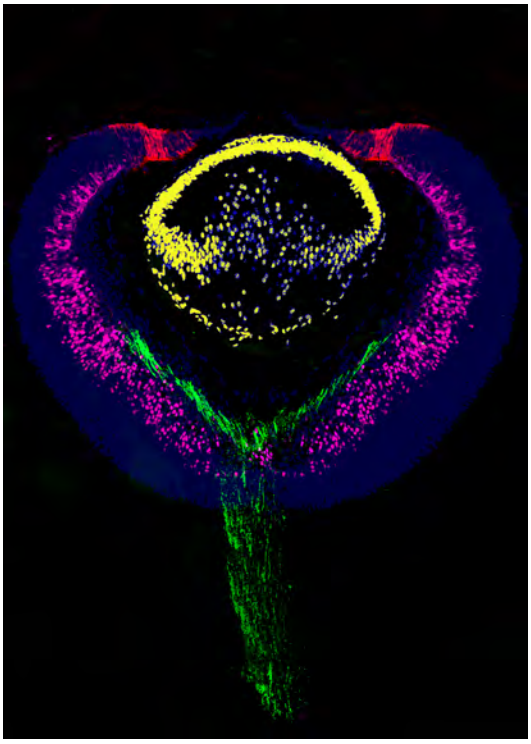


Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Development and assembly of bilateral neural circuits

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. Axon growth cones change their response as they grow and move from one intermediate target to the next one guided by the concerted action of attractive and repulsive molecules. Many of the main families of axon guidance molecules and their respective receptors involved in this process have been described but the regulatory mechanisms triggering axonal reprogramming from a decision point to the next one are poorly characterized. Growth cone plasticity is at play all over the developing nervous system and we use the mammalian visual system as a model to uncover the transcriptional, epigenetic (context-specific) and activity-dependent mechanisms that regulate axon pathfinding and circuit assembly. We also investigate to what extent our discoveries in the visual system apply to other circuits in the CNS.



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Department
Developmental Neurobiology

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Principal Investigator
Eloísa Herrera

PhD Investigators
Augusto Escalante Rodríguez
Marta Fernández Nogales
María Cruz Morenilla Palao
Verónica Murcia Belmonte
Carlos Sánchez Huertas

PhD Students
María Teresa López Cascales
Patricia Ordoño Carramiñana
Isabel Pérez Ferrer

Technical Staff
Yaiza L. Coca Ulloa
Macarena Herrera González de la Higuera

Administration
Beatriz Yunta Arce

Development, plasticity and reprogramming of sensory circuits

Guillermina López Bendito CSIC

Principal Investigator
Guillermina López-Bendito

Associated Investigator
Miguel Angel Valdeolmillos López

PhD Investigators
Francisco Martini
Teresa Guillamón Vivancos
Verónica Moreno Juan
Daniel Torres Romero
Dorien Vandael

PhD Students
Álvaro Herrero
Leticia Saiz Pérez
Irene Huerga Gómez
Mar Aníbal Martínez
Chrysoula Giasafaki
Lorenzo Puche Aroca
Pablo Castellano
Francesco Dori

Technical Staff
Luis Miguel Rodríguez Malmierca
Rafael Susín Carmona
Belén Andrés Bayón

Administration
Helena Campos Martín

Development, plasticity and reprogramming of sensory circuits

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

In the mature cerebral cortex, sensory modalities are segregated into specialized areas known as primary sensory cortices. So that cortical areas ultimately respond to a specific sensory stimulus, this segregation is thought to occur during development, and it is first instructed by intrinsic factors and later by sensory experience. We hypothesize that rewiring and plasticity events can be triggered by activity-dependent mechanisms in the sensory stations such as the thalamus or the superior colliculus.
Three major questions are been focused in the laboratory: i) the activity-dependent mechanisms involved in sensory circuits development, ii) the role of the thalamus and its connectivity in the neuroplastic cortical changes following sensory deprivation, and iii) reprogramming thalamic cells for circuit and sensory restoration. We are also developing novel animal models for determining the role of thalamocortical input in cortical functional specification and plasticity.
Within these projects we are using several experimental programmes, these include: functional neuronal imaging, manipulation of gene expression in vivo, cell and molecular biology, biochemistry, cell culture and electrophysiology. We have also used gain- and loss-of-function experiments to help unravel new mechanisms involved in the development and rewiring of this major axonal tract (see Science Advances 2021; Science 2019; CurrOpiNeurob 2018; NatComm 2017; Cerebral Cortex 2016; EMBO Reports 2015; Current Biology 2014, Nature Neuroscience 2012, Journal of Neuroscience 2012, Current Biology 2011, Neuron 2011, PLoS Biology 2009, J Neurosci 2007, Cell 2006, Nat Rev Neurosci 2003).

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

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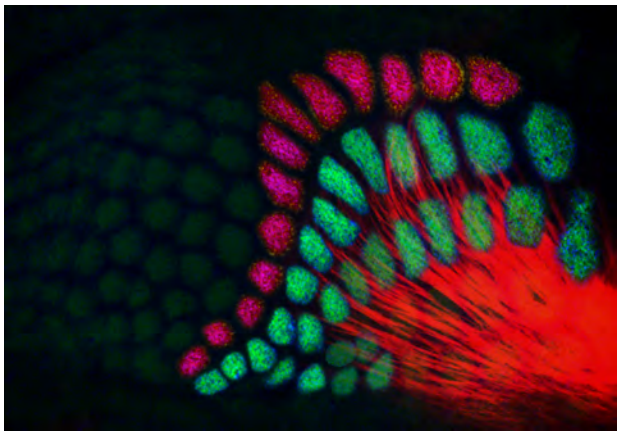

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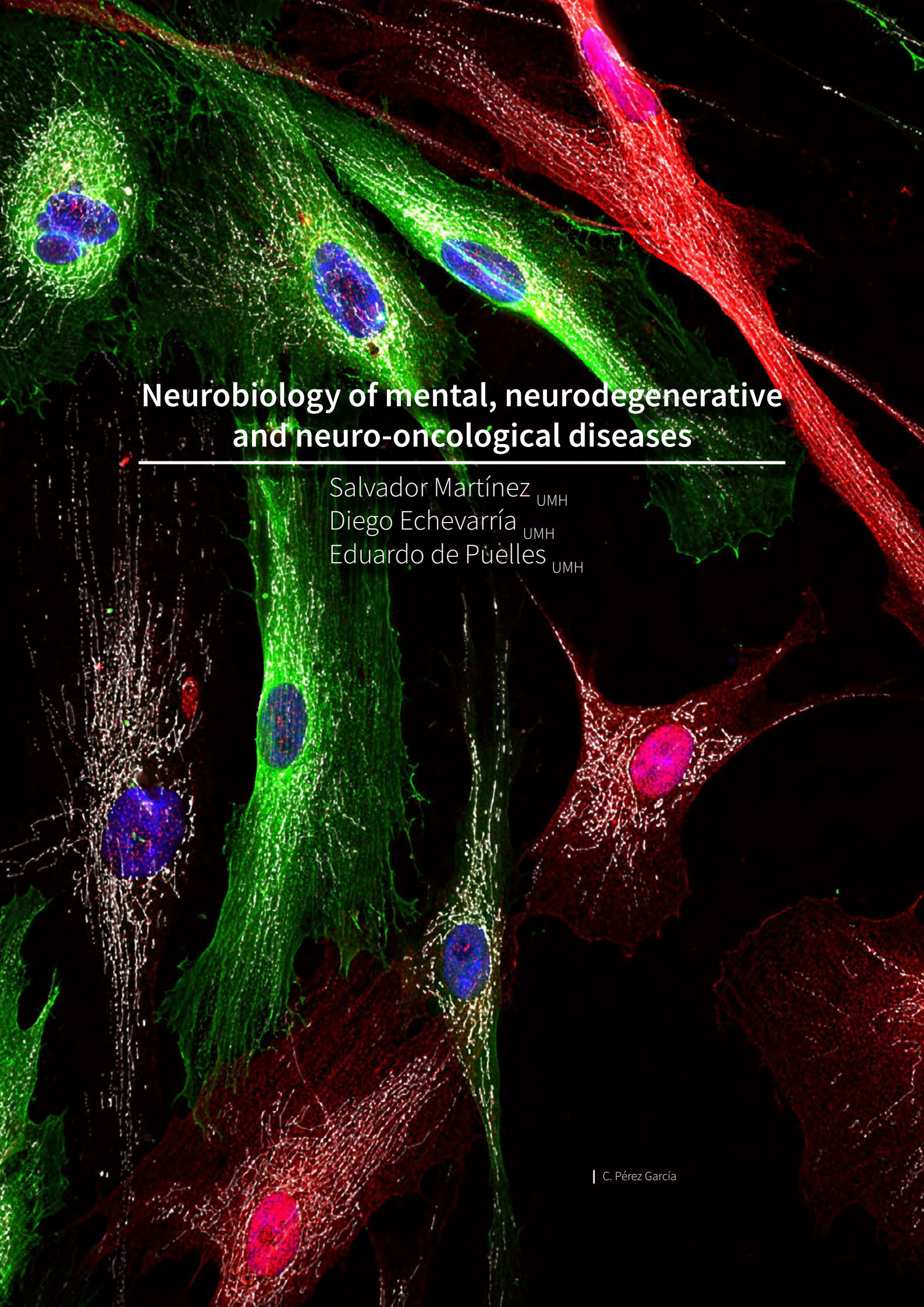


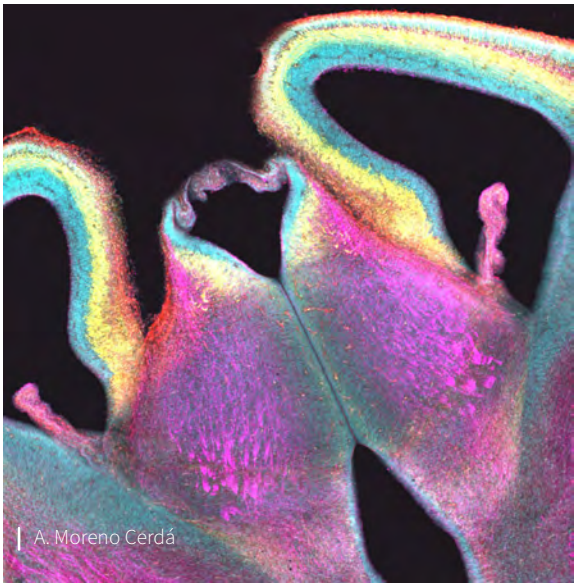
Neurobiology of mental, neurodegenerative and neuro-oncological diseases

Salvador Martínez UMH
Diego Echevarría UMH
Eduardo de Puelles UMH

C. Pérez García

Neurobiology of mental, neurodegenerative and neuro-oncological diseases

Our laboratory studies the structural and functional development of the cerebral cortex and associated circuits. Through experimental and genetic manipulations, we address the study the molecular and cellular mechanisms of the brain development of motor and limbic cortical regions, including their connectivity and basic circuitry setup and postnatally the functional roles. The results obtained experimentally and by the generation of murine and human cell models of neurodegenerative diseases (amyotrophic lateral sclerosis, multiple sclerosis, lissencephaly, cerebellar ataxias, autistic spectrum disorders, etc.), are also of our interest for building bridges of knowledge for the initiation and implementation of cell therapies and future clinical trials. Based on similar experimental approaches we study the mechanisms of infiltration and immunological conditioning of Glioblastoma multiforme.



A. Moreno Cerdá

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Developmental Neurobiology

Abnormalities in Cortical GABAergic Interneurons of the Primary Motor Cortex Caused by Lis1 (Pafah1b1) Mutation Produce a Non-drastic Functional Phenotype. Domínguez-Sala E, Valdés-Sánchez L, Canals S, Reiner O, Pombero A, García-López R, Estirado A, Pastor D, Geijo-Barrientos E, Martínez S. (2022) **Front Cell Dev Biol**. 2;10:769853. doi: 10.3389/fcell.2022.769853. eCollection 2022.

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Principal Investigator
Salvador Martínez
Diego Echevarría
Eduardo de Puelles

PhD Investigators
Ana Pombero
Raquel García-López
Abraham Andreu
Nicanor Morales

Professor Colaborator
Emilio Geijo
Diego Pastor
Francisco Carratalá
Mª Carmen Lillo
Verónica Company

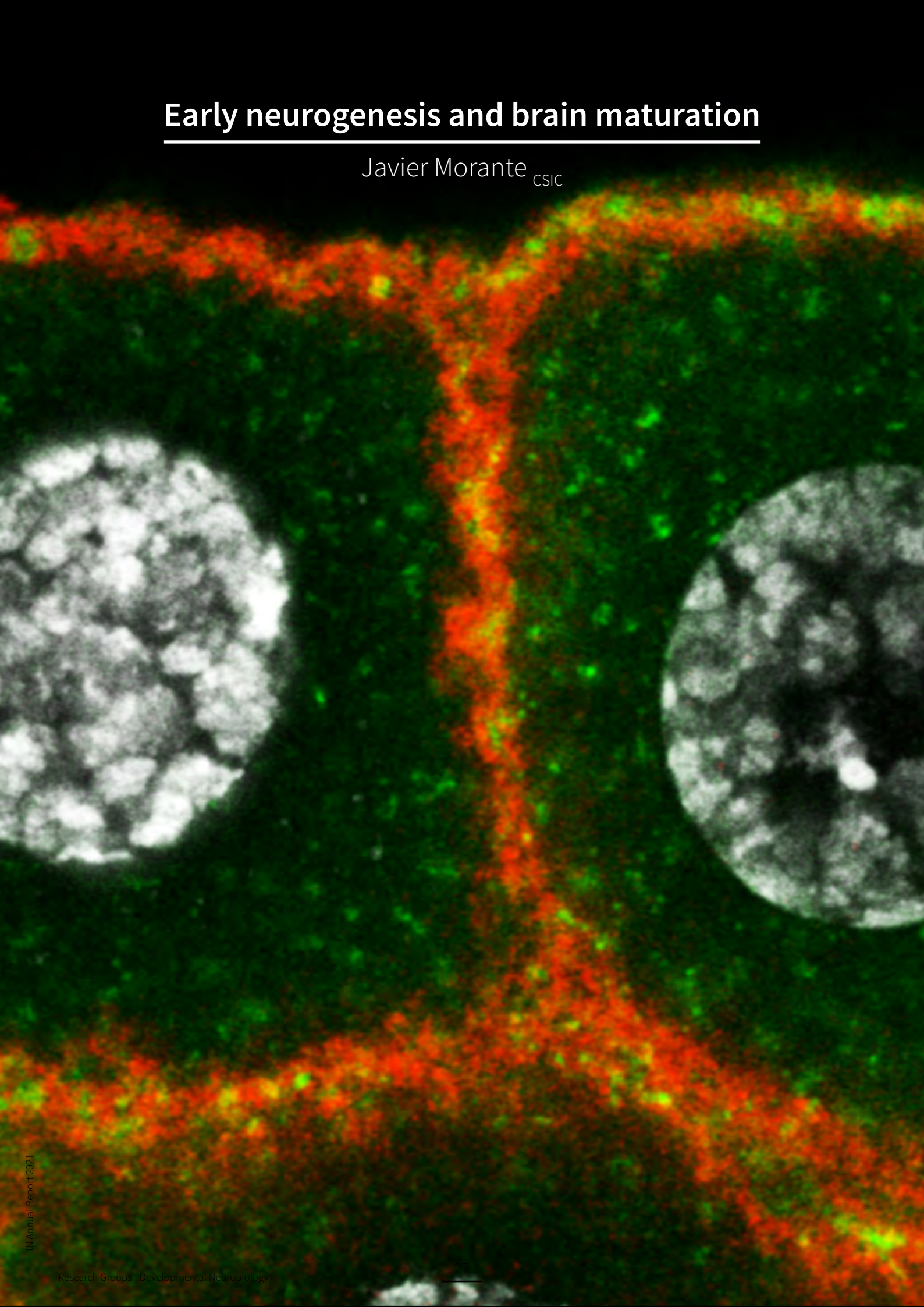
PhD Students
Antonio Guillermo Almenar Lluch
Claudia Pérez García

Technical Staff
Francisca Almagro García
Mónica García Abad

Administration
Mª Jesús Arencibia

Early neurogenesis and brain maturation

Javier Morante CSIC



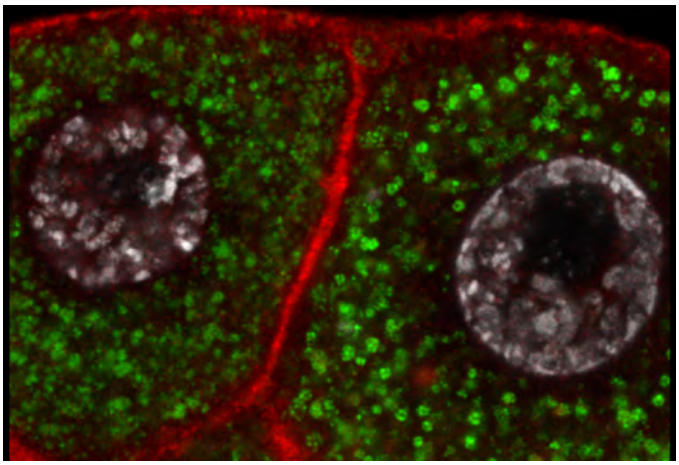
Early neurogenesis and brain maturation

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

How exactly these external and internal cues are integrated to dictate when an animal can reach sexual maturity, as well as what molecular and cellular mechanisms acting at the level of neuroendocrine cells trigger this critical decision, remains a fascinating mystery.

Childhood obesity, the prevalence of which is increasing to pandemic proportions, has been associated with precocious puberty in girls. On the other hand, malnutrition and intensive physical training can delay puberty. Previous work in mice and humans has also shown that a deficiency of leptin, a hormone secreted by fat cells, or its receptors, which signal the amount of energy stores in the body in neuroendocrine circuits, leads to hyperphagia, early-onset obesity and delayed or complete inability to initiate the pubertal transition.

By using *Drosophila*, we aim to uncover the molecular and cellular mechanisms and neuroendocrine circuits required for the regulation of sexual maturation and body weight control.



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Developmental Neurobiology

Body-Fat Sensor Triggers Ribosome Maturation in the Steroidogenic Gland to Initiate Sexual Maturation in *Drosophila*. S. Juarez-Carreño, DM Vallejo, M. Palomino-Schätzlein, P. Ramon-Cañellas, R. Santoro, J. Carranza-Valencia, E. de Hartog, D. Ferres-Marco, A. Romero, H. Payette Peterson, E. Ballesta-Illan, A. Pineda-Lucena, M. Domínguez*, J. Morante* (2021) **Cell Reports** 37(2):109830

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Principal Investigator
Javier Morante

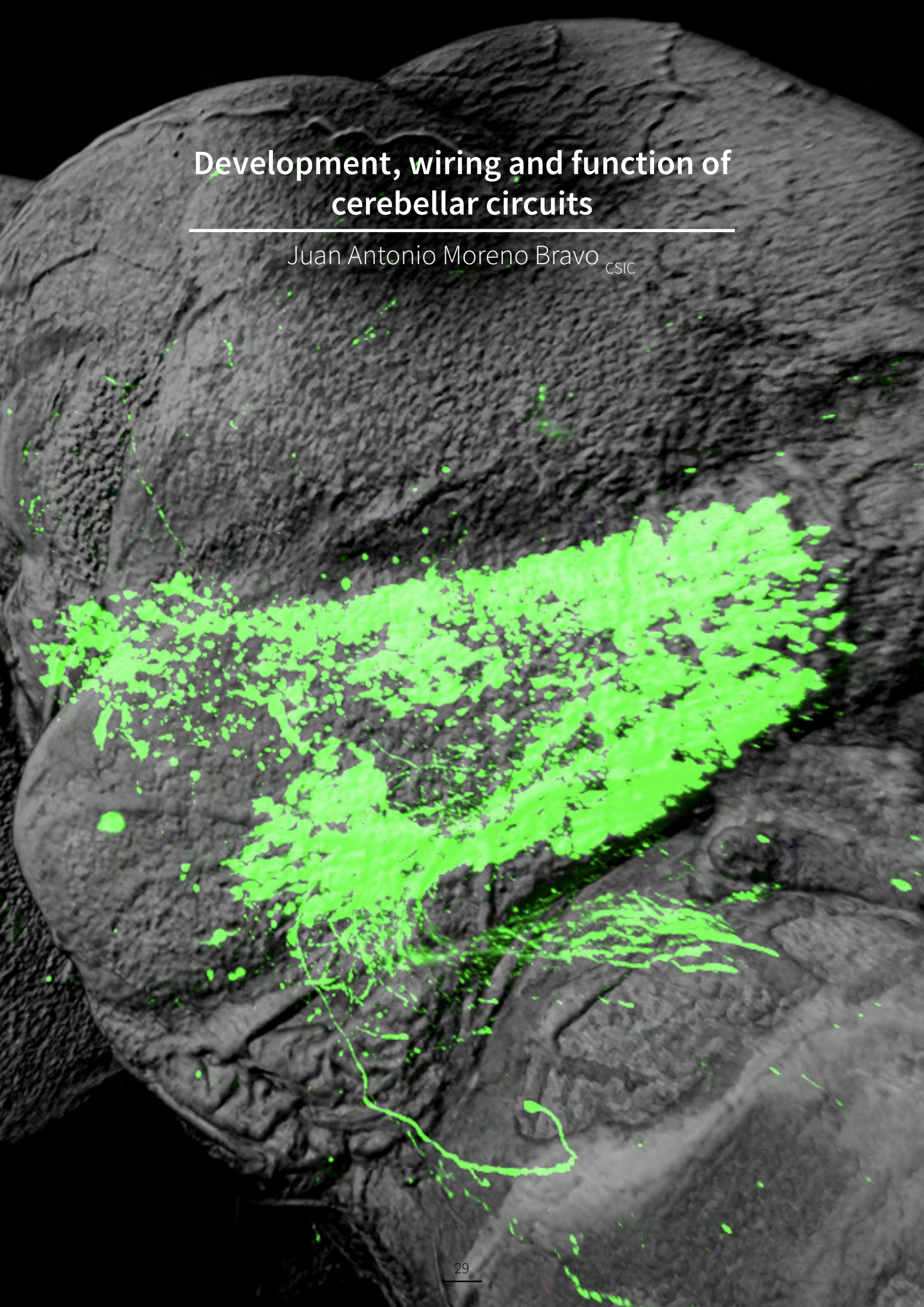
PhD Investigator
Luis García-Alonso

PhD Student
Juan Carranza Valencia

Master Student
Juan Ramon Guirado Roig

Development, wiring and function of cerebellar circuits

Juan Antonio Moreno Bravo CSIC



Development, wiring and function of cerebellar circuits

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

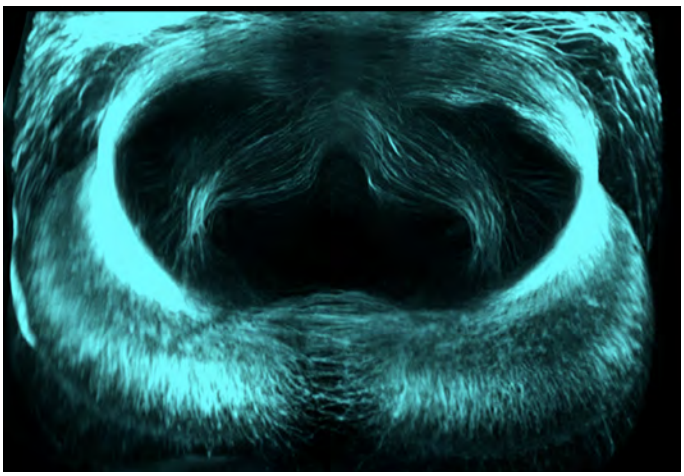
We combine mouse genetics to develop animal models with cerebellar alterations, state-of-the-art histological, cellular, molecular biology methods and techniques, transcriptomics and functional analyses.

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

Our research is focused in two main research lines:

- Understanding cerebellar long-range connectivity that relays cerebellar output to diverse brain areas. We aim to elucidate how the cerebellum influences the development and function of remote brain circuits, with particular interest on the cerebellar modulation of the developing cortical circuits.

- Investigating the development and assembly of local cerebellar circuits. We seek to determine basic regulatory mechanisms underlying the formation and function of these circuits and how alterations in these processes derive in an abnormal function of the cerebellum.



Visit the group website for more information

Principal Investigator
Juan Antonio Moreno Bravo

PhD Student
Sara Camacho García

Master Student
Victor Martin Aguiar

Tecnical Staff
Raquel Murcia Ramón

Administration
Jorge Mallor Cortés

Department
Developmental Neurobiology

Neural Stem Cells Direct Axon Guidance via Their Radial Fiber Scaffold. Kaur N*,Han W*, Li Z*, Madrigal MP, Shim S, Pochareddy S, Gul-den FO, Li M, Xu X, Xing X, Takeo Y, Li Z, Lu K, Imamura Kawasawa Y, Ballester-Lurbe B, Moreno-Bravo JA, Chédotal A, Terrado J, Pérez-Roger I, Koleske AJ, Sestan N. (2020) **Neuron** doi: 10.1016/j.neuron.2020.06.035.

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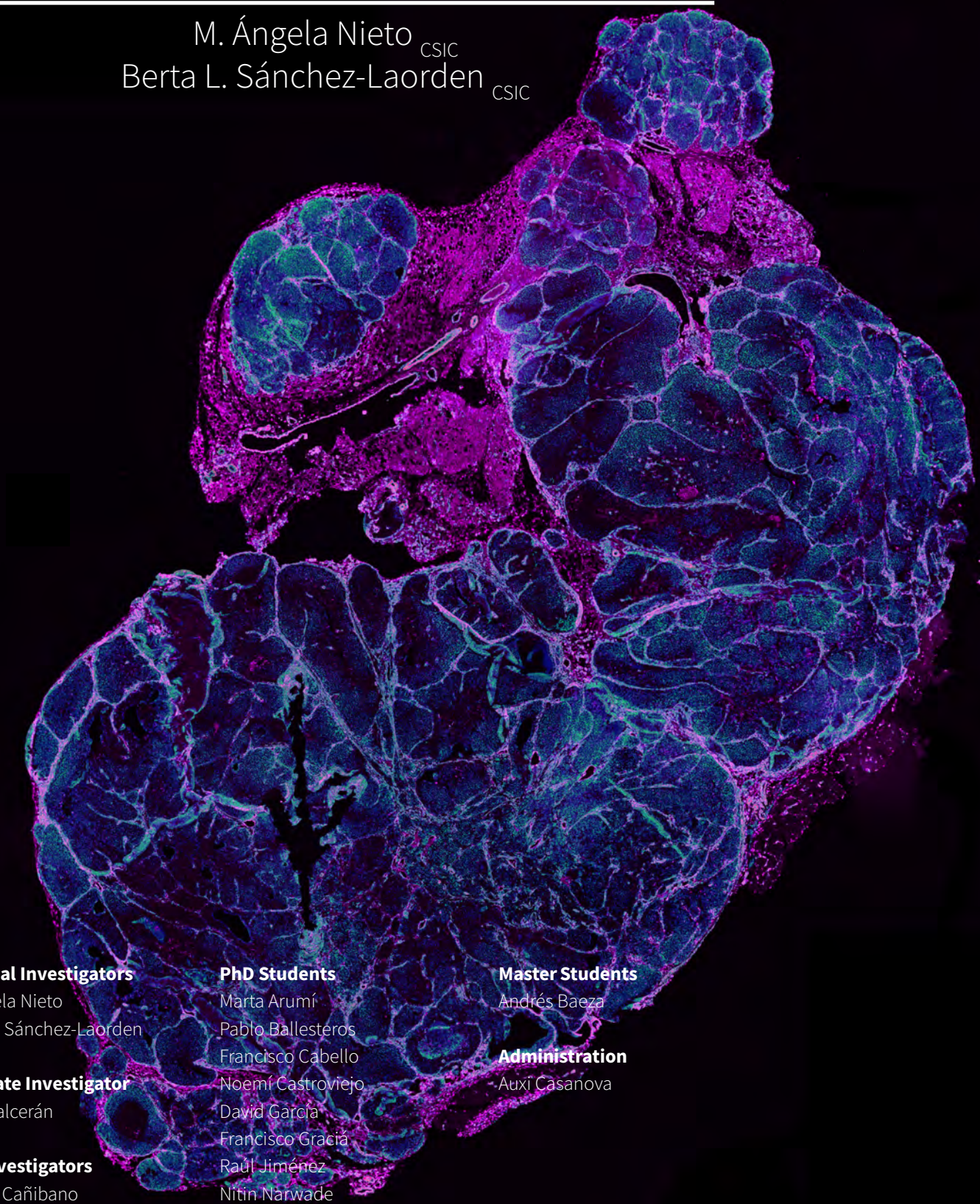
Cell plasticity in development and disease

M. Ángela Nieto CSIC
Berta L. Sánchez-Laorden CSIC



Principal Investigators
M. Angela Nieto
Berta L. Sánchez-Laorden

Associate Investigator
Joan Galcerán

PhD Investigators
Alberto Cañibano
Francisco García-Asencio
Ainara González-Iglesias
Khalil Kass Youssef
María Angeles Núñez
Francisco Javier Rodríguez-Baena
Marilyn Scandaglia
Sonia Vega

PhD Students
Marta Arumí
Pablo Ballesteros
Francisco Cabello
Noemí Castroviejo
David García
Francisco Graciá
Raúl Jiménez
Nitin Narwade
Noelia Yelo Torrano
Sanjay Vasudaven

Technical Staff
Mar Francés
Teresa Gómez
Cristina López-Blau
Cristina Minaya
Aurelia Torregrosa

Master Students
Andrés Baeza

Administration
Auxi Casanova

Cell plasticity in development and disease

For the last almost 30 years, the group has been studying cell movements and plasticity in health and disease. We study the epithelial to mesenchymal transition (EMT), a fundamental process during embryonic development to allows cells to delaminate and migrate towards their final destinations. We described how different transcription factors, the so-called EMT-TFs, are activated in different vertebrates to regulate massive cell movements during gastrulation, neural crest migration or organ positioning. We have extended our studies to biomedical research, as we found that pathological activation of these factors in the adult leads to several prominent pathologies, including cancer and fibrosis. As such, an aberrant activation of the EMT programme in tumours leads to acquisition of invasive and migratory properties, required for cancer dissemination and progression to the metastatic disease.

The EMT is a very complex process in which different EMT transcription factors (EMT-TFs) promote different plasticity programs in embryonic and cancer cells. How the EMT-TFs orchestrate these programs and, specially, how the highly plastic partial EMT states can trigger the development of fibrosis or influence metastatic potential and therapy resistance is not well understood. We are characterizing the programmes induced by different EMT-TFs and have developed new models to investigate EMT-TF expression codes and signalling pathways that can discriminate EMT states and predict cell behaviour and prognosis in pathological contexts, including organ fibrosis, breast cancer and melanoma. We are also characterizing novel functions of these EMT-TFs during neural crest development, neuronal differentiation, vascular integrity and brain metastasis. In summary, our main contribution has been showing how reactivation of developmental programmes in the adult leads to the progression of devastating pathologies. This aberrant reactivation can be considered a sign of defective homeostasis, leading to diseases whose prevalence increases with aging, such as cancer and organ degeneration by fibrosis.

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

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50+ shades of EMT in 20 years of embryo-cancer bonding. Nieto, M.A. (2020) **Nat. Rev. Mol. Cell. Biol.** 21, 563

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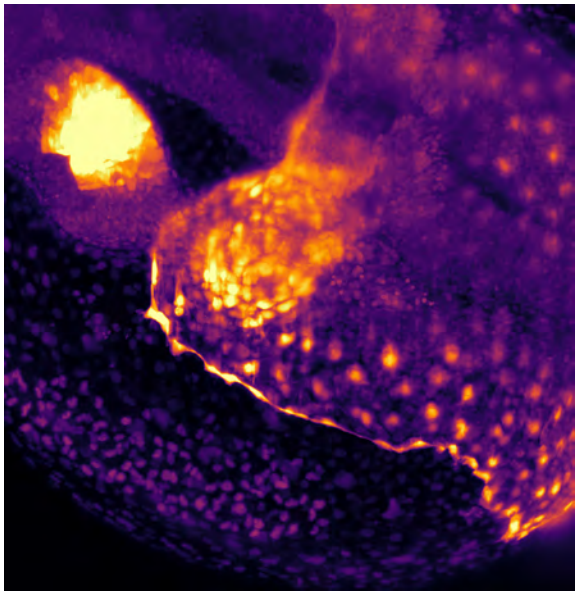

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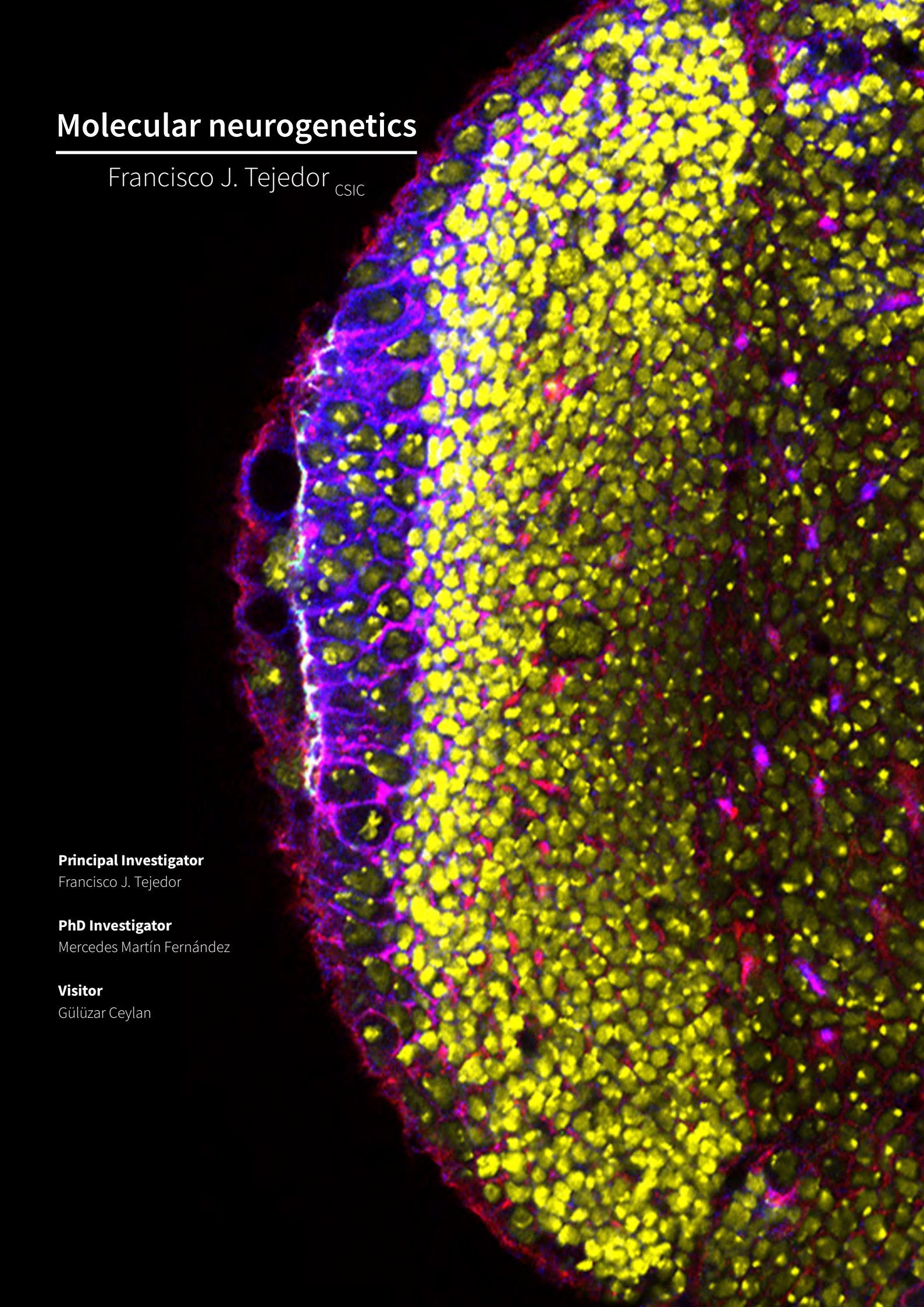
Molecular neurogenetics

Francisco J. Tejedor CSIC



Principal Investigator
Francisco J. Tejedor

PhD Investigator
Mercedes Martín Fernández

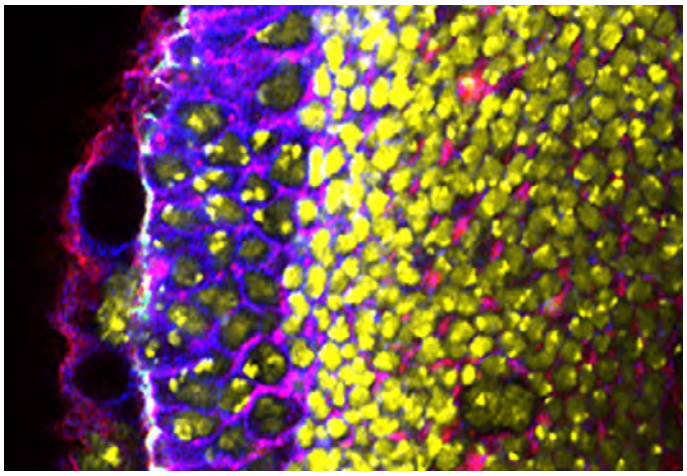
Visitor
Gülüzar Ceylan

Molecular neurogenetics

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

Following this approach, we identified the gene *minibrain* (*mnb*, also called *Dyrk1A* in vertebrates) as a major regulator of neural progenitor cell proliferation and neurogenesis in *Drosophila*. *Mnb/Dyrk1A* encodes a very well evolutionary conserved protein-kinase, which play several functions through brain development. We are focusing on its roles in the regulation of neural proliferation, cell cycle, neurogenesis, and neuronal differentiation, unravelling the underlying molecular mechanisms. Remarkably, haploinsuficiency of *DYRK1A* causes an intellectual disability syndrome characterized by microcephaly. *Mnb/Dyrk1A* has also raised great interest because it is one of the most interesting candidate genes for the neuropathologies of Down Syndrome (DS). As a matter of fact, the MNB/DYRK1A kinase is presently considered a suitable drug target for DS neuropathologies. We are using experimental models to determine what cellular functions and molecular mechanisms are altered by an excess and a loss of *Mnb/Dyrk1* function to generate neurobiological alterations reminiscent of DS and microcephaly neuropathologies. We are also testing the suitability of MNB/DYRK1A kinase inhibitors to interfere with neuronal functions as a prospect to apply pharmacological therapeutic approaches to DS neuropathologies.

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



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Department
Developmental Neurobiology

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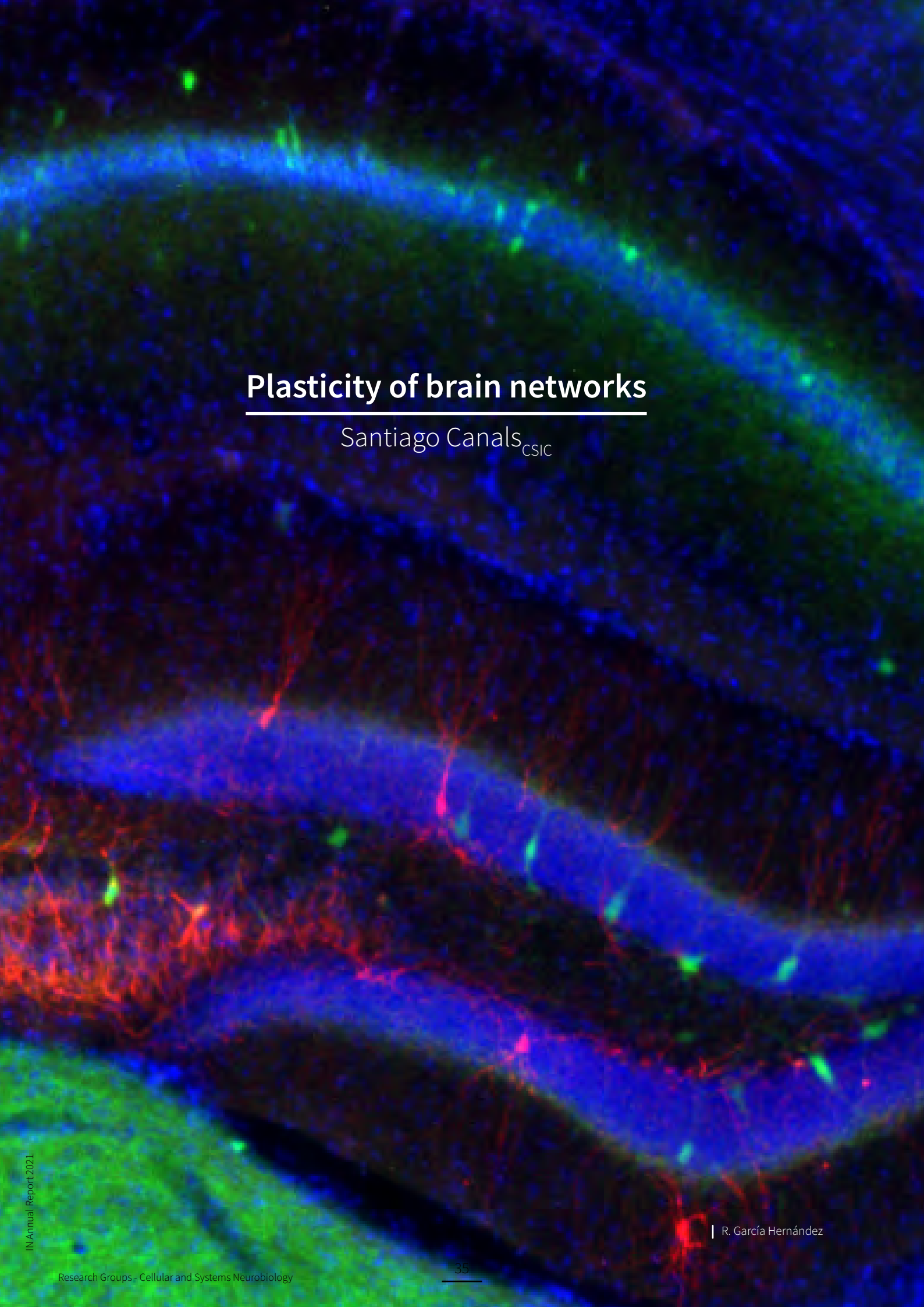
Plasticity of brain networks

Santiago Canals[CSIC]



R. García Hernández

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 behavioral adaptation. Little is known, however, about how synapse dynamics are transformed into network dynamics. We have demonstrated that brain circuits involved in learning and memory are functionally reorganized after local potentiation of synaptic transmission in the hippocampus. We are currently investigating the mechanisms underlying this network reorganization, focusing on short- and long-term synaptic plasticity and 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 behavior 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.

Department
Cellular and Systems Neurobiology

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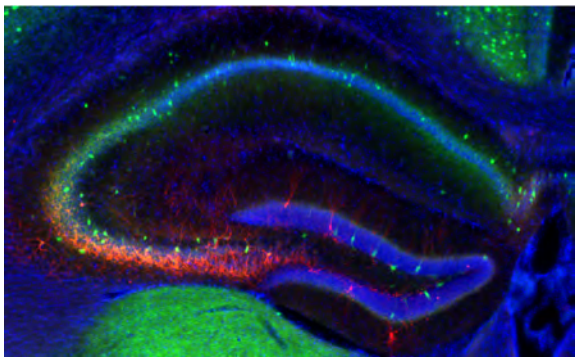


Visit the group website for more information

Principal Investigator
Santiago Canals

PhD Investigators
Encarni Marcos

PhD Students
José María Caramés
Víctor J. López Madrona
Laura Pérez Cervera
Elena Pérez Montoyo
Andrés Pérez Segura
Raquel García Hernández
Mohamed Kotb Mohamed Abdelmaboud Selim
Antonio Cerdán Cerdá
Cristian Estarellas Martín
Aarón Cuevas López

Technical Staff
Begoña Fernández Nuñez
Analía Rico Rodríguez
Clara Serrano Navarro

Administration
Rosa María Sánchez Cayuela

Sensory transduction and nociception

Elvira de la Peña UMH
Ana Gomis CSIC
Félix Viana CSIC

Principal Investigators
Elvira de la Peña
Ana Gomis
Félix Viana

Associate Investigators
Laura Almaraz
Salvador Sala

PhD Investigator
Jorge Fernández-Trillo

PhD Students
Ana Gómez del Campo Sancho
Pablo Hernández Ortego
Khalid Oudaha
Manuela de las Casas Felgueroso

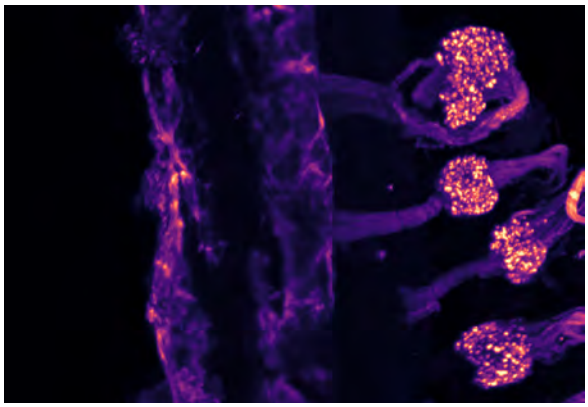
Technical Staff
Mireille Tora
Clara Serrano
Eva Quintero

Sensory transduction and nociception

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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Department
Cellular and Systems Neurobiology

Constitutive Phosphorylation as a Key Regulator of TRPM8 channel function. Bastian Rivera, Claudio Moreno, Boris Lavanderos, Ji Yeon Hwang, Jorge Fernández-Trillo, Kang-Sik Park, Patricio Orio, Félix Viana, Rodolfo Madrid and María Pertusa. (2021) **The Journal of Neuroscience** 41:8475-8493 DOI:10.1523/JNEUROSCI.0345-21.2021.

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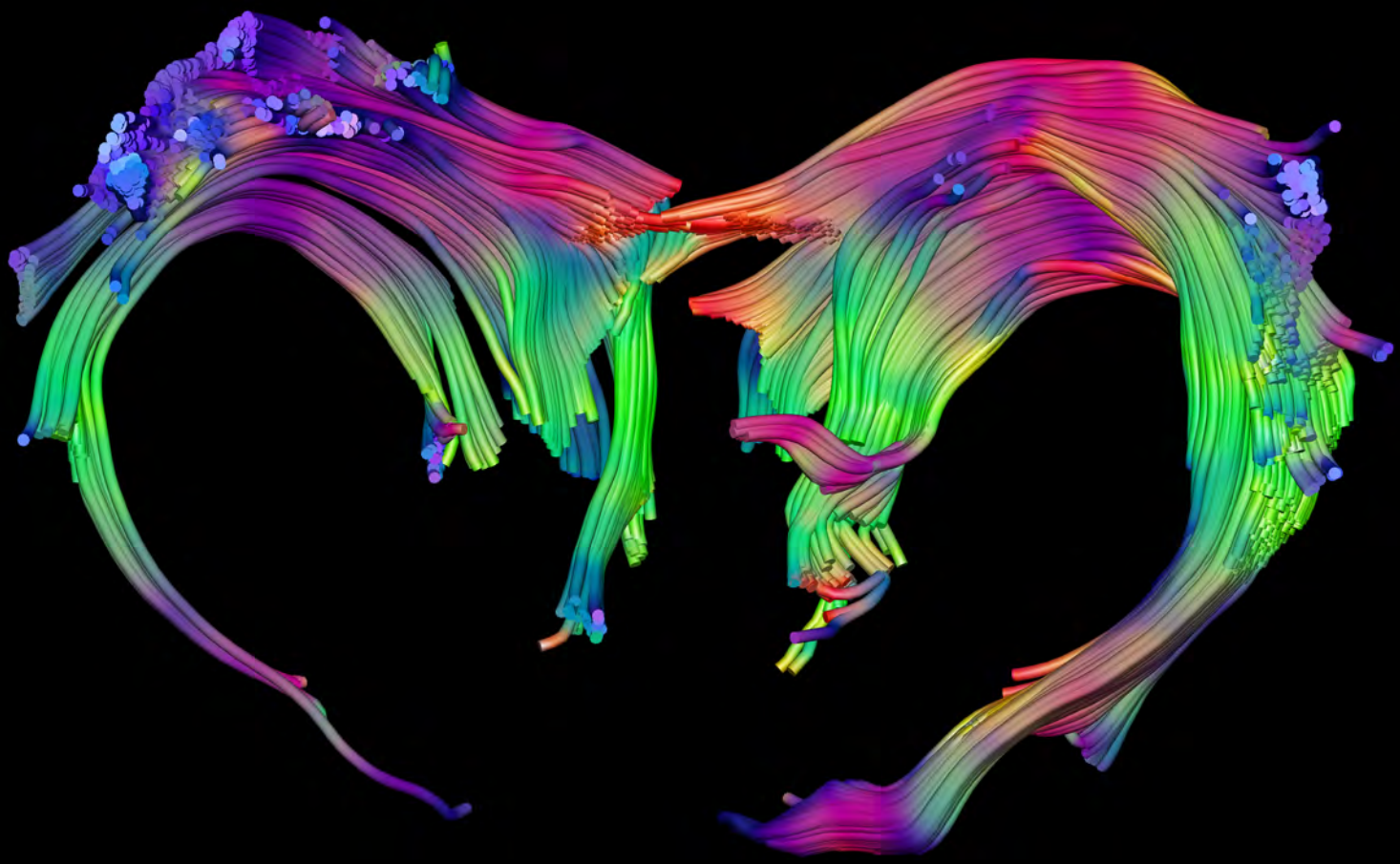

Translational imaging biomarkers

Silvia De Santis CSIC

A. Cerdán Cerdá

Translational imaging biomarkers

Neuroinflammation and neurodegeneration are hot topics for brain research, and have become very promising targets for the development of novel treatments with the potential to intervene in pathological conditions. In order to characterize both aspects of brain tissue in both preclinical and human models, non-invasive tools are needed to measure biomarkers of the inflammatory state, such as glia morphology, and salient features of the microstructure, such as the level of myelination, the axonal diameter and cell density.

Our research focuses on the development, optimization, and application of innovative magnetic resonance imaging tools relevant to both basic and clinical research. These tools allow to obtain maps of several microstructural characteristics in a non-invasive way and with a translational approach, valid both in humans and in preclinical models (mice and rats).

With these tools, we intend to characterize biomarkers of structural integrity throughout life, with special attention to healthy aging, as well as to identify early biomarkers, which can precede and predict diseases such as multiple sclerosis and Alzheimer's, all taking into account the gender dimension. An additional line of research is dedicated to developing computational approaches based on machine learning so that the methodologies developed can be transferred to the clinic.

Department
Cellular and Systems Neurobiology

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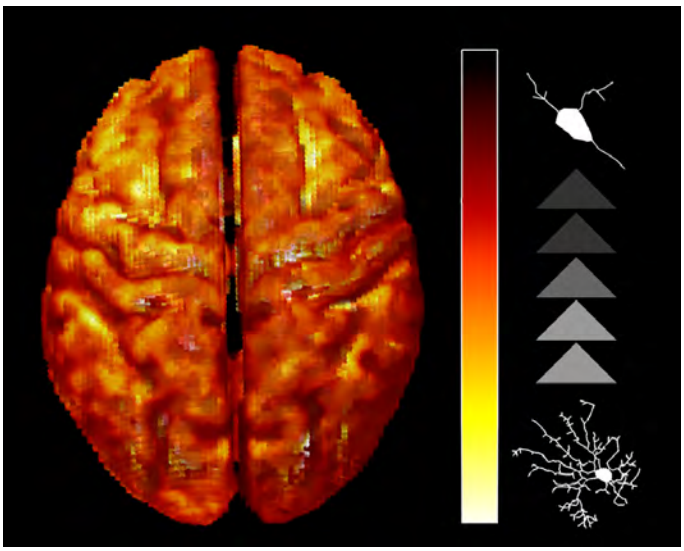


Visit the group website for more information

Principal Investigator
Silvia De Santis

PhD Students
Antonio Cerdán Cerdá
Patricia Martínez Tazo

Technical Staff
Aroa Sanz Maroto

Ocular neurobiology

Juana Gallar UMH
Mª Carmen Acosta UMH
Víctor Meseguer UMH

Principal Investigators
Juana Gallar
Mª Carmen Acosta
Víctor Meseguer

Assistant Professor
Adolfo Aracil Marco

PhD Investigators
Ariadna Díaz Tahoces
José A. Gómez Sánchez
Susana Quirce Vázquez

PhD Students
Fernando Aleixandre Carrera
David Ares Suárez
Miguel Delicado Miralles
Almudena Íñigo Portugués
Laura Rincón Frutos
Enrique Velasco Serna

Master Students
Vicente Miralles Liborio

Technical Staff
Carolina L. Luna García

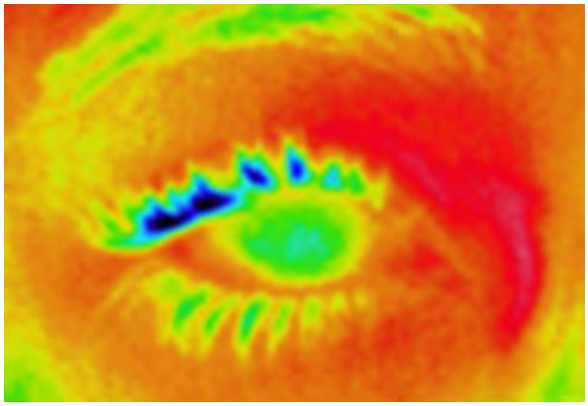
| A. Íñigo Portugués

Ocular neurobiology

The main interest of the Ocular Neurobiology Group (ONG) is to study the functional activity of sensory nerves from the ocular surface, responsible for the genesis of sensations evoked by stimulation of ocular tissues as well as for the trophic maintenance and protective reflexes ensuring the correct moisturizing of the ocular surface. Using morphological techniques (studying corneal nerve morphology in fixed and living tissue), electrophysiological techniques (recording nerve activity of sensory receptors in nerve endings and axons, as well as extracellular recording of trigeminal ganglion neurons and CNS neurons along the trigeminal pathway) and pharmacological and opto-pharmacological tools to modulate neurons' activity, and psychophysical studies (analyzing the characteristics of the sensations evoked by selective stimulation of the ocular surface), the ONG investigates the functional characteristics of the primary, thalamic and cortical neurons innervating the anterior surface of the eye with particular attention to those neurons participating in ocular sensations of eye dryness, discomfort and pain.

The ONG has described 1) the sensitivity of the ocular surface to selective stimulation in healthy subjects and its changes with ageing, 2) the correlation between the electrical activity of specific types of ocular sensory nerves and the different sensations evoked in humans, 3) the changes in ocular sensitivity in different pathologies, after ocular refractive surgery or with the use of different ophthalmic drugs, and 4) the role of the ocular surface nerve activity in regulation by CNS of basal and reflex tearing, and blinking.

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



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Department

Cellular and Systems Neurobiology

Scientific collaborators

María Merino

Oftalmología, Hospital de la Marina Baixa

Javier Belmonte

Oftalmología, Hospital General Universitario de Alicante

José Ángel Pastor-Zaplana

Departamento de Patología y Cirugía, UMH

Fernando Borrás Rocher

Departamento de Estadística, Matemáticas e Informática, UMH

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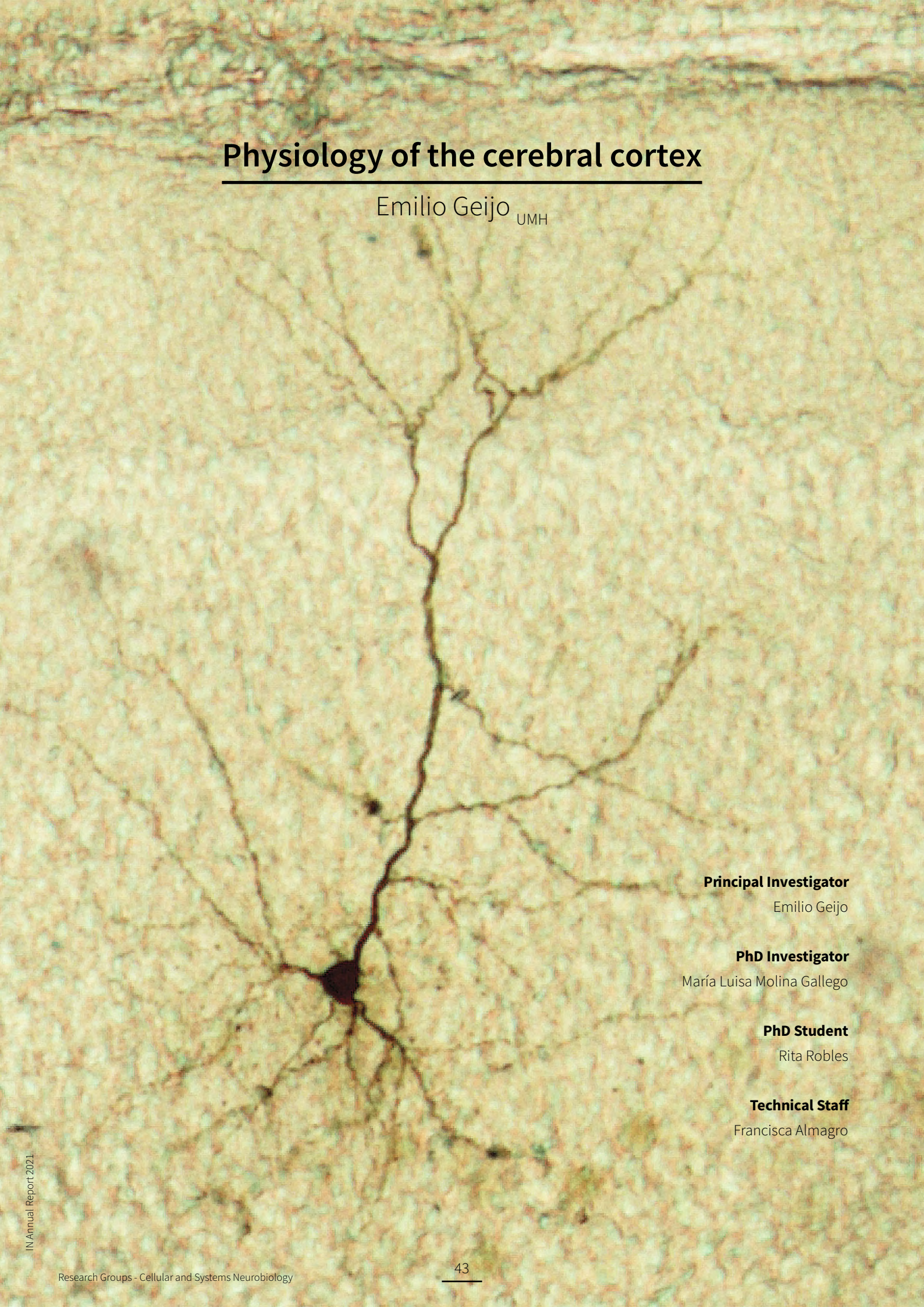
Physiology of the cerebral cortex

Emilio Geijo UMH



Principal Investigator
Emilio Geijo

PhD Investigator
María Luisa Molina Gallego

PhD Student
Rita Robles

Technical Staff
Francisca Almagro

Physiology of the cerebral cortex

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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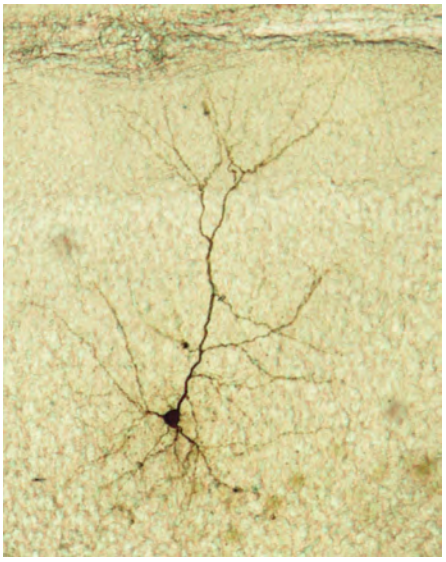
Cellular and Systems Neurobiology



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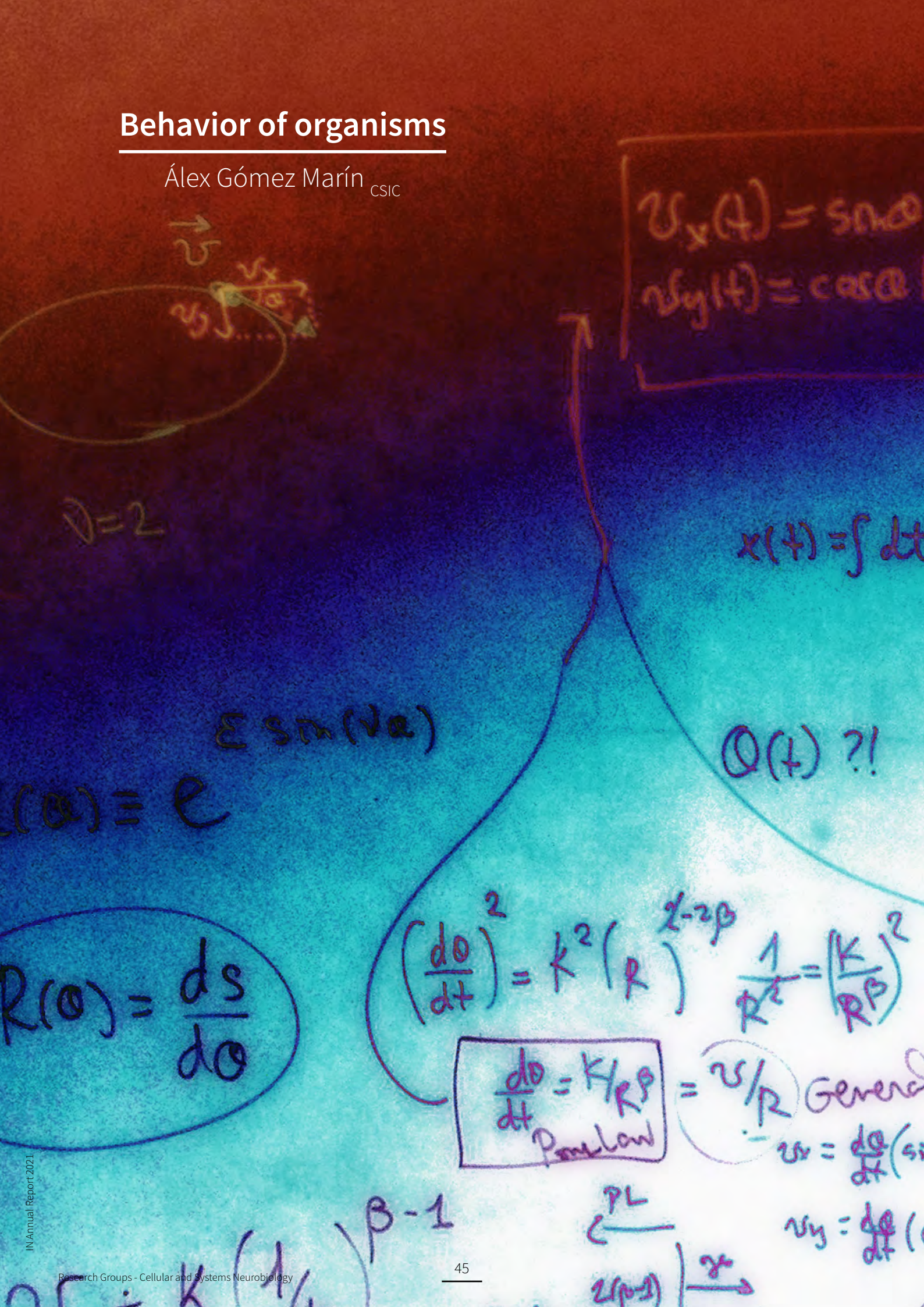
Behavior of organisms

Álex Gómez Marín CSIC



Behavior of organisms

We search for principles of life & mind in animals and humans. Combining high-resolution experiments, computational and theoretical biology, and continental philosophy, we study action-perception loops across species, from flies and worms to mice and robots. Our most recent research concentrates on human cognition and consciousness in the real world

Visit the group website for more information

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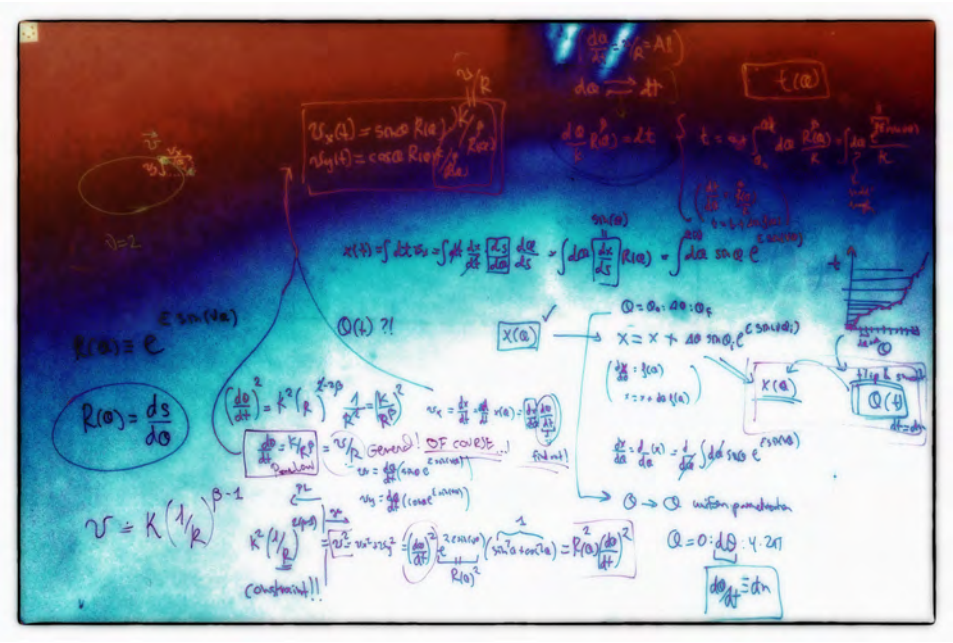
Cellular and Systems Neurobiology



Principal Investigator
Alex Gomez-Marin

PhD Students
Adam Matic
Saurabh Gupta
María Regina Zaghi Lara

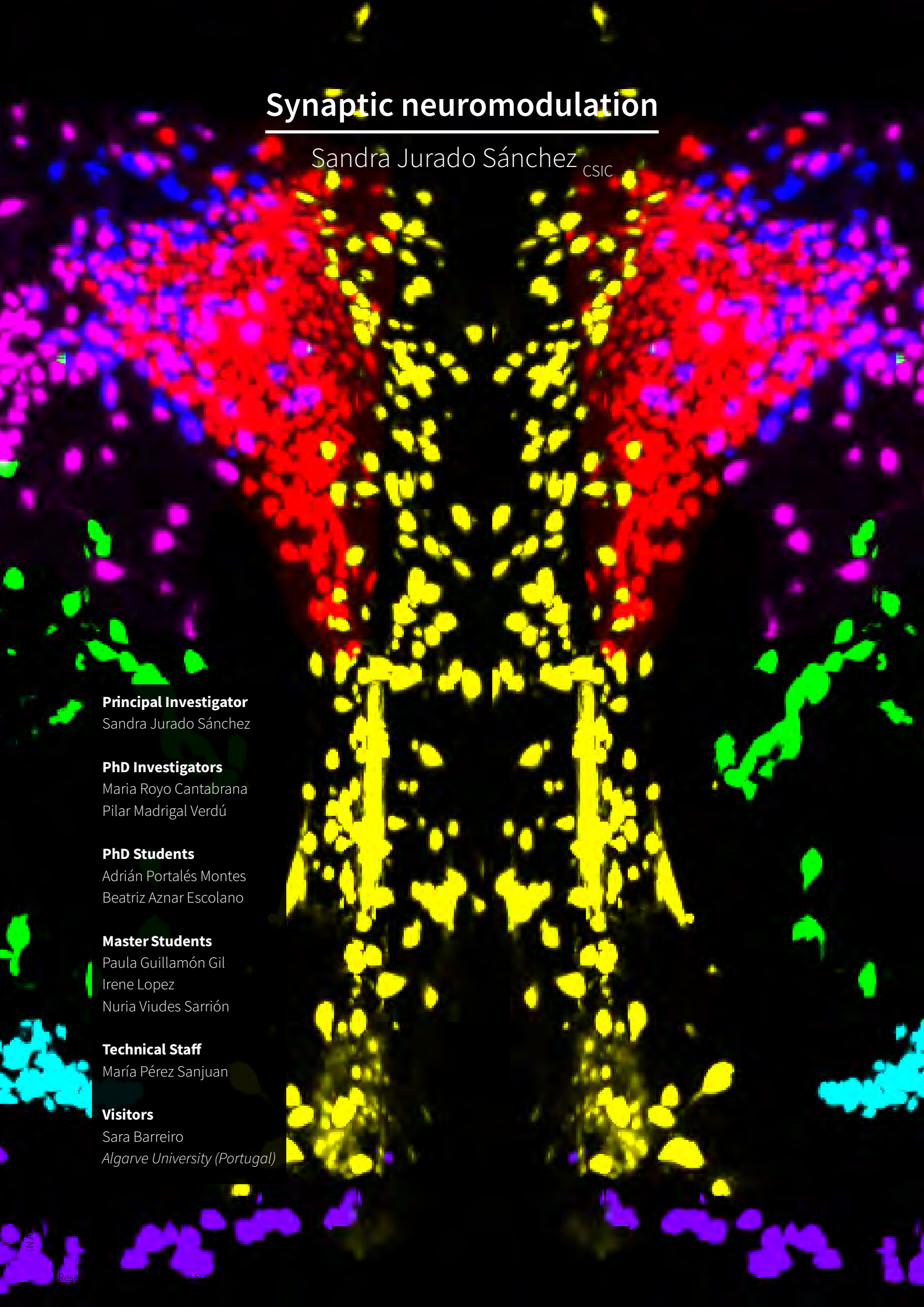
Master Students
Antonio Micó
Ángela González
Mercedes Rosillo Galera

Graduate Students
Fernando Casanova

Undergraduate Students
Alex Sospedra

Synaptic neuromodulation

Sandra Jurado Sánchez CSIC



Principal Investigator
Sandra Jurado Sánchez

PhD Investigators
Maria Royo Cantabrana
Pilar Madrigal Verdú

PhD Students
Adrián Portalés Montes
Beatriz Aznar Escolano

Master Students
Paula Guillamón Gil
Irene Lopez
Nuria Viudes Sarrión

Technical Staff
María Pérez Sanjuan

Visitors
Sara Barreiro
Algarve University (Portugal)

Synaptic neuromodulation

Neuromodulators expand the abilities of neuronal networks to process information and to perform fine-tuning computations that impact cognition, emotion, and behavior. Despite their key role, the molecular mechanisms orchestrating neuromodulatory function in the central nervous system (CNS) are much more unknown than those of inhibitory and excitatory transmission. This scenario is largely due to the technical challenge of unambiguously link specific neuromodulator release events to their physiological and behavioral functions. To address this question, our group is implementing a multidisciplinary strategy to explore different aspects of neuromodulatory function to understand how these circuits are affected during natural aging and neurodegeneration. We currently work on three main research lines:

1) Hypothalamic neuropeptides: Release mechanism and synaptic function

We employ live cell imaging technologies to explore neuropeptide-containing vesicle dynamics and release. We focus on oxytocin and vasopressin, two hypothalamic neuropeptides which mediate vital homeostatic functions as well as complex behaviors such as social interaction. Our laboratory combines imaging and electrophysiological methods to explore the exocytic machinery involved in their release, in order to elucidate their action on synaptic transmission and plasticity.

2) Formation and plasticity of neuromodulatory circuits

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

3) Impact of aging and neurodegeneration on neuromodulatory circuits

One major focus of our group is on mechanisms governing brain function under healthy and pathological aging. To this aim, we have implemented animal models of neurodegeneration (APP/PSEN1) and senesce (naturally aged mice over 20 months-old) that allow us to explore the modifications of neuromodulatory circuits in the aged brain. Here, we mainly focus on the olfactory system, as this brain region is early affected during aging and neurodegeneration.

Methodological approaches

In order to accomplish these aims, we have implemented a research program which combines state-of-the-art imaging techniques such as 3D ultra-resolution circuit mapping and vesicle dynamic/exocytosis visualization, electrophysiology, optogenetics, in vivo viral-based manipulations and animal behavioural testing.

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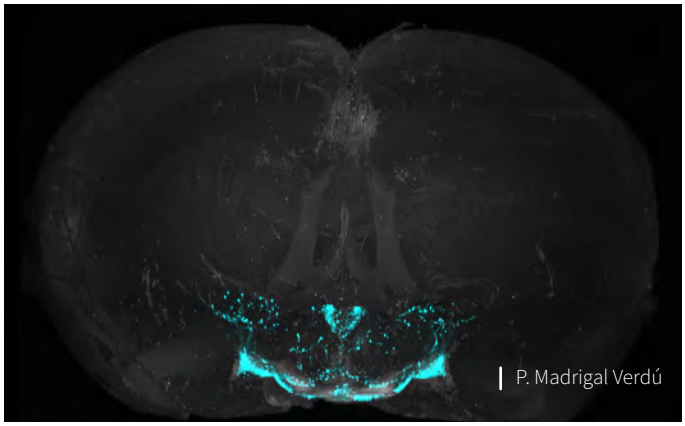
Specification of oxytocinergic and vasopressinergic circuits in the developing mouse brain. Madrigal MP, Jurado S (2021) **Communications Biology** doi: 10.1038/s42003-021-02110-4.

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

AMPA Receptor Function in Hypothalamic Synapses. Royo M, Escolano BA, Madrigal MP, Jurado S. (2022) **Front Synapti Neurosci.** doi: 10.3389/fnsyn.2022.833449.



Visit the group website for more information

Department
Cellular and Systems Neurobiology

Synaptic physiology

Juan Lerma CSIC

Principal Investigator
Juan Lerma

PhD Investigators
M. Isabel Aller
Ana V. Paternain

PhD Students
Sofía Degiorgi
Beatriz Fernández-Arroyo
Alvaro García
Amr Fwcy Kamel

Techincal Staff
Mónica Llinares

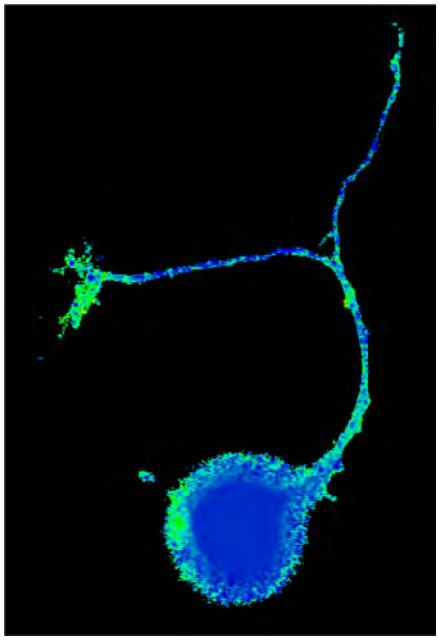
Administration
Laura Navio

Synaptic physiology

Neurons communicate with each other by means of releasing neuroactive substances that activate specific proteins situated at the postsynaptic membrane. This is a finely regulated process on which the correct performance of our brain depends, which is to say ourselves. Our group works on the structure and function of glutamate receptors, the most important signalling system in the brain since it mediates more than 90% of the excitatory neurotransmission. We described for the first time the existence in central neurons of a type of functional glutamate receptors, the kainate receptor (KAR) and demonstrated that KAR proteins form functional channels. Since then, we and other groups have addressed specific questions on the physiological role of KARs. But their role in both physiology and particularly pathology is still elusive. New data, however, indicate their involvement in mood disorders. De novo copy number variation (deletion or duplication of a chromosomal region) of synaptic genes has been recently implicated as risk factors for mental retardation or autism. Amongst them is *GRIK4*, a gene coding for a glutamate receptor subunit of the kainate type. We generated transgenic mice overexpressing *Grik4* in the forebrain. These mice displayed social impairment, enhanced anxiety and depressive states, accompanied by altered synaptic transmission in the hippocampus and the amygdala. Normalizing gene and protein levels results in total rescue of both functional and behavioural abnormalities. Following a similar strategy, we identified that triplication of the KAR encoding gene *GRIK1* is the cause of spatial memory impairment observed in Down syndrome. Normalization of *Grik1* dosage in Ts2Cje mice specifically restored spatial memory and reversed bidirectional alterations to CA1 inhibition, but not the changes in synaptic plasticity or the other behavioral modifications observed. We have proposed that modified information gating caused by disturbed inhibitory tone rather than generalized over-inhibition underlies some of the characteristic cognitive deficits in Down syndrome.

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

Department
Cellular and Systems Neurobiology



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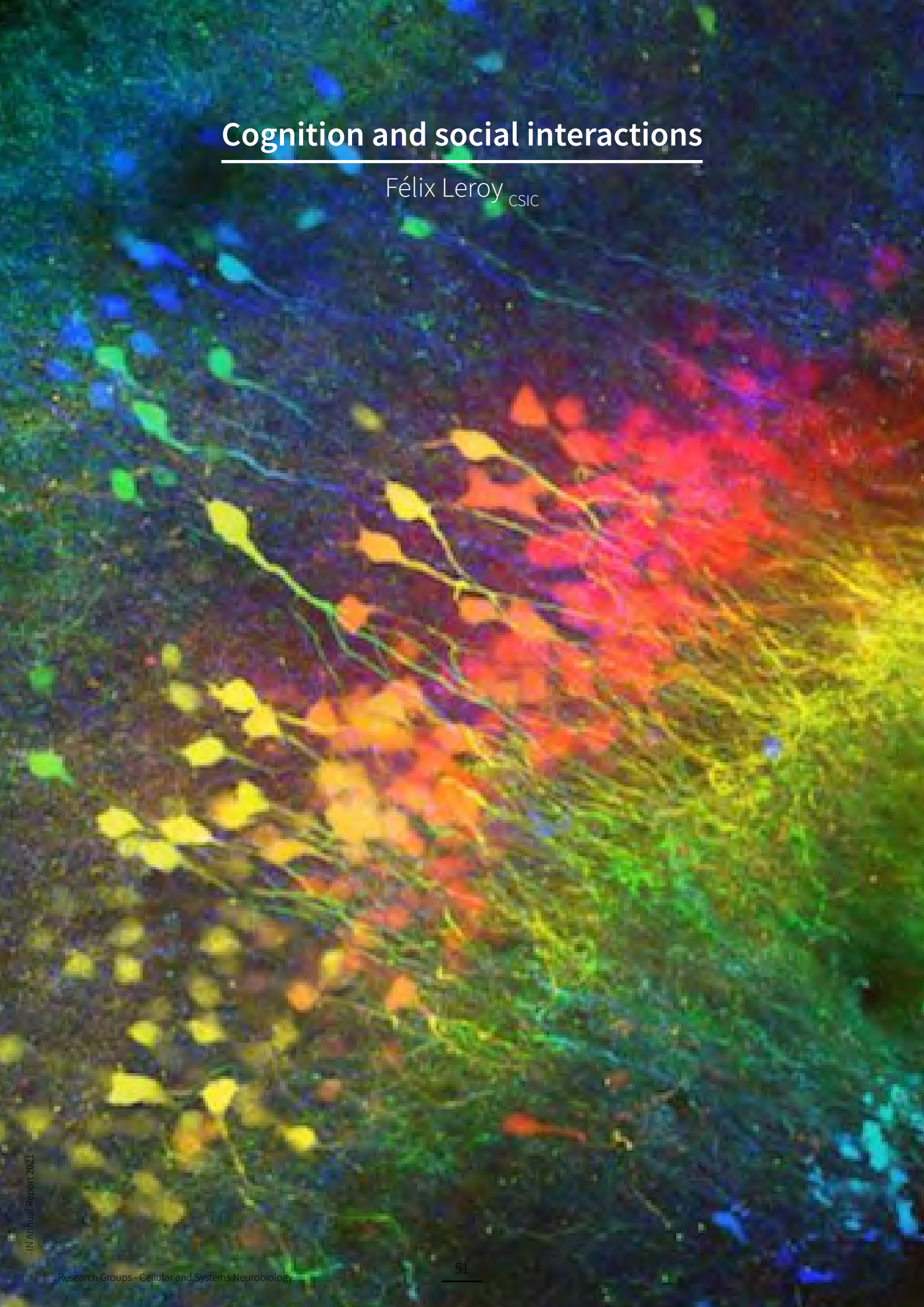
Cognition and social interactions

Félix Leroy CSIC



Cognition and social interactions

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

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

Principal Investigator
Félix Leroy

PhD Investigator
Noelia Sofia de León Reyes

Master Students
Paula Andrea Sierra Díaz
Auriane Gerbelot-Barrillon

Technical Staff
Antonia Ruiz Pino
Yuki Nomura

Administration
Javier Paniagua

Department
Cellular and Systems Neurobiology

Corticotropin-releasing hormone signaling from prefrontal cortex to lateral septum supports social novelty preference. Noelia Sofia de León Reyes, Paula Sierra Díaz, Ramon Nogueira, Antonia Ruiz-Pino, Yuki Nomura, Christopher de Solis, Jay Schulkin, Arun Asok, Félix Leroy (2022) **BiorXiv** 2022.03.15.484224; doi: 10.1101/2022.03.15.484224

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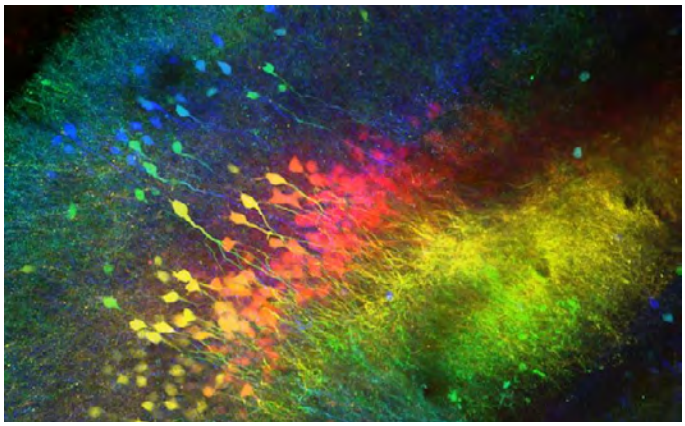

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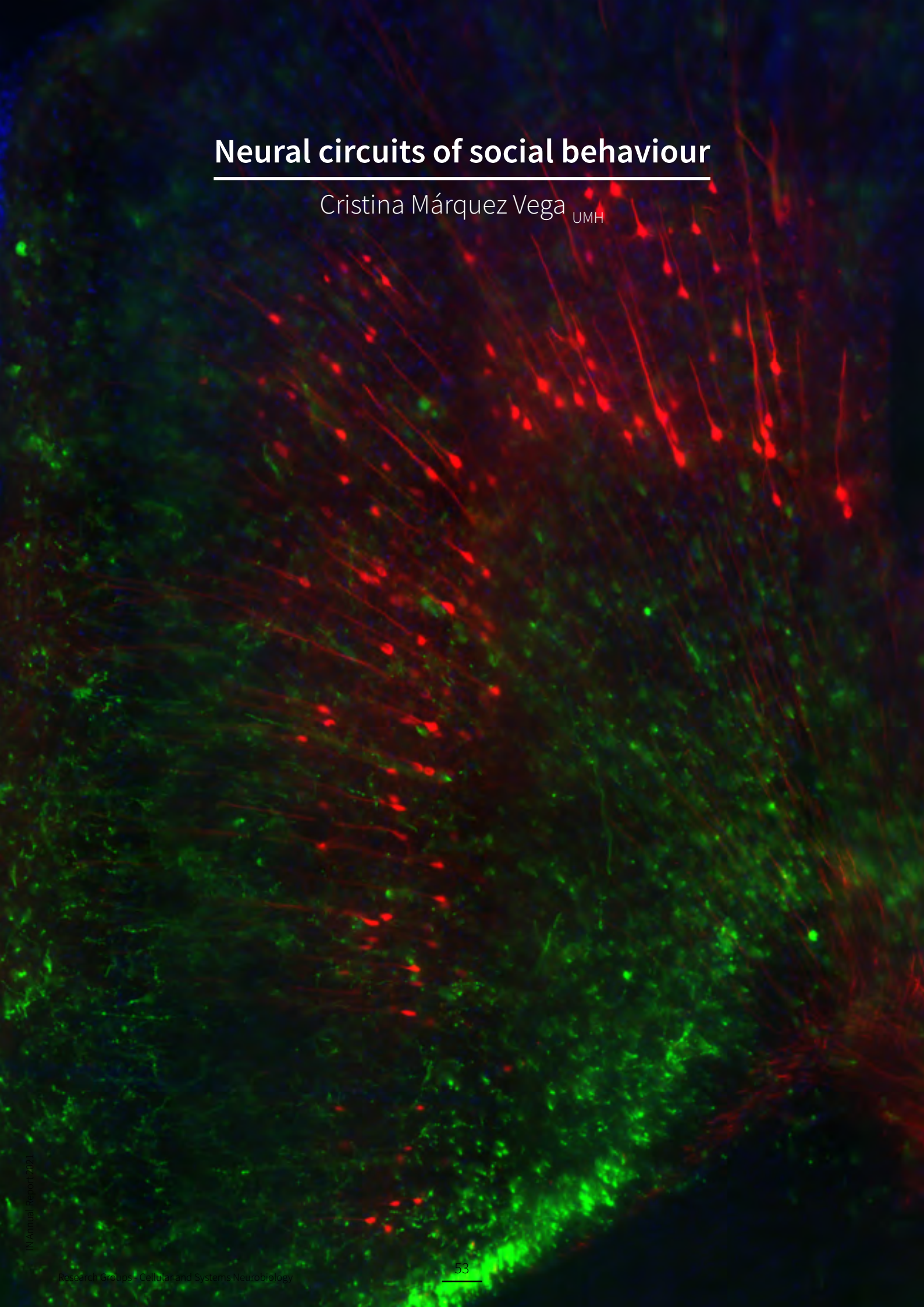
Neural circuits of social behaviour

Cristina Márquez Vega UMH



Neural circuits of social behaviour

Social interactions shape the way we perceive, feel and learn about the world, and despite its importance for social species, we still know very little about how the brain computes social information. Our lab is interested in understanding the mechanisms of how social behaviour shapes our brain, and for this, we focus on cooperative social interactions in rodents. We were pioneers in the demonstration that Norway rats display prosocial behaviours in food foraging context, providing food to conspecifics, and identified the proximal mechanisms at the level of behaviour.

Current and future projects aim to identify the neural circuits responsible for this fascinating social decision-making, using a combination of behavioural, anatomical, pharmacological, imaging and optogenetic tools in rodents.

Principal Investigator
Cristina Márquez Vega

PhD Investigator
Kevin Caref

PhD Students
Diana Costa
Michael Gachomba
Joan Esteve-Agraz
Helena Bortolozzo

Technical Staff
Aroa Sanz Maroto
Mar Francés Pérez

Department
Cellular and Systems Neurobiology

Multimodal cues displayed by submissive rats promote prosocial choices by dominants. Michael Joe Munyua Gachomba, Joan Esteve-Agraz, Kevin Caref, Aroa Sanz Maroto, Maria Helena Bortolozzo-Gleich, Diego Andrés Laplagne, Cristina Márquez * (2022) **Current Biology** (in press). *Corresponding Author

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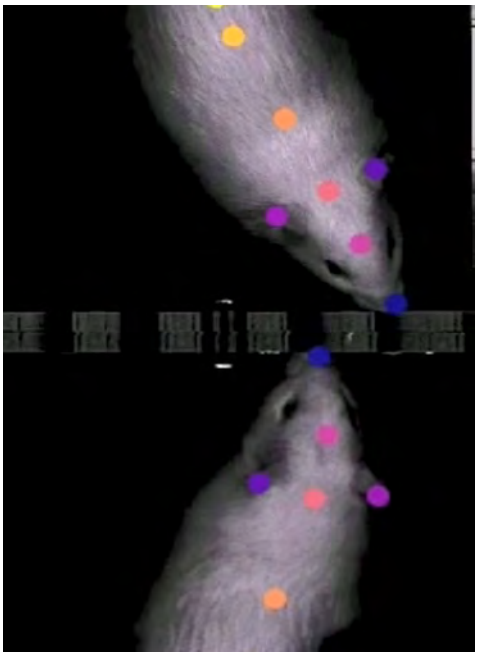

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Visual analogy laboratory

Luis M. Martínez CSIC

Visual analogy laboratory

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

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

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

Visit the group website for more information

Principal Investigator
Luis M. Martínez

Department
Cellular and Systems Neurobiology

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

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Plasticity and remodeling of neural circuits

Isabel Pérez Otaño CSIC

Principal Investigator
Isabel Pérez Otaño

PhD Investigators
Oliver Crawley
Federica Giona
Remy Verhaeghe

PhD Students
Alice Staffa
Ana Isabel Navarro Navarro
Gloria Carruana Salas
Mª José Conde Dusman
Oscar Elía Zudaire
Carmen García-Lira
Moumita Chatterjee

Master Student
Bárbara Corral

Technical Staff
Diana Baeza
Manuel Giner

Plasticity and remodeling of neural circuits

Brain function generates cognition, thought and adaptive behaviors through coordinated actions of circuits that are hard-wired during development with others that retain remarkable plasticity into adulthood. A fundamental question is how experiences shape these neural circuits, so the individual learns and interacts adequately with its environment. Over postnatal stages, most remodeling involves formation, strengthening or elimination of synapses to build, maintain or reshape neural assemblies. Synaptic remodeling occurs throughout life but is maximal during "so-called" critical periods—a stage of postnatal development when synapses have a high potential for plasticity and massive formation and elimination of synapses refines initially redundant circuitry. Yet this plasticity potential needs to be "tamed" so the correct synaptic partners are specified during postnatal circuit refinements and to support precise learning and cognitive-guided behaviors. Understanding how this is achieved is one major goal of our lab.

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

Other areas of investigation include:

1) *Targeting circuit plasticity and cognition:* Neurons rely on translational control to direct persistent modifications to selected synapses, but the mechanisms affording synapse and temporal specificity had been elusive. We have discovered neuronal GIT1/mTORC1 complexes that nucleate protein synthesis at synapses and whose assembly is negatively regulated by GluN3A expression, imposing limits on memory capacity. Regulated interactions between GluN3A and GIT1 determine which memories will be persistently stored, opening an entry point for modulating cognition (*eLife* 2021).

2) *Identifying plasticity niches in non-neuronal cells*

Control of protein synthesis and memory by GluN3A-NMDA receptors through inhibition of GIT1/mTORC1 assembly. Conde-Dusman MJ, Dey, PN, Elía-Zudaire, O., Rabaneda, LG, García-Lira, C.; Grand, T., Briz, V., Velasco, ER, Andero, R., Niñerola, S., Barco, A., Paoletti, P., Wesseling, J.F., Gardoni, F., Tavalin, SJ, Perez-Otaño, I. (2021) **eLife**. 10:e71575

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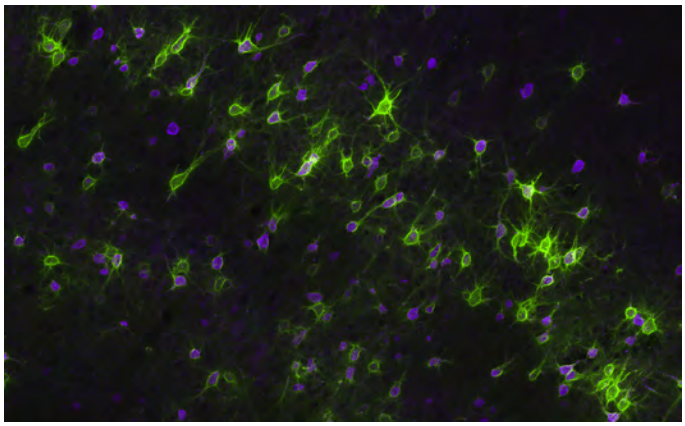

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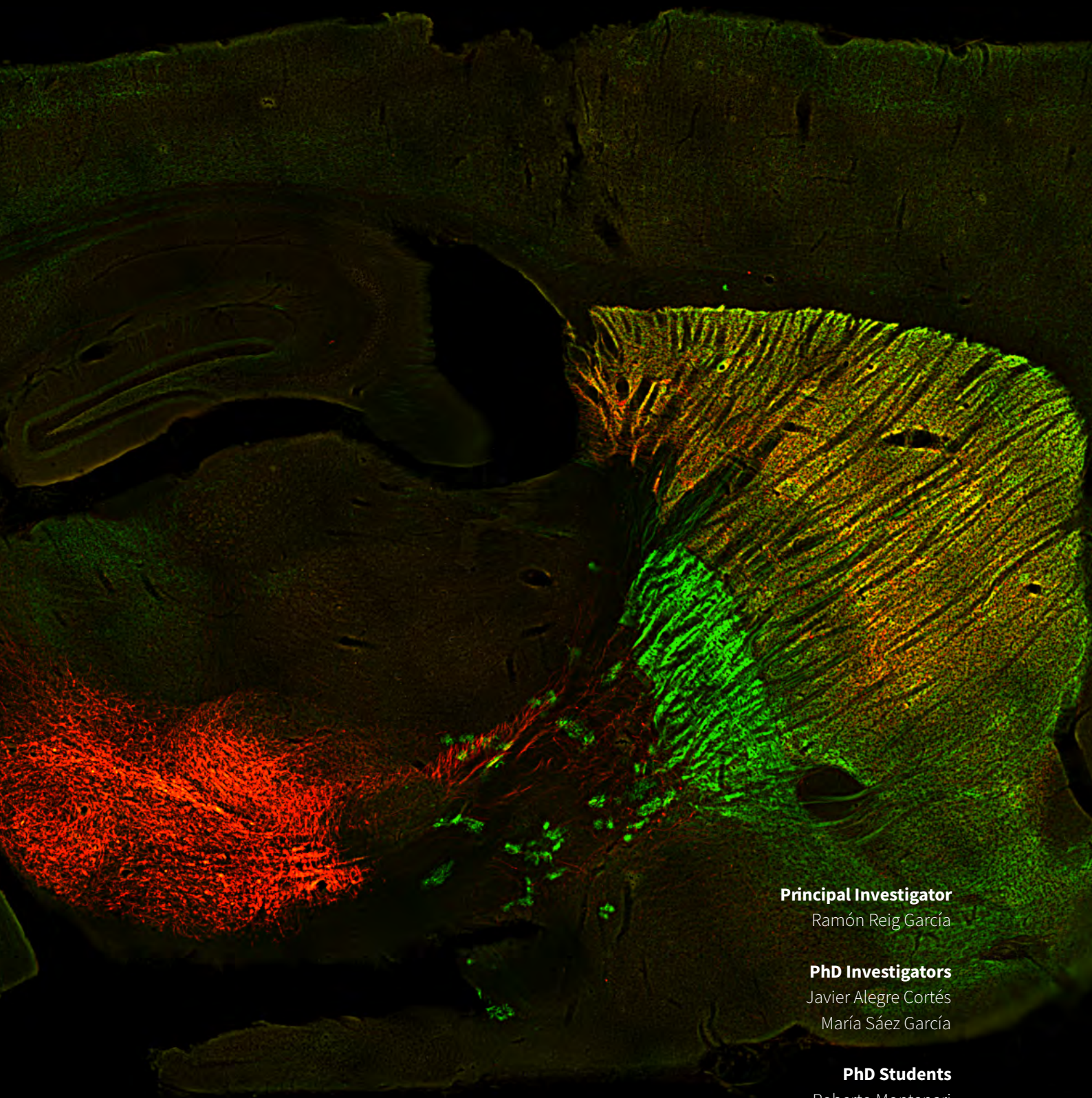
Department
Cellular and Systems Neurobiology

Sensory-motor processing by subcortical areas

Ramón Reig García CSIC



Principal Investigator
Ramón Reig García

PhD Investigators
Javier Alegre Cortés
María Sáez García

PhD Students
Roberto Montanari
Alicia Alonso Andrés

Technical Staff
Ismael Navarro Andreu

Sensory-motor processing by subcortical areas

The basal ganglia (BG) are involved in a wide range of functions such as decision-making, reward motor learning, selection motor sequences, as well as cognitive and emotional functions, most of them require the integration of sensory information. Problems in the basal ganglia function can generate numerous and diverse neurological disorders as for example Parkinson's and Huntington's diseases, Tourette syndrome, obsessive-compulsive disorder (OCD), dystonia, attention-deficit hyperactivity disorder (ADHD), and different types of addictions.
The basal ganglia are composed of several subcortical nuclei (striatum, globus pallidus, substantia nigra and subthalamic nucleus) interconnected with the cerebral cortex, thalamus and other brain areas.

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

The striatum is best known for its role in planning and selecting motor sequences. But selection of proper motor sequences also requires the prioritizing of sensory information. Sensory information from different modalities such as tactile, visual, auditory and olfactory converges in the striatum. All of these simultaneous inputs have to be processed, filtered and integrated in order to select the appropriate ones. How striatal neurons process the information is largely unknown. We aim to study the role of the striatum in sensory processing and its interplay with motor functions. At the same time, we aim to understand different neurological diseases or disorders such as Parkinson's or ADHD, related with the striatal function. To answer this question we use complementary electrophysiological, behavioral, optical and anatomical methods.

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

A new micro-holder device for local drug application during in vivo whole-cell recordings. Sáez M, Ketzef M, Alegre-Cortés J, Silberberg G, Reig R. (2018) **Neuroscience** 318, 115-123

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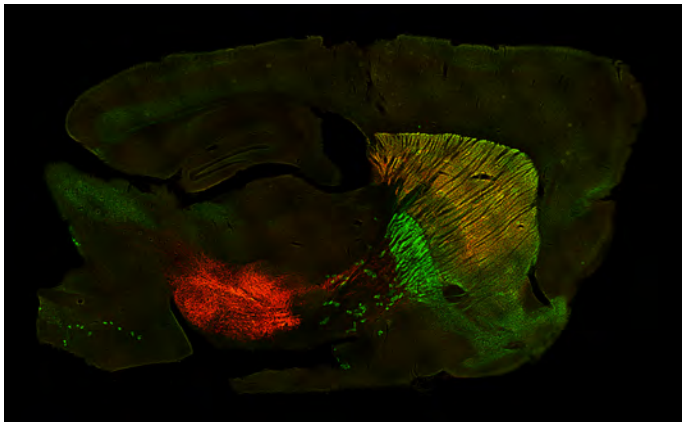

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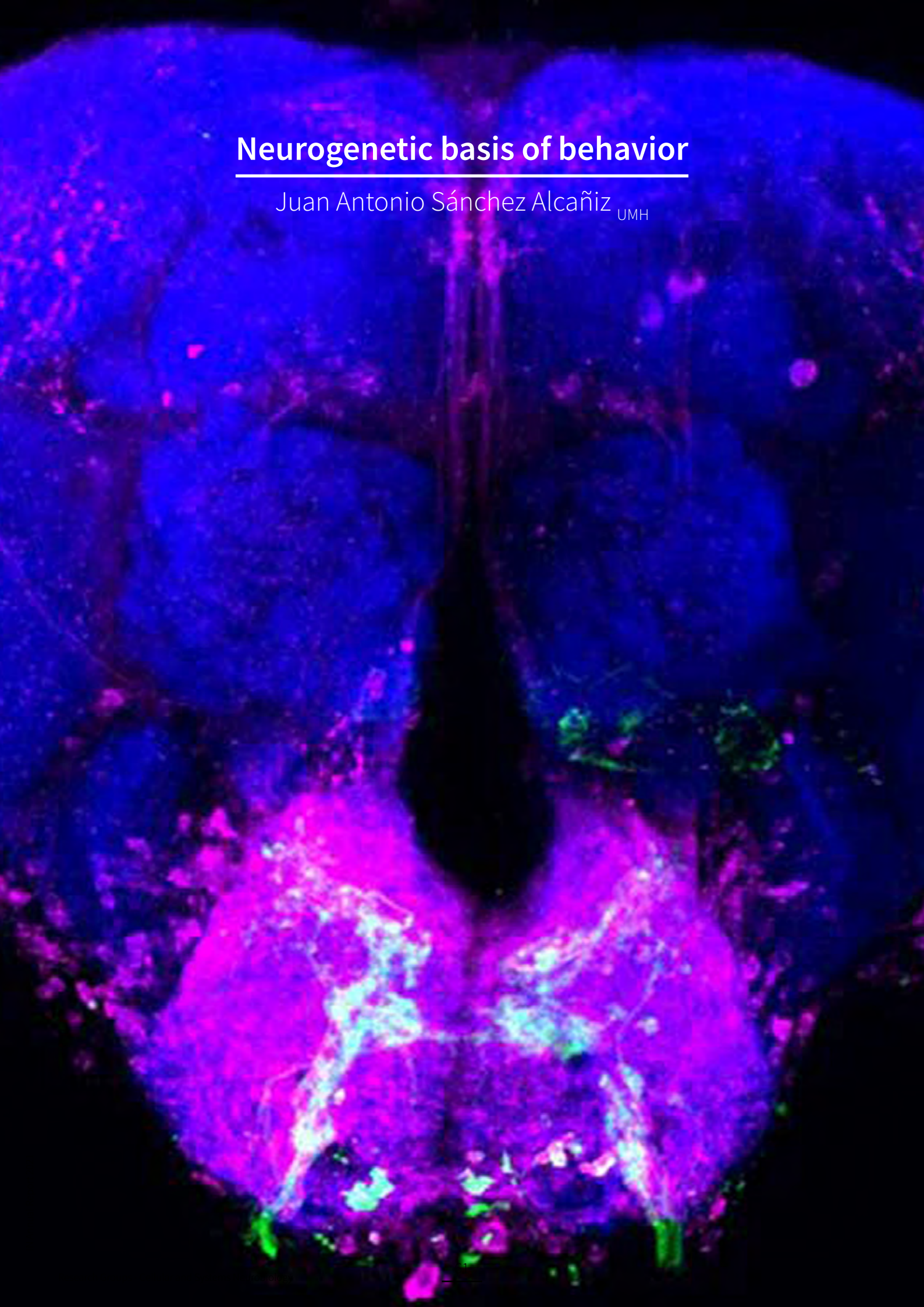
Department
Cellular and Systems Neurobiology

Neurogenetic basis of behavior

Juan Antonio Sánchez Alcañiz UMH



Neurogenetic basis of behavior

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

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

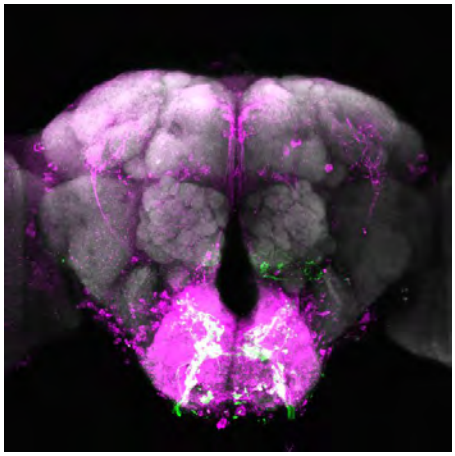
Department
Cellular and Systems Neurobiology

Principal Investigator
Juan Antonio Sánchez Alcañiz

PhD Investigator
Pol Ramón Cañellas

PhD Student
Rubén Molla Albaladejo
José María Buil Gómez
Manuel Jiménez Caballero

Technical Staff
María Pérez Sanjuan



Visit the group website for more information

Behavior individuality: A focus on *Drosophila* melanogaster. Molla Albaladejo R and Sánchez-Alcañiz JA (2021) **Frontiers in Physiology** DOI: 10.3389/fphys.2021.719038

An expression atlas of variant ionotropic glutamate receptors identifies a molecular basis of carbonation sensing. Sánchez-Alcañiz JA, Silbering A, Croset V, Zappia G, Sivasubramaniam AK, Abuin L, Sahai SY, Münch D, Steck K, Auer TO, Cruchet S, Neagu-Maier L, Sprecher SG, Ribeiro C, Yapici N and Benton R (2018) **Nature Communications** DOI: 10.1038/s41467-018-06453-1

Multisensory neural integration of chemical and mechanical signals. Sánchez-Alcañiz JA and Benton R (2017) **BioEssays** DOI: 10.1002/bies.201700060

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Wiring and function of somatosensory circuits

Francisco José Taberner Sanchís CSIC

Principal Investigator
Francisco José Taberner Sanchís

PhD Student
Chiara Nappi

Technical Staff
Espe Selva González

Wiring and function of somatosensory circuits

Specialized subsets of primary sensory neurons innervating different body tissues detect and transduce different environmental cues into itch, touch, temperature or pain information. When these signals eventually reach the brain, they generate the sensory percept and evoke the convenient physiological and behavioural responses for the survival of the animal. On its way to the brain, this sensory information undergoes an initial processing at the spinal cord. In healthy individuals, local excitatory and inhibitory spinal cord interneurons form modality specific processing microcircuits. These circuits dynamically tune down or amplify the sensory signals in response to other sensory modalities or to brain descending signals. However, in certain pathologies like nerve injury or in different inflammatory conditions, the normal processing at the spinal cord is altered and unconventional maladaptive circuits are wired up, resulting in chronic pain and itch. Due to the intrinsic complexity of the spinal cord circuitry, and the lack of an appropriate tool set for capturing and interrogating the spinal cord neuronal ensembles in behaving animals, our knowledge on the cellular and molecular substrates that constitute the sensory microcircuits and facilitate maladaptive changes are still largely unknown.

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

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

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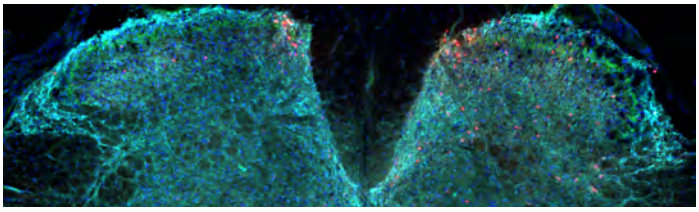

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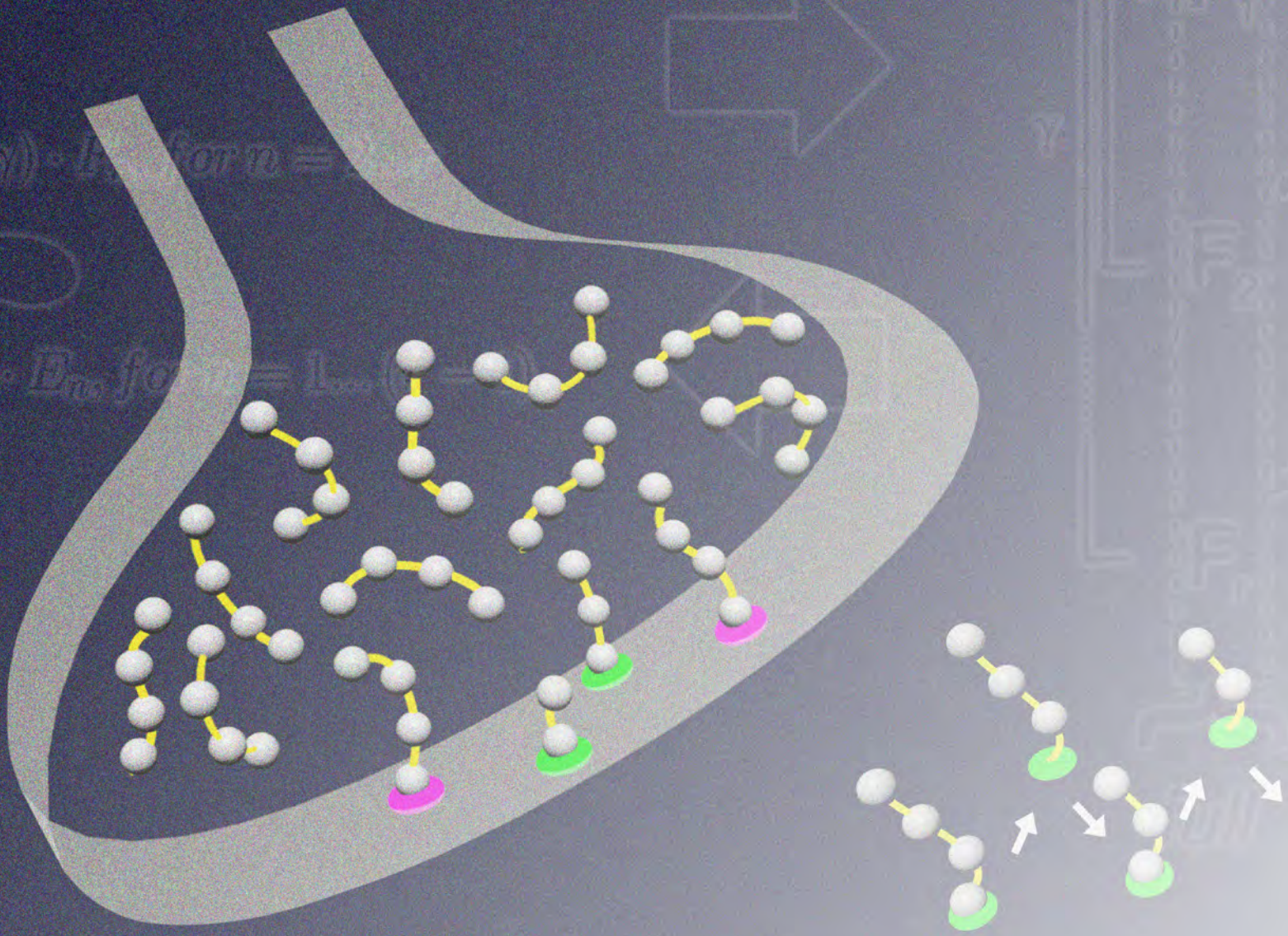
Department
Cellular and Systems Neurobiology
Scientific Program

Molecular and cellular physiology of synaptic transmission

John F. Wesseling CSIC



Molecular and cellular physiology of synaptic transmission

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

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

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

Department
Cellular and Systems Neurobiology

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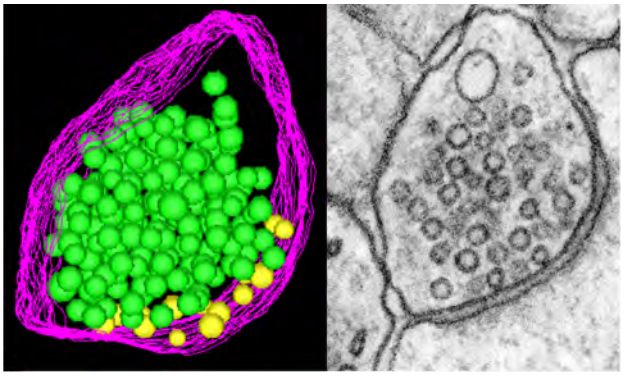

Visit the group website for more information

Principal Investigator
John F. Wesseling

PhD Students
Sergio Del Olmo Cabrera
Juan José Rodríguez Gotor
Doris Santiago

Technical Staff
Diana Baeza Soler

Transcriptional and epigenetic mechanisms of neuronal plasticity and its disorders

Ángel Barco CSIC

Principal Investigator
Ángel Barco

PhD Investigators
Beatriz del Blanco
Juan Paraíso Luna

PhD Students
Ana Martín-González
Marta Alaiz Noya
Sergio Niñerola Rives
Miguel Fuentes Ramos
Samanta Ortuño Miquel

Master Students
María Consuelo López Gómez
Isabel Bustos Martínez

Technical Staff
Román Olivares
Carina Racovac

Transcriptional and epigenetic mechanisms of neuronal plasticity and its disorders

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

We currently work on two main lines of research:

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

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

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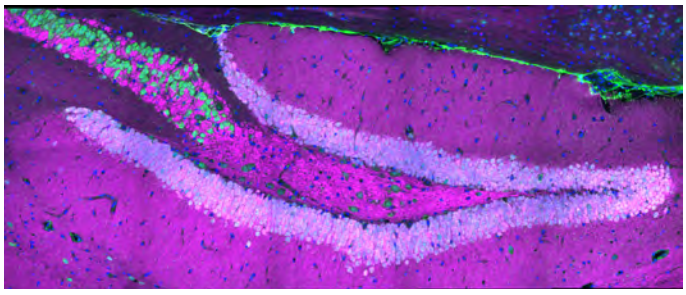

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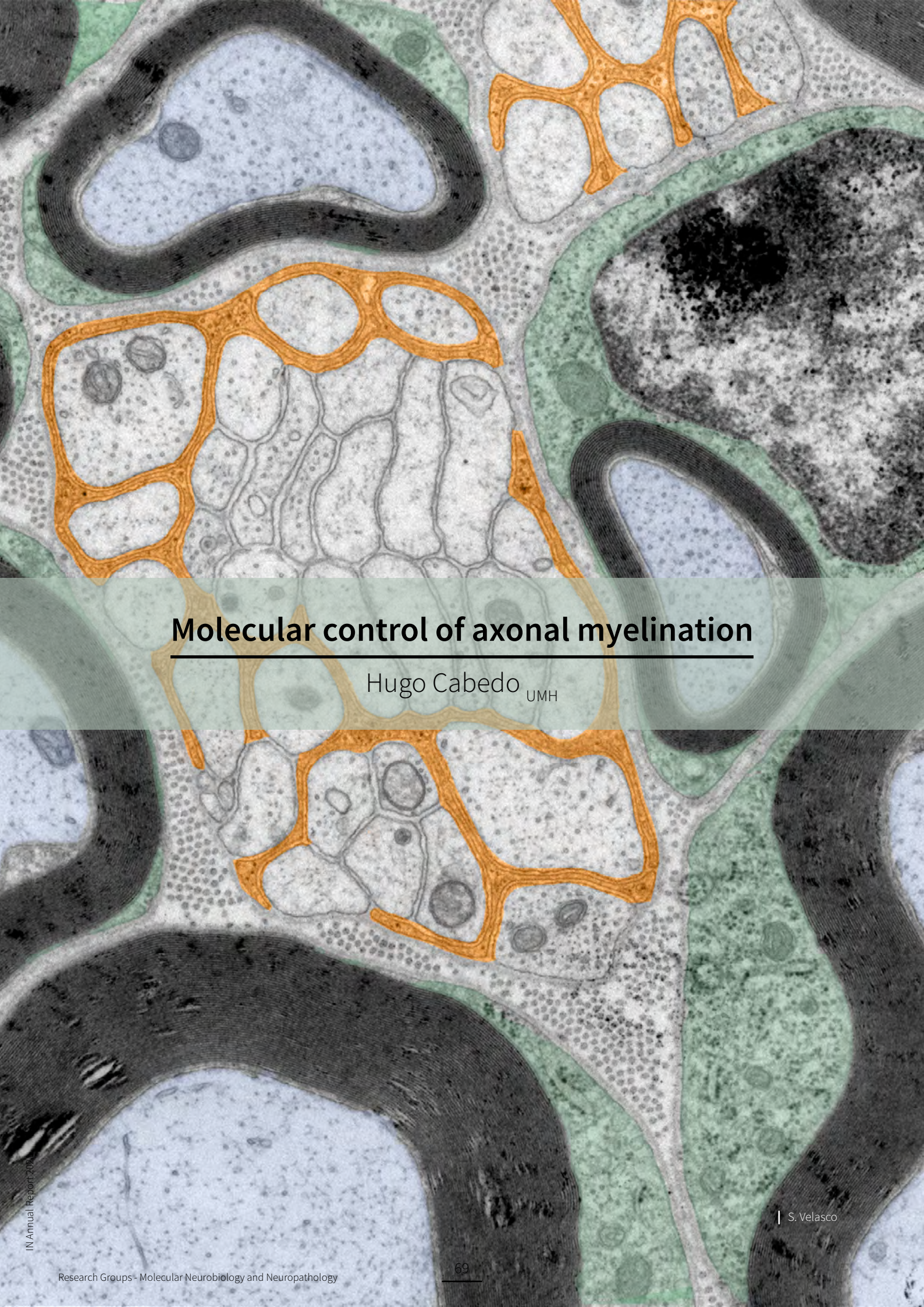
Department

Molecular Neurobiology and Neuropathology



Molecular control of axonal myelination

Hugo Cabedo UMH

S. Velasco

Molecular control of axonal myelination

Nerve conduction velocity is inversely proportional to the electrical resistance of the axon and the capacitance of the plasma membrane that surrounds it. To increase nerve impulse velocity some invertebrates (such as squids) decrease resistance of the axon by greatly increasing its diameter. In more complex nervous systems, like higher vertebrates, this would increase by more than a hundred times the volume of the nervous system. To increase nerve conduction velocity without changing the axonal diameter (and nervous system volume) it is necessary to reduce the capacitance by increasing the thickness of the lipid membrane surrounding the axon. This has been achieved in vertebrates by depositing large amounts of plasma membrane of specialized hypertrophied neighboring cells (oligodendrocytes or Schwann cells). Rudolf Virchow first described this membrane, known as "myelin", in 1854. In our group we try to elucidate the molecular mechanisms controlling the axonal myelination. Our goal is to use this information to develop new strategies in the treatment of demyelinating diseases such as multiple sclerosis in the central nervous system, and Charcot-Marie-Tooth in the peripheral nervous system. We also use this information to try to improve nerve regeneration after traumatic injuries. In order to achieve our goals we use state-of-the-art technologies such as Next-Generation Sequencing of patient's DNA and genetic modification of mice to generate animal models of disease.

Department

Molecular Neurobiology and Neuropathology

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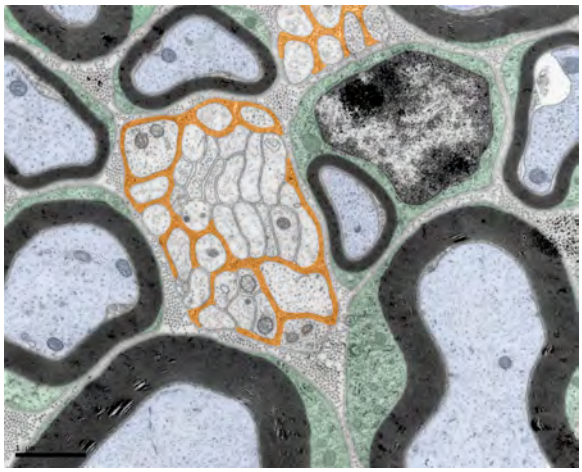


Visit the group website for more information

Principal Investigator

Hugo Cabedo

PhD Investigator

Jose A. Gómez-Sánchez

PhD Students

Sergio Velasco Avilés

Mariam Blanco Cantó

Nikiben Patel

Professor Colaborator

Carmen Díaz Marín

Visitors

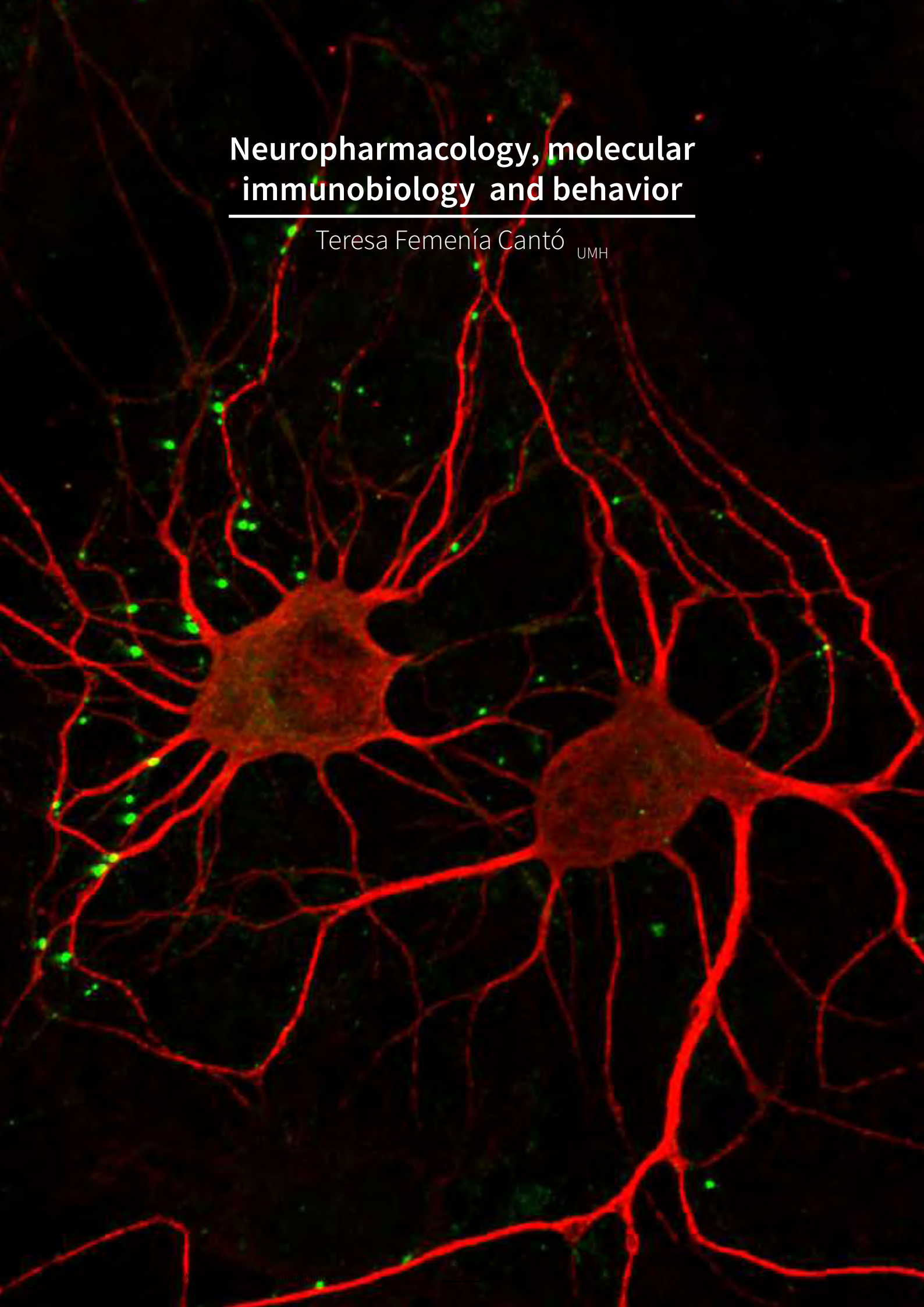
Dra. Katharina Scherschel

Clara Mutschler

Aysun Üçer

Neuropharmacology, molecular immunobiology and behavior

Teresa Femenía Cantó UMH



Neuropharmacology, molecular immunobiology and behavior

Our research group aims to understand how pathophysiological brain circuit function, with emphasis on psychiatric and neurological disorders, is mediated by mechanisms related with the immune system. We aim to determine: 1) how innate immune system receptors, such as the Pattern Recognition Receptors (PRRs; e.g. Toll-like receptors) operate during molecular signaling to regulate emotional and cognitive functions and 2) how crosstalk with the periphery affects these functions by evaluating the functional impact of immune alterations linked to stress or diseases accompanied with low-grade inflammation such as metabolic disorders, which are commonly associated with mood and anxiety disorders.

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

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

Department
Molecular Neurobiology and Neuropathology

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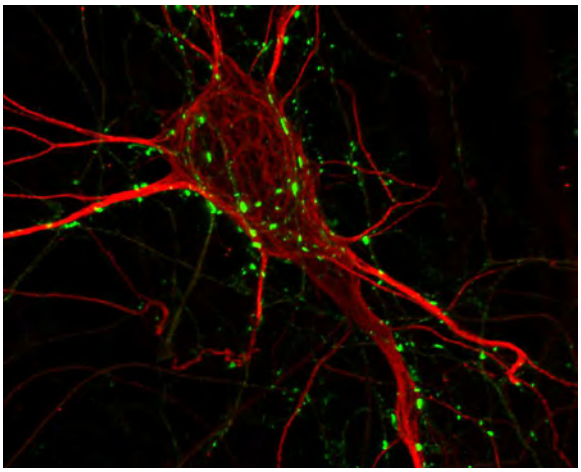


Visit the group website for more information

Principal Investigator
Teresa Femenía Cantó

PhD Students
Álvaro Morcuende Campos

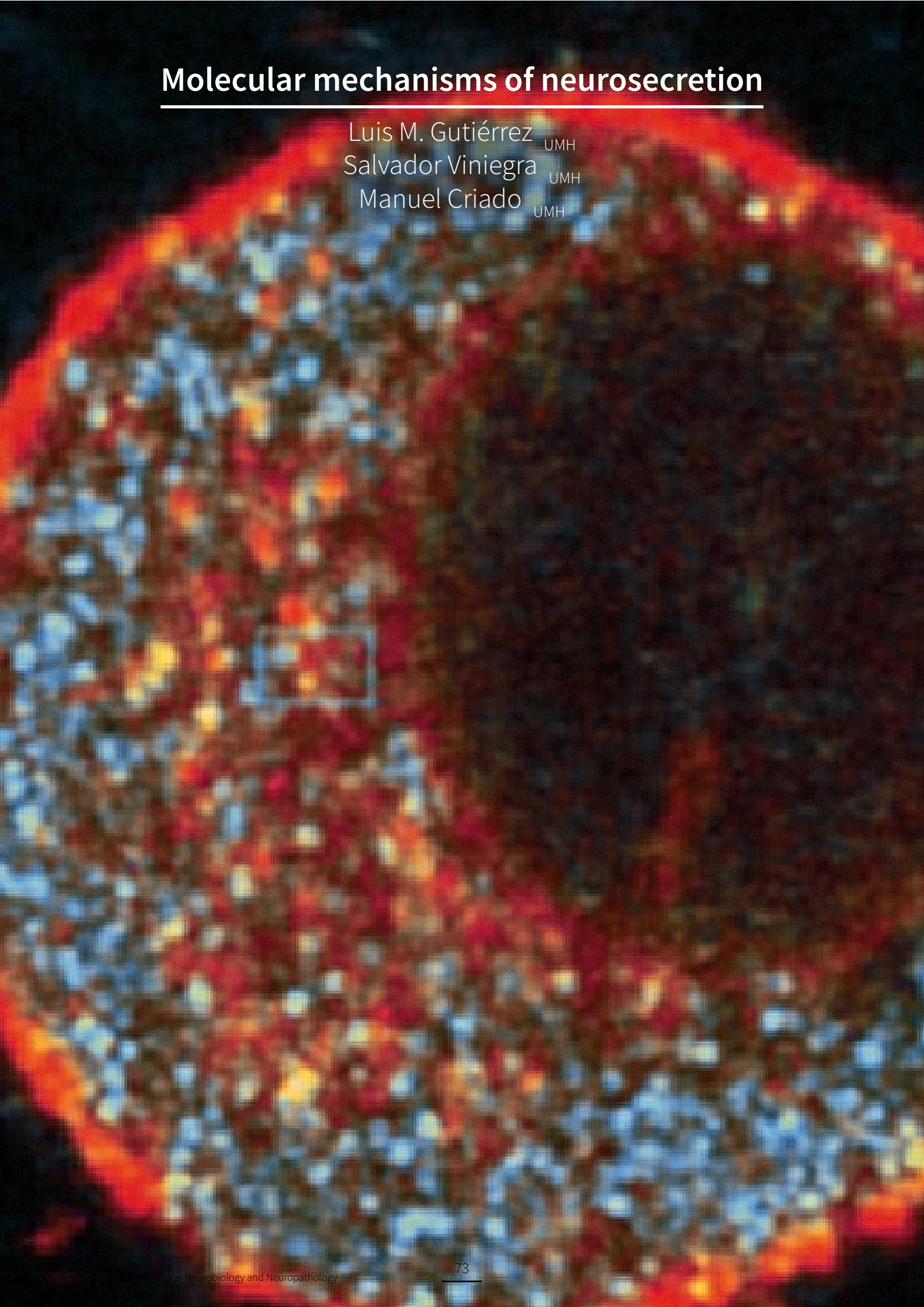
Master Students
Elena Nieto Chumillas
Sofía Antón López

Technical Staff
María Pérez Sanjuan
Claudia Llinares Monllor

Visitor
Andriana Perdikou
Lucía Suárez Serrano

Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH
Manuel Criado UMH



Molecular mechanisms of neurosecretion

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.

Department
Molecular Neurobiology and Neuropathology

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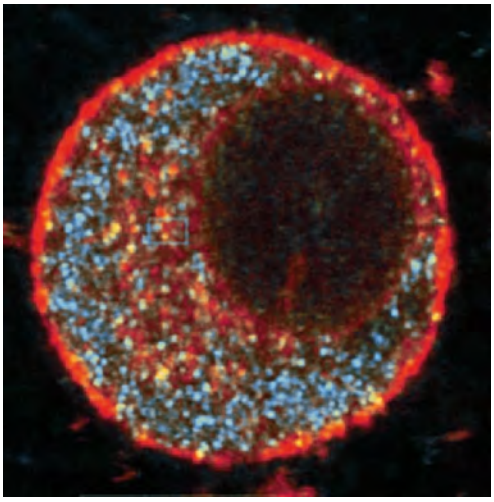


Visit the group website for more information

Principal Investigator
Luis M. Gutiérrez
Salvador Viniegra
Manuel Criado

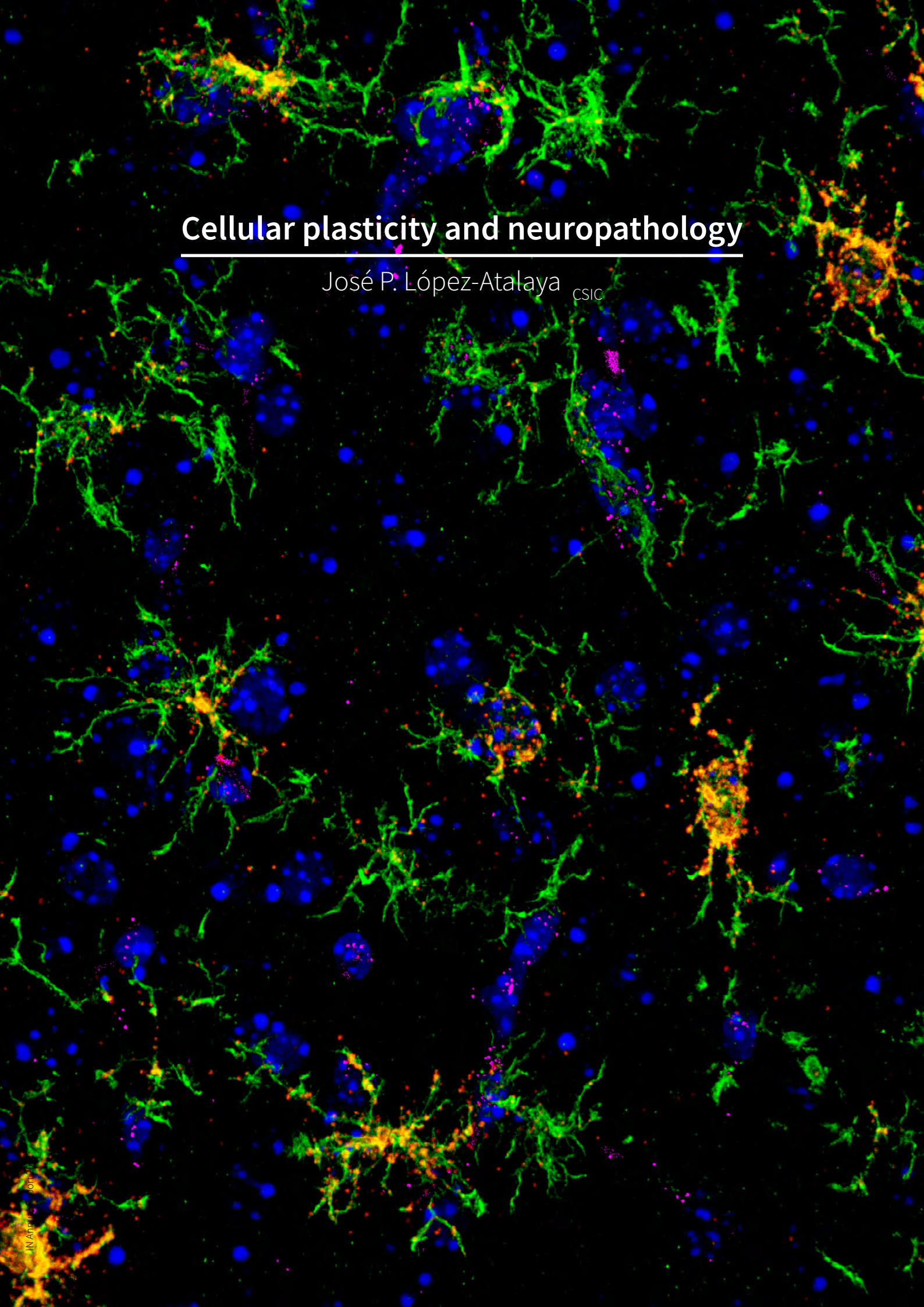
PhD Investigator
José Heliodoro Villanueva

PhD Student
Yolanda Giménez-Molina

Technical Staff
María del Mar Francés

Cellular plasticity and neuropathology

José P. López-Atalaya CSIC



Cellular plasticity and neuropathology

Aging constitutes a major risk factor for most common neurodegenerative disorders, including Alzheimer's disease. Neuroinflammation is a prominent feature of aging and is central to neurodegenerative diseases. However, the role of neuroinflammation in age-related cognitive decline, as well as its contribution to the onset and progression of neurodegenerative dementias is not well understood. We investigate the mechanistic links between neuroinflammatory processes in brain aging and neurodegenerative diseases. We seek to understand how brain's innate immune cells integrate within neural circuits to influence brain function in health and disease. Our research focuses on elucidating how microglia cells interpret cues from their tissue microenvironment to adopt specialized roles. We have particular interest in unveiling the core gene regulatory networks regulating the transitions and maintenance of distinct phenotypic and functional states of brain's innate immune cells. To this aim we combine genetic mouse models of Alzheimer's disease and postmortem brain samples from patients, genome-wide transcriptomics and epigenomic profiling at population and single-cell level, and state-of-the-art histological, cellular and molecular biology methods. Our ultimate goal is to develop novel effective approaches to help older adults ward off age-related cognitive impairment, and to open new avenues for therapeutic intervention to delay or prevent the progression of most prevalent neurodegenerative conditions.

Department

Molecular Neurobiology and Neuropathology

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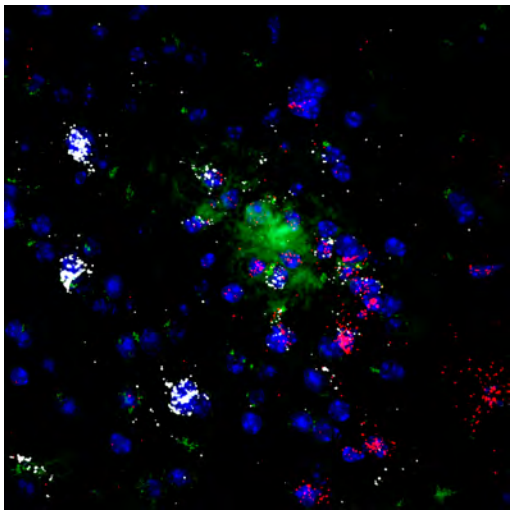


Visit the group website for more information

Principal Investigator

José P. López-Atalaya

PhD Students

Carmen M. Navarrón Izquierdo

Angel Márquez Galera

Aysha M. Bhojwani Cabrera

Verónica López López

Master Students

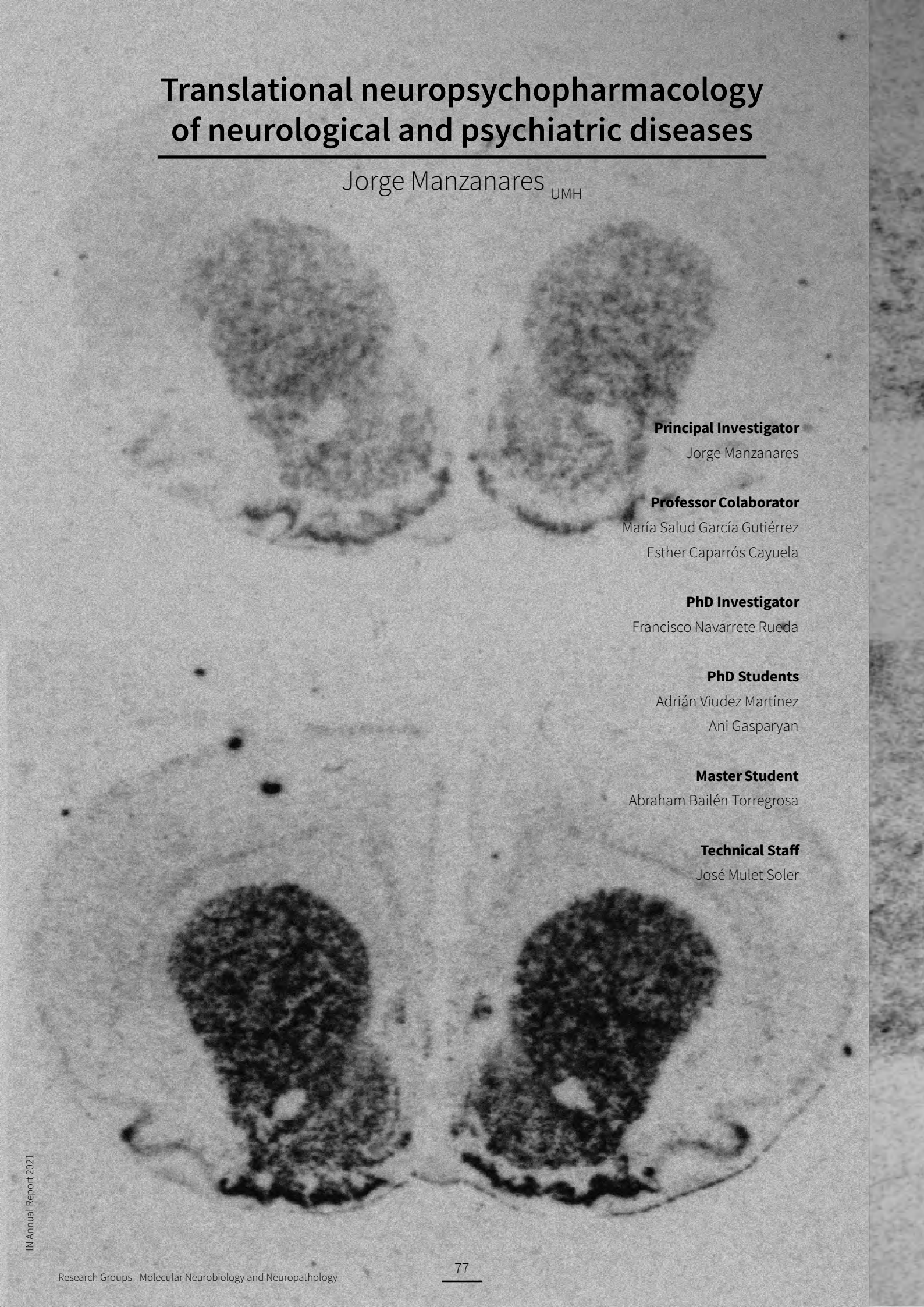
Daniel Oppermann Peixoto

Technical Staff

Manuel Alejandro Expósito Coca

Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH



Principal Investigator
Jorge Manzanares

Professor Colaborator
María Salud García Gutiérrez
Esther Caparrós Cayuela

PhD Investigator
Francisco Navarrete Rueda

PhD Students
Adrián Viudez Martínez
Ani Gasparyan

Master Student
Abraham Bailén Torregrosa

Technical Staff
José Mulet Soler

Translational neuropsychopharmacology of neurological and psychiatric diseases

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 behavior, we analyze 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.

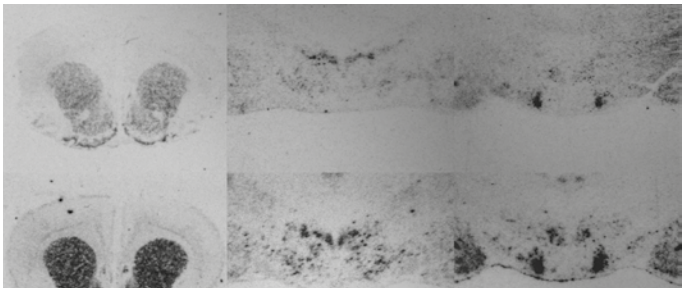
Alterations in Gene and Protein Expression of Cannabinoid CB2 and GPR55 Receptors in the Dorsolateral Prefrontal Cortex of Suicide Victims. María S. García-Gutiérrez, Francisco Navarrete, Gemma Navarro, Irene Reyes-Resina, Rafael Franco, Jose Luis Lanciego, Salvador Giner, Jorge Manzanares (2018) **Neurotherapeutics** 15:796-806

Cannabidiol regulates behavioural alterations and gene expression changes induced by spontaneous cannabinoid withdrawal. Francisco Navarrete, Auxiliadora Aracil-Fernández, Jorge Manzanares (2018) **British Journal of Pharmacology** 175:2676-2688

Cannabidiol reduces ethanol consumption, motivation and relapse in mice. Adrián Viudez-Martínez, María S. García-Gutiérrez, Carmen María Navarrón, María Isabel Morales-Calero, Francisco Navarrete, Ana Isabel Torres-Suárez, Jorge Manzanares (2018) **Addiction Biology** 23:154-164

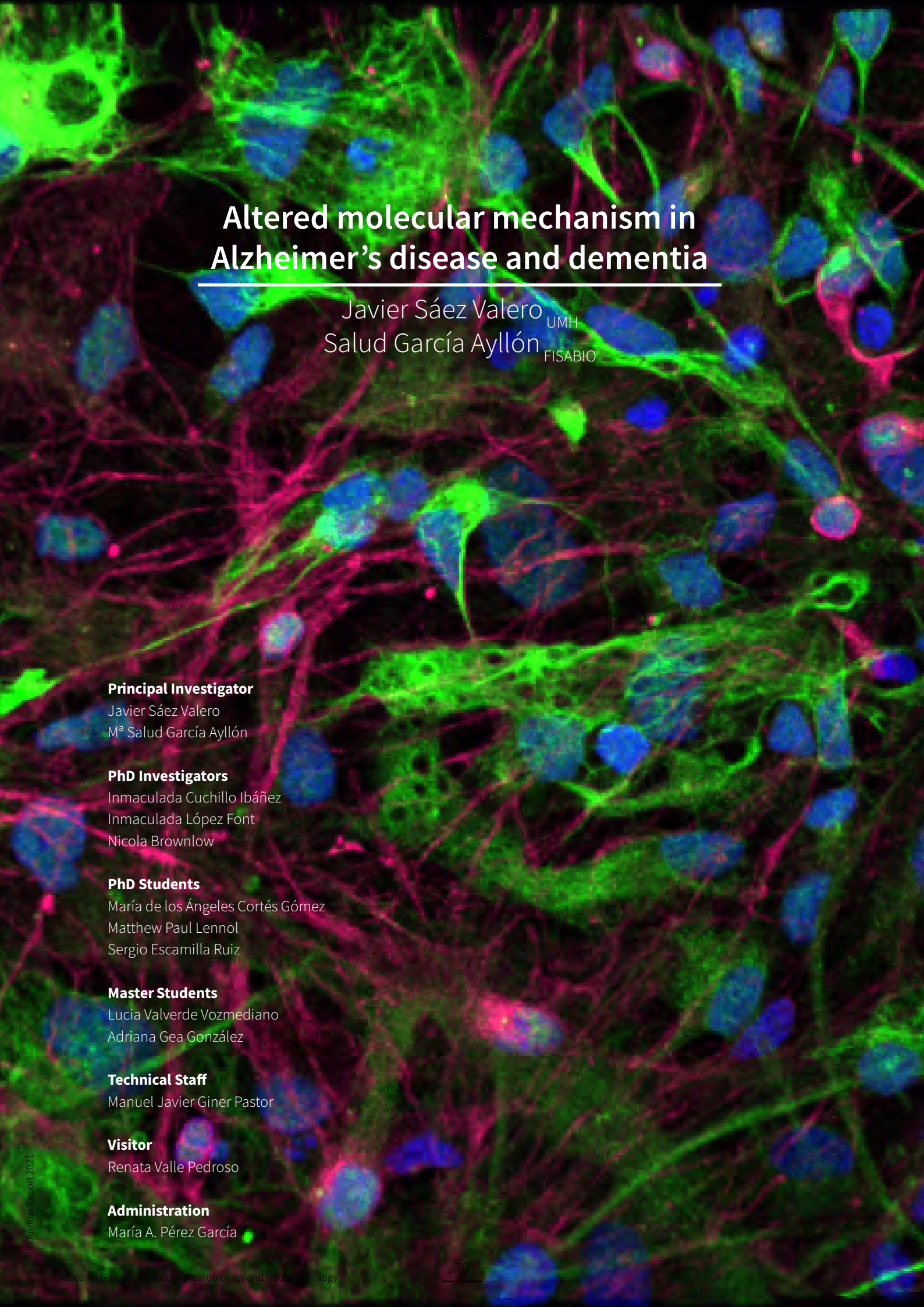
Effects of cannabidiol plus naltrexone on motivation and ethanol consumption. Adrián Viudez-Martínez, María S García-Gutiérrez, Ana Isabel Fraguas-Sánchez, Ana Isabel Torres-Suárez, Jorge Manzanares (2018) **British Journal of Pharmacology** 175:3369-3378

Increased vulnerability to ethanol consumption in adolescent maternal separated mice. María S. García-Gutiérrez, Francisco Navarrete, Auxiliadora Aracil, Adrián Bartoll, Isabel Martínez-Gras, José L. Lanciego, Gabriel Rubio, Jorge Manzanares (2016) **Addiction Biology** 21:847-858



Visit the group website for more information

Department
Molecular Neurobiology and Neuropathology



Altered molecular mechanism in Alzheimer's disease and dementia

Javier Sáez Valero UMH
Salud García Ayllón FISABIO

Principal Investigator
Javier Sáez Valero
Mª Salud García Ayllón

PhD Investigators
Inmaculada Cuchillo Ibáñez
Inmaculada López Font
Nicola Brownlow

PhD Students
María de los Ángeles Cortés Gómez
Matthew Paul Lennol
Sergio Escamilla Ruiz

Master Students
Lucia Valverde Vozmediano
Adriana Gea González

Technical Staff
Manuel Javier Giner Pastor

Visitor
Renata Valle Pedroso

Administration
María A. Pérez García

Altered molecular mechanism in Alzheimer's disease and dementia

Our research line is focused in Alzheimer's disease (AD), but with interest in other neurodegenerative disorders. Translationality of our research lies in our aim to clarify the pathological mechanisms which underlie the disease, searching potential diagnostic tools and/or processes with therapeutic relevance. Our group is part of CIBERNED (an ISC-III Center for Networked Biomedical Research focused in neurodegenerative diseases) with members from FISABIO (Foundation for the promotion of health and biomedical research of the Valencian Community) and ISABIAL (Institute of Health and Biomedical Research of Alicante). In recent years, we have been involved in a project of the EU Joint Programming in Neurodegenerative Disease, BIOMARKAPD, a European consortium that aimed to validate classical markers and refine protocols for analysis. Our group is part of the "Society for CSF analysis and clinical neurochemistry".

Our expertise comprises i) biochemical characterization of PTM for brain/CSF proteins, including glycosylation, phosphorylation, and characterization of proteolytic processing; ii) characterization of ligand-receptor interaction associated to signaling pathways; iii) assessment of sustained inhibition of key enzymes such as cholinesterases and secretases.

Among the recent studies there are: i) β-amyloid (Aβ) and tau hyperphosphorylation (P-tau) cross-talk, role for the reelin protein. Reelin is a signaling protein that modulates synaptic function and plasticity in the brain through interaction with apolipoprotein E receptors. ApoE is the major genetic risk factor for sporadic AD. We demonstrated a novel mechanism by which Aβ regulates reelin expression and glycosylation, thereby influencing its signaling cascade. We also described a new apolipoprotein E receptor that influenced amyloid processing. ii) Interaction and modulation of acetylcholinesterase by P-tau and the role of presenilin 1 in the glycosylation and functional location of acetylcholinesterase. iii) Development of new CSF biomarkers, evaluating the diagnostic potential of particular glycoforms of proteins (including APP), which improve sensitivity and specificity of the biomarkers. We also identify in the CSF several secretases and APP photolytic fragments. We are part of the team involved in the report of the new ADAM10 Tyr167* nonsense mutation in familial AD.

Plasma ACE2 species are differentially altered in COVID-19 patients. García-Ayllón MS, Moreno-Pérez O, García-Arriaza J, Ramos-Rincón JM, Cortés-Gómez MÁ, Brinkmalm G, Andrés M, León-Ramírez JM, Boix V, Gil J, Zetterberg H, Esteban M, Merino E, Sáez-Valero J. (2021) **FASEB J** 35, e21745

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The apolipoprotein receptor LRP3 compromises APP levels Cuchillo-Ibañez I, Lennol MP, Escamilla S, Mata-Balaguer T, Valverde-Vozmediano L, Lopez-Font I, Ferrer I, Sáez-Valero J. (2021) **Alzheimers Res Ther** 13, 181

Increased P2×2 receptors induced by amyloid-β peptide participates in the neurotoxicity in alzheimer's disease Godoy PA, Mennickent D, Cuchillo-Ibáñez I, Ramírez-Molina O, Silva-Grecchi T, Panes-Fernández J, Castro P, Sáez-Valero J, Fuentealba J. (2021) **Biomed Pharmacother** 142, 111968

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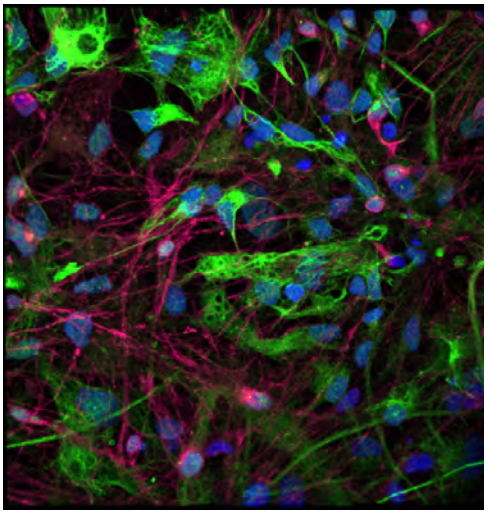
Department

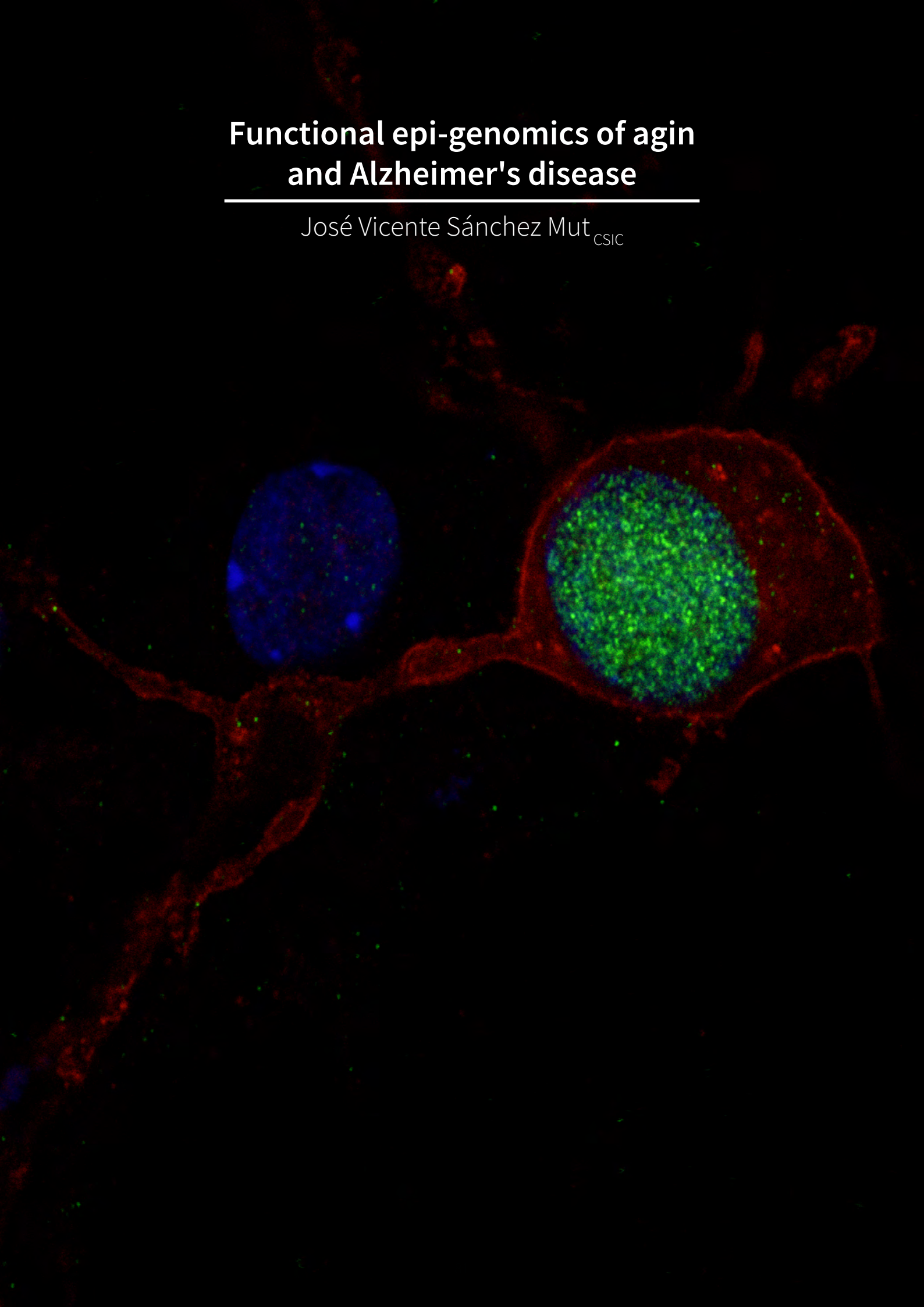
Molecular Neurobiology and Neuropathology



Visit the group website for more information

Functional epi-genomics of agin and Alzheimer's disease

José Vicente Sánchez Mut CSIC

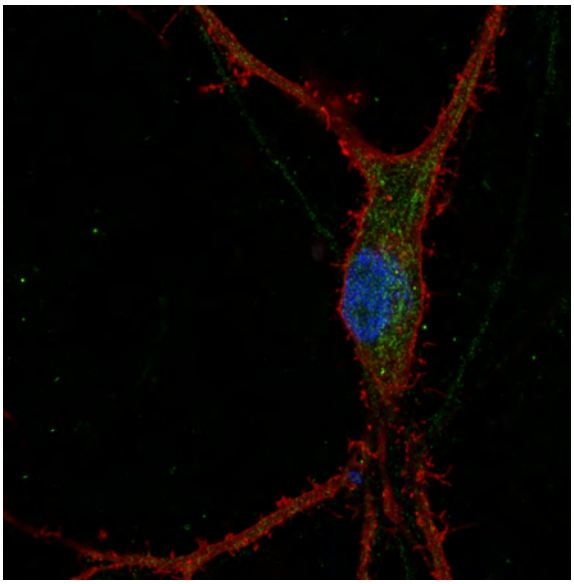


Functional epi-genomics of aging and Alzheimer's disease

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

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

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



Visit the group website for more information

PM20D1 quantitative trait locus is associated with Alzheimer's disease. Sanchez-Mut JV , Heyn H, Silva BA, Dixsaut L, Garcia-Esparcia P, Vidal E, Sayols S, Glauser L, Monteagudo-Sánchez A, Perez-Tur J, Ferrer I, Monk D, Schneider B, Esteller M, Gräff (2018) **Nat Med** doi: 10.1038/s41591-018-0013-y

Human DNA methylomes of neurodegenerative diseases show common epigenomic patterns. Sanchez-Mut JV , Heyn H, Vidal E, Moran S, Sayols S, Delgado-Morales R, Schultz MD, Ansoleaga B Garcia-Esparcia P, Pons-Espinal M, Martinez de Lagran M, Dopazo J, Rabano A, Avila J, Dierssen M, Ira Lott, Ferrer I, Ecker JR, Esteller M (2016) **Transl Psychiatry** doi: 10.1038/tp.2015.214

Epigenetic Alterations in Alzheimer's Disease. Sanchez-Mut JV , Gräff J (2015) **Front Behav Neurosci** doi: 10.3389/fnbeh.2015.00347

Promoter hypermethylation of the phosphatase DUSP22 mediates PKA-dependent TAU phosphorylation and CREB activation in Alzheimer's disease. Sanchez-Mut JV, Aso E, Heyn H, Matsuda T, Bock C, Ferrer I, Esteller M (2014) **Hippocampus** doi: 10.1002/hipo.22245

DNA Methylation Map of Mouse Brain Identifies Targets of Epigenetic Disruption in Alzheimer's Disease. Sanchez-Mut JV , Aso E, Panayotis N, Lott I, Dierssen M, Rabano A, Urdinguio RG, Fernandez AF, Astudillo A, Martin-Subero JI, Balint B, Fraga MF, Gomez A, Gurnot C, Roux JC, Avila J, Hensch TK, Ferrer I, Esteller M (2013) **Brain** doi: 10.1093/brain/awt237

Department
Molecular Neurobiology and Neuropathology

Principal Investigator
José Vicente Sánchez Mut

PhD Investigator
Aida Giner De Gracia

PhD Student
Alejandro González Ramón
Victoria Pozzi Ruiz

Servicies and Facilities

| E. Saez Carrión

Imaging Facility

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

Visit the facility website for more information

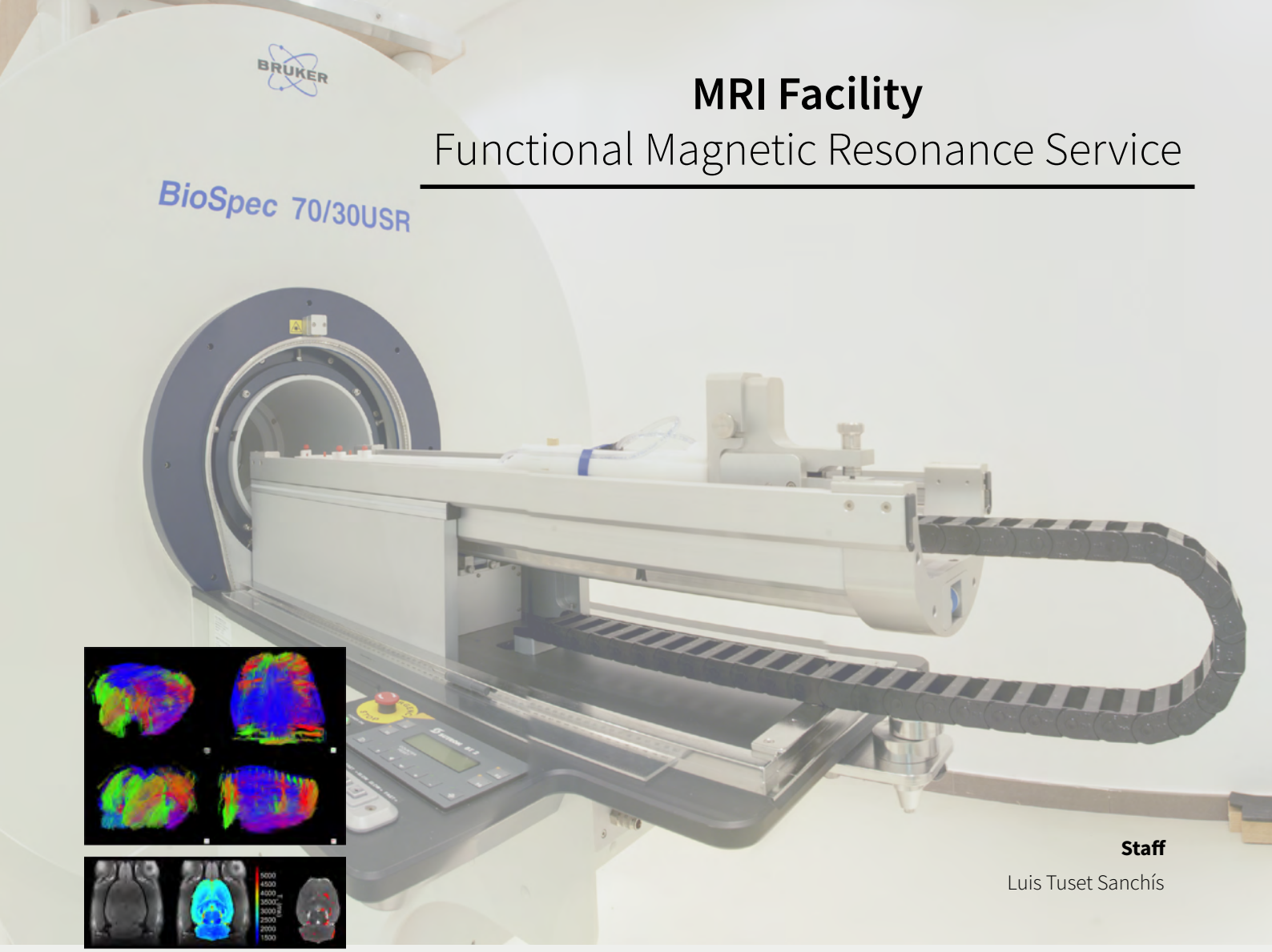
Staff

Giovanna Expósito Romero

Verona Villar Cerviño

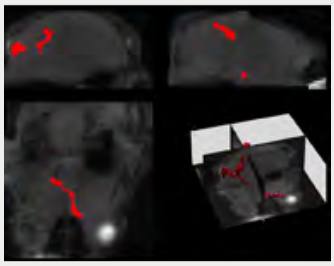
MRI Facility

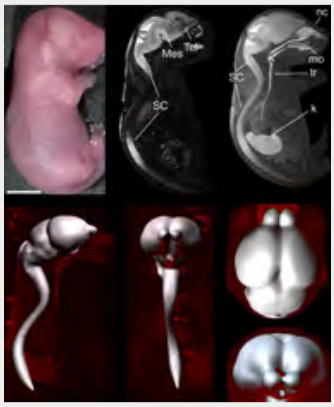
Functional Magnetic Resonance Service

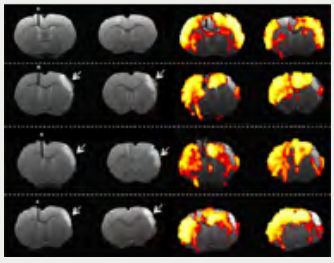


Staff

Luis Tuset Sanchís







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

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

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

Visit the facility website for more information

Animal Housing Facilities

SPF Animal House

The Unit for Genetically Modified Mice is one of 3 animal facilities at the Animal Experimentation Service of the UMH. It is a specific pathogen free facility with capacity for around 15,000 mice. The IN has full control of this facility and set up a service for in-house embryo cryopreservation, mouse genotyping and to generate transgenic mice.

Zebrafish Facility

***Drosophila* Stocks and Media Preparation Facility**

Visit the facility website for more information

Veterinary Staff

Tomás García Robles
Gonzalo Moreno del Val

Animal House

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

Animal Research Facilities

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.

Visit the facility website for more information

Drosophila Service

Laura Mira Valdelvira
Irene Oliveira Ávalos

Zebrafish Facility

Cristina Minaya Ramírez
Alba Olmos Franco

Genotyping

Mª Trinidad Gil García
Eva Mª Sabater Sánchez

Wieland Brendel

Omics Facility

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

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

Staff

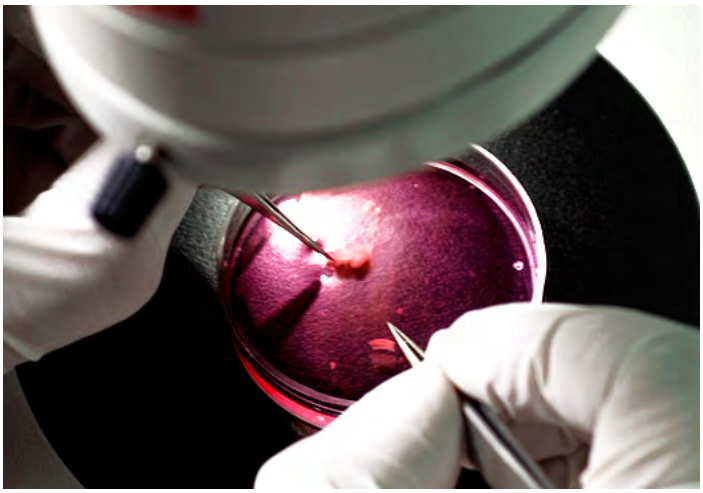
Antonio Javier Caler Escribano

Visit the facility website for more information

Cell Culture Facilities

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

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



Staff

Sara Carratalá Gosálbez

Rosa García Velasco

Visit the facility website for more information

SHARE Service

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

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

Staff

Víctor Javier Rodríguez Milán

SHARE
Scientific Hardware & Electronics Service

Visit the facility website for more information

Neurotropic Vectors

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

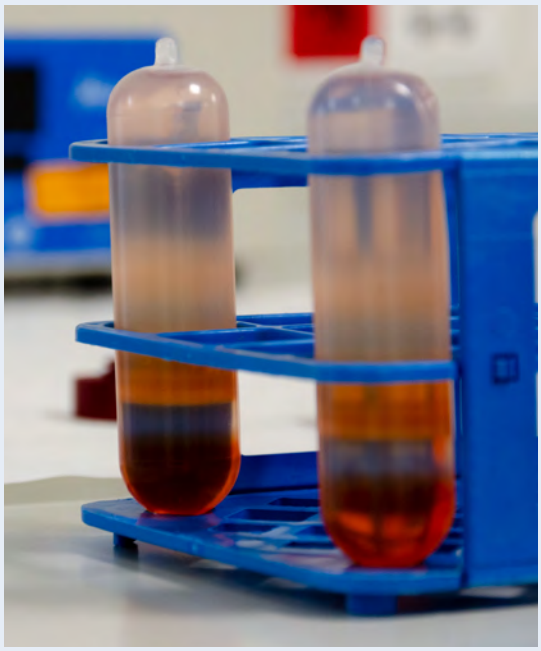
In recent years the delivery of molecular tools into neurons has become an essential approach to understand the mechanisms underlying brain function and brain disorders.

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

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

Staff

Cristina García Frigola



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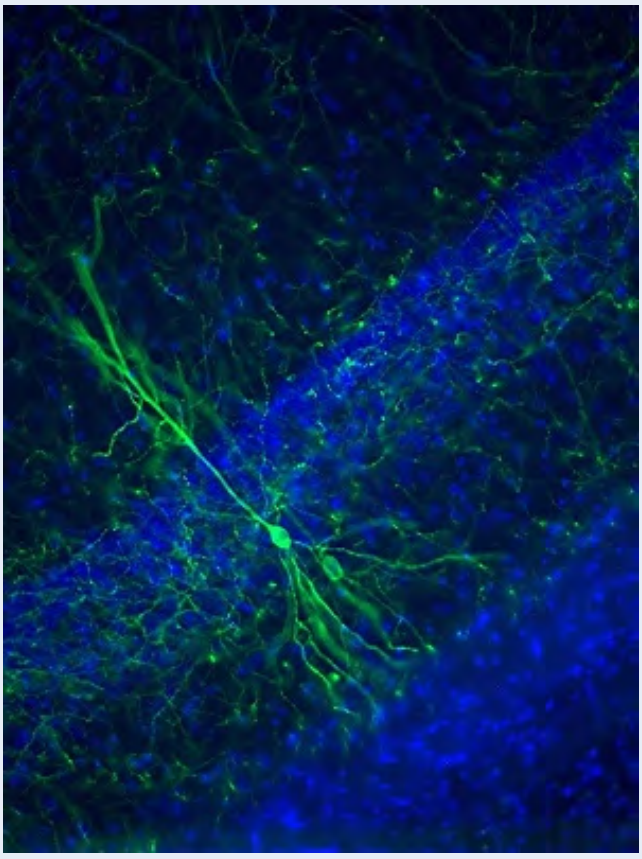


Hippocampal cell infected with a EGFP expressing AAV.

Administration and Service Staff

Manager

Mª Teresa García Hedo

Administration

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

Maintenance

Jesús Campos Roldán
Álvaro Daniel Fenoll Esclápez

Computing

Mª Isabel Sánchez Febrero

Audiovisual Service and Graphic Design

Sergio Javaloy Ballestero

Glassware and Autoclaving

Trinidad Guillén Carrillo

A. González Iglesias

Research Highlights

Medium spiny neurons activity reveals the discrete segregation of mouse dorsal striatum.

Alegre-Cortés et al. **eLife 2021**

URL: https://bit.ly/3sNeCHk

The research led by Dr. Ramón Reig advances in the understanding of the problems in the activity of striatal circuits that generate motor, cognitive and emotional symptoms in both rodents and humans.

Astrocytes and neurons share region-specific transcriptional signatures that confer regional identity to neuronal reprogramming.

Herrero-Navarro et al. **Sci Adv 2021**

URL: https://bit.ly/385CHSC

The work of Dr. Guillermina López-Bendito's laboratory opens the door to recovering the sensory circuits of sight or hearing damaged in early stages of life.

Sublayer- and cell-type-specific neurodegenerative transcriptional trajectories in hippocampal sclerosis.

Cid E, et al. **Cell Rep. 2021**

URL: https://bit.ly/3PAm2re

The research of Dr. José López-Atalaya, co-led by Liset Menéndez de la Prida of the Cajal Institute, shows that epilepsy-associated atrophy is characterized by the death of a specific subpopulation of pyramidal neurons in the hippocampus.

Body-fat sensor triggers ribosome maturation in the steroidogenic gland to initiate sexual maturation in *Drosophila*.

Juárez-Carreño et al. **Cell Rep. 2021**

URL: https://bit.ly/3wvDrtr

The work led by Drs. Javier Morante and María Domínguez explores the communication mechanisms between body fat and the brain that regulate the onset of puberty.

The apolipoprotein receptor LRP3 compromises APP levels.

Cuchillo-Ibáñez et al. **Alzheimers Res Ther. 2021**

URL: https://bit.ly/3Pr81fr

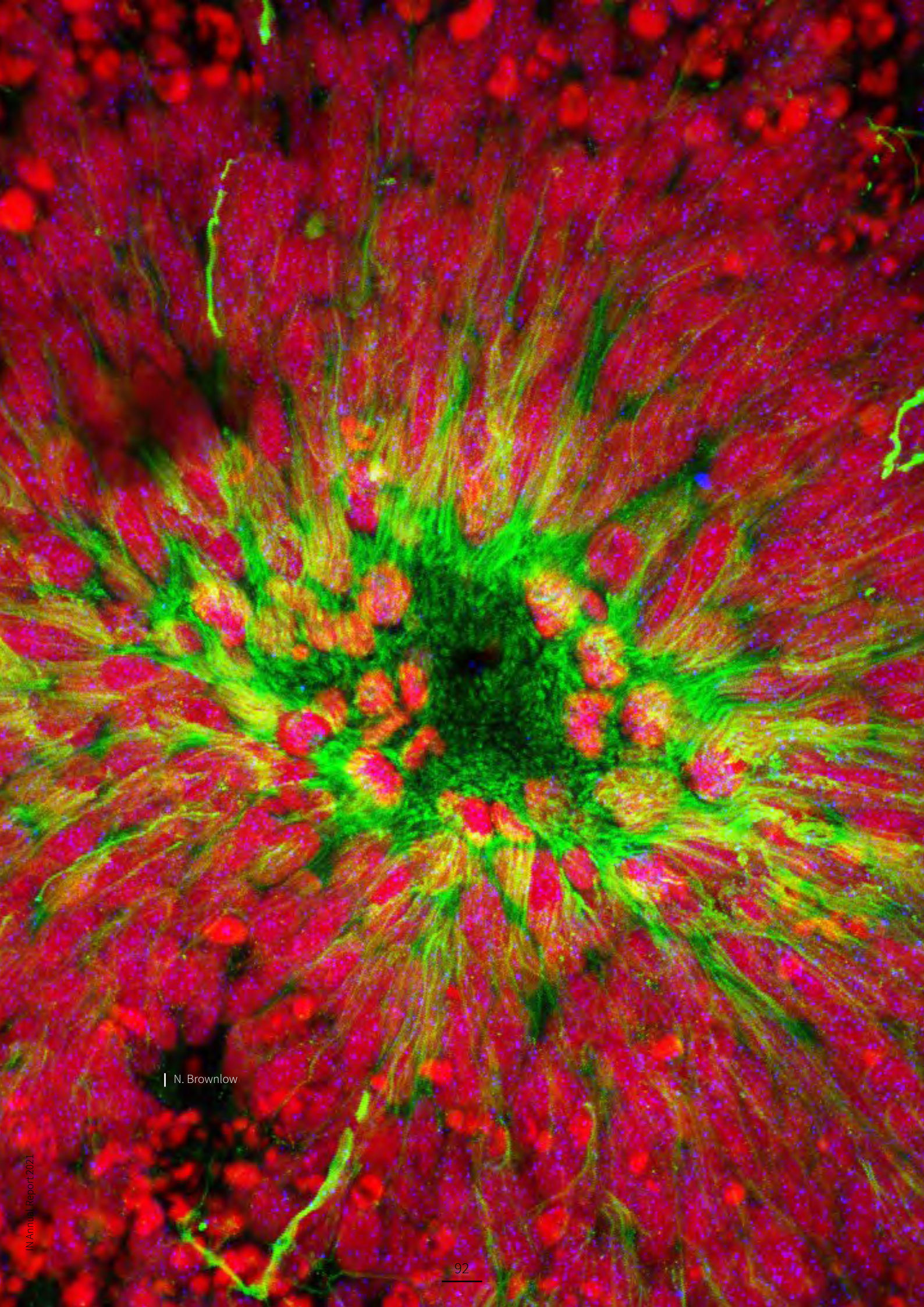
The work of the group led by Dr. Javier Sáez relates the LRP3 protein to a reduction in the accumulation of amyloid beta, which identifies this protein as a new therapeutic target in Alzheimer's Disease.

Control of protein synthesis and memory by GluN3A-NMDA receptors through inhibition of GIT1/mTORC1 assembly.

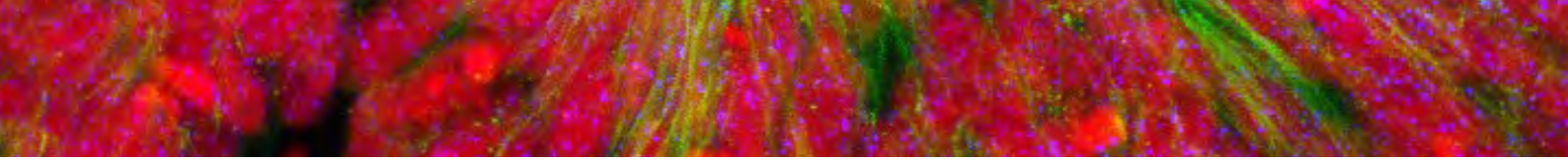
Conde-Dusman et al. **eLife 2021**

URL: https://bit.ly/3wBUw3L

The work led by Dr. Pérez-Otaño has characterized the complexes that regulate the protein synthesis needed for the consolidation of associative and spatial memories in mice.



N. Brownlow



Scientific Meetings

IN researchers are very active in organizing scientific meetings. As a result of this activity, Alicante has become an essential European hub for activities in the field of neuroscience. Although face-to-face activities in 2021 have still been greatly reduced due to the COVID-19 pandemic, dozens of doctoral students, postdoctoral researchers, and group leaders from all over the world visited our institute and/or the city of Alicante to participate in These events. Some of these events have been broadcast on our YouTube channel, further increasing their reach.

IN Seminar Program

The IN runs a highly successful international seminar program in which dozens of leading scientists from around the world interact with our researchers. Due to the COVID-19 pandemic, most of the talks in 2021 took place online, including conferences from the United States, China, England, Germany, France, Switzerland, etc. See annex for the complete list.

The most outstanding meetings, conferences and workshops organized in 2021 were:

February 11: International Day of Women and Girls in Science

The conference organized by Dr. Sandra Jurado, could be followed live through the Institute's YouTube channel. IN researchers Carmen Navarrón, Dr. Verónica Moreno, Dr. Teresa Guillamón and Dr. Diana Vallejo, as well as Professor Carmen Sandi, from the Lausanne Institute of Technology (Switzerland), presented the results of their research and discussed the main challenges that as women they face in their professional careers.

Symposium The Neural Basis of Rodent Social Behaviors (October 7 and 8)

This scientific symposium coordinated by Drs. Cristina Márquez, Félix Leroy, and Juan Lerma, took place over 2 days and gathered in San Juan de Alicante an international list of leading researchers in the study of social behavior in rodents. The talks were complemented by a poster session.

14th Progress Report Workshop

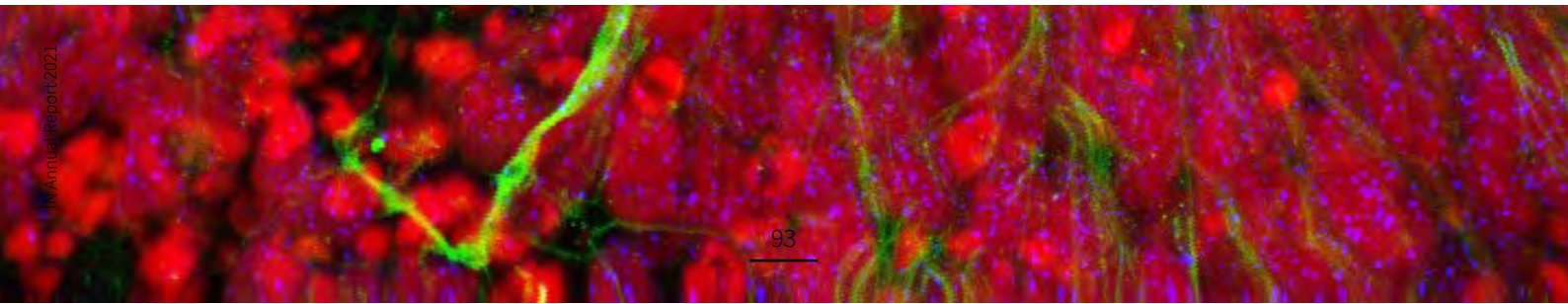
The IN conference took place on October 14 and 15, in the Institute's Assembly Hall, and included the presentation of the work carried out in the last two years by 15 Principal Investigators of our Institute

International Workshop on Chronic Pain and Itch: Mechanisms and Circuits

This scientific workshop organized by Drs. Félix Viana, Elvira de la Peña, Augusto Escalante, Asia Fernández, Ana Gomis, and Francisco Taberner took place on October 20, 21 and 22 at the San Juan Complex facilities, a few meters from the IN. The meeting took place in person and online. More than 10 world leaders in the investigation of chronic pain and itching participated in it.

XVIII Christmas Meetings

This scientific meeting coordinated by Drs. Teresa Femenia, Felix Leroy, and Javier Morante, took place on December 20 and 21. The meeting, organized by the IN every year around Christmas, brings together young researchers who work abroad and who are interested in learning about the IN as a possible new destination in their scientific careers. During the two days, researchers present their main scientific achievements, meet our staff, and visit our facilities. During the meeting, a poster session is held in which young IN researchers presented the research carried out in 2021.



Scientific Meetings

Training and Education Master and PhD Program

Master in Neurosciencies: from the bench to the bedside

(provided by UMH)

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

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

The following subjects are covered:

Mandatory subjects:

- Advances in genetic analysis and embryology 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 courses (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).

MiN Master in Neurosciences
FROM THE BENCH TO THE BEDSIDE
UNIVERSITAS Miguel Hernández

Visit the Master website for more information

Master Research Project:

- Original laboratory research work (15 ECTS).

Development of the 2020-2021 academic year

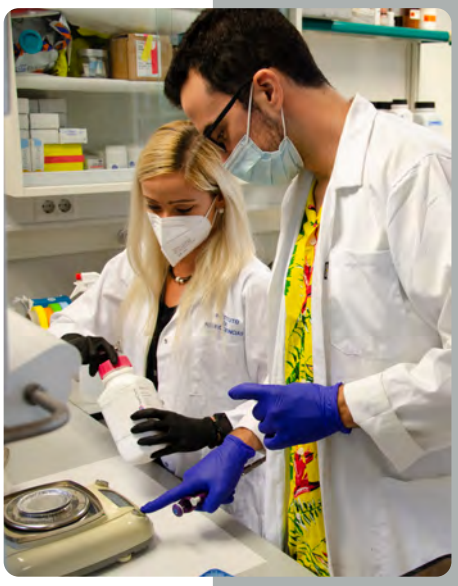
The partnership and exchange of master's students with the Institute Pasteur (University La Sorbonne, Paris) and the SOCE-funded International Scholarships to attend our Master program has favored internationalization despite the extraordinary circumstances imposed by the pandemic. Due to the health crisis and the restrictions caused by COVID-19, all teaching activities were conducted in an online or face-to-face format depending on the instructions received from the UMH. A total of 14 students completed the master's degree and conducted a research project (TFM) within IN research groups.

Training and Education Master and PhD Program

PhD program (RD 99/2011)

The PhD program in Neurosciences is designed to stimulate the initiative and abilities of the students, helping to orient the development of their scientific careers. The program also is an important vehicle for the internationalization of the Institute. The community of PhD students is gender-balanced (50%) and internationalization is increasing (22% foreigners in 2021), particularly considering the mobility restrictions in this period.

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. According to the current law, students require a total of 300 ECTS credits to be admitted. On average 20 new PhDs are admitted yearly.



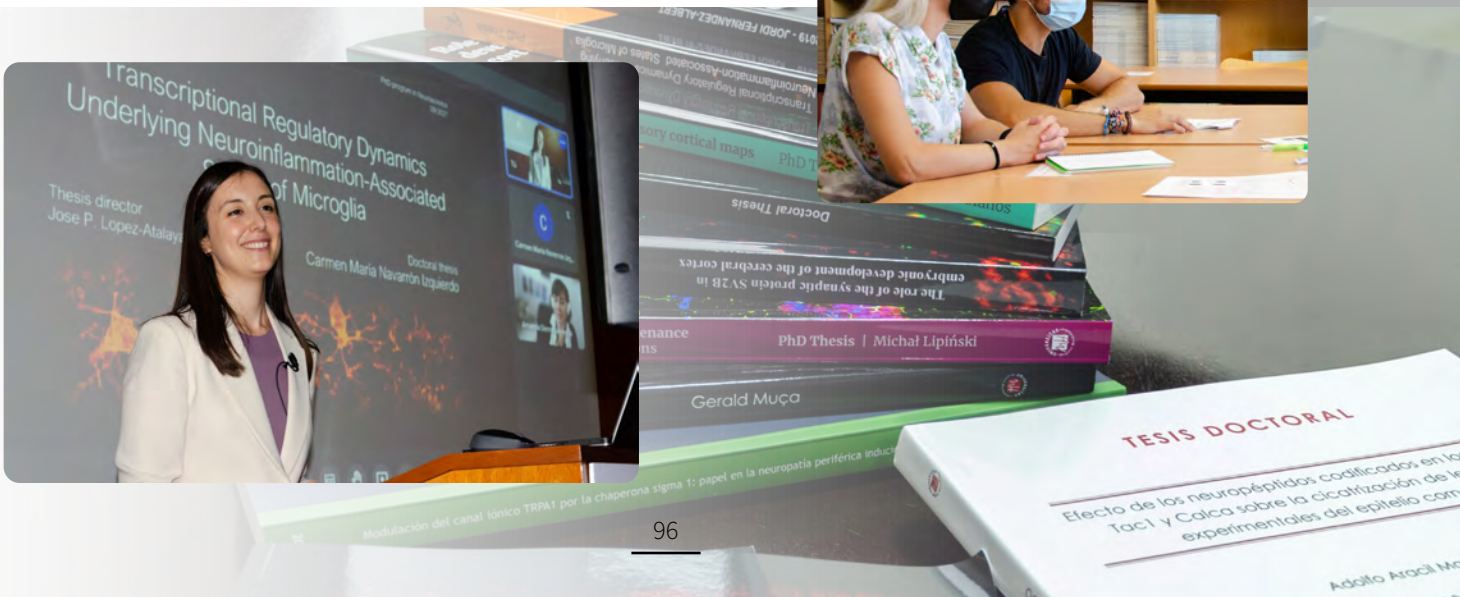
The program offers a variety of Training activities like:

- 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.

Development of the 2020-2021 academic year

During the 2020-2021 course, we had 105 young researchers registered, including 25 that initiated their thesis this course. In total, 14 doctoral theses have been defended (50% gender-blanced), three of them with international mention.

Visit the PhD program website for more information



Innovation: UCIE

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

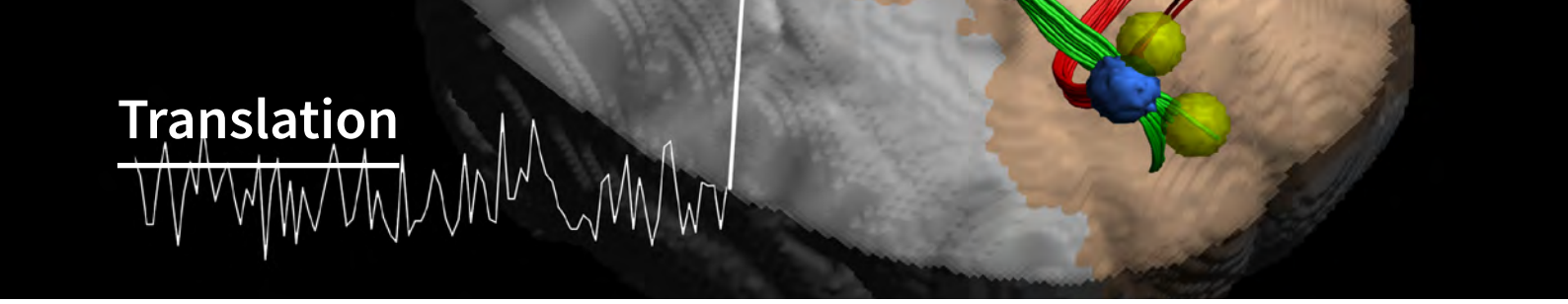
Although the main activity of the IN is the generation of new knowledge through basic research on the development and function of neuronal circuits, their genetic programmes, and cognitive capacities, many of these research programmes have produced important results that can be transferred to society, both through the health system and to the productive sector. The innovation axis of the IN, supported by **IN.pulse**, is responsible for identifying and accompanying these projects in their transfer process, as well as promoting innovation activities at the IN. Ongoing projects include the development of biomarkers for Alzheimer's disease, treatments to improve eye comfort, new drug delivery vectors for the treatment of glioblastomas, and the use of AI to improve the definition of treatments in parkinsonism, the phases of disease or mood and loneliness in the elderly.

IN.pulse
UNIDAD CIENTÍFICA DE INNOVACIÓN EMPRESARIAL

Visit the IN.pulse website for more information

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

GENERALITAT VALENCIANA | TOTS A UNA VEU
AVI AGÈNCIA VALENCIANA DE LA INNOVACIÓ
CSIC
INSTITUTO DE NEUROCIENCIAS



Translational research at the Instituto de Neurociencias UMH-CSIC

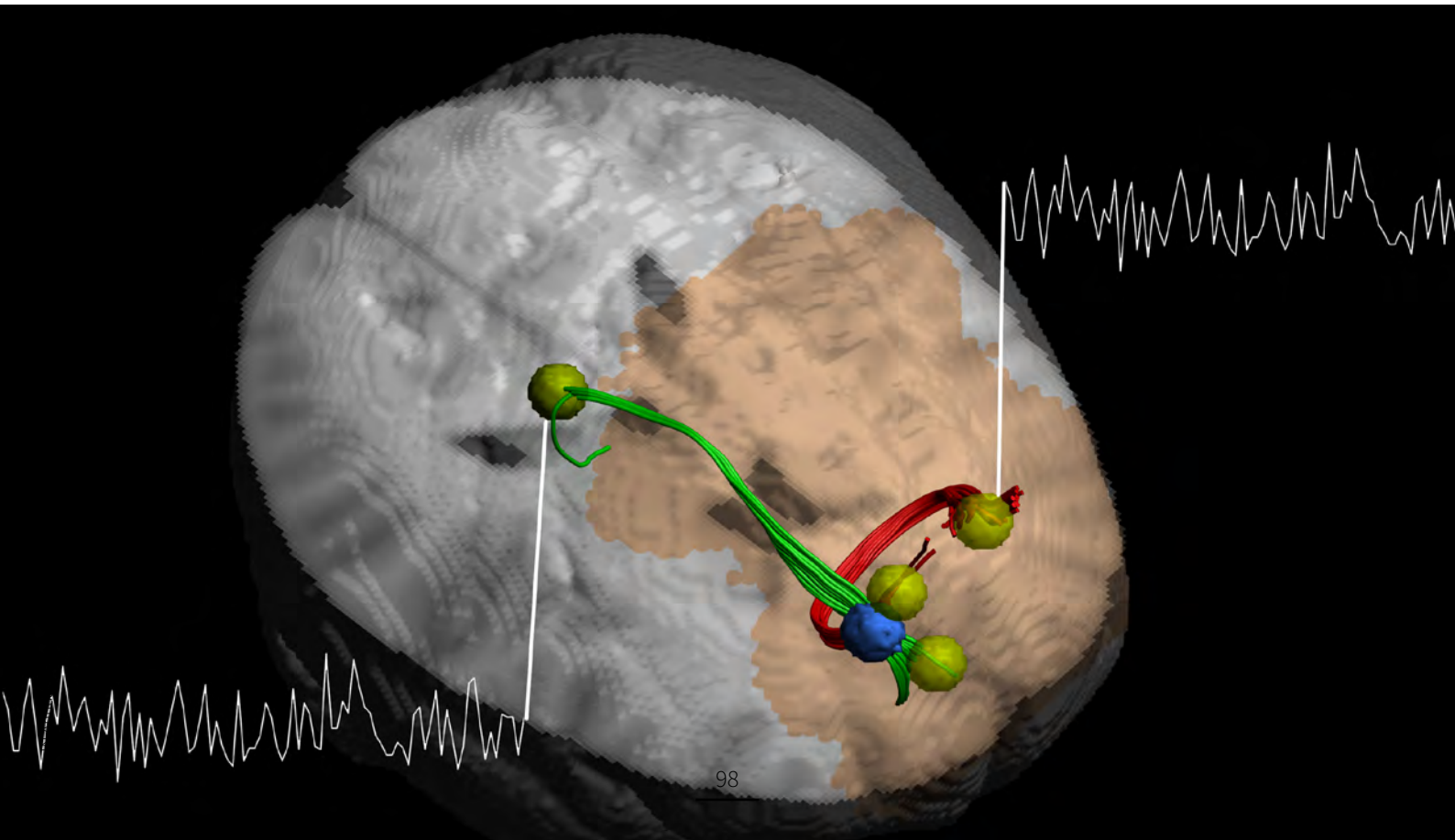
One of our main objectives is to turn the research carried out at the IN into novel therapies for diseases of the nervous system. To do this, we conduct research on nerve regeneration, demyelinating diseases, Parkinson's disease, Alzheimer's, ALS and chronic pain, among others. IN researchers have developed lines of translational research in close collaboration with doctors from local and national hospitals and other health institutions. The axis aims to promote these collaborations through the organization of meetings and the establishment of collaboration agreements between the IN and organizations of professionals and patients, and institutes dedicated to clinical research such as the Institute of Health and Biomedical Research of Alicante (**ISABIAL**), the Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (**FISABIO**) and different networks dependent on the **ISCIII** (CIBER and RICOR) aimed at coordinating Spanish research on the most prevalent human diseases.

ISABIAL
INSTITUTO DE INVESTIGACIÓN SANITARIA Y BIOMÉDICA DE ALICANTE

Fundació Fisabio

ciber isciii

Visit the Translation website for more information



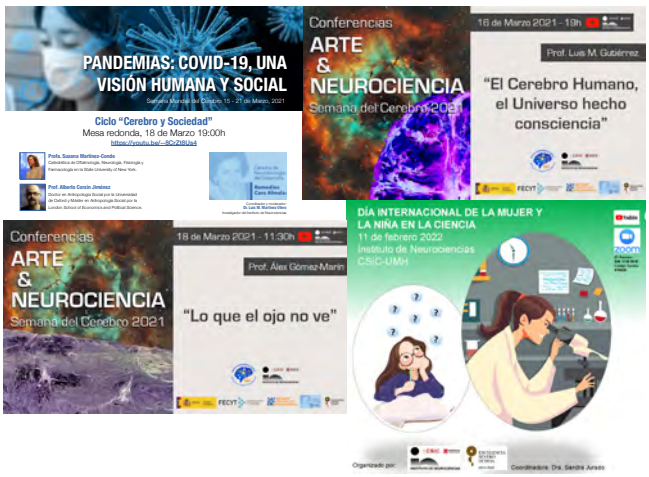
Outreach activities

We increased our proximity to society during 2021 through several actions:

- **Open doors activities**

We annually organize the **Brain Awareness Week** (BAW) in collaboration with the European DANA Alliance for the Brain. The main activity is an open house and science fair in which the whole institute, from PIs and PhD students to administration officers, get involved. The number of visitors surpassed 3,000 in 2019. Unfortunately, we had to switch to a smaller format in 2021 in which we combined a public exhibition of art and science in a central venue in Alicante with several online events (conferences and round table) that were largely attended. Additional outreach activities are organized in the **International Day of Women and Girls in Science**. We also run a visit program for schools that attracts hundreds of students, but that had to be discontinued during 2021.

Visit the BAW website for more information



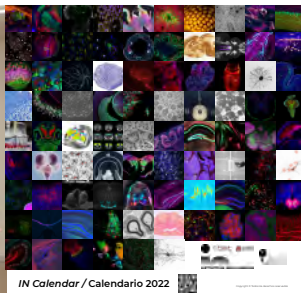
- **Presence in social networks**

The number of Twitter followers increased in more than 2,000 followers in 2021. We also created numerous new contents for our YouTube channel. We recently opened an Instagram account to show attractive scientific photos. In addition, it took place the **I Scientific Photography Contest of the IN**, organized by the post-doctoral organization of the Institute of Neurosciences (OPINA) in collaboration with the IN social media team, with the aim of creating among all the IN community a joint catalogue of scientific photography

@instituto_neurociencias

13,324 views in 2021
223 new subscribers in 2021

Winners of the I Scientific Photography Contest of the IN



2022 IN calendar, made with the photos of the contest

- **Presence in traditional media**

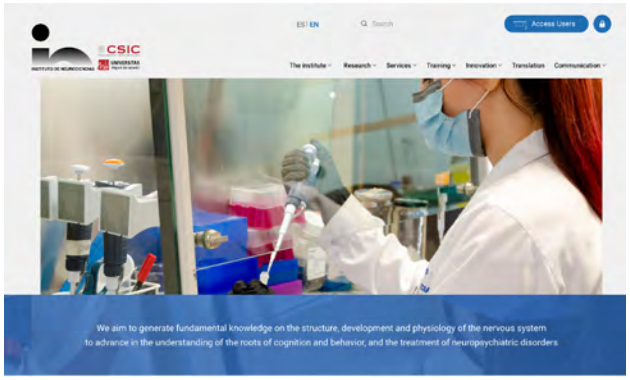
The Instituto de Neurociencias UMH-CSIC appeared **619 times in the media** in 2021, slightly exceeding that registered in 2019 (607). The trend of increasing impacts that began in 2017 seems to be recovering. These impacts have been the result of 14 press releases sent to the media in 2021.

Access the full report on media impacts 2021

- **Renewal of our website**

We have renewed our website, enhancing its attractiveness and accessibility by adding multimedia material.

Visit the new IN website for more information



Awards and Distinctions 2021

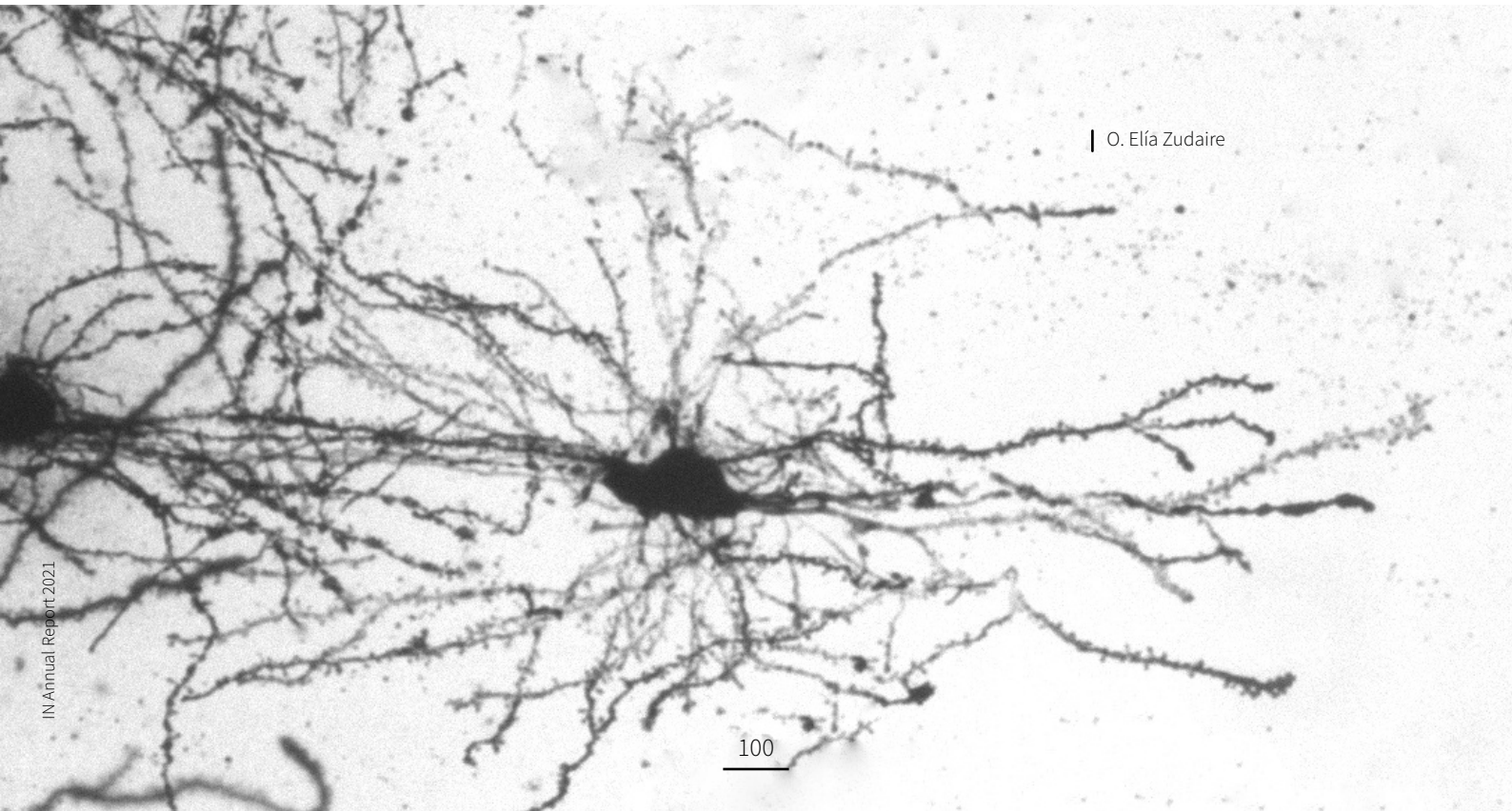
Dr. Ángela Nieto Toledano, winner of the l'Oréal-UNESCO For Women in Science Award.

Dr. Guillermina López Bendito, election as a member of the Mediterranean Science Selection by MEDNIGHT.

Dr. Juan Antonio Moreno Bravo, Olympus Award for young researchers.

Dr. Juan Lerma, election as Vice-Chair of the European Brain Council.

Dr. Felix Leroy, election as a member of the European Academy of Young Researchers.



O. Elía Zudaire

Collaborations and Alliances

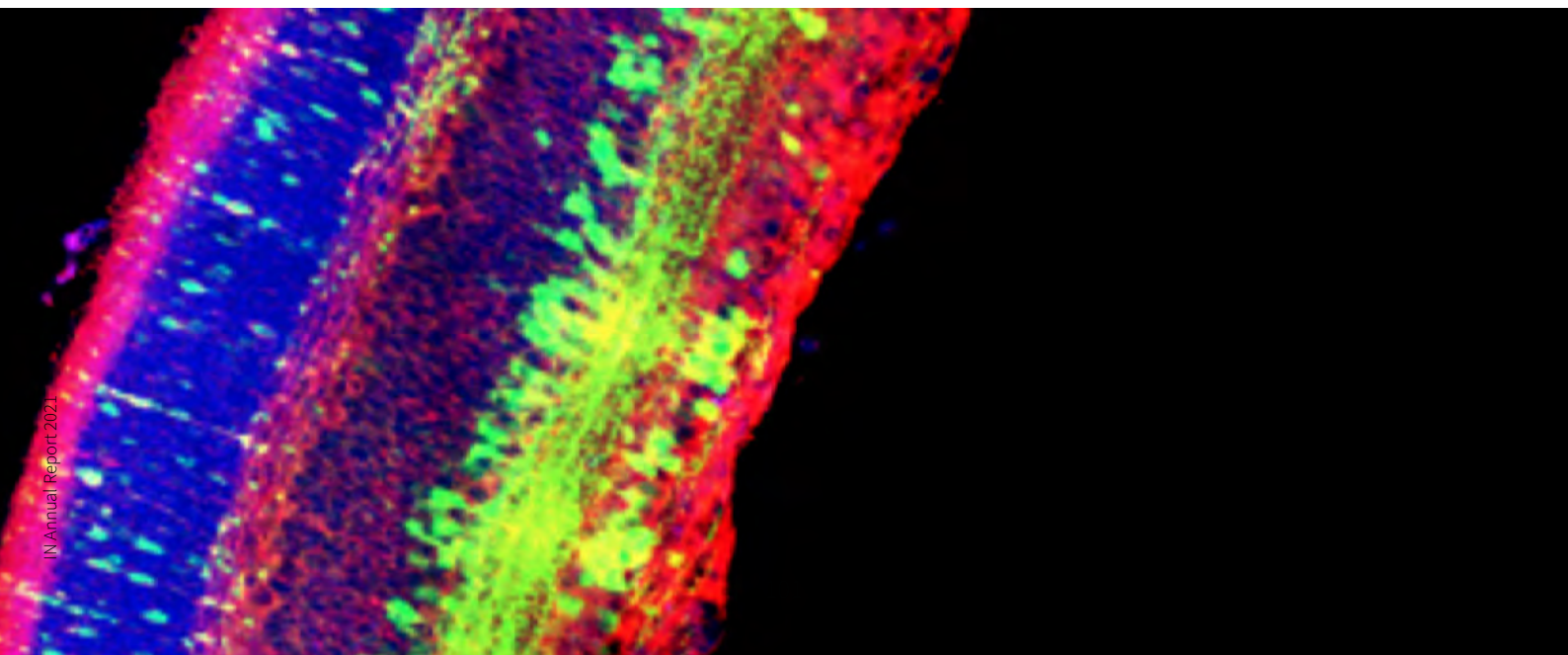
There are regular collaborations between IN researchers and scientists of the most prestigious biomedical research institutions. The participation of the IN researchers is fostered in European Networks of Excellence, Integrated Projects and International Training Networks (ITNs) as well as in high-throughput technological platforms, to facilitate mobility with partner labs.

The "Remedios Caro Almela" Prize in Developmental Neurobiology, supported by private funds, is awarded by the IN. This prominent and well-regarded international prize has been consistently sought by leading Europe-based neuroscientists, has reliably identified some of the very top leaders in European developmental neuroscience, and has succeeded in bringing attention to the Institute.

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

- Agencia Valenciana de Innovación (AVI-GVA)
- ISABIAL, FISABIO and other clinical research institutes
- Asociación Española Contra el Cáncer
- Universidad San Pablo CEU
- Universidad Católica de Murcia (UCAM)

The international character of our teaching programs, Master and PhD, is fundamental to expand our presence in the first stages of training of researchers, and compete for the best students.



SOMMa and “Severo Ochoa” acreditation of Excellence

The IN, a Severo Ochoa Center of Excellence

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

These centers together with the "María de Maeztu" Units of Excellence constitute **SOMMa**: **The "Severo Ochoa" Centres and "María de Maeztu" Units of Excellence Alliance**. This alliance aims to attract and nurture scientific talent and promote ground-breaking research, following principles of excellence, integrity, external peer-review, competitiveness, and international cooperation.

Visit the SOMMa website for more information

EXCELENCIA
SEVERO
OCHOA

Chair of Neurobiology

Remedios Caro Almela

Richard Morris & Constantino Sotelo

Remedios Caro Almela Chair of Neurobiology

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

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

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

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

Professor Richard Morris (2013-present) Professor of Neuroscience at the University of Edinburgh and Member of the Royal Society.

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

Visit the website for more information

Remedios Caro Almela Prize

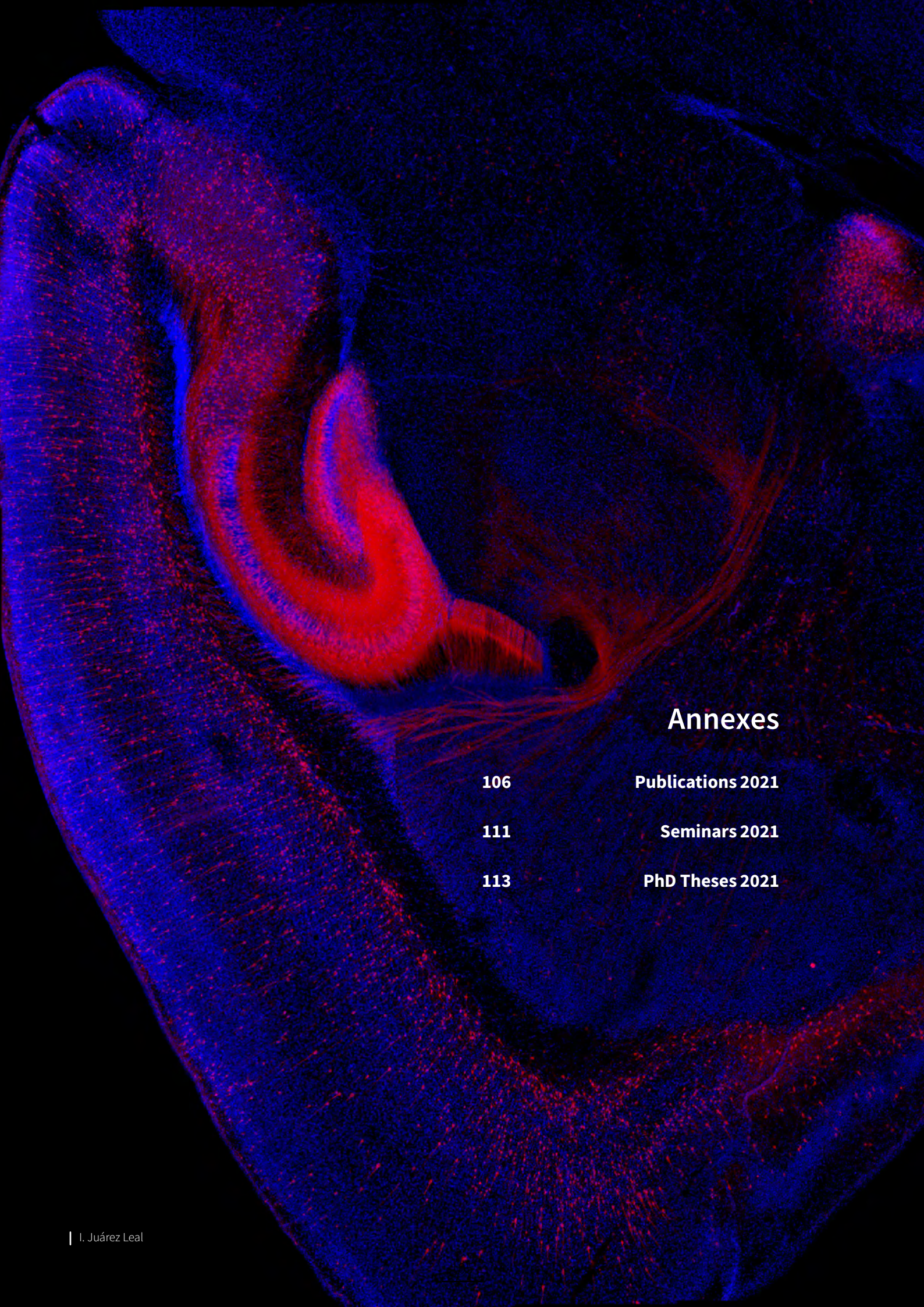
Dr. Pierre Vanderhaeghen, 2021

The jury of the **Remedios Caro Almela Prize** awarded the X Prize to Professor **Pierre Vanderhaegen**, Director of the Stem Cell and Developmental Neurobiology Laboratory of the VIB-KU Leuven Center for Research on the Brain and its Diseases (Belgium).

Dr. Vanderhaegen was awarded for his work pioneering the implantation of pluripotent stem cells into functional circuits, which represents a new approach to investigate the mechanisms of neural development and opens up numerous possibilities for cell therapy in the nervous system. Particular emphasis was placed on *"the originality of his work, the relevance of his numerous contributions to the field of developmental neurobiology, and his focused work on a big problem over many years. In particular, his pioneering work on the implantation of pluripotent stem cells in functional brain circuits opened up numerous possibilities for cell therapy in the nervous system. His research has also contributed to revealing basic aspects of development that allow us to better understand how a structure with the complexity of the human cerebral cortex has appeared".*

This prestigous Prize was previously awarded to Barry Dickson (2006), François Guillemot (2007), Rüdiger Klein (2008), Steve Wilson (2009), Christine Holt (2011), Magdalena Götz (2013), Silvia Arber (2015), Alain Chedotal (2017) and Óscar Marín (2019).

Visit the Remedios Caro Almela Prize website for more information



Annexes

I. Juárez Leal

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The Search for Biomarkers in Psychiatry. Garcia-Gutierrez MS, Manzanares J, Navarrete F 2021 **Front Psychiatry** 12, 720411. 10.3389/fpsyt.2021.720411

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Book Chapters and Reviews

Are You Interested or Afraid of Working on EMT? Nieto MA 2021 **Methods Mol Biol** 2179, 19-28. 10.1007/978-1-0716-0779-4_4

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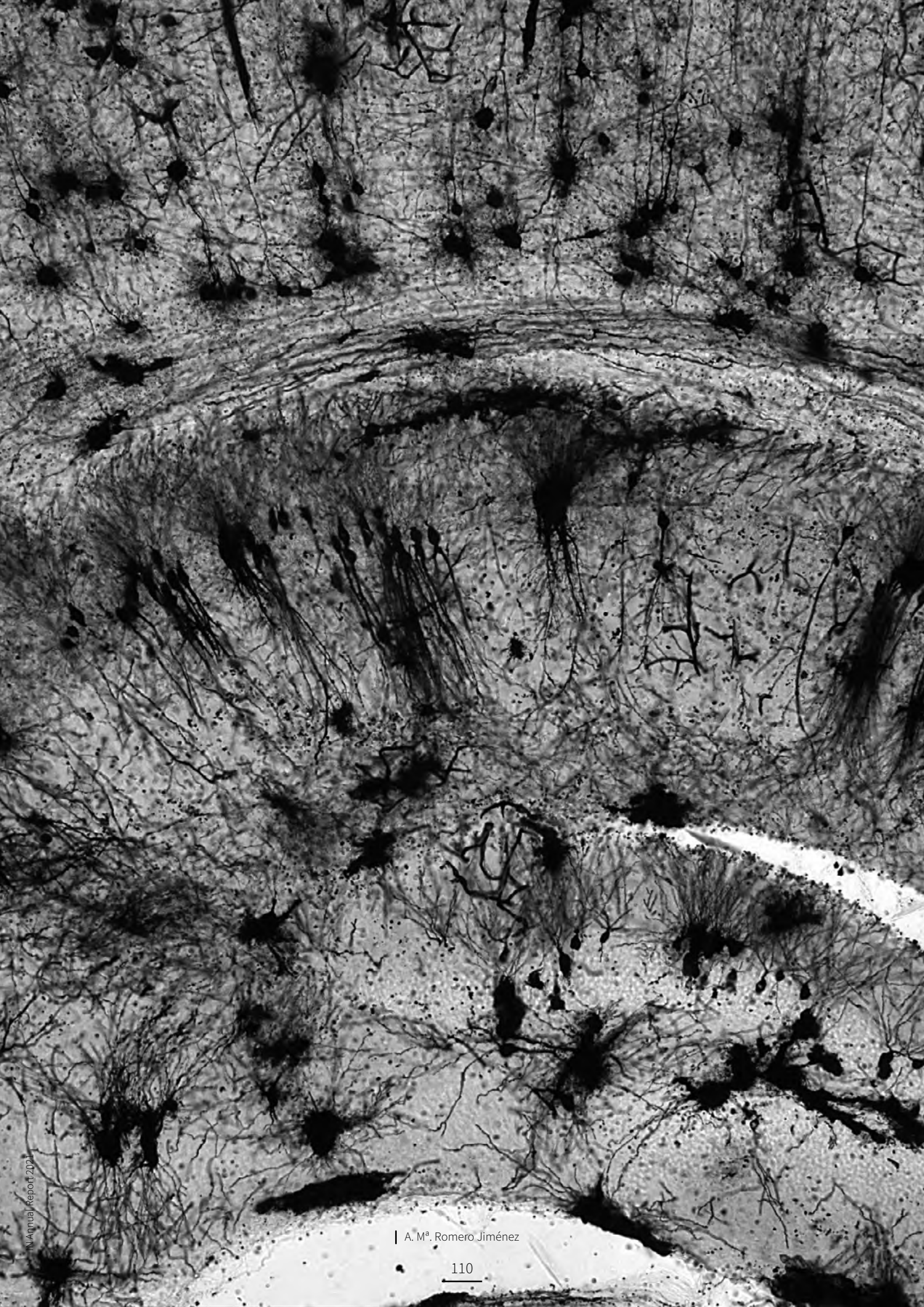


A. Mª. Romero Jiménez

Seminars

Dr. Luis Martínez-Otero Instituto de Neurociencias, Alicante *Material Minds: Exploring the Interactions between Predictive Brains, Cultural Artefacts, and Embodied Visual Search.*

Dr. Jaime de la Rocha IDIBAPS, Barcelona *The dynamics of evidence accumulation during decision making.*

Dr. Diego Gomez-Nicola School of Biological Sciences, University of Southampton, Southampton, UK *Microglial dynamics in health and disease*

Dr. Luis Puelles Universidad de Murcia, Murcia *Critical comparison of prosomeric and columnar brain models*

Dr. Ivan Rodríguez Geneva University, Geneva, Switzerland *The sick sense is in the nose.*

Dr. María Robles Institute of Medical Psychology, LMU, Munich, Germany *Sleep-wake cycles shape proteome and phosphoproteome dynamics in brain.*

Dr. Oliver Collignon Université Catholique de Louvain, Louvain-la-Neuve, Belgium *Brain development under sensory deprivation and restoration.*

Dra. Irene Miguel-Aliaga Imperial College London, London, UK *The second brain of a simpler gut.*

Dr. Francesco Papaleo IIT Central Research Labs Genova, Genova, Italy *Circuits of Emotion Discrimination.*

Dr. Maria Llorens-Martin Centro de Biología Molecular Severo Ochoa-CSIC-UAM, Madrid A*dult hippocampal neurogenesis in physiology and disease.*

Dra. Monika Schönauer University of Freiburg, Freiburg, Germany *Imaging Memory Consolidation in Wakefulness and Sleep.*

Dr. Laura Cancedda Italian Institute of Technology, Genova, Italy *Treating neurodevelopmental disorders: challenges, issues, problems, concerns, difficulties, harms, worries, doubts, but we need to start from somewhere.*

Dr. Juan Antonio Moreno-Bravo Instituto de Neurociencias, Alicante *Local and Long-range Cerebellar Connectivity.*

Dr. Xiang Yu School of Life Sciences, Peking University, Peking, China *Regulating of early wiring of the sensory cortices by experience and molecules.*

Dr. Jose Carlos Pastor Pareja School of Life Sciences, Tsinghua University, Beijing, China A*typical basement membranes: secretion, assembly and roles in the nervous system.*

Dr. Paola Arlotta Harvard University, Cambridge, USA *Molecular Logic of Cortical Development.*

Dr. Ian Wickersham Brain and Cognitive Sciences, MIT, Cambridge, USA *Viral techniques for studying neural circuitry.*

Dr. Felix Leroy Instituto de Neurociencias, Alicante *CRH release from the pre-frontal cortex to the lateral septum regulates social recognition*

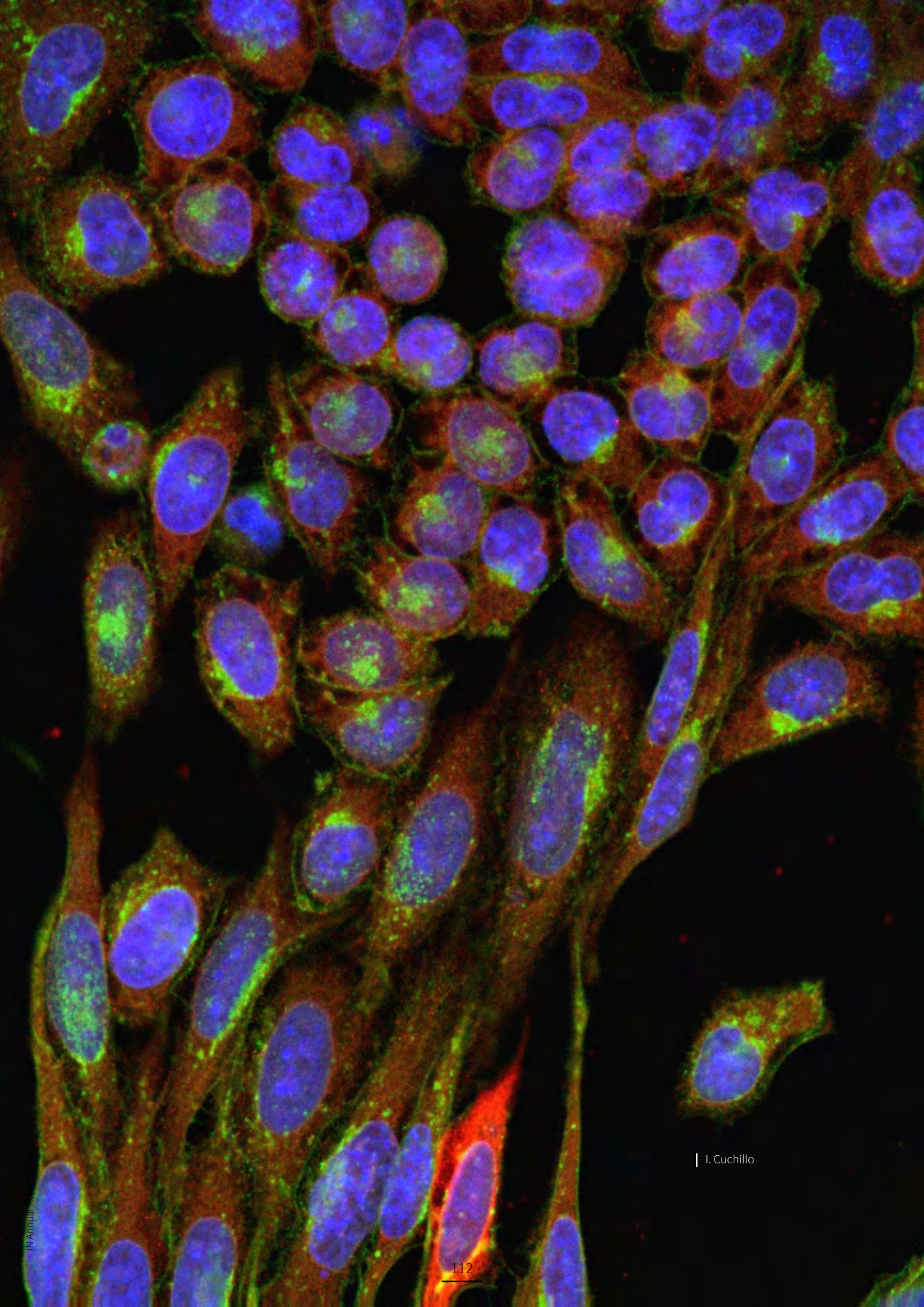
Dr. Rohini Kuner University of Heidelberg (Heidelberg, Germany) *Sumoylation in sensory neurons regulates neuropathy and pain.*

Dr. Albert Quintana Universitat Autònoma de Barcelona (UAB), Barcelona *Dissecting neuropathology in mitochondrial disease: one neuron at a time.*

Dr. Pierre Vanderhaeghen VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium *Remedios Caro Almela Lecture 2021 - Linking development and evolution of the human brain*

Dr. Tansu Celikel School of Psychology, Georgia Tech, Atlanta, US *Deconstructing the sense of touch.*

Dra. Francesca Bartolini Columbia University, New York, USA *Emerging Roles of the Microtubule Cytoskeleton in Synaptic Pathology and Axonal Degeneration.*



I. Cuchillo

PhD Theses

Chinnappa, Kaviya
Regulation of Cerebral Cortex Development and Expansion by MIR3607
Dr. Víctor Borrell Franco

Company Devesa, Verónica
New Insights into Development of the Habenular Complex and the Fasciculus Retroflexus
Dr. Eduardo De Puelles Martínez
Dr. Diego Echevarría Aza

Conde Dusman, María José
GluN3A-NMDA Receptors regulate protein synthesis by controlling the assembly of GIT1-mTORC1 complexes.
Dra. Isabel Pérez Otaño

Eed, Amr Fawzy Kamel
Functional and Structural Substrates of Increased Dosage OG Grik4 Gene Elucidated Using Multi-modal MRI.
Dr. Juan Lerma Gómez

García Asencio, Francisco
The Role of Prrx1 In Mouse Development and Vascular Biology
Dra. Ángela Nieto Toledano

García López, Lucía
Role of PI3K/AKT/PTEN in tumorigenesis: A link between inflammation and reprogramming of the host metabolism.
Dra. María Domínguez Castellano
Dr. Santiago Nahuel Villegas Nieto

Gasparyan, Ani
Efectos del Cannabidiol en un nuevo modelo animal de trastorno de estrés postraumático.
Dr. Jorge Manzanares Robles
Dr. Francisco Navarrete Rueda

González Iglesias, Ainara
Intron Detention As A Mechanism To Tightlly Control The Timing Of Neural Differentiation.
Dra. Ángela Nieto Toledano

Gupta, Saurabh
Hierarchy and Flexibility in Caenorhabditis Elegans Foraging.
Dr. Alejandro Gómez Marín

Herrero Navarro, Álvaro
Region Specific Glia-To-Neuron Reprogramming:A Step Forward To Neuroan Repair.
Dra. Guillermina López Bendito

Murillo Bartolomé, Álvaro
Effects of Glun3A silencing in Huntington's disease and systematic mapping of its expression in the mouse forebrain.
Dr. Isabel Pérez Otaño

Navarrón Izquierdo, Carmen
Transcriptional Regulatory Dynamics Underlying Neuroinflammation-Associated States of Microglia.
Dr. José Pascual López-Atalaya Martínez

Robles Picó, Rita Mariana
Local Circuits of the Mouse Granular Retrosplenia Cortex.
Dr. Salvador Martínez Pérez
Dr. Emilio Geijo Barrientos

Sáez García, María
The Impact Dopamine on Multisensory Information Processing in the Associative Striatum.
Dr. Ramón Reig García

Valiño Pérez, Arturo José
Divergence-Convergence ratios govern functional circuitry in the early visual pathway.
Dr. Luis Miguel Martínez Otero
Dr. Jorge Brotons Mas

Velasco Aviés, Sergio
Papel de las HDACs de la clase lla en la biología de las Células de Schwann.
Dr. Hugo Cabedo Martí

Annual Report 2021

INSTITUTO DE NEUROCIENCIAS
Consejo Superior de Investigaciones Científicas (CSIC)
Universidad Miguel Hernández (UMH)
http://in.umh-csic.es/

Av. Santiago Ramón y Cajal s/n
03550 San Juan de Alicante
Alicante

Diseño y maquetación: Sergio Javaloy Ballestero