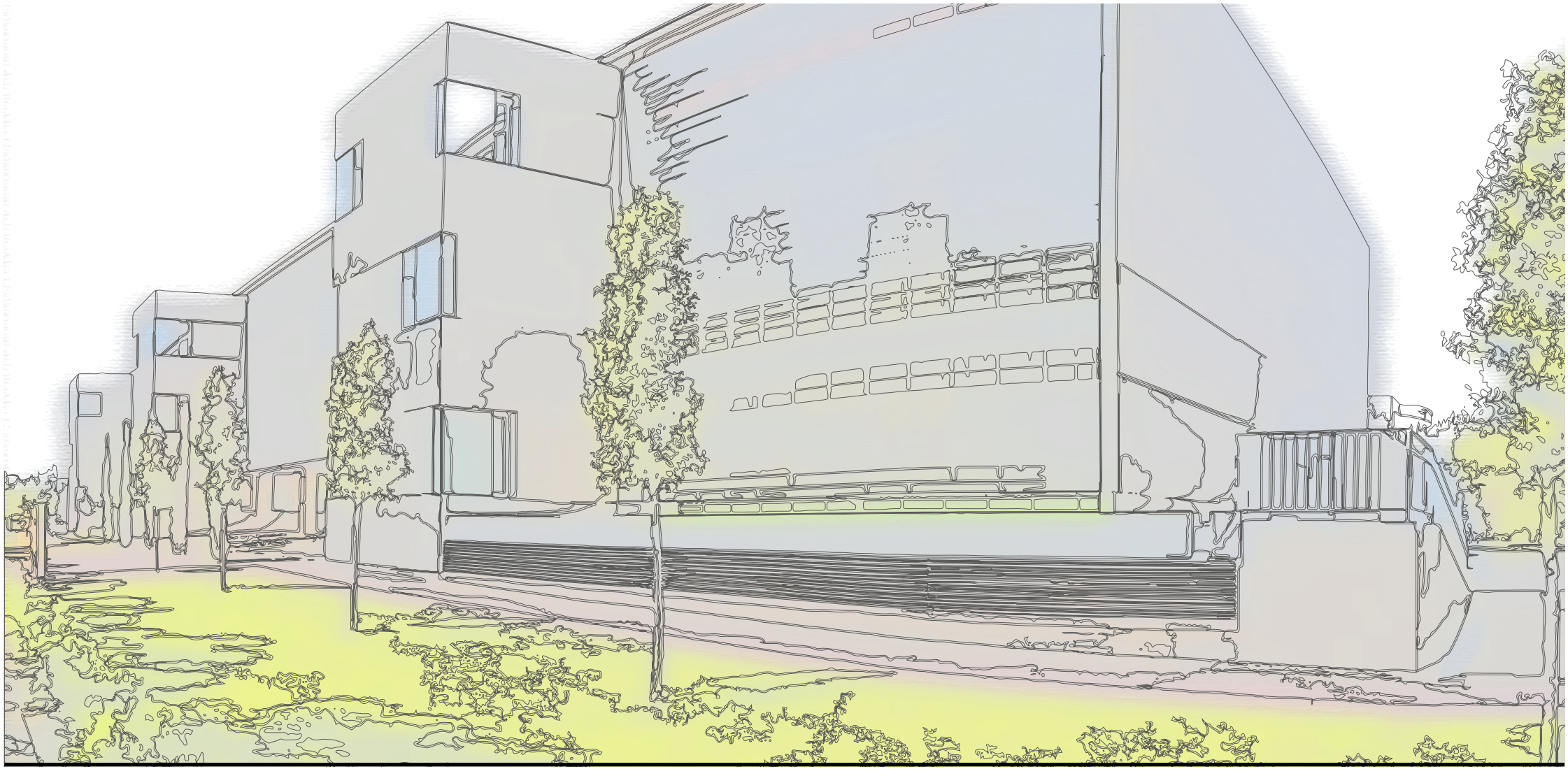
INSTITUTO DE NEUROCIENCIAS

ANNUAL REPORT 2016



EXCELENCIA
SEVERO
OCHOA

ANNUAL REPORT 2016

CSIC
Consejo Superior de Investigaciones Científicas

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

EXCELENCIA SEVERO OCHOA

Salutation

Salvador Martínez Pérez : Director

The year 2016 has been a year of institutional stabilization for the Institute of Neurosciences, which continues to maintain a good level of published work, project income and achievement of important scientific milestones. All this thanks to the effort of the staff of the Institute that with its scientific, technical and administrative competence allows us to reach the levels of excellence for which we are recognized nationally and internationally. Moreover, the high level of competitive funding, thanks to the scientific talent and quality of the projects of our research groups, allows us to maintain the quality of all services and research support units. Finally, the accreditation as a "Severo Ochoa Center of Excellence" (since July 2014), continues to allow us to undertake new initiatives and recruit talent researchers.

During 2016 there has been a relay in the Director of the Institute of Neurosciences. The professor of the UMH, Salvador Martínez was democratically elected by the Institute of Neurosciences Claustrum on January 21 and appointed Director on April 21. We thank to Juan Lerma, the Director of our center since 2007, his strong contribution to develop in a very significant way the scientific quality of the Institute. It should be noted that in September the Board of the Institute unanimously approved the Gold Medal of the Institute of Neuroscience to Juan Lerma. A scientific meeting was organized for the presentation on October 10, in which Miguel Maravall, Alfonso Araque and Oscar Herreras participated as speakers; and gave a more personal talks Ana Valero and Carlos Belmonte, expressing gratitude and friendship to Juan Lerma.

On December 16, 2015, the New Agreement between the CSIC and the UMH was signed for the regulation of the Institute of Neurosciences and the Institute's Internal Regulations were revised, which the actualize and renew the management bodies.

As a result of competitions of places of researchers of the CSIC for the Institute of Neurosciences we are going to incorporate three new scientists: Isabel Pérez Otaño as Research Professor, who comes from the CIMA of Navarra; Sandra Jurado as Titular Scientist, who comes from the University of Maryland; and Berta López Sánchez-Laorden also as Titular Scientist, and that was already in the IN as Contract Ramón y Cajal. Also, José López-Atalaya has obtained a Ramón y Cajal Contract.

The good road mapped out by Carlos Belmonte and Juan Lerma, both in stimulating quality research and the policy of scientific excellence as a principle for the incorporation of new researchers, has led our center to achieve high levels of scientific leadership and competitiveness international. With the new additions and the development of the professional career of the members of the IN, the talent of our researchers represents its outstanding value. Adequate development also depends on the good work done and the professionalism of the research support and administrative staff, which make the experimental work and the economic resources of the researchers more efficient.

On the other hand, the classification of the personnel indicates that we maintain a stable proportion of approximately 60% of women and 40% of men, and around 20% of our personnel come from other countries. Remarkably, more than 30% of our contracted researchers continue to have non-Spanish origin, which speaks of the degree of internationalization of our center.

Fulfilling the mission of IN to generate knowledge about the brain and its mechanisms, this last year the IN has made a number of relevant findings, a selection of which the reader can find in the specific section of this report.

In terms of productivity, this year there is an improvement over the previous year, although within a stability both in the number of articles and in the average impact factor (7.21 in 2016) of the journals in which they are published, and continue harvesting a good number of appointments.

In the past year, the IN has been the subject of a series of relevant actions. Several members of the IN have achieved significant recognition of their research work, congratulations to all. With this, the IN and its members continue to strengthen their national and international presence.

In 2016, IN groups have continued with some degree of expenditure containment, probably due to the erratic and disparate calls for projects in Spain. Logically, it is necessary to look for strategies that prevent the crisis of financing of science in Spain threatens the most fundamental structures of the Institute. The successful participation of several researchers in the calls for proposals of the European Research Council and other Horizon 2020 programs is the natural way out of the Spanish crisis. The sustained effort to incorporate to the Center the most modern techniques and technology that allow our researchers to carry out the most advanced experiments and to advance in the knowledge of the brain in equality with our European or American colleagues.

In the educational aspect the International Masters in Neuroscience of the IN and the UMH, has been partially coordinated with the Masters

of Developmental Neurobiology of the Pasteur Institute and the University Paris VI (Pierre et Marie Curie), giving 3 ECTS Exchange Credits. This has led to an important increase in the visibility and internationalization of Master's students. Also, this year Emilio Geijo has been appointed coordinator of the Master.

In 2016 we have continued to collaborate with the World Brain Week through the organization of various outreach events and open days that has allowed the Institute to visit more than 1,500 people, with UMH and RNE live radio and television broadcasts. We want to emphasize that the intimate knowledge of the brain will have significant repercussions in the construction of the society of the future and therefore, Neuroscience is called to modify the human attitudes and customs towards higher levels of well-being and adaptation to the new circumstance that confronts the humanity. In this task, I would like to thank once again all those who, through their commitment and effort, in one or another position throughout this year, have contributed to the IN mission by placing it at the scientific level in which it is located, and institutions to which we belong, CSIC and UMH, for the continuous support to our research activity.

Salvador Martínez
Director.

A Bit of History

In 1990 the Valencian Government formally recognised the Instituto de Neurociencias at the Universidad de Alicante as a University Institute formed by a group of its researchers that, since 1985, had been dedicated to the study of the structure and function of the nervous system. Moving beyond the typical university departmental structure, members of the new Institute began to share not only their ideas but also funding and resources in order to improve their research environment. At the same time a Ph.D. Programme was created to train young scientists in the field of neuroscience.

Five years later the Institute became an "Associated Unit" of the Instituto Cajal del Consejo Superior de Investigaciones Científicas (CSIC) that moved two of its research groups to Alicante. In 1996, the Institute along with the Faculty of Medicine was transferred to the newly created University Miguel Hernández of Elche (UMH). During this period the Institute was physically located in the Faculty of Medicine building on the San Juan Campus site.

The IN was formally made a Joint Centre of the UMH and CSIC in 2000. Since then the IN incorporated tenured scientific staff from the CSIC and host young researchers through the Ramon y Cajal Research Programme. The UMH initiated the construction of a new building specifically planned to house the IN in 2001. The work was completed with additional funding from the Health Department of the Valencian Government. Furniture and laboratory equipment was provided by the CSIC. Researchers finally moved into the new premises in 2004, whilst building was officially inaugurated on the 26th of September 2005 by Her Royal Majesty Queen Sofía of Spain.

Where We Are

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

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

What We Do

One of the greatest challenges facing today's science and society is to understand the brain and the biological basis for human behaviour, including functions as wide as language, consciousness, emotions, sensations or movement control. Psychiatric and neurodegenerative neurological illnesses represent a growing health problem and an important social burden in developed Western countries. Unfortunately there is still relatively little known about the causes of these illnesses and for this reason there is an increasing interest on the study of the nervous system.

The IN is a publicly funded centre dedicated to brain research in both normal and pathological conditions. This is achieved through a multidisciplinary approach towards the study of the structure, function and development of the nervous system at the molecular, cellular, and integrative levels. The Institute is organised into three research Departments: Developmental Neurobiology, Cellular and Systems Neurobiology and Molecular Neurobiology and Neuropathology. Each Department is formed by scientists that share general research interests and technical approaches.

There is a second level of organization based on research lines. These lines constitute a horizontal organisation grouping members of different research units around more specific research subjects. This horizontal-vertical structure facilitates greater interactions between institute members, through an understanding of the brain from different viewpoints, disciplines and techniques.

The IN undertakes an important training activity through its International PhD Programme in Neuroscience, which has been awarded with a mention as "Programme of Excellence" by the Ministry of Education. It also strives to be a centre

of reference in terms of both national and international collaborations between clinical and basic research groups from a wide range of disciplines.

During the Academic Year 2015-2015 we started the International Master in Neuroscience: from bench to bedside. This is a one year course totalling 60 ECTS on both basic and advanced aspects of neuroscience offered in several courses by University and CSIC lecturers, in collaboration to Developmental Biology Master of the Instituto Pasteur and the University Paris VI (Pierre et Marie Curie).

The years following the relocation of the IN to its new building have seen an important period of expansion, resulting in the IN becoming the largest Spanish institute monographically dedicated to the study of the nervous system and its pathologies. The significant increase in personnel has been in both young to senior researchers, several of them of recognized international prestige. The IN currently has 35 tenured researchers (20 from the UMH and 17 from the CSIC), 10 non-tenure scientists, 217 doctoral and postdoctoral researchers and 95 technical and administrative staff (See graphic IN in Numbers: Personnel).

IN scientists have achieved both national and international recognition, as judged by their participation in diverse national and international programmes, and their success in obtaining funding and awards. The number and quality of publications generated not only for the preceding period, but in 2012-2015 place the IN as one of the highest-ranking research centres in Spain with a competitive level in Europe (See graphic Impact Factors and Budget growth).

Where We Are Going

In 2010, the IN implemented its second Strategic Plan, which at the request of the CSIC was elaborated in 2009. The previous Plan shaped the IN along the last five years (2005-2009). The second outlines the guidelines for consolidation, with the clear goal of becoming a center of excellence in the European Research Area. The 3rd Action Plan, started in 2014, reaffirmed the IN's pursuit of excellence, and its intention to strengthen and specify some of lines of research aimed at studying the nervous system. We moved towards multi-disciplinary approaches and strengthen research around to pathologies of the nervous system. This is being carried out by incorporating appropriate technology and the pursuit of partnerships with hospitals and agents of the health system. The incorporation of cutting-edge technology platforms, such as imaging techniques aimed at studying and exploring the brain, is another goal of IN. The institute has an international vocation and continues to seek the incorporation of leading scientists from all countries and intensive collaboration with other research centers, particularly in Europe. The increase of our international docent offer, initiated with our Master, and the interaction with technological institutes to stimulate innovation platforms, are two lines of work to drive new challenges in the Plan of Action of the IN of 2017.

Most Relevant Scientific Milestones

- We have described a critical mechanism for the initial formation of the External Subventricular Zone (OSVZ) during the embryonic development of the mammalian cerebral cortex. For as little as 2 days, apical Radial Glia cells produce a lot of Radial Glial basal, which are the founding cells of the OSVZ. This process is dependent on a transient decrease in the function of the Cdh1 and Trnp1 genes. (Martinez-Martinez et al., **Nature Comm**. 7: 11812, 2016).

- We have described the ability of the most peripheral area of the eye to generate ganglion cells. (Marcucci et al., **Cell Reports** 17: 3153-3164, 2016).

- We have shown that a group of neurons that are part of the accessory olfactory bulb and are essential for proper processing of the olfactory function originate in the thalamic lateral eminence. (Ruiz-Reig et al., **Cerebral Cortex,** 2016. Epub ahead of print).

- We have shown that interfering with the biogenesis of microRNAs disrupts homeostatic mechanisms that protect neurons from overactivation,thereby revealing a new role for the microRNA system in the regulation of neuronal response thresholds. (Fiorenza et al., **Cerebral Cortex** 26: 1619-33, 2016).

- We have described the role of kainate synaptic receptor helper proteins in the receptor synaptic localization. (Palacios-Filardo et al., **Cerebral Cortex,** 6: 1464-1472, 2016).

- We have described that Presenilin-1 (PS1) can be detected in cerebrospinal fluid, in the form of aggregates or complexes, as diagnostic biomarkers for Alzheimer's disease (AD). (Sogorb-Esteve et al., **Mol Neurodegener** 29: 11: 66, 2016).

- We have outlined the paradoxical effects of deep brain stimulation (DBS) of the nucleus accumbens for treatment of alcoholism combining behavioral, pharmacological and brain imaging studies. (Hadar et al., **Transl Psychiatry** 6: 840, 2016).

- We have described the mechanism of increased activity in cold sensitive neurons in a dry eye model, due to altered expression of partner and potassium channels in the corneal terminals. (Kovács et al., **Pain,** 157: 399-417, 2016).

- We have described the role of Minibrain (DYRK1A) in regulating the neurogenesis process by controlling mechanisms involved in cell cycle and neural differentiation. (Shaikh et al., **Development,** 143: 3195-3205, 2016).

- We have shown that the Piezo2 ion channel is the main transducer channel in proprioception. Essential function in the balance, coordination of movements and position of the extremities. (Florez-Paz et al., **Scientific Reports** 6: 25923, 2016).

- We have shown in human brain extracts the interaction of Aβ oligomers with Reelin. Reelin levels are higher in the brains of AD subjects, but their biological function seems to be affected by Aβ. (Cuchillo-Ibanez et al., **Scientific Reports,** 17: 6: 31646, 2016).

- We have described the contribution of histone hypoacetylation to the neuropathology caused by polyglutamines through the biochemical and molecular characterization of several animal and cellular models of Huntington's disease. (Guiretti et al., **Neurobiol Dis** 89: 190-201, 2016).

- We have demonstrated the ability of bone marrow-derived mesenchymal cells to induce myelin regeneration in an experimental model of chronic demyelination. (Cruz-Martinez et al., **Cell Death Dis.** May 12, 7: e2223, 2016).

Main review work:

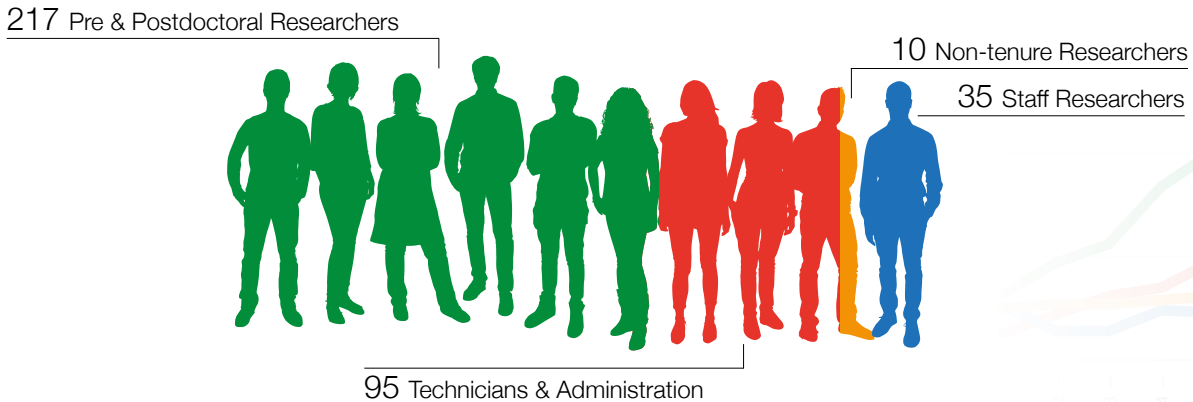
- Nieto et al., **Cell.** 166: 21-45. 2016.

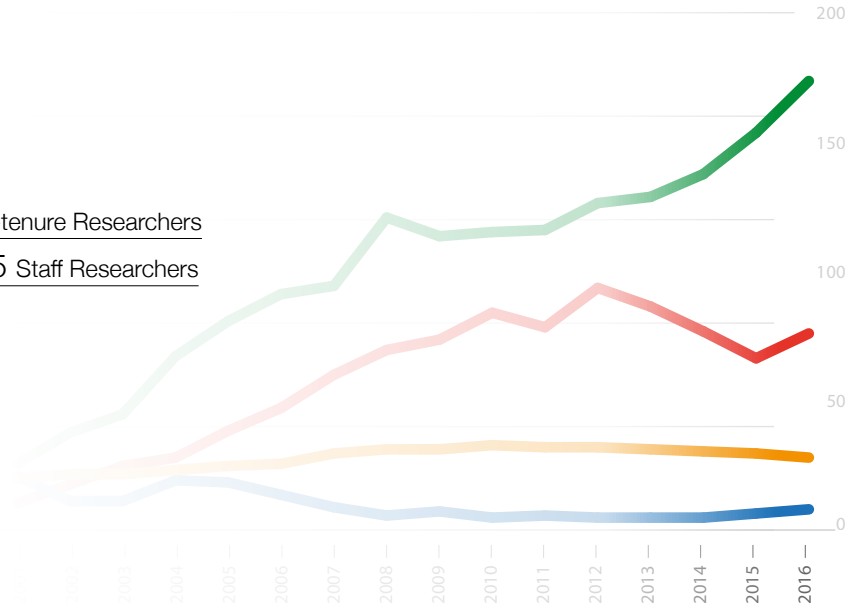
- Valbuena and Lerma, **Neuron.** 92: 216-329. 2016.

- Meunier and Gutierrez, **TINS.** 39: 605-613. 2016.

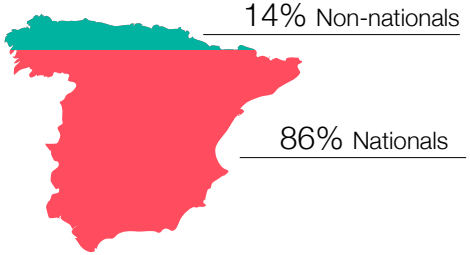
The Institute in Numbers

Personnel by Category

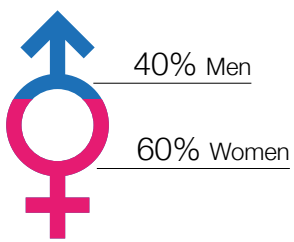




by Origin

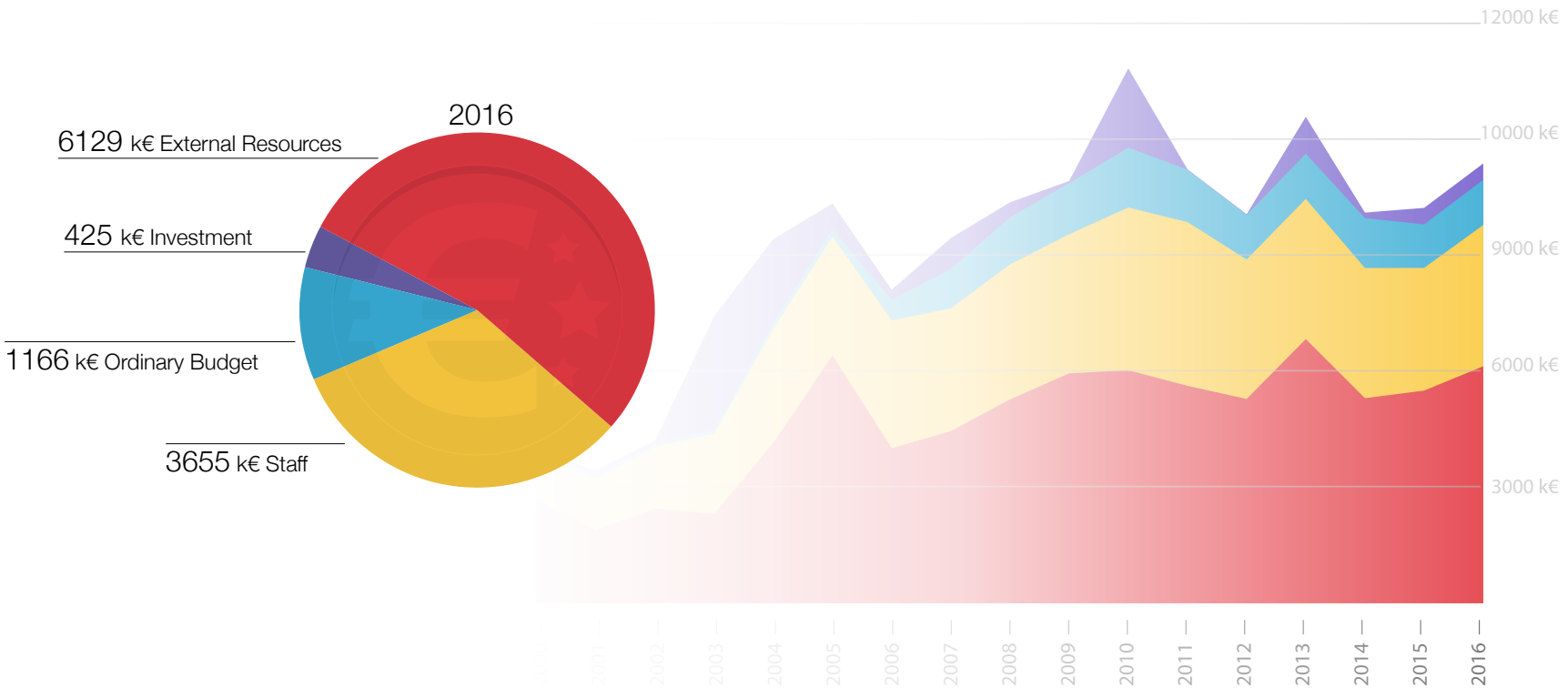


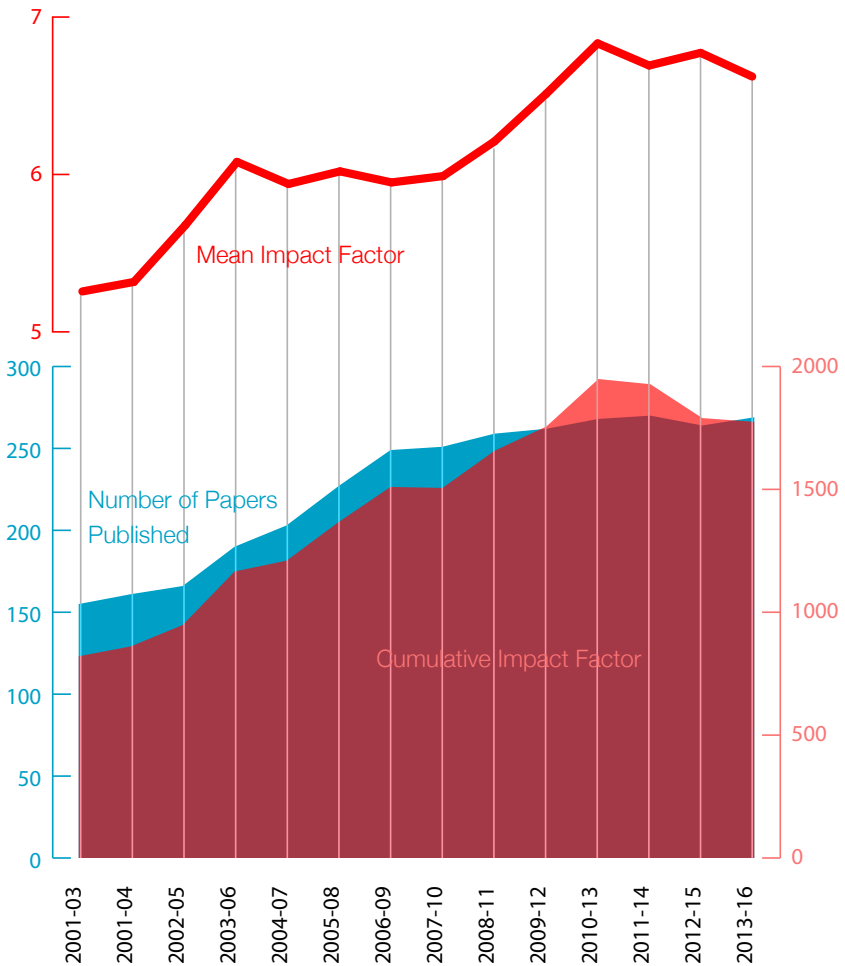
by Gender

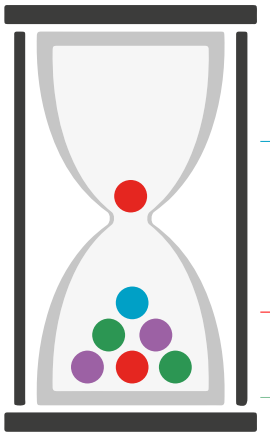


The Institute in Numbers

Budget Growth in Thousands of Euros







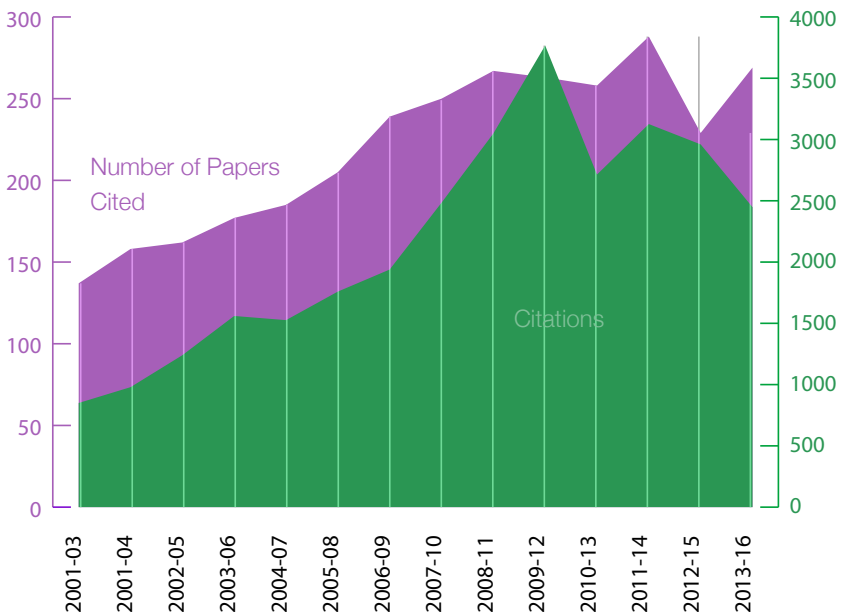
269 Papers Published

6,62 Mean Impact Factor

2448 Citations

for the period 2013-2016

Q&A Pending for Julio:
Number of Papers Published different to cited IMHO



Research Units

Cellular & Systems Neurobiology

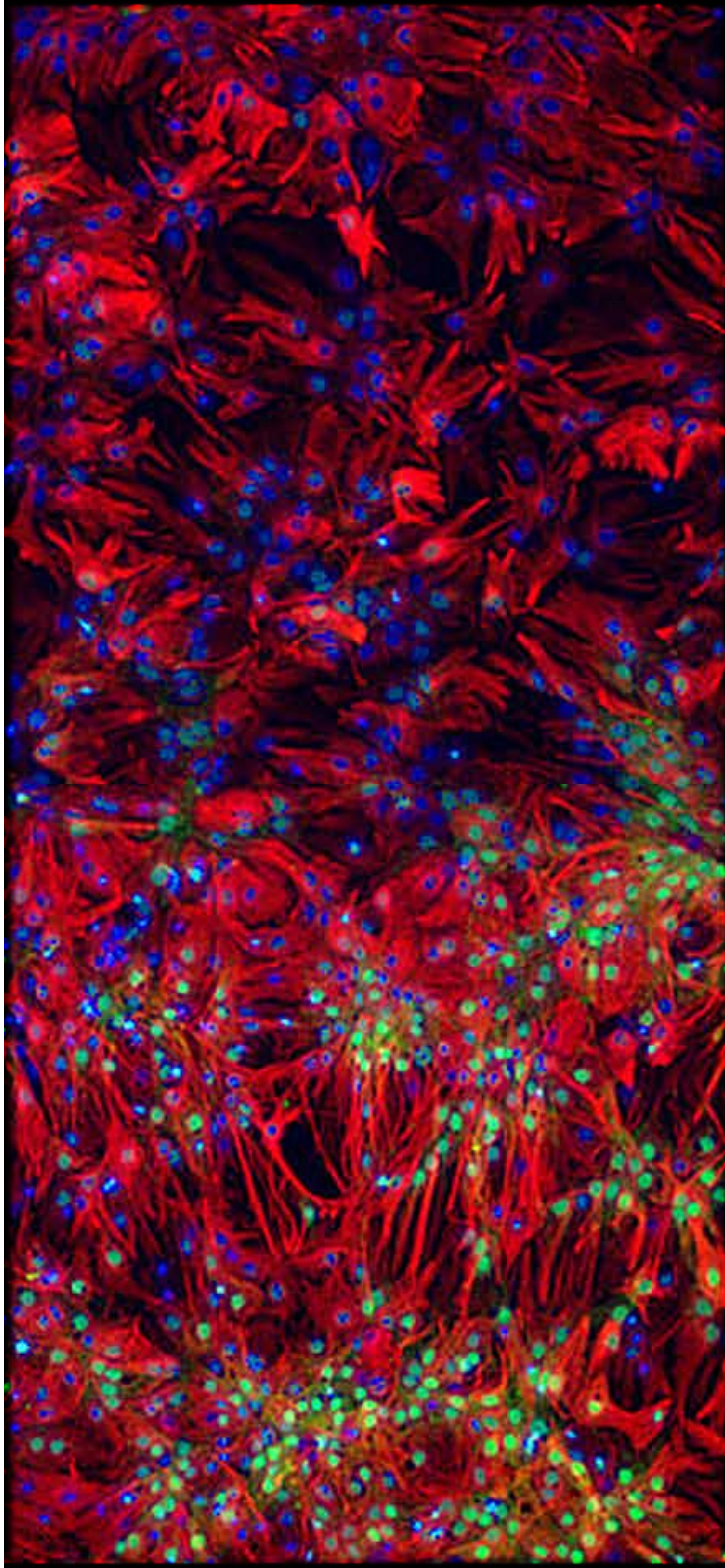
The Cellular and Systems Neurobiology Unit consists of nine groups whose research focuses on the function of the cerebral cortex and several sensory systems, primarily using electrophysiological, computational and imaging approaches.

Developmental Neurobiology

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

Molecular Neurobiology

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



Research Lines

Morphogenesis

The morphogenesis of the central and peripheral nervous system requires that progenitor cells make the correct decisions as to whether proliferate, differentiate, move or die. The genes and mechanisms that regulate and coordinate these decisions are the main emphasis of the sublines that this research line encompasses.

Synaptic Transmission & Plasticity

The study of synaptic transmission and synaptic plasticity is considered a key to understanding the function of the nervous system. Sublines within this line address the study of neurotransmitters receptor proteins, including glutamate and nicotinic receptors, the cellular and molecular mechanisms controlling the development of neural wiring as well as the genetic programs activated by neuronal activity, required to maintain long-lasting changes in synaptic plasticity and memory.

Sensory Transduction

This research line is devoted to study the cellular and molecular basis of the transduction and encoding of thermal, mechanical and chemical stimuli in the somatosensory system of mammals. We are particularly interested in the role played by different classes of ion channels in modulating the excitability of primary sensory neurons and their relevance to the pathophysiology of neuropathic and inflammatory pain. In addition, we have a keen interest in peripheral and central mechanisms of thermoregulation.

Neuronal Migration & Circuit Assembly in the Cerebral Cortex

The neural assembly underlying the formation of functional networks in the cerebral cortex arises during development through the interaction of two distinct neuronal types, glutamatergic projection neurons and GABAergic interneurons. Our research largely concentrates on the analysis of the mechanisms controlling the the migration, final allocation and connectivity of the different classes of cortical neurons.

Nervous System Pathology

This line of research arises from the necessity to have a more direct understanding of central nervous system development and neurodevelopmental related diseases. It fulfils one of the objectives of the IN: to contribute to solving neurological diseases. Therefore the conducting nexus of this research line is the experimental emphasis in the pathology and physiopathology of nervous system.

Systems Neurobiology

Systems neurobiology benefits from the combination of latest-generation computational, molecular and imaging techniques. Research in this line examines the architecture of neuronal circuits in order to address the structural and functional underpinnings of perception and behaviour.

Research Groups

Involvement of nicotinic acetylcholine receptors in chronic kidney disease
Juan J. Ballesta UMH

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders
Angel Barco CSIC

Neurogenesis & cortical expansion
Víctor Borrell CSIC

Molecular control of axonal myelination
Hugo Cabedo UMH

Plasticity of brain networks
Santiago Canals Gamoneda CSIC

Signaling networks underlying asymmetric cell division
Ana Carmena CSIC

Molecular neurobiology of neuronal nicotinic receptors
Manuel Criado UMH

Cellular & conductual neuroscience
Carmen de Felipe UMH

Mechanisms of growth control & cancer in Drosophila
María Domínguez CSIC

Neurobiology & neuromodulation of the opioid actions
Clara C. Faura Giner UMH

Ocular Neurobiology
Juana Gallar UMH
Mª Carmen Acosta UMH

Developmental Neurogenetics
Luis García-Alonso CSIC

Physiology of the cerebral cortex
Emilio Geijo UMH

Mechanotransduction in mammals
Ana Gomis CSIC

Behavior of Organisms
Alex Gomez-Marin CSIC

Molecular mechanisms of neurosecretion
Luis M. Gutiérrez UMH
Salvador Viniegra UMH

Development & assembly of bilateral neural circuits
Eloísa Herrera CSIC

Synaptic physiology
Juan Lerma CSIC

Cellular Plasticity & Neuropathology
José P. López-Atalaya CSIC

Cellular & molecular mechanisms of brain wiring
Guillermina López-Bendito CSIC

Translational neuropsychopharmacology of neurological and psychiatric diseases
Jorge Manzanares UMH

Neural Circuits of Social Behaviour
Cristina Márquez Vega UMH

Experimental Embryology
Salvador Martínez UMH
Constantino Sotelo UMH

Visual Neuroscience Laboratory
Luis M. Martínez CSIC

Early neurogenesis & brain maturation
Javier Morante CSIC

Cell movements in development & disease
M. Angela Nieto CSIC

Sensory-motor processing by subcortical areas
Ramón Reig García CSIC

Altered molecular mechanism in Alzheimer's disease & dementia
Javier Sáez Valero UMH

Molecular neurogenetics
Francisco Tejedor CSIC

Sensory transduction and nociception
Félix Viana CSIC
Carlos Belmonte UMH

Involvement of nicotinic acetylcholine receptors in chronic kidney disease

Juan J. Ballesta UMH

Neuronal nicotinic receptors (nAChR) are a heterologous class of cationic channels present throughout the CNS, muscle and non-neuronal tissues. Neuronal nicotinic receptors are involved in cognitive functions such as learning and memory, attention and executive function. Moderate to severe cognitive impairment is highly prevalent in chronic kidney disease (CKD) and end stage renal disease (ESRD) patients. Cognitive domains relevant for daily function are deteriorated in these patients. Nevertheless, presently there is no treatment of cognitive impairment in CKD and ESRD patients. Uremic myopathy is a common alteration in patients with ESRD. However, the pathogenesis of uremic myopathy remains

unclear. Uremia is also associated with sensory and motor polyneuropathy. Neuromuscular transmission occurs when acetylcholine from the nerve ending is released and binds to muscle-type nAChRs on the postjunctional muscle membrane. The nAChRs respond by opening channels for the influx of Na^+ ions and subsequent endplate depolarisation leads to muscle contraction. The cholinergic antiinflammatory pathway is a physiological mechanism that modulates host inflammatory responses by stimulating the vagus nerve. The CAP acts via α7 nAChRs.

In this context we are involved in the study of the role of nAChRs in: (1) the cognitive impairment of CKD, (2) the uremic myopathy and neuropathy, and (3) the pathogenesis of CKD.

Principal Investigator

Juan J. Ballesta

Clinical Collaborator

Carlos del Pozo

Ballesta, J.J., Cremades, J., Rodriguez-Muñoz, M., Garzón, J., Faura, C.C. (2012) **Sensitivity to μ Opioid Receptor Mediated Antinociception is Determined by Cross–regulation Between μ and δ Opioid Receptors at Supraspinal level** **British Journal of Pharmacology** *166: 309-326*

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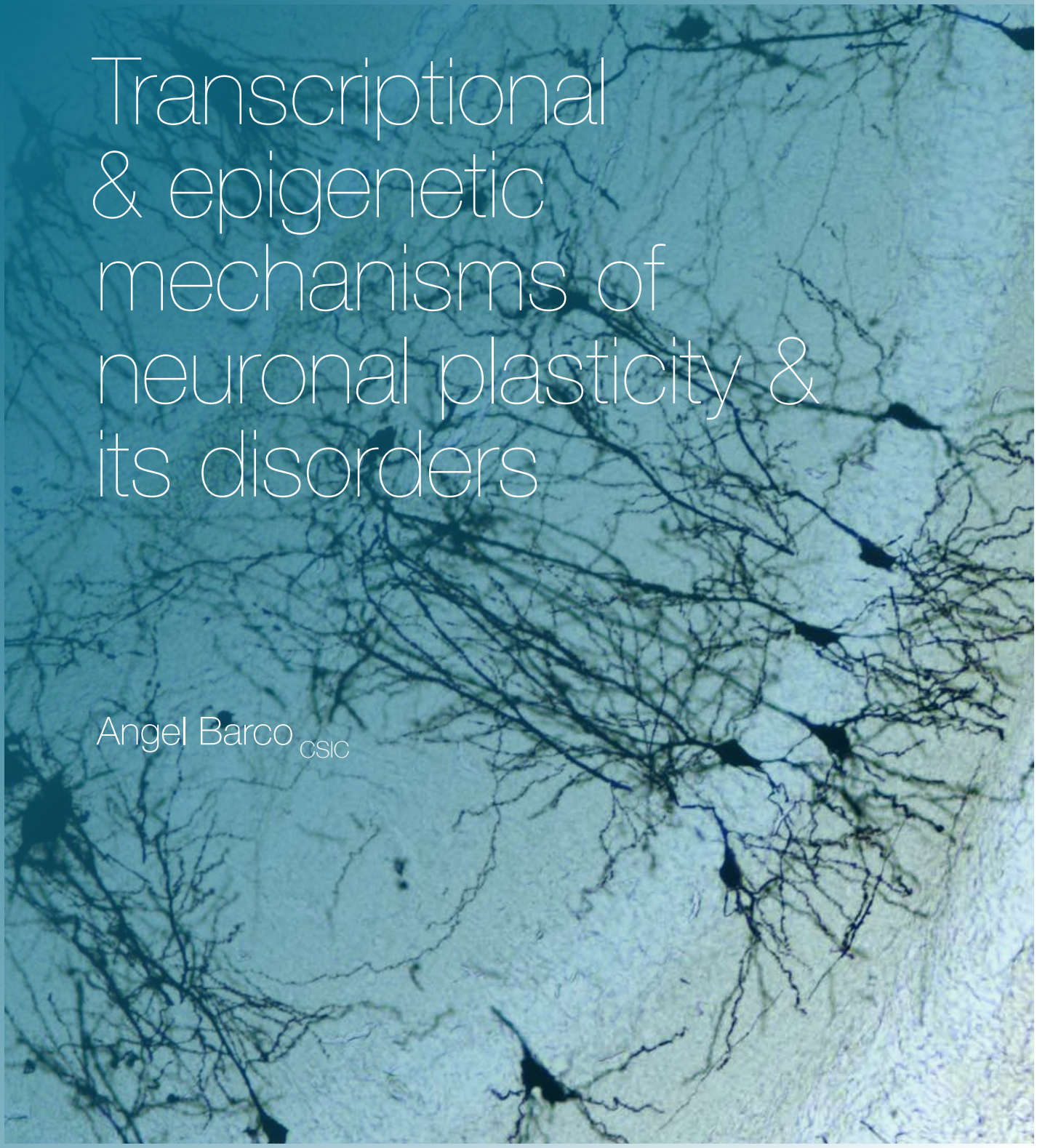

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Angel Barco CSIC

Our research focuses on the molecular bases of neuronal plasticity, learning and memory, and other long-lasting modifications of the animal's behavior. More precisely, we are investigating the role of specific transcription and epigenetic factors in these processes. We also aim to determine how the malfunction of epigenetic mechanisms leads to different pathological situations in the nervous system. To tackle these questions, we use a multidisciplinary approach that combines mouse genetics, genomics, behavioral and electrophysiological analyses and molecular and cellular biology techniques. From the methodological point of view, we are particularly interested in the application of genomic profiling techniques based on next generation sequencing (NGS) and epigenetic editing approaches in the nervous system.

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

We currently work on two main lines of research:

- Interplay of transcriptional and epigenetic mechanisms in activity-dependent transcription: Alterations in the patterns of neuronal gene expression are thought to underlie the long-lasting changes in the strength of synaptic connections responsible for the encoding of memories in the nervous system. We are investigating the participation of specific activity-regulated transcription factors, such as CREB and SRF, and epigenetic enzymes, such as CBP and p300, in this process. We are also interested in determining the role of the covalent modification of chromatin in neuroplasticity.

- Contribution of epigenetic mechanisms to intellectual disability (ID) disorders: We investigatethe contribution of epigenetic mechanisms, such as histone acetylation and methylation, to the pathoetiology of different neurological conditions associated with cognitive impairments and autism, including Rubinstein-Taybi syndrome and X-linked intellectual disability. Towards this end, we generate and characterize mouse models for these conditions, explore the molecular causes of the disease and tackle new therapies.

Principal Investigator

Angel Barco

PhD Investigators

Beatriz del Blanco
Romana Tomasoni

PhD Students

Jordi Fernández-Albert
Deisy Guiretti
Michal Lipinski
Alejandro Medrano-Fernández
Marilyn Scandaglia

Technical Staff

Román Olivares
María Teresa López Cascales
Nuria Cascales Picó

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Fiorenza A, Lopez-Atalaya JP, Rovira V, Geijo-Barrientos E and Barco A. (2016) **Blocking miRNA biogenesis in adult forebrain neurons enhances seizure susceptibility, fear memory and food intake by increasing neuronal responsiveness.** **Cereb Cortex** *26(4):1619-33*

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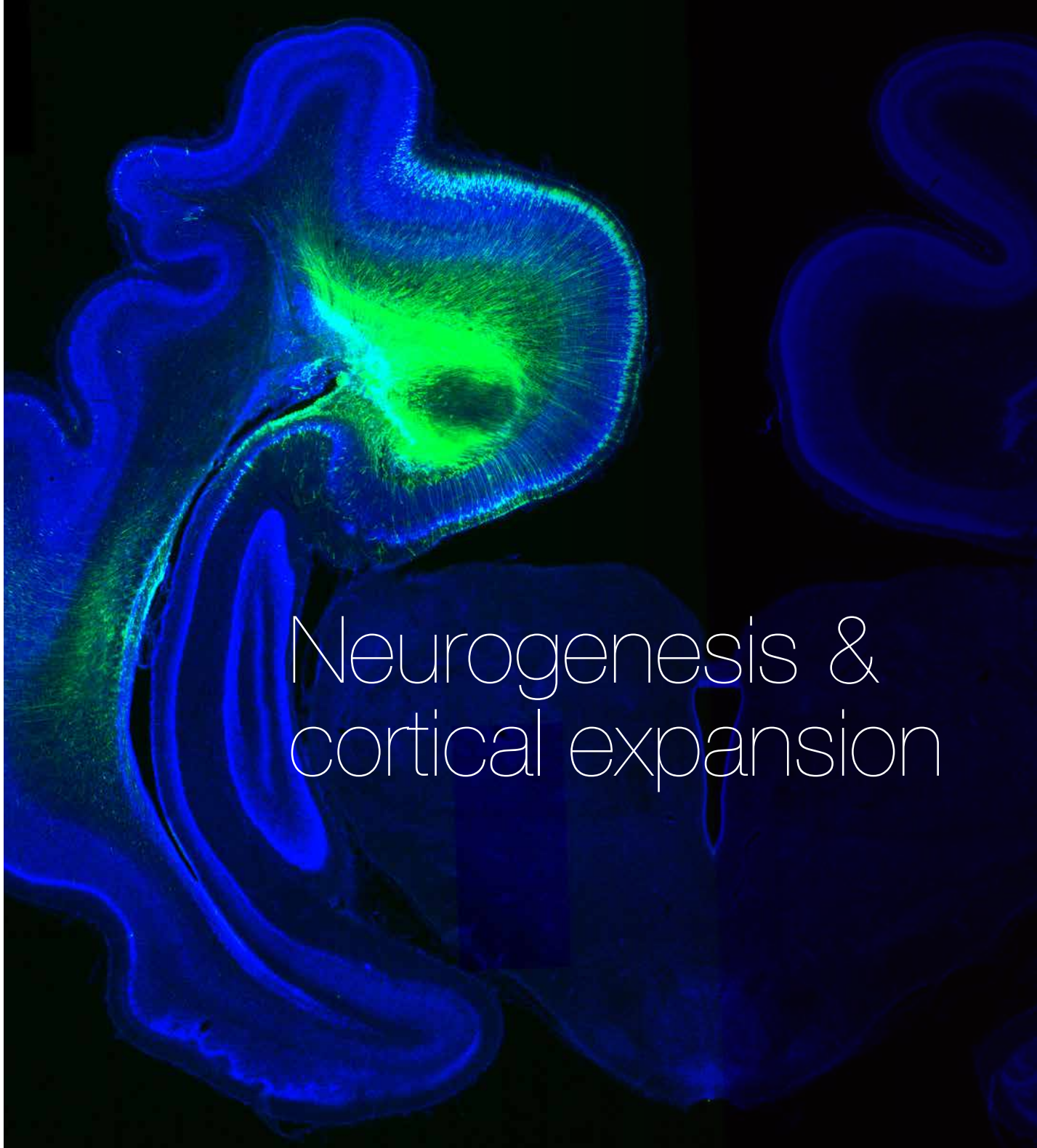
Víctor Borrell CSIC

Our laboratory is interested in understanding the cellular and molecular mechanisms governing the expansion 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.



Neurogenesis & cortical expansion

Neurogenesis & cortical expansion

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

We are interested in the identification and understanding of the cellular and molecular mechanisms involved in the expansion and folding of the mammalian cerebral cortex in health and disease. To study this we combine genetic tools (in vitro and in vivo electroporation, viral vectors, transgenic and knock-out mice), experimental embryology, state-of-the-art imaging techniques and standard histological, cellular and molecular biology methods, using various species as experimental models. Currently, our efforts are focused on understanding the role played by distinct types of progenitor and stem cells in the tangential vs. radial expansion of the cerebral cortex, and the genetic and molecular mechanisms regulating this process.

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Neurogenesis & cortical expansion

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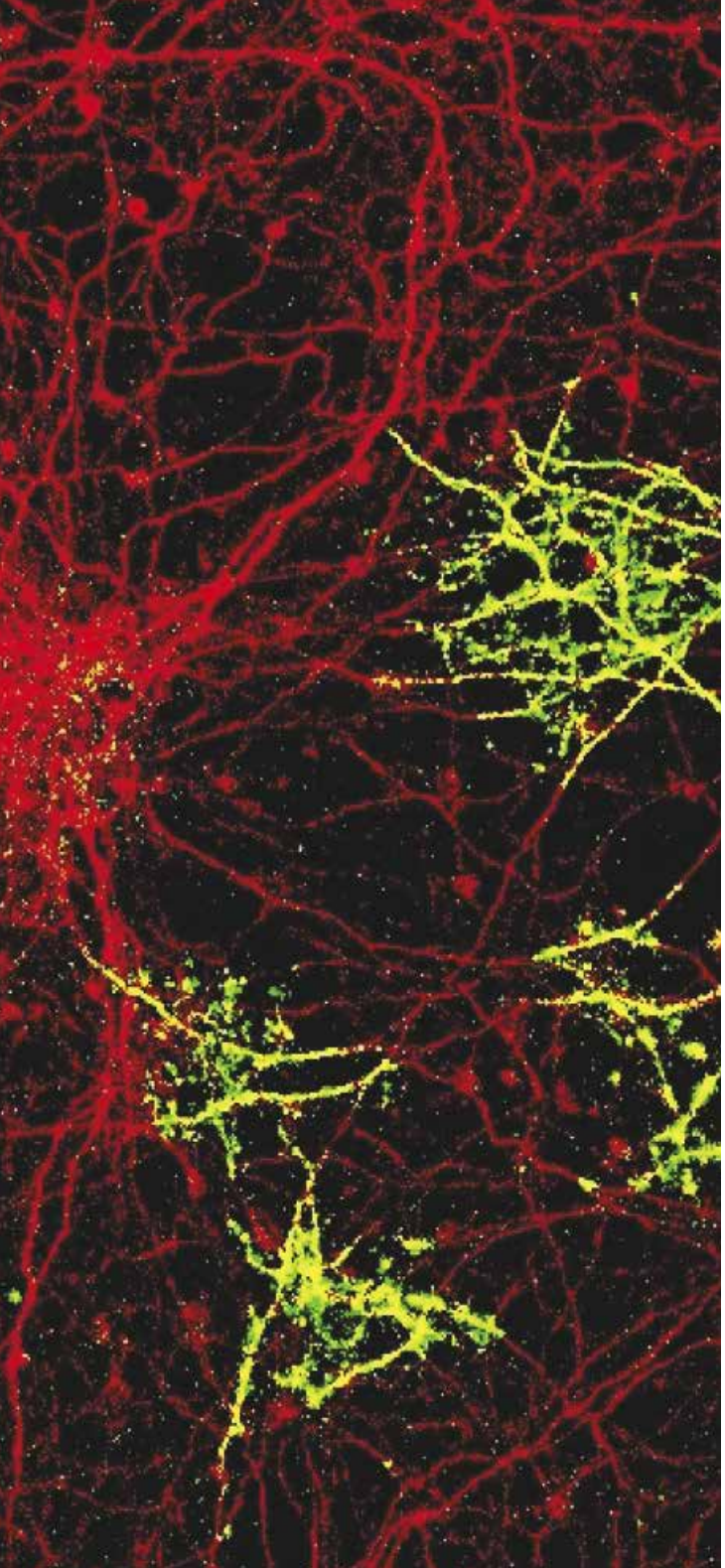

Molecular control of axonal myelination

Hugo Cabedo UMH

Nerve conduction velocity is inversely proportional to the electrical resistance of the axon and the capacitance of the plasma membrane that surrounds it. To increase nerve impulse velocity some invertebrates (such as squid) decreases resistance of the axon by greatly increasing its diameter. In more complex nervous systems, like higher vertebrates, this would increase by more than a hundred times the volume of the nervous system. To increase nerve conduction velocity without changing the axonal diameter (and nervous system volume) it is necessary to reduce the capacitance by increasing the thickness of the lipid membrane surrounding the axon. This has been achieved in vertebrates by depositing large amounts of plasma membrane of specialized hypertrophied neighboring cells (oligodendrocytes or Schwann cells). Rudolf Virchow first described this membrane, known as “myelin”, in 1854. Recently it has been established that the decision whether or not an axon is "myelinated" as well as the thickness of the myelin sheath depends on the axonal levels of a particular type of protein of the family of “neuregulins”.

Molecular control of axonal myelination

In our group we try to elucidate the molecular mechanisms controlling the axonal myelination. Our goal is to use this information to develop new strategies in the treatment of demyelinating diseases such as multiple sclerosis or Canavan disease in the central nervous system, and Charcot-Marie-Tooth in the peripheral nervous system. We also use this information to try to improve nerve regeneration after traumatic injuries. In order to achieve our goals we use state-of-the-art technologies such us Next-Generation Sequencing of patient's DNA and genetic modification of mice using both conventional and the CRISPR/CAS9 technology.

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Molecular control of axonal myelination

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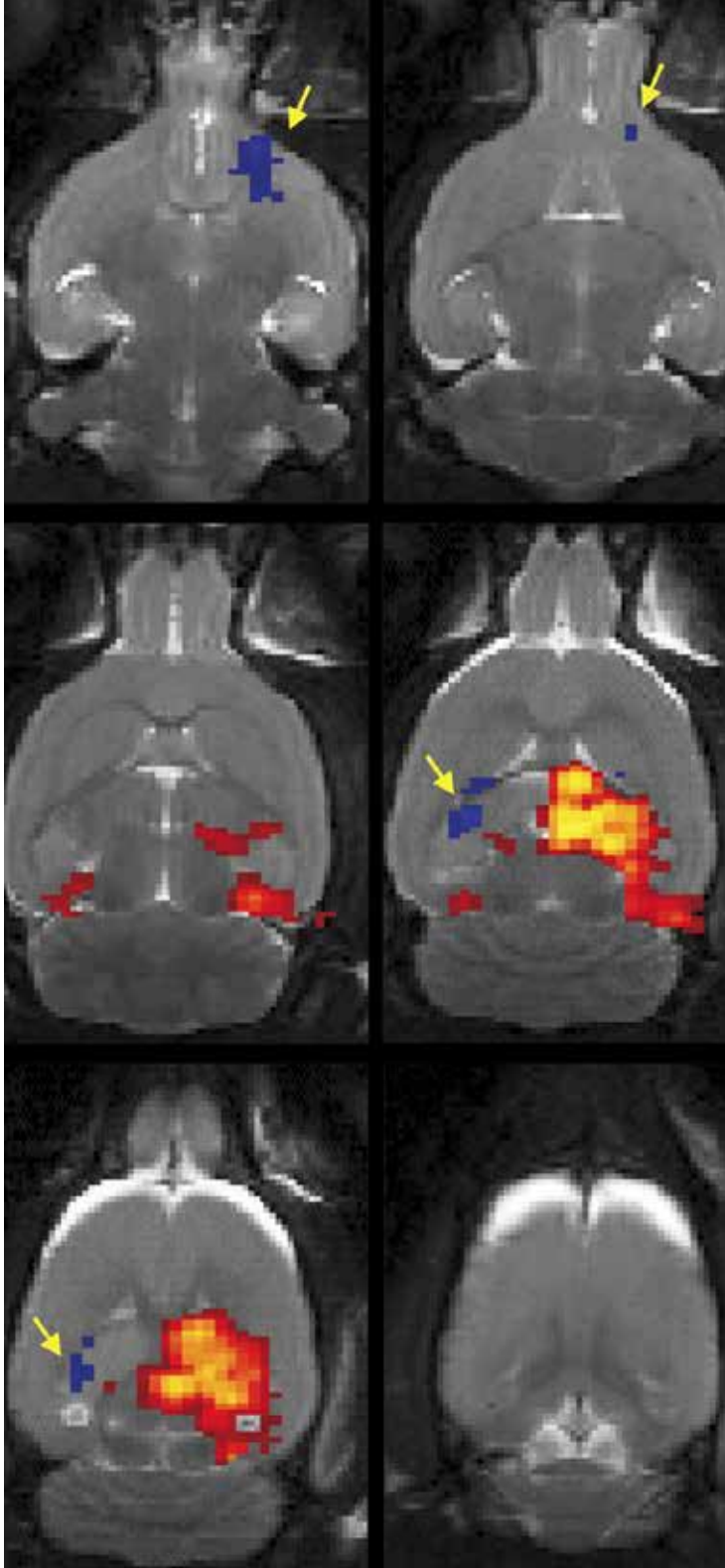
Plasticity of brain networks

Santiago Canals Gamoneda CSIC

The work of our group focuses on two research lines: plasticity of brain networks and brain energetics.

How are memories encoded, stored and retrieved in our brains? Experience-dependent modulations of synaptic strength shape the functional structure of the brain, recruiting relevant networks in a particular context and supporting behavioural adaptation. Little is known, however, about how synapse dynamics are transformed into network dynamics. Recently we have demonstrated that brain circuits involved in learning and memory are functionally reorganized after local potentiation of synaptic transmission in the hippocampus. In our present project we aim at investigating the mechanisms underlying this network reorganization, focusing on short- and long-term synaptic plasticity and neuromodulation. To this end we combine functional magnetic resonance imaging (fMRI) with electrophysiological techniques and deep brain microstimulation, in murine models of learning and memory.

The same cellular mechanisms that mediate



experience-dependent neuroplasticity and allow learning from, and react to, changes in the environment can also be activated by drugs of abuse. Human and animal studies indicate that the refractory nature of addiction results from drug-induced stimulation of reward-related learning networks. As a consequence, drug seeking behaviour becomes hard-wired in the addict's brain. By applying the same multidisciplinary approach, we are investigating the functional reorganization of brain networks supporting addiction and relapse.

In the second research line we aim at investigating the neurometabolic and neurovascular coupling mechanisms that sustain brain function. Here our interest is twofold; we want to understand the metabolic energy requirement of neuronal signalling and its impact on brain physiology (efficient coding strategies) and pathology (i.e. stroke, anoxia, concussion). On the other hand, we want to know the precise and quantitative neurophysiologic basis of the blood-oxygen-level-dependent (BOLD) signal to improve the interpretation of fMRI data.

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Plasticity of brain networks

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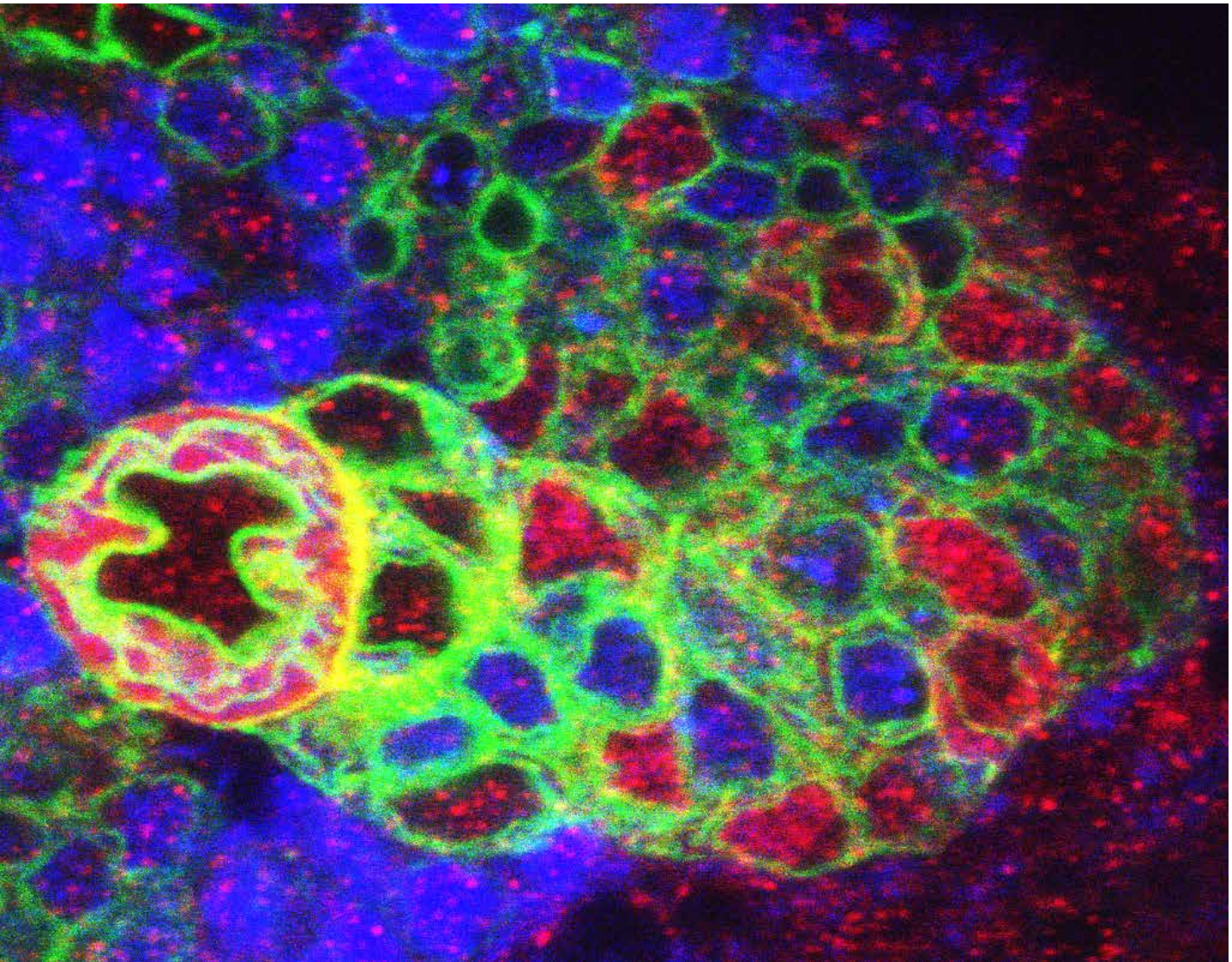
Signaling networks underlying asymmetric cell division

Ana Carmena CSIC



One of the big challenges in Developmental Neurobiology is to understand how the immense variety of neural types that constitute the nervous system is generated. Asymmetric cell division is a universal and key mechanism to generate cellular diversity during Development, and it is also an important process in Cancer and Stem Cell Biology. Our lab is currently focused on analyzing in depth this process. Specifically, we are interested in studying and contributing to

answering three fundamental questions in the field:

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

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

- Which are the connections between asymmetric cell division and tumorogenesis? Our model system are the type II neuroblasts of the Drosophila larval brain

The Approach: Today it has become apparent that signal transduction pathways are not mere linear cascades. Conversely, they are organized into complex signaling networks. The aim of our research is to unveil the functional signaling networks underlying the autonomous and non-autonomous mechanisms that regulate asymmetric cell division. In this context, we consider PDZ (*P*SD-95, Dlg, ZO-1) domain-containing proteins are excellent candidates as hubs of cross-talk between signaling pathways. Hence, we analyze the function of PDZ proteins, including the protein Canoe/AF-6, as signal integrators within signaling networks during asymmetric cell division. We achieve our research integrating Genetic, Cell Biology, Biochemistry, Molecular Biology and Proteomic techniques.

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Signaling networks underlying asymmetric cell division

Keder, A. Rives-Quinto, N. Aerne, B., Franco, M., Tapon, N. and Carmena, A. (2015) The Hippo Pathway Core Cassette Regulates Asymmetric Cell Division **Current Biology** *25, 2739-2750*

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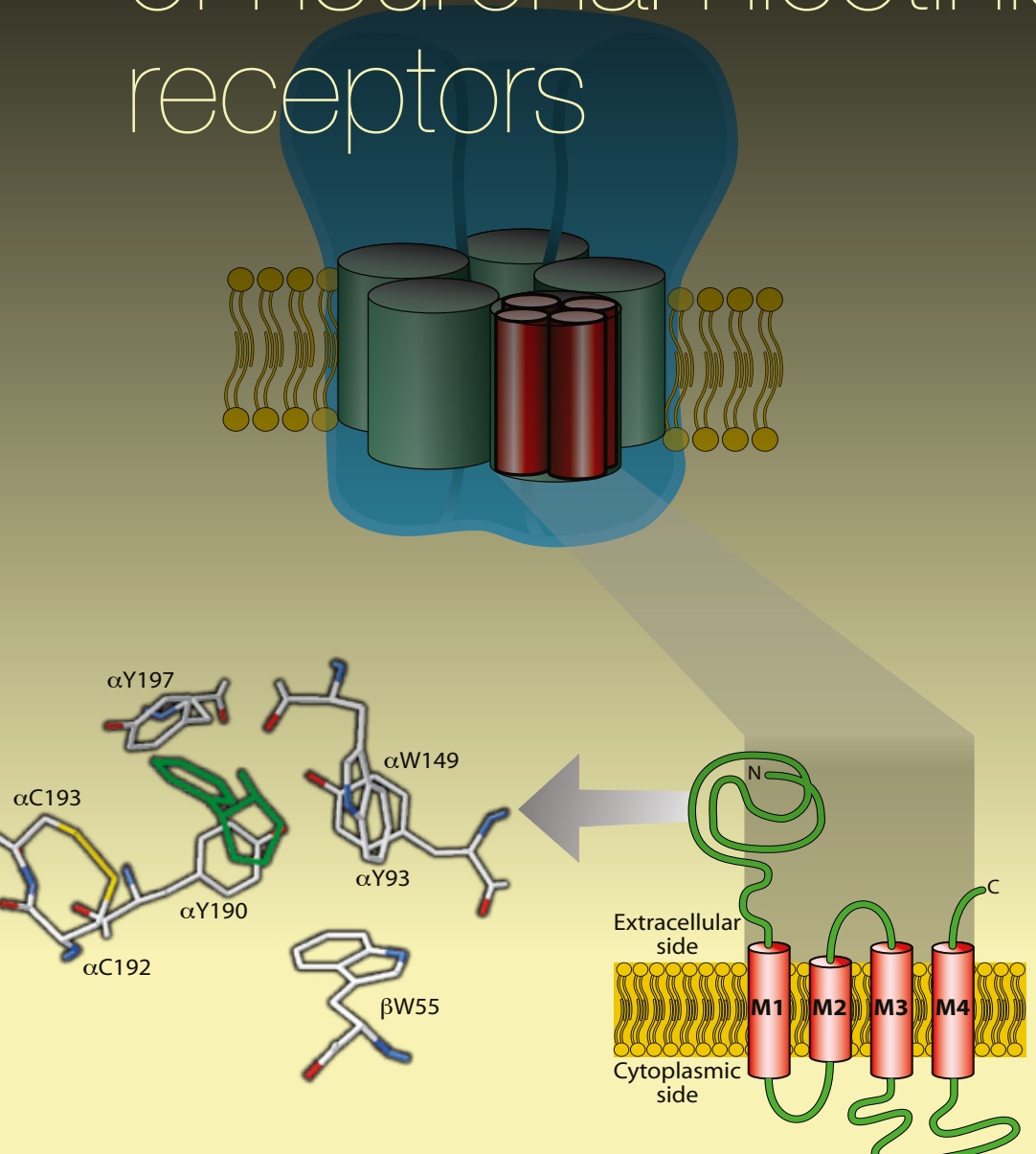
Molecular neurobiology of neuronal nicotinic receptors



Manuel Criado UMH

The nicotinic acetylcholine receptor is widely distributed in the central and peripheral nervous systems. Important functions and pathologies specific of the nervous system, such as memory, anxiety, analgesia, cerebral circulation, nicotine addiction and Alzheimer disease, could be better understood and/or treated through the study of the mechanisms which regulate the function and expression of nicotinic receptors. We use cell and molecular biology techniques in the following main projects:

Molecular neurobiology of neuronal nicotinic receptors

Mechanisms governing the functional expression of nicotinic receptors. By using specific mutants we study subunit assembly and receptor gating.

Study of proteins able to regulate receptor biogenesis and function. Synthesis, assembly and localization of nicotinic receptors are complex processes that need the action of specific proteins. At present we characterize the interaction of some proteins with specific nicotinic receptor subtypes.

Search and characterization of ligands able to modify the activity of neuronal nicotinic receptors. Antagonists as well as positive allosteric modulators are being studied.

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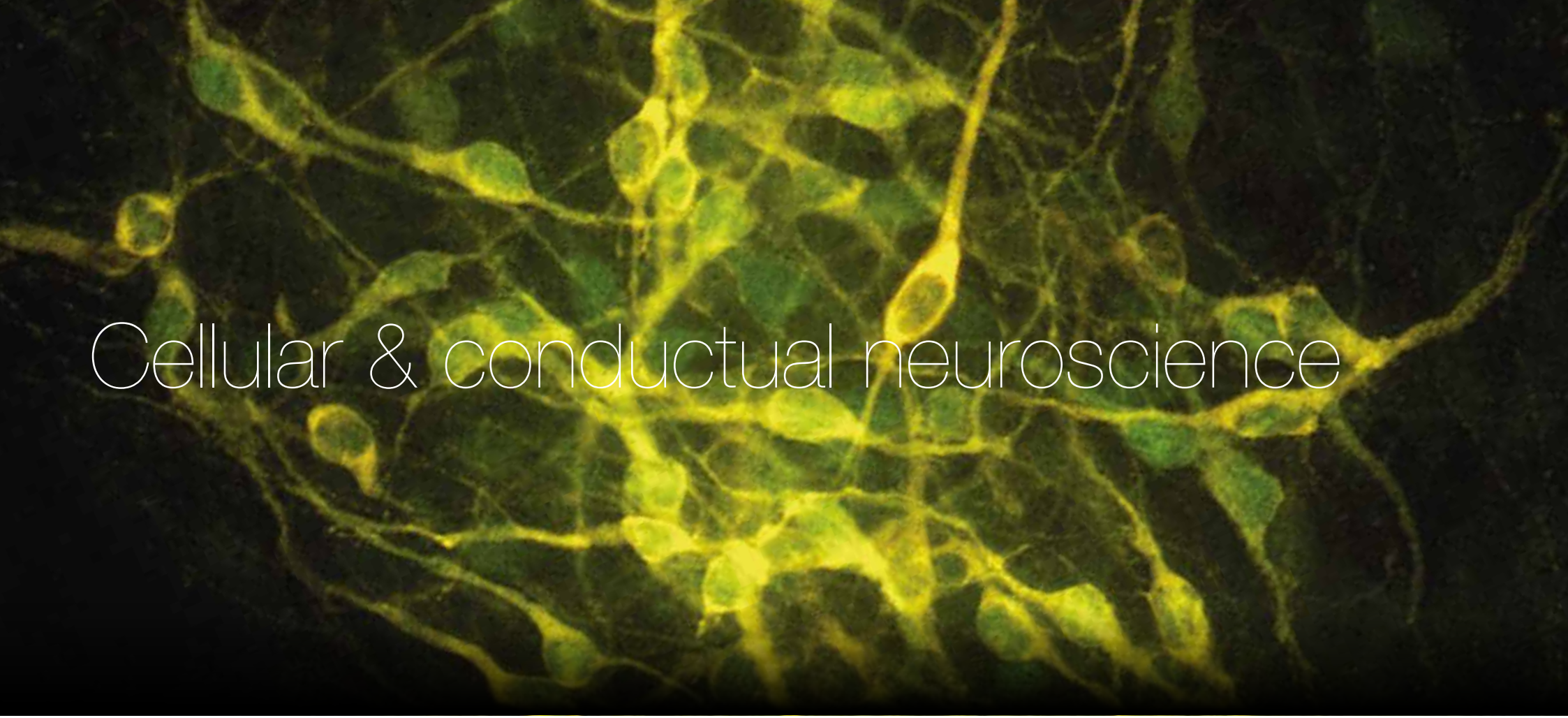

Cellular & conductual neuroscience

Carmen de Felipe UMH

The role of substance P in pain, tolerance and dependence mechanisms to opiates. We study the role of SP in tolerance effects, reward and drugs of abuse dependence, using KO animals for the NK1 gene. We investigate the molecular and behavioural effects of morphine, comparing to cocaine and amphetamine, which also induce addiction and analgesia, and the morphological

localization of the areas of the brain involved. We analyse the possible association and / or dissociation of neural basis which mediate the diverse effects of morphine: analgesia, reward, tolerance, dependence, motor behaviour, withdrawal signs. Besides, we study the neural basis involved in relapse and compulsive drug self-administration behaviour.

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

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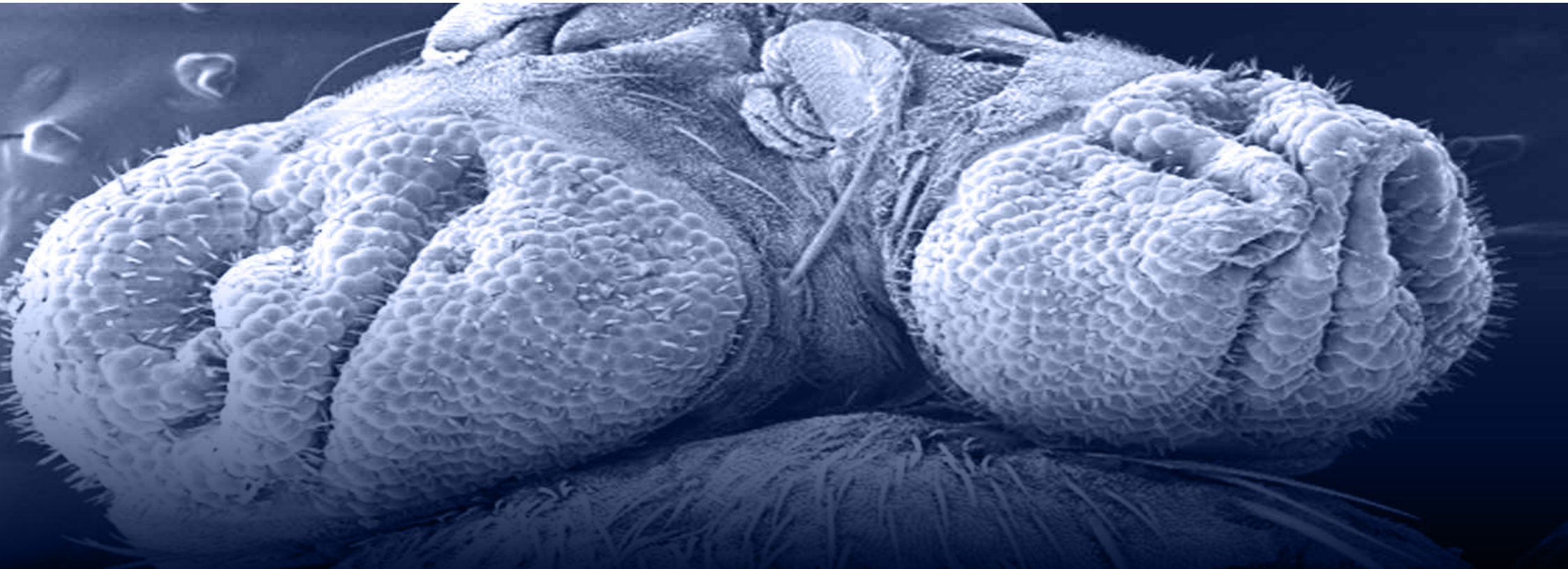
Mechanisms of growth control & cancer in Drosophila

María Domínguez CSIC

Our studies are focused on three complementary research projects:

- The brain keeps body size in check: Animal size is remarkably constant within species and this constancy is even more striking when we consider how our legs or arms, or the wings of an insect, are matched in size and shape. Genetic errors, diseases and environmental insults can perturb developmental growth programs that



may cause deviations and variability, in the sense that identical body parts would display imperfect symmetry and size. In order to limit the resultant variation, juvenile organisms buffer variability through homeostatic mechanisms, so that the correct final size is attained. Recently we have reported that the *Drosophila* brain mediates such homeostatic control via an insulin-like peptide Dilp8 binding to the relaxin hormone receptor Lgr3. Lgr3 neurons, acting as a neural 'hub', distribute Dilp8 'growth' information to other neuronal populations (insulin-producing cells and PTTH-producing neurons) thereby adjusting the levels of hormones insulin, ecdysone, and juvenile hormone, in a manner that stabilizes body and organ size.

At the organ level, the proper control of growth is linked to specialized domains known as "organizers" (i.e. conserved signalling centres). Local activation of Notch and Hedgehog signalling pathways along the dorsal-ventral (DV) and anterior-posterior (AP) axes, respectively, of the growing organs establish these organizers. The DV and AP organizers emit signals that promote global organ growth, patterning and cell fate specification. The DV (Notch) and AP (Hedgehog/Dpp) organizers promote growth non-redundantly within an organ, yet how the distinct organizer signals are integrated to ensure proper growth has remained unknown. Our recent work revealed that the Hedgehog receptor, Boi, is negatively regulated by Notch signalling thereby restraining Hedgehog signalling within Notch's DV domain. Conversely, Hedgehog signalling limits the organizing activity and growth by the Delta-Notch signalling. Our findings also uncovered a hitherto unsuspected tumour suppressor role for hedgehog signalling and unravelled unanticipated cooperative antagonisms between two pathways extensively used in growth control and cancer. Similar organizing signals are used repeatedly to promote growth and patterning in widely different organs (e.g. the neural tube, somites, limbs, eyes, etc.). We have shown that organ specificity is achieved through the activation of the organ-specific transcription factors by the organiser signals. Thus, the transcription factor Eyegone [homologue of human PAX6(5a)] and the secreted factor Four-jointed [Fjx in vertebrates] are activated by and mediate growth downstream of the Notch's organizer. Our findings also redefine the human PAX6 (5a) isoform, which is the structural homolog of Eyegone, as an oncogene and identify Four-jointed as a regulatory node integrating global growth control by Notch organizer and the cell-autonomous control by the tumour suppressor pathway Hippo/MST.

- Genome-wide screen for novel cancer genes and mechanisms: we have been pioneered in formulating high-throughput genetic screens for identified novel cancer-causing genes using sensitize (prone to cancer) genetic background. Through these screens, we have identified novel nexus of cancer including the cooperation between Notch and epigenetic silencers in malignant transformation or the cooperation between Notch and the Pten/PI3K/AKT pathway in promoting tumour invasion. Importantly, the Notch-Akt/Pten axis is conserved during human leukemogenesis and mutational loss of *PTEN* is responsible for resistance of T-cell acute lymphoblastic leukemic cells to inhibitors of the Notch pathway. In collaboration with Dr. Borggrefe, we have shown that the histone demethylase Lid/KDM5A is a core component of Notch silencing complex in tissue growth and tumorigenesis. Our screens also identified the conserved microRNA mir-8 (called miR-200 in humans) as a key modulator of Notch pathway activity in development and metastatic cancers. More recently, we have also shown in collaboration with A. Ferrando and I. Ainfantis that downregulation of the histone methyltransferase E(z) facilitates tumorigenesis by the Notch signalling pathway. This mechanism is also well conserved during

human leukemogenesis. Together these data link, for the first time, the Notch signal transduction pathway to the epigenetic silencing pathways, the Pten/PI3K/AKT pathway and the cell-cycle control during the process of tumorigenesis.

- Imaging tumour invasion and metastasis: The fruit fly Drosophila melanogaster has been a workhorse of genetics and developmental biology for almost a century, but its true potential for the genetic and cell biology analysis of tumour metastasis has only recently been realised. We are developing novel cancer-sensors based on the novel insulin/relaxin-like peptide identified in our laboratory that enable rapid and robust quantification of tumour burden for use in high-throughput cancer screens.

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Mechanisms of growth control & cancer in Drosophila

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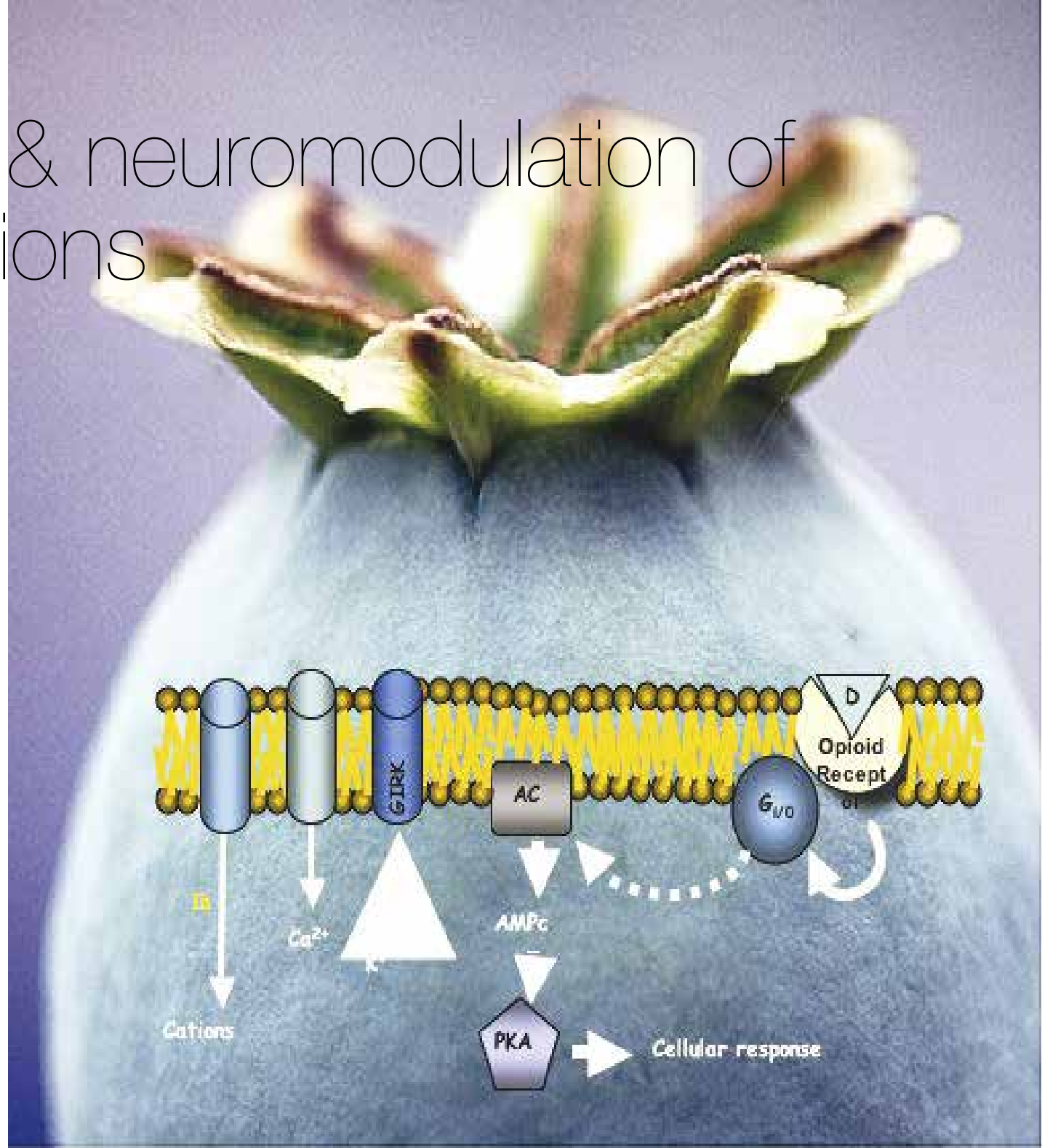
Neurobiology & neuromodulation of the opioid actions

Clara C. Faura Giner UMH

The improvement in the benefit–risk ratio for analgesic therapies is a relevant issue. Opioids are still the most potent and prescribed analgesic drugs. However, their clinical and non-clinical uses still have serious problems such as variability in the analgesic response, tolerance, dependence, addiction and locomotive alterations. It is important to know the neurological basis of opioid actions and the possible manipulation of them in order to improve analgesic efficacy and decrease unwanted effects.



Neurobiology & neuromodulation of the opioid actions

The variability in analgesic efficacy and other opioid responses may be due to modifications in the functionality of the opioid receptors originated either in the endogenous opioid system or the receptors themselves (cooperativity or oligomerization). The variability could also be due to a different neuromodulation, which can be caused by different factors. The neuropeptide FF system can be a candidate influencing endogenous opioid peptides.

To address these issues we are trying to determine the involvement of changes in opioid receptors as well as pre-receptor mechanisms in opioid responses. We are assessing changes in receptor transduction and in the density, functionality, efficacy and oligomerization of opioid receptors in CNS. In addition, we are studying the implication of endogenous opioid peptides and other neuropeptide systems in opioid variability through behavioural assays.

The potential contributions and applications of work in this area are very relevant. The clarification of mechanisms involved in unwanted opioid actions would establish the basis for its control and would allow the optimization of analgesic treatments.

On the other hand, the group has collaborations with internationals researchers (Drs Kalso, McQuay and Moore) and with researchers from the same Institute (Drs Ballesta and Berbel)

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J J Ballesta, J Cremades, M Rodríguez-Muñoz, J Garzón C CFaura. (2012) Sensitivityto μ Opioid Receptor Mediated Antinociception is Determined by Cross–regulatio nBetween and Opioid Receptors at Supraspinal level. **Br J Pharmacol** *DOI: 10.1111/j.1476-5381.2011.01750.x*

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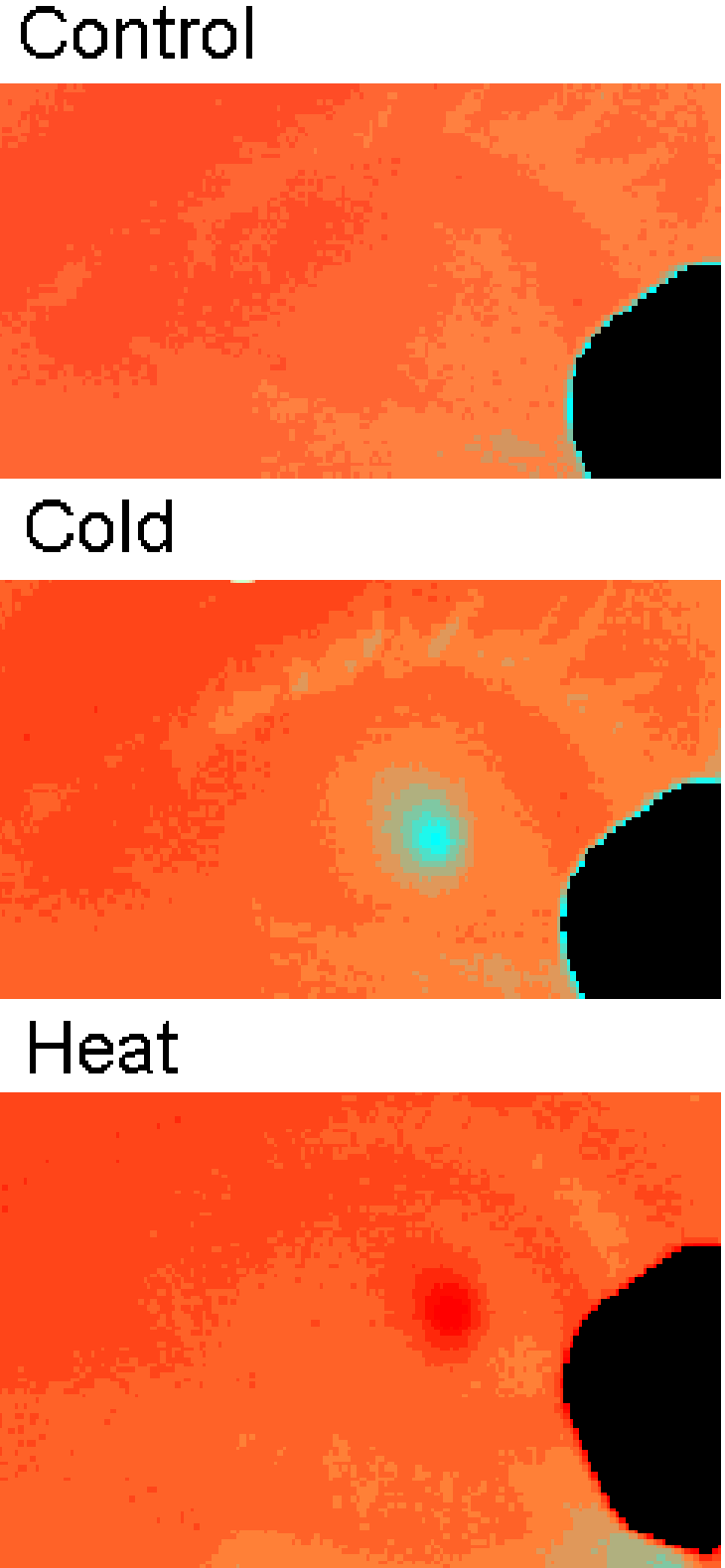

Ocular Neurobiology

Juana Gallar UMH

Mª Carmen Acosta UMH

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

with particular attention to those neurons participating in ocular sensations of eye dryness, discomfort and pain.

The ONG has described 1) the sensitivity of the ocular surface to selective stimulation in healthy subjects and its changes with age, 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 innervation in blinking and in basal and reflex tearing.

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

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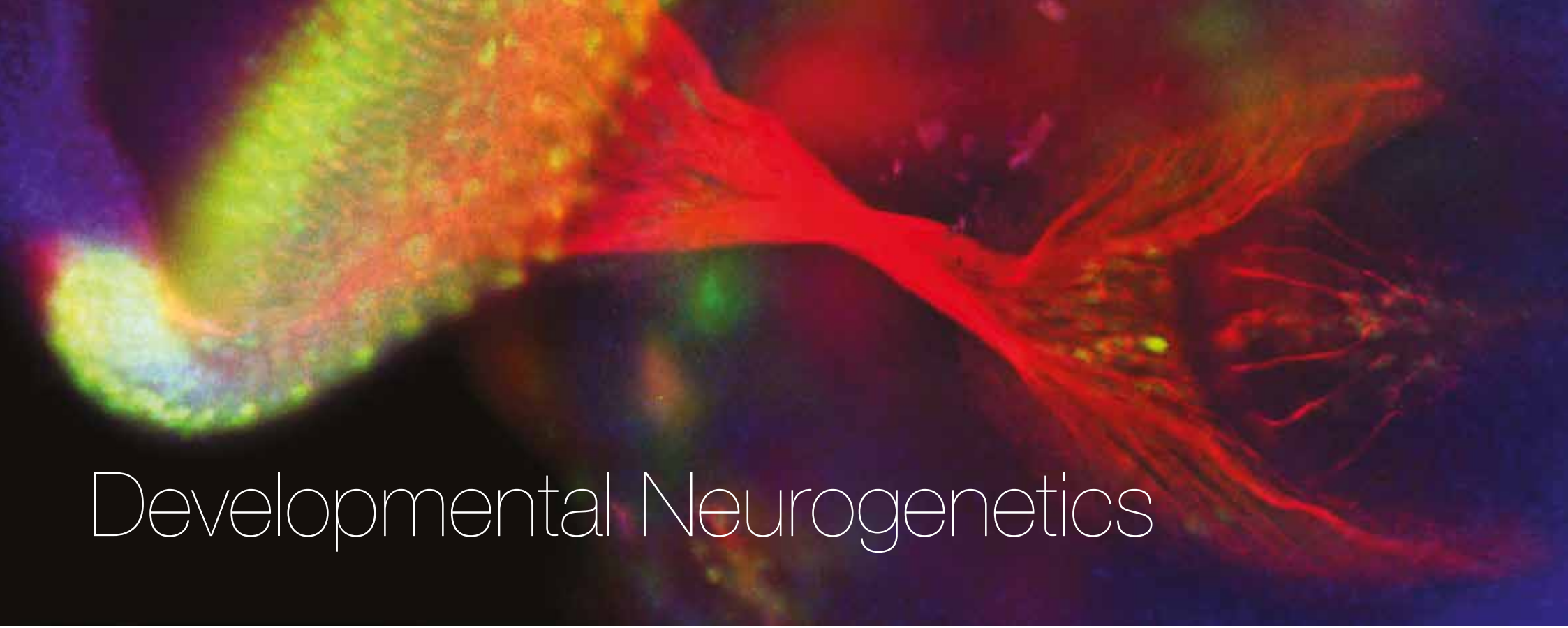

Developmental Neurogenetics

Luis García-Alonso CSIC

Function of the Nervous System is determined by the number of neurons and its network architecture. During embryonic development, billions of neural connections are formed with exquisite precision and fidelity. This process is driven by the genetic program and established in three steps: growth and neurogenesis, to generate an organ with a characteristic size, shape and neural pattern; stereotyped guidance and synaptogenesis of each axon and dendrite with specific target cells; and plasticity and remodeling of synaptic connections to adapt to particular environments. Every one of these steps is critically controlled by cell communication mechanisms. Our lab is interested in the cell communication mechanisms that determine morphogenesis and neural connectivity, its specificity and its fidelity.

Developmental Neurogenetics

We approach the study of these mechanisms using Drosophila melanogaster as animal model.

Our work focuses on the study of functional cellular mechanisms dependent on L1- and NCAM-type proteins, two cell adhesion molecules that belong to different families of the immunoglobulin protein superfamily. These proteins are present in arthropods and chordates, from flies to humans, and are co-expressed during the growth of specific organs and axon tracts. Both, L1- and NCAM-type proteins function in cell communication mechanisms as modulators of FGF and erbB receptors. Our work reveals that the specificity of both L1- and NCAM-type proteins as modulators of FGF and erbB receptors has been conserved along evolution. The co-expression of these molecules in certain epithelia and neural projections reflects a specific requirement for functional overlap to ensure fidelity of organ growth, neurogenesis and axon guidance during development. In addition, we study the function of Reelin, a vertebrate cell communication protein that was lost early during invertebrate evolution. Our work shows that Reelin control of Notch signaling can be revealed in transgenic Drosophila through its interaction with the conserved LpR1-2 receptors and the signal transduction protein Dab.

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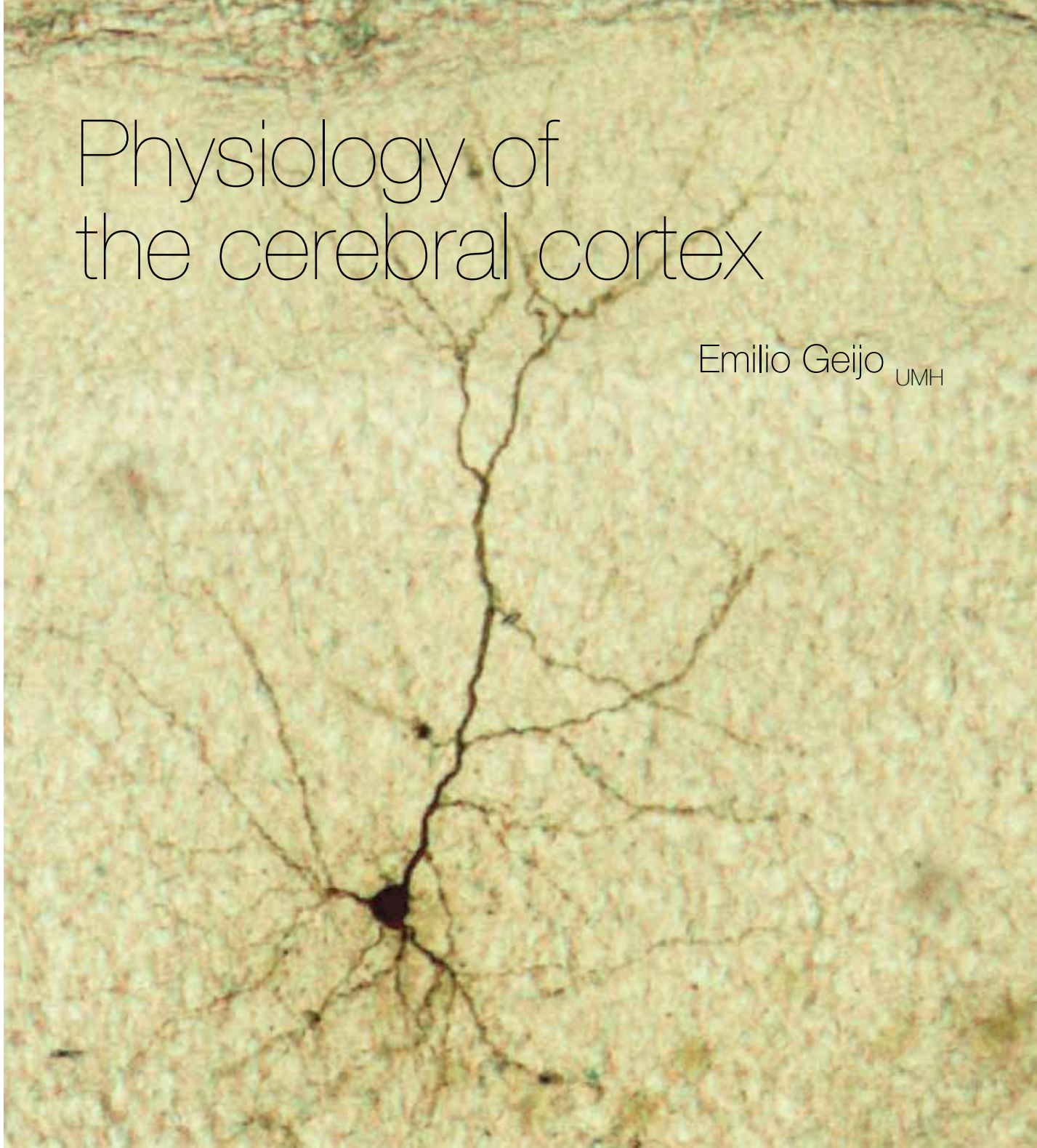
Physiology of the cerebral cortex

Emilio Geijo UMH

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



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

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

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Mechanotransduction in mammals

Ana Gomis CSIC

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

Nociceptors are primary afferent fibers of the somatosensory system specialized in the detection of noxious stimuli. They are critically involved in the initial steps of pain sensation. Transient Receptor Potential (TRP) channels have been recognized as key molecular detectors of thermal and chemical stimuli in the somatosensory system. Upon activation, these polymodal cationic channels depolarize sensory terminals and bring them to the threshold for action potential discharge. In contrast, the molecular identity of mechanosensitive channels responsible for low and high threshold mechanodetection is not completely known. In

addition to several TRP channels, other ion channels, including the family of Piezo proteins may play important roles.

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

We are interested in identifying the receptor molecules expressed in specific populations of sensory neurons and asking how they participate in mechanosensation in physiological and pathophysiological conditions. A second goal is to study the interaction of ion channels involved in nociception and mechanotransduction with defined components of the extracellular matrix. Finally, we also study the effects of drugs and blockers of sensory channels on sensory afferents of the knee joint recorded in anesthetized rats. This last step is very important in the establishment of new therapies against pain.

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

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Mechanotransduction in mammals

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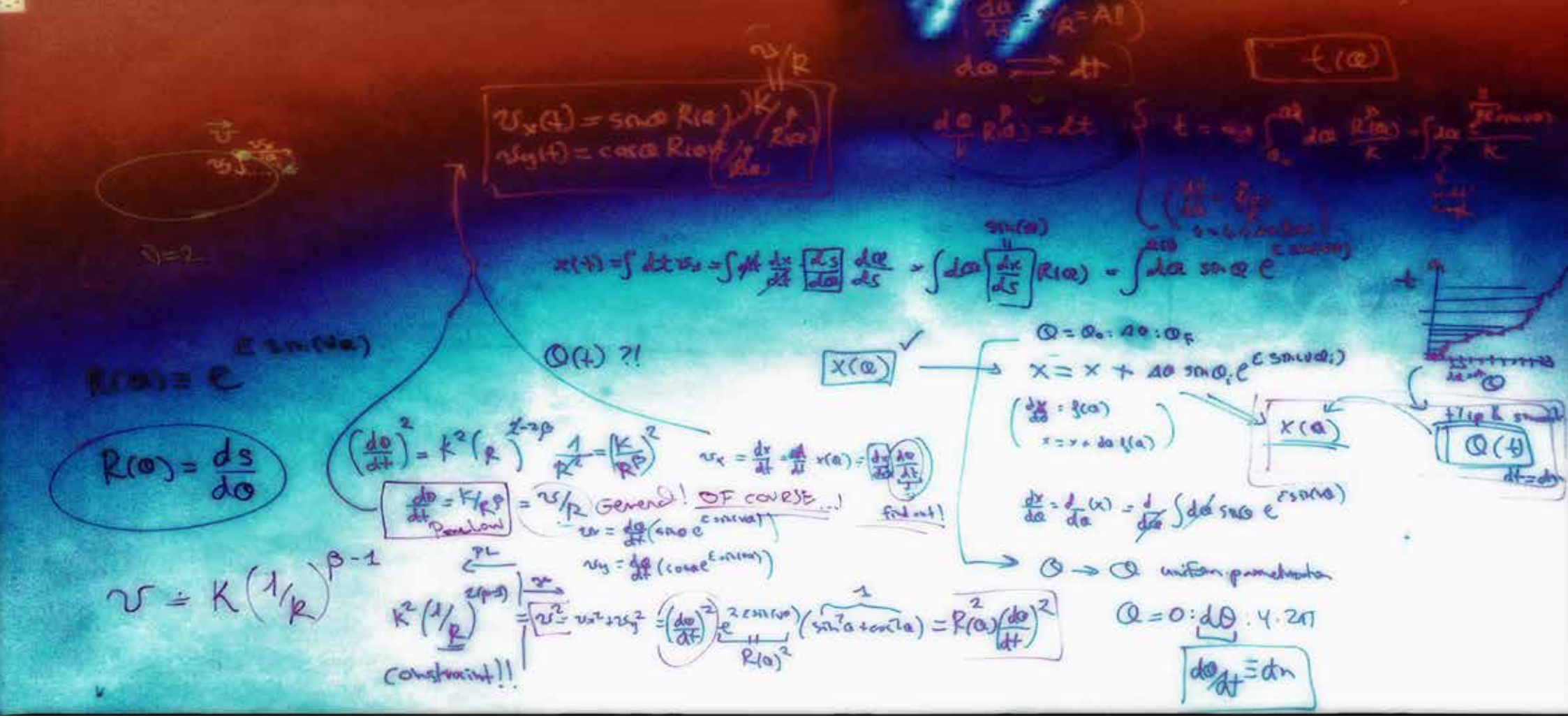

Behavior of Organisms

The behavior of animals is not the behavior of their brains, but the processes emerging from the interaction between neural activity, body biomechanics and environmental constraints.

Alex Gomez-Marin CSIC

Recent advances in neuroscience comprise a wide range of "big tools" enabling the collection of "big data", both being promissory notes for understanding the brain and explaining behavior. This has lead to much emphasis on techniques and causal accounts of explanation in the flavour of the latest interventionist techniques and reductionist views, thus giving the impression that detailed studies of behavior and its algorithmic composition are less important. However, dissecting "necessary and sufficient" neural circuits for behavior is no shortcut to the proper study of behavior itself. After all, to ask how the brain works is different than (and requires) to ask what it is for — neurons indeed compute information yet nervous systems evolved to produce adaptive behavior. Thus, in the lab we try to avoid missing the forest for the trees.

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

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

Behavior of Organisms

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M. Zago, F. Lacquaniti, A. Gomez-Marin^ (2016) The speed-curvature power law in Drosophila larval locomotion. **Biology Letters** *12: 20160597*

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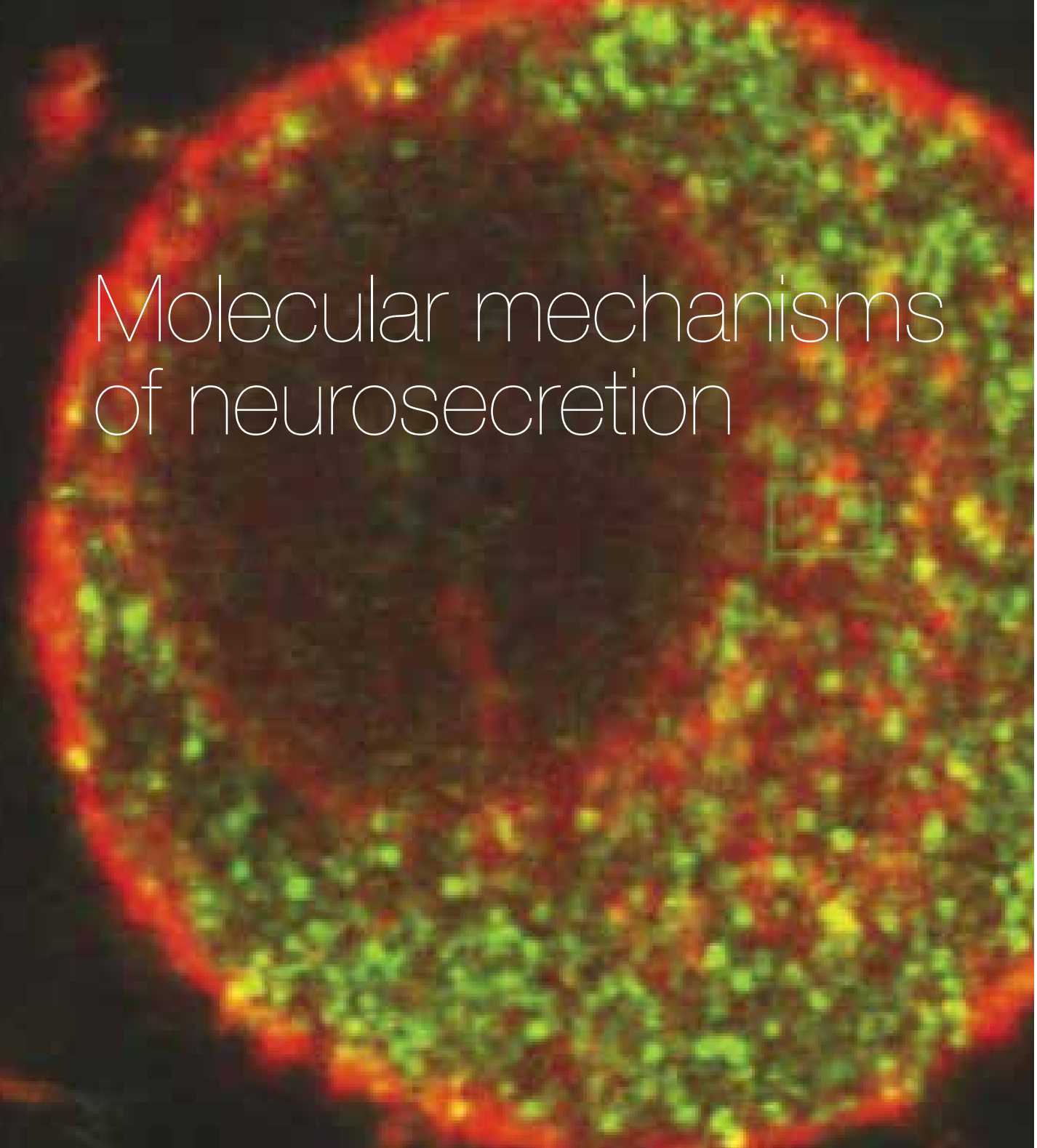

Molecular mechanisms of neurosecretion

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

Molecular mechanisms of neurosecretion

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.

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Villanueva, J, Viniegra, S, Gimenez-Molina, Y, Garcia-Martinez, V, Exposito-Romero, G, Frances, M, Garcia-Sancho, J, and Gutiérrez, LM (2014) **The position of mitochondria and ER in relation to that of the secretory sites in chromaffin cells** **J. Cell Sci.** *127, 5105-5114*

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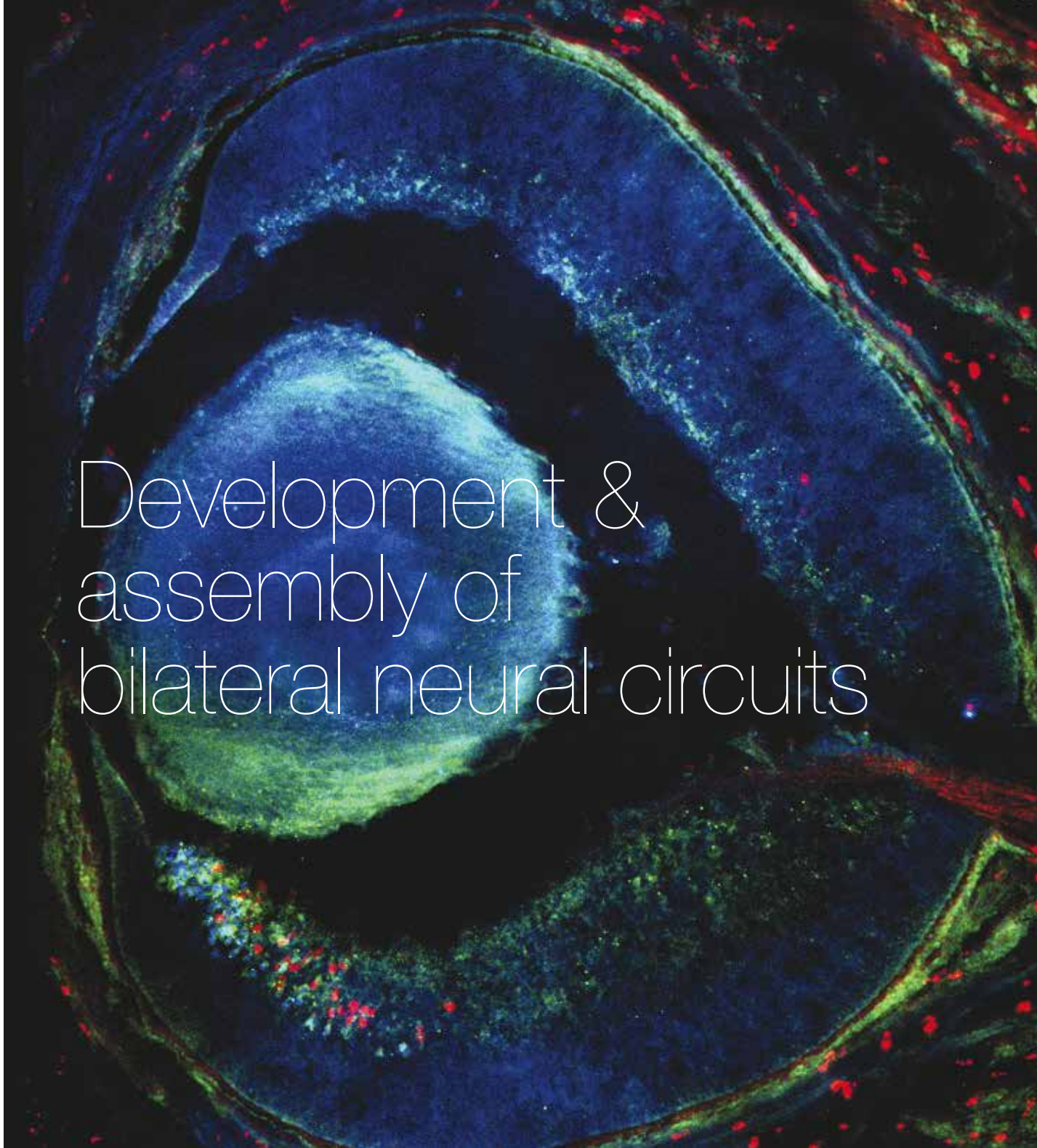
Development & assembly of bilateral neural circuits

Eloísa Herrera CSIC

Most metazoans are bilaterally symmetric and many features of mature neural function including the interpretation of sensory information and the coordination of locomotion depend on the coherent communication between the two brain hemispheres. In order to integrate sensory information from both sides



of the body and then elaborate a coordinated response, the nervous system requires both axons crossing at the midline and axons remaining in the ipsilateral side of the brain. Alterations in the axonal decision of crossing the midline or in the assembly of bilateral inputs in the brain may perturb the proper establishment of laterality in the nervous system circuitry leading for instance, to pathological consequences in vision or motor coordination.

We use the development of the visual system and the spinal cord in mammals as models to understand the molecular mechanisms that govern axonal divergence at the midline and the assembly of bilateral circuits in the target tissues.

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Development & assembly of bilateral neural circuits

Marcucci F, Murcia-Belmonte V, Wang Q, Coca Y, Ferreiro-Galve S, Kuwajima T,Khalwid S,Ross M.E,Mason C and Herrera E (2016) The Ciliary Margin Zone of the Mammalian Retina Generates Retinal Ganglion Cells **Cell Reports** *17(12): 3153–3164 (Cover caption)*

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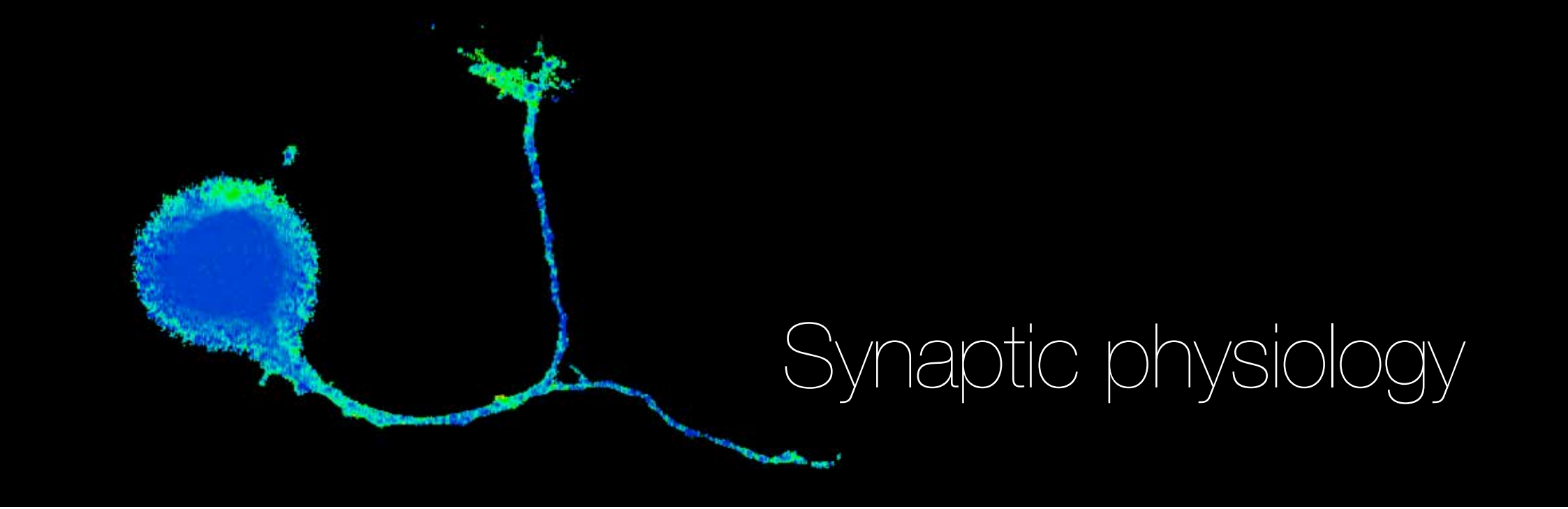

Synaptic physiology

Juan Lerma CSIC

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

In the frame of defining the molecular structures mediating neuronal communication, we described for the first time the existence in central neurons of another type of functional glutamate receptors, the kainate receptor (KAR). We have demonstrated that KAR proteins form functional receptor channels in hippocampal neurons and also provided the tool

by which these receptors could be further studied, the drug 2-3-benzodiazepine, GYKI 53655, which allows its pharmacological isolation. Indeed, this finding paved the way for progress in the field. Since then, we and other groups have addressed specific questions on the functional role of KARs. We have characterized these receptors in cultured neurons and brain slices and described their fundamental role in controlling neuronal tissue excitability and epileptogenesis. We have demonstrated that these receptors have a dual mechanism for signalling: in addition to their expected capability of acting as ion channels, they trigger a second messenger-mediated cascade, involving a G-protein. This and subsequent work put forward the new concept that ion channel-forming receptors are also able to signal through a G-protein, opening new vistas on the mechanisms by which glutamate receptors of the ionotropic type work. Taken together, our data has helped to understand why KAR activation is proconvulsive and pointed them as targets for new treatments of epileptic disease.

The idea that KARs activate a G-protein has encouraged us to study interacting proteins that may influence their correct targeting and their signalling capacities. Therefore, one the main objectives of the lab has been to identify and to evaluate the role of interacting proteins in the signalling properties of KARs using a number of model systems. Using proteomic techniques, including two-dimensional gels and mass spectrometry analysis, we have identified a set of over 20 proteins that take part of the "interactome" of these receptors and analysed the impact of some of them on the roles of kainate receptors likely play have in neuronal physiology. Among the identified proteins are SNAP25, which we have shown plays a key and unexpected role in endocytosis of these receptors from the synaptic membrane. Indeed, it is responsible for a type of long-term synaptic plasticity of the kainate receptor-mediated synaptic component. Also, CRMP2 and CRMP4 were also identified as interactors of GluK5. Indeed KARs influence neuronal maturation and neuritic proliferation through these proteins in a bidirectional manner. We have also identified the subunit of the receptor that positively interacts with a Go protein, and that is most likely responsible for non-canonical signaling of these receptors. The regulation of receptors by all these proteins provides innovative strategies to finely influence its function and may constitute targets for development of new active drugs in problems of excitability, such as epilepsy.

These are salient properties of KARs but their role in both physiology and pathology is still limited. New data, however, indicate their involvement in mood disorders. De novo copy number variation (deletion or duplication of a chromosomal region) of synaptic genes has been recently implicated as risk factors for mental retardation or autism. Amongst them is *GRIK4*, a gene coding for a glutamate receptor subunit of the kainate type. The understanding of brain diseases requires the definition of the molecular, synaptic and cellular disruptions underpinning the behavioural features that define the disease. For this reason, we generated transgenic mice overexpressing *grik4* in the forebrain. These mice displayed social impairment, enhanced anxiety and depressive states, accompanied by altered synaptic transmission in the hippocampus. Together, these data indicate that a single gene variation in the glutamatergic system results in behavioural symptomatology consistent with autism spectrum disorders as well as in alterations in synaptic function in regions involved in social activity.

Synaptic physiology

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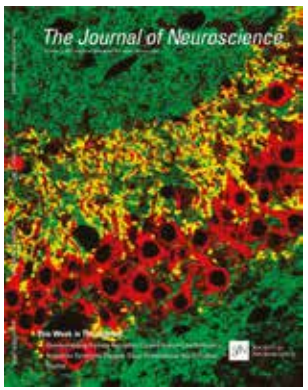

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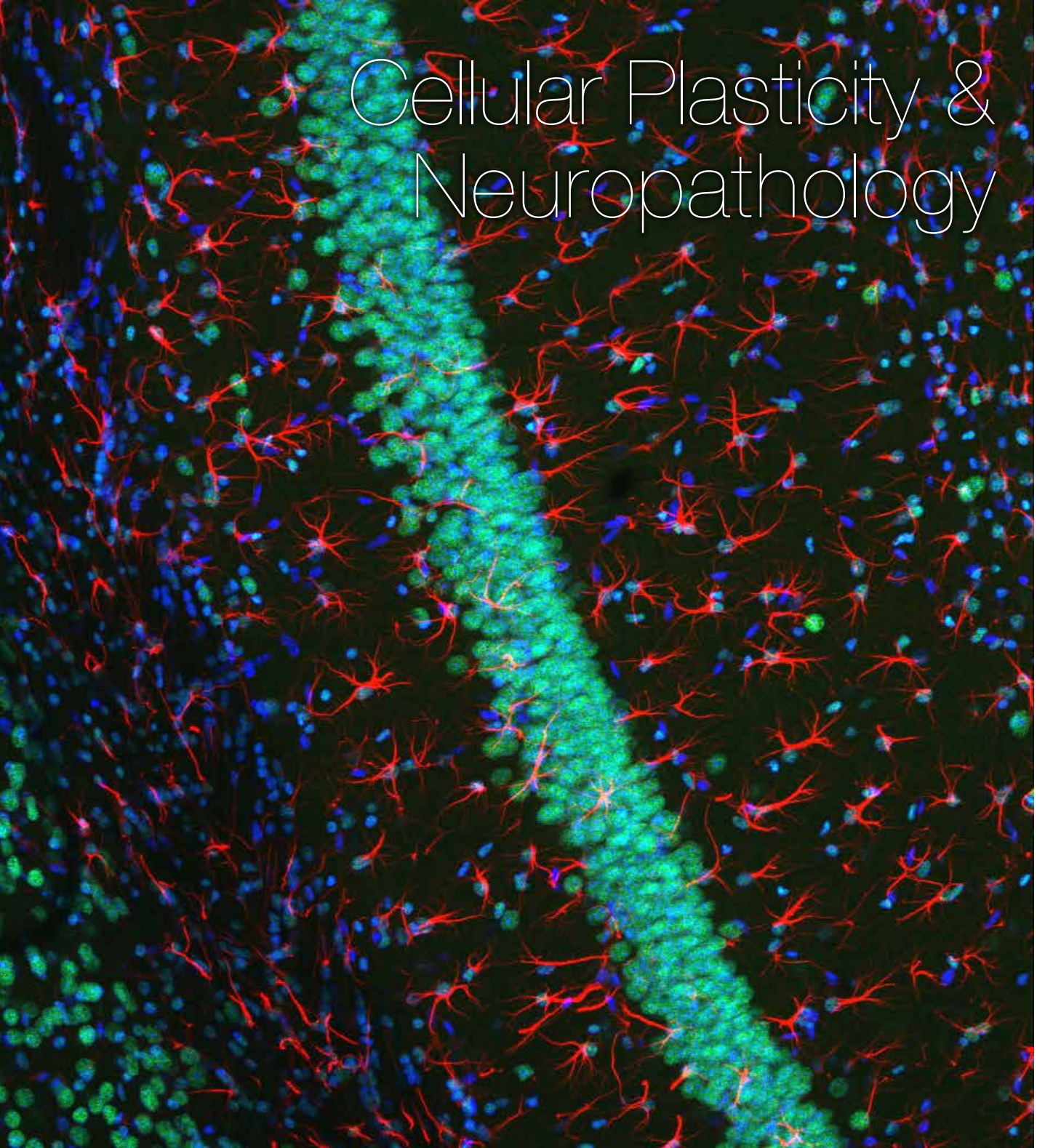

Cellular Plasticity & Neuropathology

José P. López-Atalaya CSIC

Cell identity is a reflection of a cell type-specific transcription factor network that governs complex patterns of gene expression. In eukaryotic cells, these transcriptional profiles are maintained by alterations in chromatin structure that include covalent modifications of the DNA and histone proteins, and nucleosome positioning. More recent evidence suggests that the three-dimensional genome architecture may also be critical for achieving proper spatio-temporal patterns of gene expression during cell differentiation and contributes to the maintenance of cellular memory.

Cellular Plasticity & Neuropathology

Cells' ability to change their behaviour in response to internal or external environmental cues is a key feature of development and normal function of cells within most multicellular organisms. One of the most striking naturally occurring transitions in cellular phenotype is observed in the mammalian brain. In the brain, microglial cells play fundamental roles in neuronal physiology including regulation of neurotransmission and synapse formation and maintenance. In addition, microglia constitutes the intrinsic brain defence system. Stroke, trauma, infection or chronic neurodegeneration trigger a pronounced glial response. This dual role is associated to a profound phenotypic switch from "active" to "reactive" microgliosis. Critically, microglia and also other types of brain macrophages and astrocytes must orchestrate complex genetic programs in response to a variety of stimuli that dictate the induction of alternations in their phenotype to serve the appropriate biological functions. However, the mechanisms underlying these phenotypic transitions and the maintenance of the acquired identity remain largely unknown.

We combine mouse genetics, genomics and cell biological approaches to explore the boundaries of epigenome plasticity in differentiated cells. We use neuroglia as models to study how gene regulatory interactions control cellular state and identity. Our research may provide direct mechanistic links to neuroinflammatory processes in brain aging and neurodegenerative diseases.

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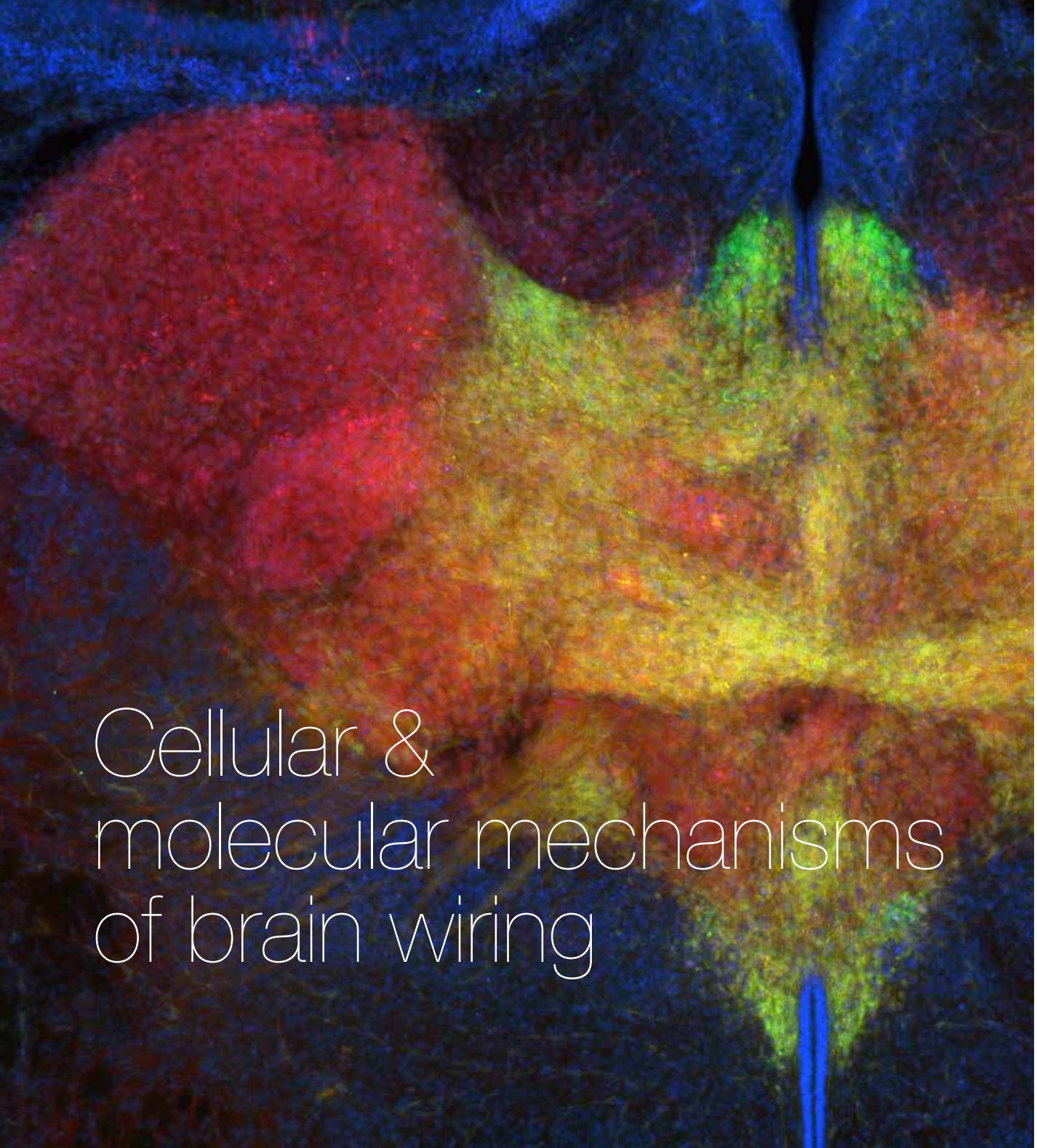

Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

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

Cellular & molecular mechanisms of brain wiring

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

Two major questions are been focused in the laboratory: i) the activity-dependent mechanisms involved in thalamocortical wiring, ii) the role of the thalamus and its connectivity in the neuroplastic cortical changes following sensory deprivation, and iii) reprogramming thalamic cells for circuit and sensory restoration. We are also developing new animal model for determining the role of thalamocortical input in cortical specification and plasticity.

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

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

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Cellular & molecular mechanisms of brain wiring

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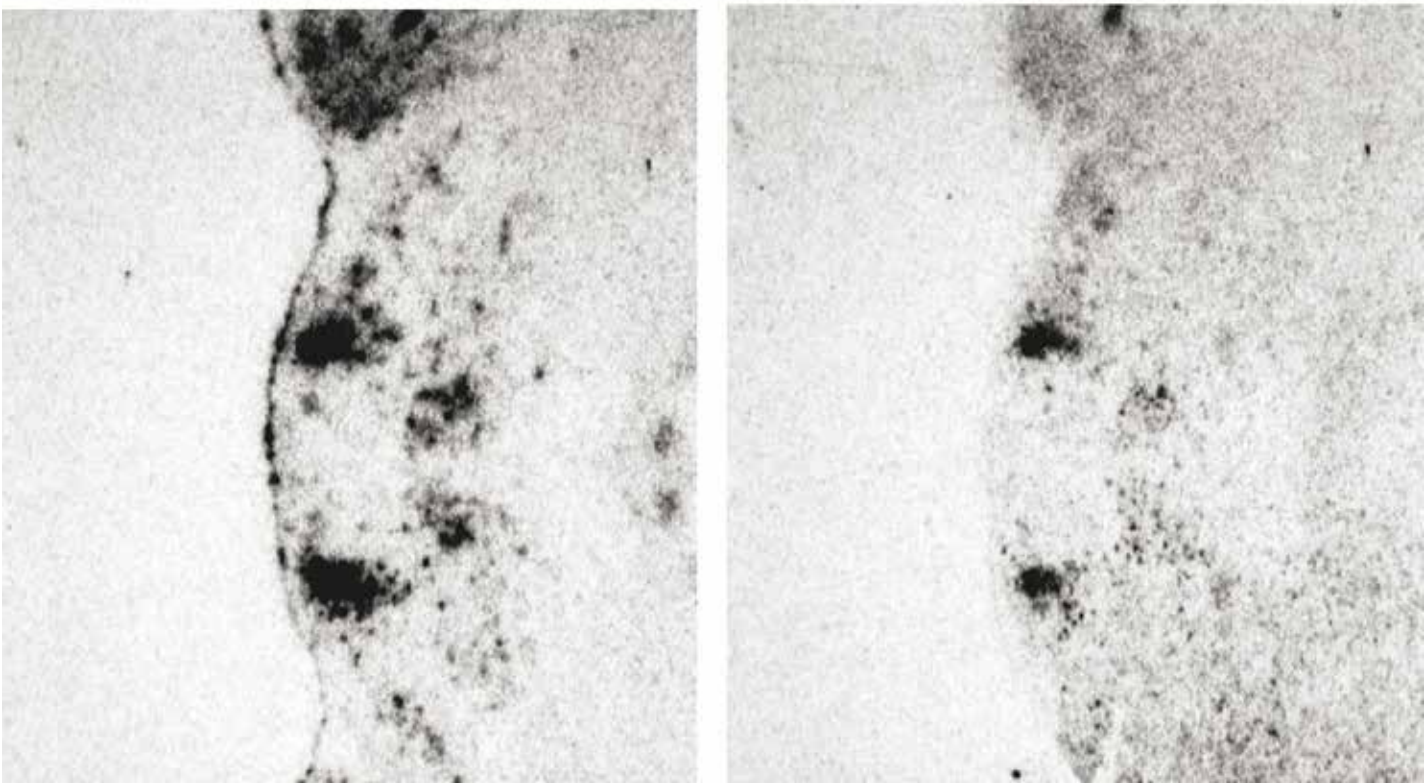
Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH



The laboratory is focused in the identification of key receptors and genes underlying behavioral and molecular alterations involved in the occurrence of neuropsychiatric disorders (anxiety, depression, drug dependence, Parkinson, etc..) and that may represent potential new targets to treat these diseases.

To this aim, one of our major interest is to work with appropriated animal models of psychiatric and neurological alterations that were able to reflect, at least in part, certain behavioral and/or neurochemical features of the illness that they are simulating and therefore result helpful to identify whether these behavioral changes are associated to specific alterations in key proteins in the brain.

In the last years, the laboratory has paid much attention to the role of the opioid and cannabinoid systems in the anxiety and depression-like behaviors, impulse control diseases (specially, excessive voluntary consumption of ethanol) and Parkinson'abs disease. We routinely used a number of methods to evaluate behavioral features of these animal models, the effects of drugs in wild type or genetically modified mice and we study functional receptor alterations using autoradiographic approaches, immunocytochemical analyses or molecular changes in gene expression by PCR or in situ hybridization techniques.

The laboratory has been in constant relationship with groups of psychiatrists and neurologists with the purpose to establish a reciprocal bridge between preclinical and clinical research and to be able to set up a fluent interchange of information that ultimately result helpful to patients developing psychiatric and neurological diseases. This effort has been reflected in several joint publications. We hope to maintain and strengthen this type of approach to continue translational research in the neuropsychopharmacological aspects of neurological and psychiatric diseases.

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Neural Circuits of Social Behaviour

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Social interactions shape the way we perceive, feel and learn about the world, and despite its importance for social species, we still know very little about how the brain computes social information.

Neural Circuits of Social Behaviour

Our lab is interested in understanding the mechanisms of how social behaviour shapes our brain, and for this, we focus on cooperative social interactions in rodents. We have recently demonstrated that Norway rats display prosocial behaviours in food foraging context, providing food to conspecifics, and identified the proximal mechanisms at the level of behaviour (Marquez et al, Current Biology, 2015). Current and future projects aim to identify the neural circuits responsible for this fascinating social decision-making, using a combination of behavioural, anatomical, pharmacological, imaging and optogenetic tools in rodents.

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Cristina Marquez* , Rennie S, Costa D, Moita M*. **Co-corresponding author* (2015) **Prosocial choice in rats depends on food-seeking behaviour displayed by recipients** **Current Biology** *25(13) , 1736 - 1745*

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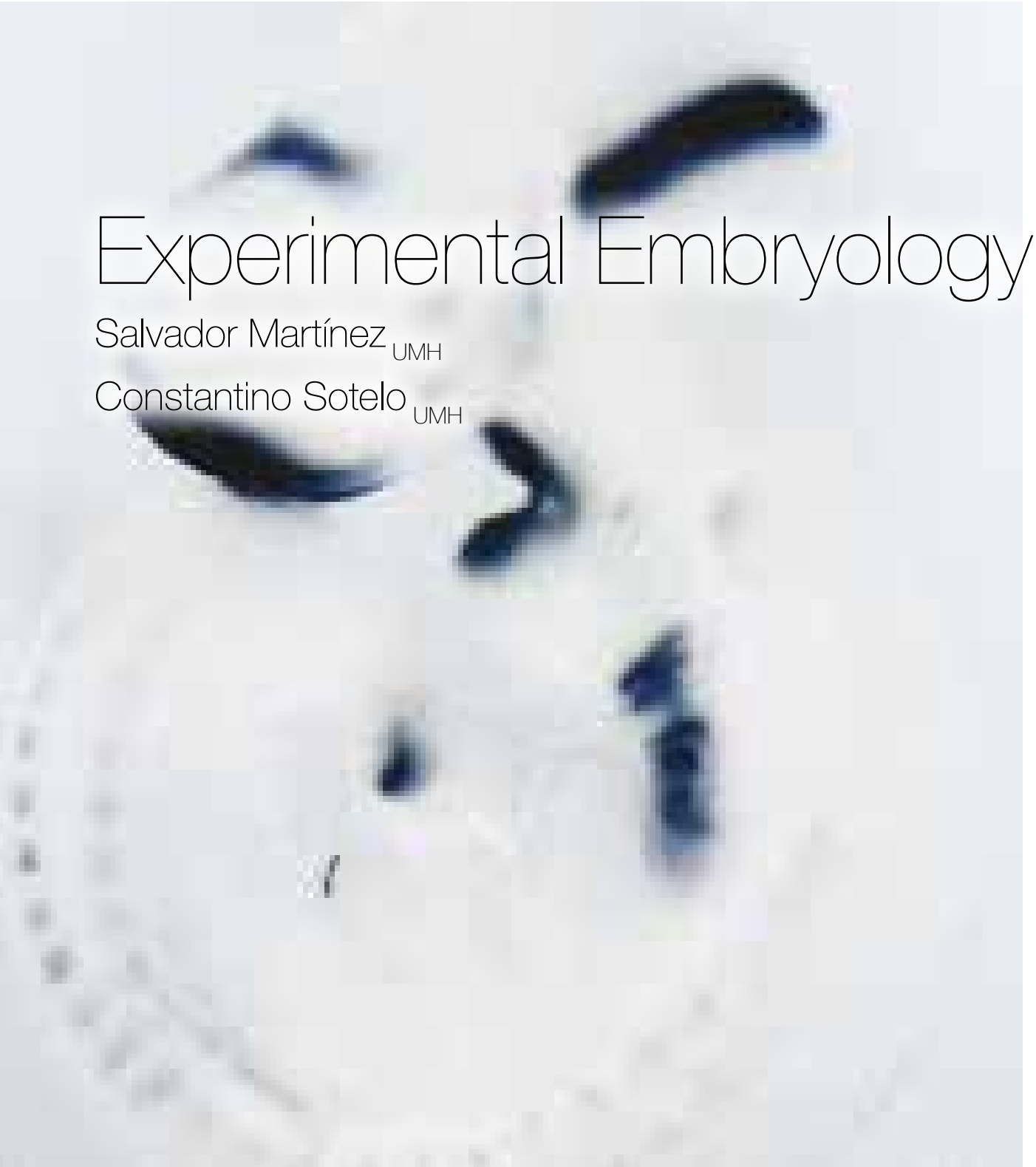

Experimental Embryology

Salvador Martínez UMH

Constantino Sotelo UMH

Our studies are focused on four research projects:

Experimental Embryology: manipulations in mouse and chick embryos allow us to study cellular and molecular factors that control the regionalization, segmentation, proliferation, differentiation and cellular migration processes of the Central Nervous System. We concentrate our research work in the understanding of the molecular factors that control the development and morphogenetic activity of the secondary

organizers of the anterior neural tube of vertebrates. Our work explores particularly the molecular action of signalling molecules like SHH, WNTs and FGFs in the Isthmic organizer, the zona limitans intrathalamic (ZLI) and the anterior neural ridge (ANR).

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

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

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

Development of the Cerebellum: (i) Precerebellar neurons migration: study of the molecular and cellular mechanisms involved in the migration of precerebellar neurons, particularly those of the inferior olive, at the origin of climbing fibers. Our studies are focused mainly on studying the molecular control of the decision adopted by these neurons of crossing or not to cross the ventral midline of the brain stem, during migration and axonal growth. (ii) Development and differentiation of Purkinje cells: The role of the thyroid hormone (T3) in the loss of the capacity of PCs to regenerate their axons towards the end of the first postnatal week was disclosed, because this loss was triggered prematurely by early exposure of mouse PCs to T3, whereas it was delayed in the absence of T3. The transcription factor Krüppel-like 9 (Klf9) was a key mediator of this effect. Klf9 is also involved in the PCs programmed cell death. In fact, in Klf9 knockout mice, the survival rate of PC is reduced by half; whereas the survival increases in PCs overexpressing Klf9. Thus, Klf9 seems to be a key molecule for the PC transition between the developing and grown-up stages

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

Experimental Embryology

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Visual Neuroscience Laboratory

Luis M. Martínez CSIC

We, like many other mammals, are essentially visual animals. Thus the visual system of our brains must achieve a daunting task: it creates, in real time, an internal representation of the external world that it is used by other parts of the brain to guide our behavior. But, how do we actually see? How does this neural system accomplish the job? A parsimonious explanation proposes that visual information is analyzed in a series of sequential steps starting in the retina

and continuing along the multiple visual cortical areas. As a result, the information captured by the approximately 105 million of photoreceptors in the back of each eye is continuously rearranged in a complex combination of points and lines of different orientations and curvatures that are defined by differences in local contrast, color, relative timing, depth, movement, etc. Ultimately, by mechanisms that remain largely unknown, these elementary features of the image are integrated into the perception (our "vision") of each individual object in the visual scene.

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

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Visual Neuroscience Laboratory

J.A. Hirsch, X. Wang, F.T. Sommer & L.M. Martinez (2015) **How inhibitory circuits in the thalamus serve vision** **Annual Review of Neuroscience** *38:309-329.*

L.M. Martinez*, M. Molano-Mazón, X. Wang, F.T. Sommer & J.A. Hirsch (2014) **Statistical wiring of thalamic receptive fields optimizes spatial sampling of the retinal image.** **Neuron** *81:943-956. Cover article.*Corresponding Author*

I. Benjumeda, A. Escalante, C. Law, D. Morales, G. Chauvin, G. Muca, J. Marquez, G. Lopez-Bendito, A. Kania*, L.M. Martinez*, E. Herrera* (2013) **Uncoupling of EphA/ephrinA signaling and spontaneous activity in neural circuit wiring.** **Journal of Neuroscience** *33:18208-18218. Cover Article. *Corresponding Authors*

V. Villar-Cerviño, M. Molano-Mazón, T. Catchpole, M. Valdeolmillos, M. Henkemeyer, L.M. Martínez, V. Borrell & O. Marín 2013)(**Contact repulsion controls the dispersion and final distribution of Cajal-Retzius cells.** **Neuron** *77: 457–471. Cover article.*

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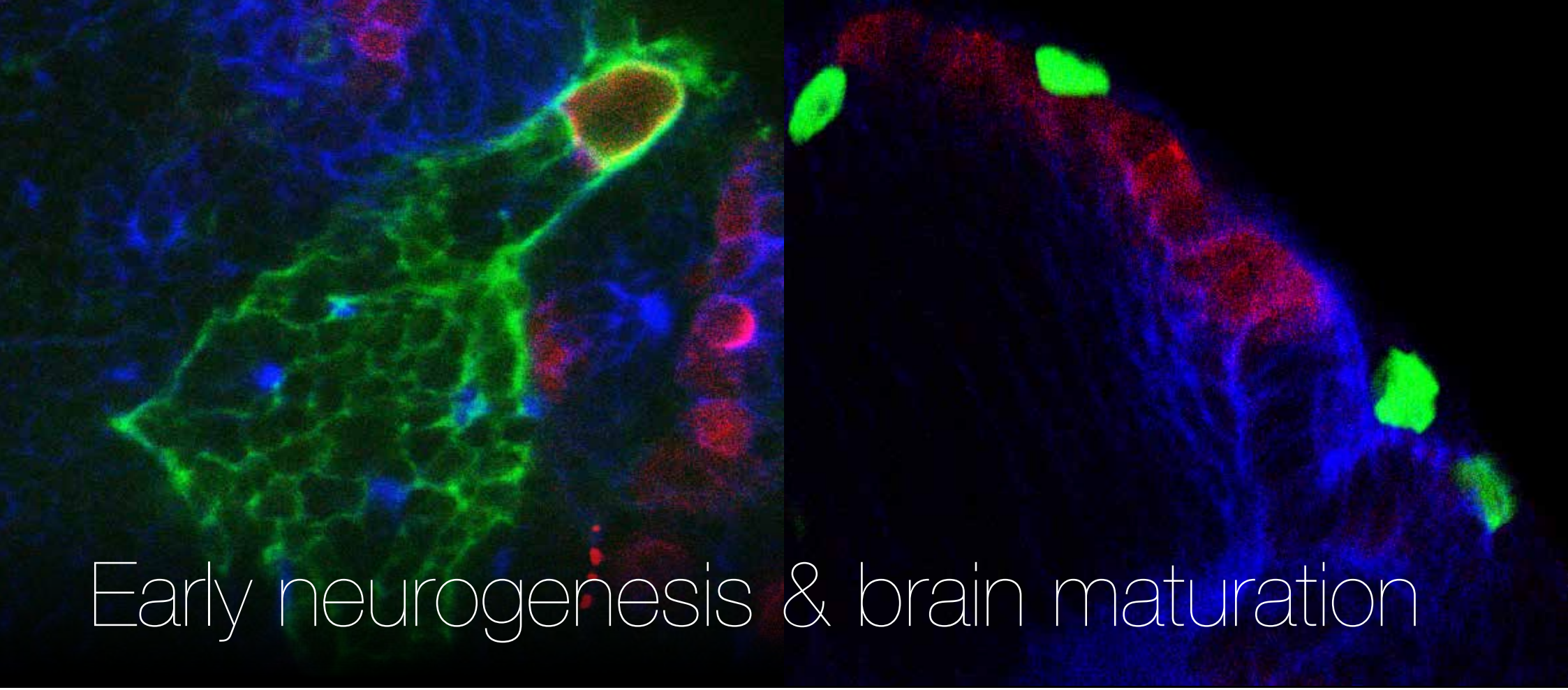

Early neurogenesis & brain maturation

Important early events in neurogenesis are proving elusive and difficult to define. One example is the events that underlie the specification of neural stem cells, both in terms of number and cell types, which is a consequence of the processes controlling neuroepithelial cell proliferation and the transition of their progeny into neural stem cells.

Javier Morante CSIC

Early neurogenesis & brain maturation

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

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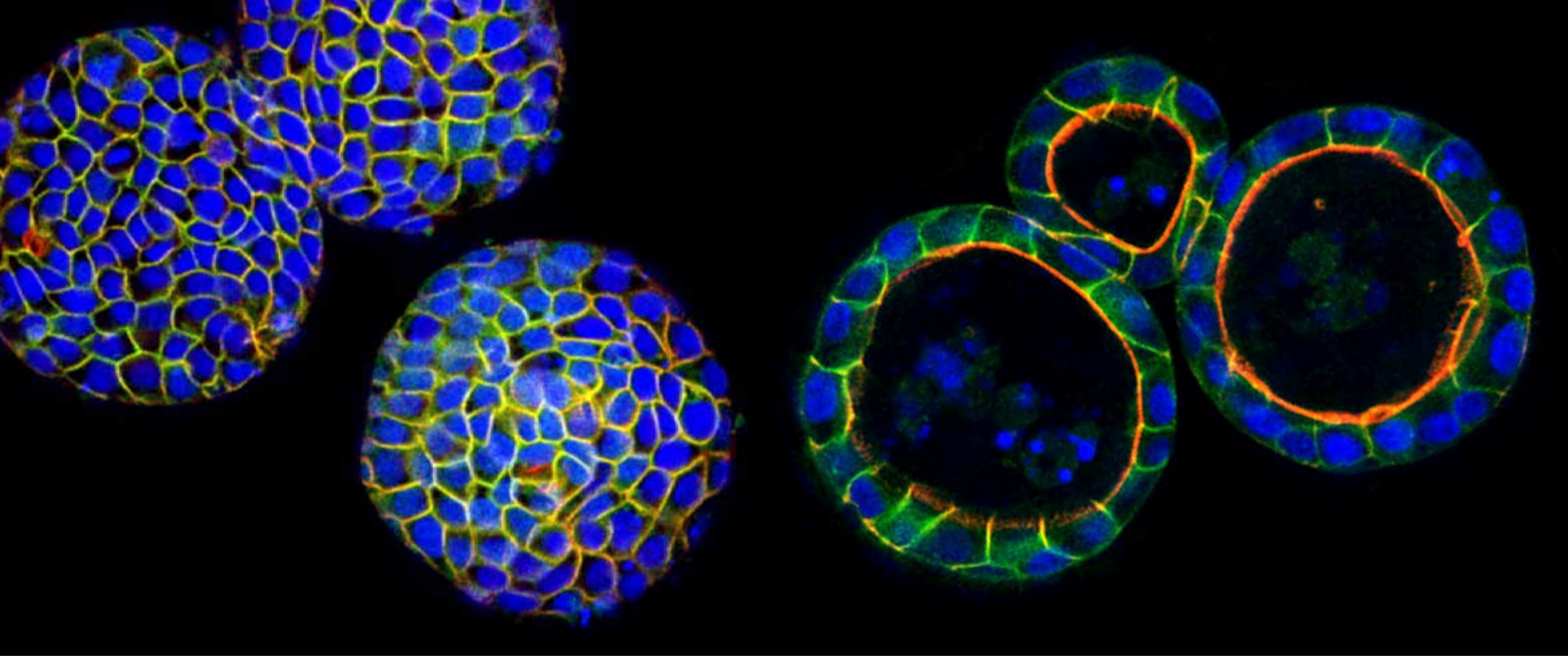


Cell movements in development & disease

M. Angela Nieto CSIC

Our main interest is the study of cell behaviour in development and disease, in particular associated with cell movements. We have been working on the functional analysis of the Snail gene family, and have shown its implication in different processes during

embryonic development in vertebrates, including the formation of the mesoderm and the neural crest, both involving the triggering of the epithelial to mesenchymal transition (EMT) and massive cell migrations. We have also found that pathological activation of Snail factors either during development or, in particular, in the adult leads to several prominent pathologies. As such, Snail aberrant activation in tumours leads to the acquisition of invasive and migratory properties (2000-2002). In addition, we have found that Snail fulfills unexpected roles in cartilage and bone. On one hand, Snail controls bone growth during foetal and postnatal development (2007) and, on the other hand, it controls bone mass in the adult (2009). The pathological aspect of Snail is also conserved in the bone, as we have found that an aberrant Snail function leads to the development of achondroplasia (the most common form of dwarfism in humans) and osteomalacia (bone demineralization in the adult). Going back to fundamental processes at early development, we have shown that the interplay between Snail factors and another transcription factor (Sox3) together with a stereotyped repression of epidermal cadherins determines embryonic territories at gastrulation (2011) and neurulation (2016).

A phylogenetic analysis of this family has allowed us to conclude that the Snail genes constitute, along with the Scratch genes, a subgroup of the C2H2 zinc-finger transcription factors. We have found that in addition to the regulation of cell movements, Snail is important for cell survival and for the attenuation of cell cycle in embryos (2004). Its role in survival we had later extended to adult hepatocytes (2010). We have found that Scratch is required for the survival of spinal cord neurons during embryonic development by antagonizing the p53 apoptotic pathway (2011) and also that it prevents postmitotic neurons from re-entering the cell cycle (2013). Therefore, cell survival and the control of cell division are ancestral functions of the Snail/Scratch superfamily with important implications in development and disease. We are currently investigating the putative role of Scratch in the adult central nervous system.

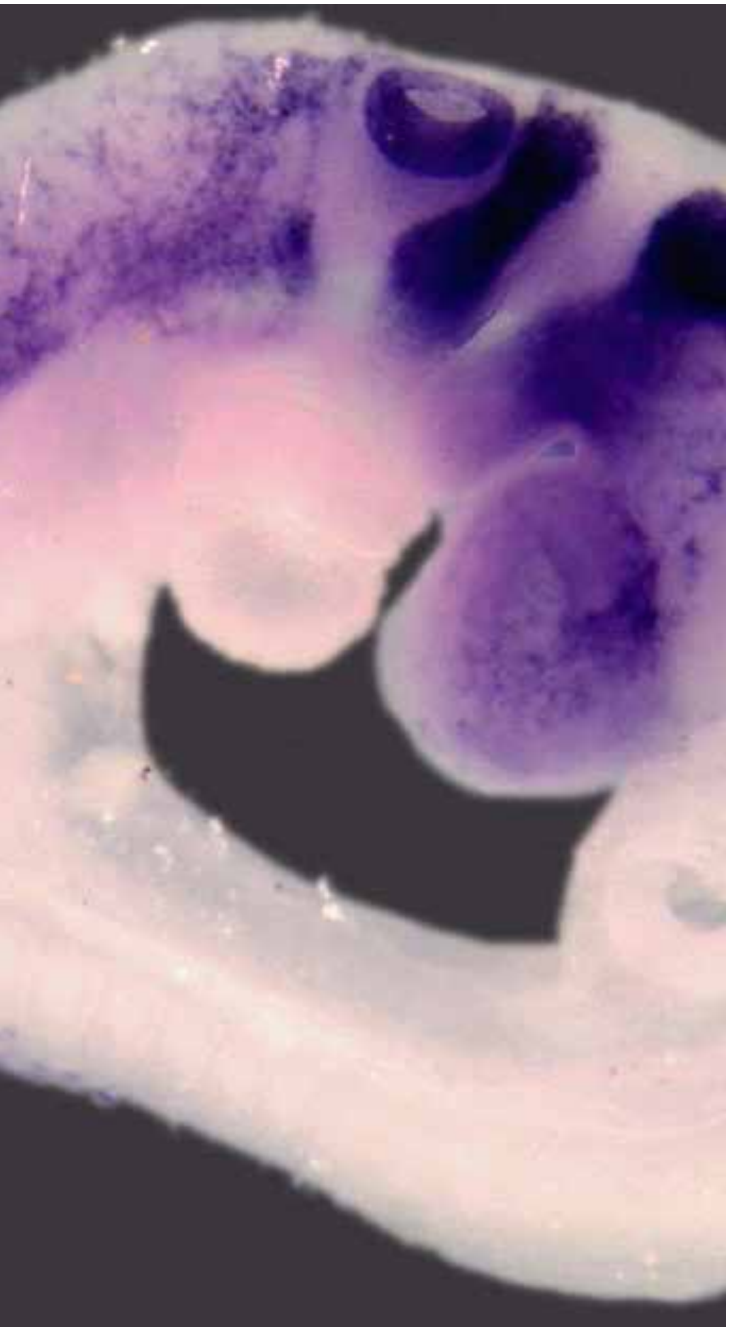
The invasive and survival properties of Snail-expressing cells provide a selective advantage to disseminate to distant territories both during embryonic development and during cancer progression, allowing cells to form different tissues and organs or distant metastasis, respectively. Interestingly, metastasis is the cause of the vast majority of cancer-associated deaths, but the underlying mechanisms remain poorly understood. The invasion and dissemination steps during carcinoma progression have been associated with EMT, which as mentioned above, endows cells with invasive abilities and also with the stem cell-like properties required to initiate the formation of a secondary tumor. However, we have shown that while EMT is important for the acquisition of motility and invasive properties in cancer cells, its abrogation is required for these migratory cancer cells to colonize distant organs and progress to the metastatic state. This also has an impact on the design of therapeutic strategies in cancer, as inhibiting EMT (and therefore, motility) when cells have already disseminated from the primary tumour will indeed favour metastasis formation (2012). We are now characterizing the EMTs induced by different EMT-TFs and their impact in the metastatic process in models of breast cancer and melanoma.

The EMT has been involved in the development of other pathologies including organ fibrosis. The development of fibrosis associated with massive accumulation of extracellular matrix, mainly collagen fibres secreted by an excess of myofibroblasts. Fibrosis appears in different organs such as the kidney, the liver, the lung

or the heart and it concurs with a progressive reduction in organ function and eventual organ failure. Renal fibrosis develops in different pathological conditions including urinary obstruction, diabetes, glomerulonephritis or deterioration of transplants. Thus, it is crucial to understand the mechanisms by which fibrosis develops and one key question is the origin of myofibroblast, that has been debated until recently. Some data indicated that they were the result of an EMT undergone by the renal epithelial cells, while lineage analysis suggested that this was not the case. Recently we have shown that the activation of EMT is required for development of organ fibrosis but, importantly, that renal epithelial cells are not the source of myofibroblasts. As such, fibrosis develops after renal epithelial cells undergo a partial EMT by which they dedifferentiate but remain integrated in the tubules. These damaged epithelial cells send signals to the interstitium that in turn favor (i) the differentiation of myofibroblasts from interstitial fibroblasts, and (ii) the recruitment of bone marrow-derived mesenchymal cells and macrophages, therefore favoring fibrogenesis and sustaining inflammation, the hallmarks of renal fibrosis. Furthermore, we have shown that fibrosis can be attenuated by the systemic injection of EMT inhibitors, opening new avenues for the treatment of fibrotic diseases (2015). We are currently investigating putative additional inhibitors and their mechanism of action.

In our studies we use mouse, chick and zebrafish as experimental models for loss or gain and function analyses together with cultured cells and samples from patients with the associated pathologies.

Cell movements in development & disease



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Cell movements in development & disease

Nieto, M.A., Huang R Y-J, Jackson, R.A. and Thiery, J.P. (2016) **EMT: 2016**. **Cell** *166,21-45*

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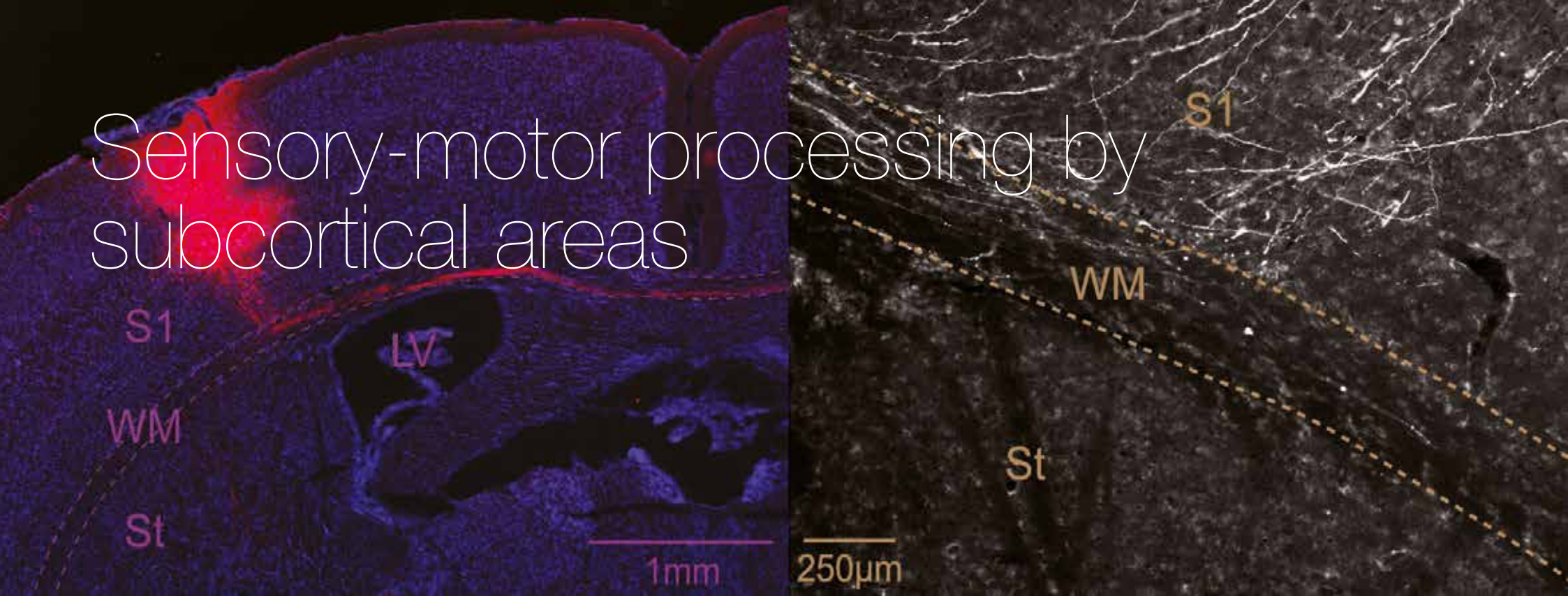
Sensory-motor processing by subcortical areas



Ramón Reig García CSIC

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

The striatum (caudate nucleus & putamen) is the "door" or input layer of the basal ganglia that receives inputs from multiple cortical areas as prefrontal, motor or sensory, and thalamus. The striatum also receives massive dopaminergic

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

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

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Sensory-motor processing by subcortical areas

Reig R, Silberberg G. **(2016)** *"Corticostriatal pathways underlying bilateral sensory integration in the mouse striatum – a whole-cell in vivo study".* **Cereb. Cortex** *26 (12): 4405-4415*

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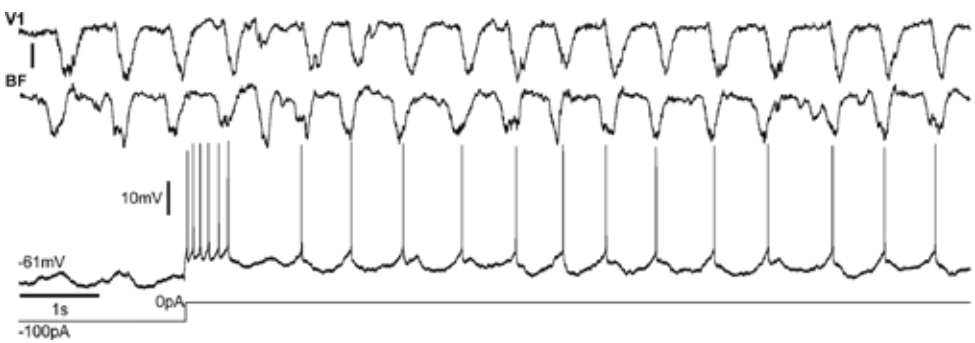
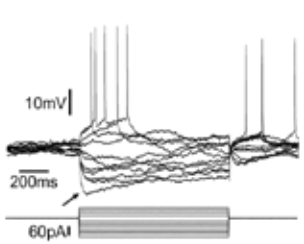
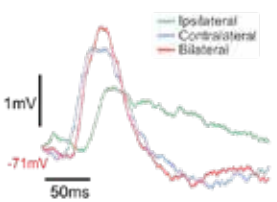
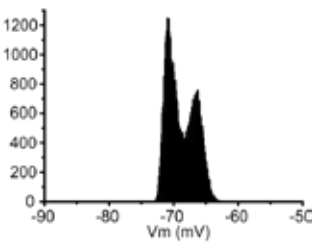




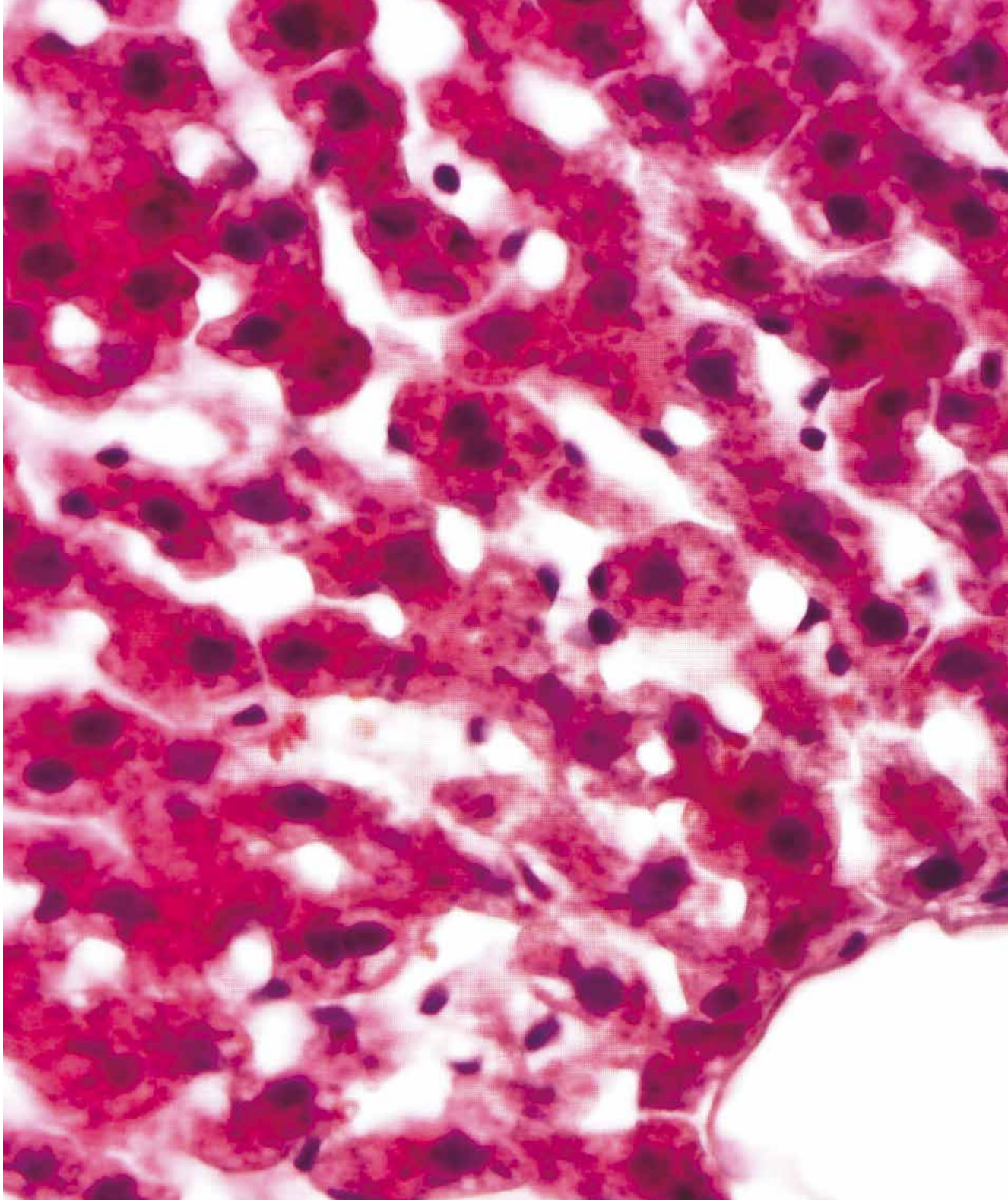




Altered molecular mechanism in Alzheimer's disease & dementia

Javier Sáez Valero UMH

Our aim at the IN is to introduce a research line into Alzheimer's disease (AD) and dementia that originated from a basic point of view but, that is relevant to the development of clinical-diagnostic applications. Therefore, the translational benefits of our research lie in the fact that we not only aim to clarify the pathological



mechanisms behind these diseases, but also to define potential diagnostic tools and/or processes with therapeutic relevance. Our group is also member of CIBERNED (an ISC-III Center for Networked Biomedical Research focused in neurodegenerative diseases).

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

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

Furthermore, we evaluate the diagnostic potential and methodological approaches for analysis of particular glycoforms of proteins, which improve sensitivity and specificity of the biomarkers. We also develop assays to identify secretase-related proteins, related with β-amyloid metabolism, in the cerebrospinal fluid. We also collaborate in the BiomarkAPD project (a JPND initiative of the UE) and the Society for CSF analysis and clinical neurochemistry in the validation and standardization of CSF biomarkers.

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Altered molecular mechanism in Alzheimer's disease & dementia

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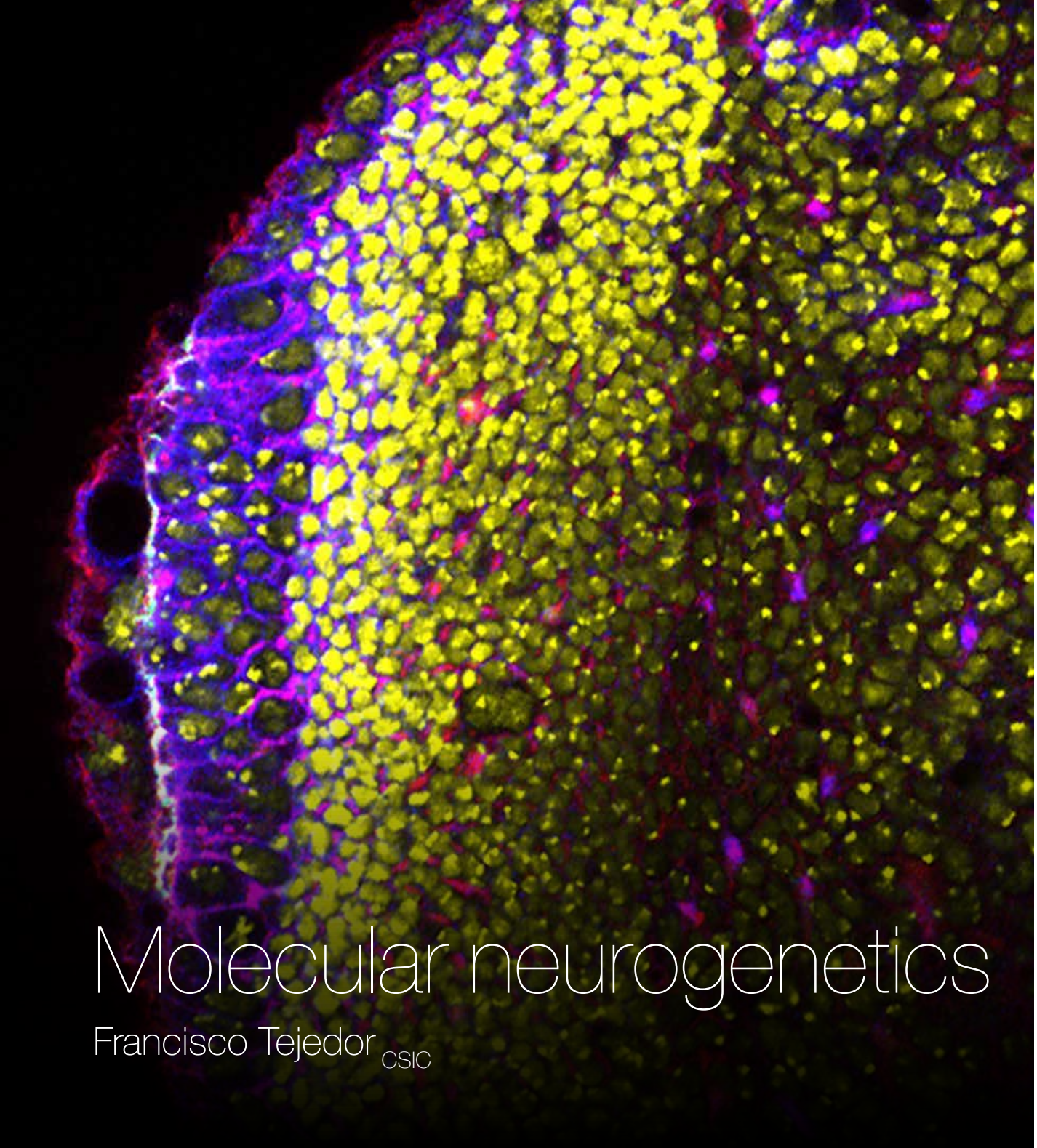

Molecular neurogenetics

Francisco Tejedor CSIC

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

Following this approach, we have identified the gene *minibrain* (*mnb*, also called *Dyrk1A* in vertebrates) as a major regulator of neural progenitor cell proliferation

and neurogenesis in Drosophila. *Mnb/Dyrk1A* encodes a very well evolutionary conserved protein-kinase, which play several functions through brain development. We are focusing on its roles in the regulation of neural proliferation, cell cycle, neurogenesis, and neuronal differentiation, unravelling the underlying molecular mechanisms. Remarkably, haploinsuficiency of *DYRK1A* causes an intellectual disability syndrome characterized by microcephaly. *Mnb/Dyrk1A* has also raised great interest because it is one of the most interesting candidate genes for the neuropathologies of Down Syndrome (DS) and neurodegeneration processes. As a matter of fact, the MNB/DYRK1A kinase is presentely considered a suitable drug target for DS neuropathologies. Since DS is originated by the triplication of chromosome 21, we are using experimental models to determine what cellular functions and molecular mechanisms are altered by an excess of *Mnb/Dyrk1* function to generate neurobiological alterations reminiscent of DS neuropathologies, particularly, neuronal deficit, dendritic atrophy and neurodegeneration. We are also testing the suitability of MNB/DYRK1A kinase inhibitors to interfere with neuronal functions as a prospect to apply pharmacological therapeutic appraoches to DS neuropathologies.

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Sensory transduction and nociception

Félix Viana CSIC
Carlos Belmonte UMH

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

Our research group is interested in the analysis of the cellular and molecular mechanisms that determine the activation of thermoreceptors, low- and high-threshold mechanoreceptors, as well as polymodal and silent nociceptors. We are trying to identify the cellular and molecular determinants of stimulus specificity, and the mechanisms that give rise to the different response thresholds. To this end, we use different experimental approaches, ranging from the transcriptional profiling of subpopulations

of sensory neurons, optopharmacology, the molecular analysis of transduction ion channels and receptor molecules, recordings of sensory nervous activity in isolated cells and single neurons in anesthetized animals to behavioral analysis in different animal models of chronic pain.

We are examining the problem of sensory transduction at different conceptual levels. From a reductionist point of view, we are trying to establish which transduction molecules and which cellular mechanisms give rise to the preferential response to a particular stimulus and how they are modulated. In a more integrative approach, we are also trying to define the functional relationships between different transduction molecules, the ion channels involved in neuronal excitability and intracellular signal transduction pathways in sensory receptor neurons. The final goal is to obtain an integrated view of their cellular mechanisms for stimulus detection and the coding of these stimuli into a discharge of nerve impulses with a defined temporal sequence. We are also exploring the biological significance of this sensory message in the regulation of bodily functions. The analysis includes the search for selective pharmacological agents capable of interfering with the different steps of the transduction process or their modulatory mechanisms. An additional important research line of our group involves the analysis of the short- and long-term cellular and molecular changes that occur in primary sensory neurons during pathological process such as lesions and inflammation.

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

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Sensory transduction and nociception

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Collaborations & Agreements

Public and Private Institutions

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

- Cátedra de Neurobiología Remedios Caro Almela
- Institute Pasteur and University Pierre and Marie Curie (Paris VI)
- Fundación Duques de Soria.
- Hospital de San Juan. Actividades de formación de personal RID e intercambio de expertos. Consejería de Salud de la Comunidad Valenciana.
- European Dana Alliance for the Brain.
- Fundación Marcelino Botin
- Asociación Española Contra el Cáncer
- The Allen Institute for Brain Science

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European Network of Neuroscience Institutes

European Research, particularly on Neuroscience, depends heavily on the creative contributions of young investigators. In recognition of this important need, fourteen major European Neuroscience Institutes formed a network, dedicated to the promotion of the independent work of young investigators. From the interactions between its different nodes, we expected a major impact on the research of the individual teams, a stronger integration of research between participating institutions, and a significant structuring effect on the Neuroscience field in the future European Research Area. All these objectives have been attained.

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

Research Professorship in Neurobiology

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

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

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

Richard Morris & Constantino Sotelo

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

This Prize has been so far awarded to Barry Dickson (2006), François Guillemot (2007), Rüdiguer Klein (2008), Steve Wilson (2009), Christine Holt (2011), Magdalena Götz (2013) and Silvia Arber (2015).

The latest Prize Ceremony was held on October 29th, 2015 at the Instituto de Neurociencias. The prize winner Dr. Silvia Arber, opened the ceremony with the Remedios Caro Almela Lecture.

Dr Barry J. Dickson
2006

Dr François Guillermot
2007

Dr Rűdiger Klein
2008

Dr Stephen Wilson
2009

Dr Christine Holt
2011

Dr Magdalena Götz
2013

Dr Silvia Arber
2015

Services & Facilities

Zebrafish Facility

Zebrafish have become an animal model of choice for the study of embryonic development, due to their transparent embryos and easy maintenance. The zebrafish facility consists of 3 independent modules housing more than a 1000 adult fish each. It is equipped with a reverse osmosis water purification system, pH, temperature and salinity control, and a live food preparation setup (Artemia). A daily supply of zebrafish embryos is available for experimental embryology, gene expression analysis or the generation of transgenic lines.

Molecular Biology & Microbiology

This service offers the equipment necessary to carry out a wide range of molecular biology techniques including: gel documentation equipment for agarose and polyacrylamide gels; CCD-based imaging system for chemiluminiscence, fluorescence and gel documentation; film developer for X-ray imaging; spectrophotometers including plate readers and small volume photometers (NanodropTM); electroporation systems; and pulse field electrophoresis. This service also allows the cultivation of microorganisms in an environment controlled by Biological Safety regulations.

The service provides incubators and orbital shakers specially designed and reserved to perform microbiology experiments with a wide variety of biological tools such as plasmids, prokaryotic expression vectors, BACs or yeast.

Centrifugation Facility

This facility has a variety of centrifuges and ultracentrifuges, and a wide range of rotors such as fixed-angle rotors, swinging-bucket rotors, vertical-tube rotors and the innovative NVTTM near-vertical-tube rotors. This equipment is suitable for preparative techniques (i.e. specific particle isolation) as well as analytical techniques, which seek to define the physical or hydrodynamic properties of a specific particle.

Experimental Embryology

(two units; one of them allocated a the genetically modified mice animal house)

This service is specifically designed to carry out experimental embryology procedures in mammals. It is equipped with a micro dissection laser, biolistic system and fluorescence stereoscopic microscope with digital image capture and processing system. The Unit also has a CUY21 electroporator system, which is designed for in utero electroporation of DNA plasmids in embryonic brains, and an ultrasonic system that allows the electroporation of DNA or the injection of cells in precise regions of the brain.

Live Cell Imaging Platform

In order to take advantage of the latest live cell imaging techniques, the IN has an imaging platform composed of: Conventional confocal microscope, which allows image acquisition of fixed material at several wavelengths.

- Inverted confocal microscope, equipped with a constant atmosphere chamber and multiple lasers, including UV. Its uses include time-lapse experiments and the precise un-caging of cage compounds.

- Multiphoton microscope, equipped with two workstations. One includes an upright microscope for rapid acquisition of images from in vivo preparations or brain slices, with simultaneous electrophysiological facilities. The other consists of an inverted microscope for long-term time-lapse experiments under controlled conditions.

- Total Internal Reflection microscope (TIRF), used for the measurement of real time kinetics of binding to sensor molecules. TIRF is a fast, non-destructive and sensitive technique suited to the monitoring of orientation changes and lateral mobility of proteins.

- Confocal electrophysiology station with resonant scanner for high temporal resolution and electrophysiology equipment.

- Laser Microdissector for microscopic high resolution scrutiny that lets to select and discard areas of tissue, individual cells, cell fragments and even chromosomes.

- Neurolucida system for neuroanatomical analysis of the brain and workstations for analysis and processing of images that allows the extraction of statistical parameters and the quantification of scientific results. This includes reconstruction of 3D images and 4D series.

Surgery Room

(two units; one of them allocated a the genetically modified mice animal house)

The surgery unit is prepared for both minor and major surgery, including stereotaxic surgery in mouse, rat and guinea pig. The Unit has a LEICA M400-E surgical microscope, an isoflurane anaesthesia machine, medical oxygen, a small anaesthesia chamber and a homeothermic blanket. There is an aesthetic gas elimination system installed. The protocols used at the Unit are approved by the Institute's Ethical Committee for Animal Experimentation.

Cell Culture Facility

The facilities are distributed in several areas of common use:

- Cell lines culture room: equipped with hoods, CO2 incubators, centrifuges, normal and fluorescence microscopes. This room is used exclusively for cell lines, which are routinely tested for mycoplasma.
- Primary culture rooms: with similar equipment, this facility is devoted to animal cell primary culture from several sources.
- Organotypic culture room: is equipped to carry out animal tissue explant cultures (microscope, vibrating microtome and tissue electroporator).

Electronics Workshop

This workshop carries out the routine testing and repair of laboratory instruments, as well as the design, construction and repair of different electronic devices. It is equipped with machinery for the construction of laboratory pieces in metal or plastic.

Fluorescence Assisted Cell Sorting

The Institute runs the latest generation "Fluorescence Activated Cell Sorting" (FACS) currently available. Our FACSAria is a digital analyzer/sorter of

high precision and sensitivity for sorting and analysis of cell populations with differently tagged structures, used in studies such as: the search for molecules involved in neuronal development and plasticity, the search for molecules implicated in tumour development, neuropsychiatric and neurodegenerative disorders, and cell therapy: stem cell isolation for transplant in animal models for neuropsychiatric and neurodegenerative diseases.

Behavioural Studies Area

Comprised of two units: one of them allocated a the genetically modified mice animal house; the other in the general animal house.

In this common area there are 6 independent spaces and a common area for washing, Equipment such as Skinner box, rotarod, treadmill, 8 arms maze, hot plate and water maze with tracking system allow researchers to study the behaviour of rats and mice (motor function, memory, learning, conditioning, etc). There are also systems for multiple electrophysiological tasks in animals chronically implanted with multiple electrodes, recording EEG, field potentials or individual neurons in animals performing different tasks such as spatial navigation or sensory discrimination.

Illustration & Photography

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

Purchase & Storage

This service manages all the institutional purchasing requirements, giving support and advice to research groups when acquiring material and equipment. The new service's space covers 200m2 with more than 900 lineal meters of shelves and specific cabins for flammables and reactive products. A stock of frequently used material for research groups and other services is maintained. The Service is coordinated with the Institute's administration in order to effectively place orders, manage their payment and assign them to the different grants.

fMR Brain Imaging

The Institute's Brain Imaging Service is equipped with a Bruker Biospec 70/30 Magnetic Resonance Imaging system with high performance (up

to 675 mT/m) gradients and capacity for the application of modern techniques of multimodal and parallel Imaging in animal experimentation (rat, mouse, rabbit and cat)

This pioneering installation combines functional MRI (fMRI) with deep brain micro-stimulation and electrophysiological recordings. This leading edge technology allows the simultaneous acquisition of neuronal activity (local field potentials, multiunit activity) and hemodynamic responses, enabling studies of neurovascular coupling, functional connectivity and neuronal plasticity.

Animal House

The IN Service of Genetically Modified Mice belongs to the UMH Animal Experimentation Service and houses about 8000 mice under specific pathogen-free conditions. It has an approximate area of 2000 square meters and it includes the following areas:

- Breeding and maintenance of lines of genetically modified mice. It houses about 300 lines of genetically modified mice. The lines are handled by specialized personnel under direct advice of researchers through a computer program designed for that purpose.
- Breeding of wild type and production of gestational age defined female mice. The area of production of non-transgenic mice serves the needs of this type of mice.
- The service defined gestational age females. Designed specifically to support experimental embryology, it provides to researchers of inseminated mice at different stages of gestation.
- Quarantine. Where are stocked animals received from other institutions. Before any eternal animal can be admitted, the Aanimals Testing Lab determines their health status and carries out embryo transfer if they are not free of pathogens.
- Laboratory of transgenesis. Where the rederivations and other procedures of assisted reproduction such as IVF and freezing of sperm and embryos of mouse are performed.
- Experimental zone. It has an area of animal stocking and comprehensive equipment for experiments involving surgery and behavioural studies within the barrier area.
- Washing and sterilization area. Centralised washing, preparation & sterilization of all materials used in the animal house.

Master & PhD Program

The PhD Program has been an ongoing activity at the Institute since its foundation, and it has played an important role in the professional formation of scientists in the field. A high percentage of students completing the program have subsequently been incorporated into national research teams or have taken up overseas postdoctoral positions. The program is intended for graduate students to complete a PhD thesis based on experimental work in neuroscience. The Program offers the official title of PhD in Neurosciences as established by the Real Decreto 1393/2007 and has received the "Quality Mention" of the Spanish Ministry of Education. This year the PhD program was under the RD 99/2011 normative.

The Program is closely linked to the ongoing research projects at the IN directed by its staff members (CSIC researchers and University professors) working in several areas of neurosciences. The study of neuroscience requires a broad multidisciplinary approach given the wide-ranging techniques required for the study of the nervous system and neurological diseases. Postgraduate training at the IN covers such diverse fields as neurophysiology, cellular biology, molecular biology, genetics and behavioural studies.

During the Academic Year 2012-2013 we started the Master in Neuroscience: from bench to bedside. This is a one year totalling 60 ECTS on both basic and advanced aspects of neuroscience offered in several courses by University and CSIC lecturers.

Master in Neuroscience: from Bench to Bedside.

Introduction to the Study of the CNS.

- Advances in embryology and the genetic analysis of the nervous system.
- New developments in the study of the organization and cellular components of the nervous system.

Neuroscience Today.

- Current topics in neuroscience a multidisciplinary view: scientific seminars and activities of the INA.

Functional Concepts in Neurosciences.

- Electrical Signaling in the Nervous System.
- Intracellular Signaling.
- Synaptic transmission.
- Neural Systems.

Neuropathology and Therapy.

- Neuropathology.
- New therapies.

Advanced Studies in Neuroscience.

- Developmental Neurobiology: from Neurogenesis to neural circuits formation.
- Sensory Transduction.
- Information processing.

Techniques in Neurosciences.

- Basic aspects of the use of shared resources in research. Animal facilities and cell culture.
- Functional image acquisition and image analysis. Functional fMR in small animals.
- Tools in neuroscience: Tools for Bioinformatics Analysis of Gene Expression and Evolution.
- Statistical tools in neuroscience. Annotated brain atlas.

Master Research Work

PhD Program

After completion of these credits in this or another equivalent Master, students can enrol in his/her PhD thesis project within a research group at the IN (see http://in.umh.es/unidades.aspx).

Students of the program are eligible to diverse sources of fellowships linked to the ongoing research projects of the IN and the JAE, and Consolider programs of the CSIC.

The Program belongs to the Network of European Neuroscience Schools (NENS) a formal structure within the Federation of European Neuroscience Societies (FENS).

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Zebrafish Facility

Diana Abad Bataller
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Publications

Article

Alvarez-Alonso MJ., Jurado-Barba R., Martinez-Martin N., Espin-Jaime JC., Bolaños-Porrero C., Ordoñez-Franco A., Rodriguez-Lopez JA., Lora-Pablos D., De la Cruz-Bertolo J., Jimenez-Arriero MA., Manzanares J., Rubio G. Association between maltreatment and polydrug use among adolescents. **Child Abuse Negl.** *51:379-389*

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Seminars

08/01/16 **Development of the CRISPR-Cas technologies**
Dr. Francis Mojica *Universidad de Alicante*

15/01/16 **Understanding muscle stem cell regenerative decline in aging**
Dra. Pura Muñoz *UPF, Barcelona*

22/01/16 **Insights from genetic and genomic approaches into the understanding of brain cortical development**
Dr. Jamel Chelly *Institut de Génétique et de Biologie Moléculaire et Celulaire, Université Strasbourg, France*

29/01/16 **Using zebrafish to study myelinated axons in vivo**
Dr. David Lyons *Centre for Neuroregeneration, University of Edinburgh*

05/02/16 **Sex Circuits and Brain Maps**
Dr. Greg Jefferis *MRC Laboratory of Molecular Biology, Cambridge, UK*

12/02/16 **The retinal pigment epithelium: close interaction partner of the photoreceptors and interface between retina & the body system**
Dr. Olaf Strauss *Charité- Universitätsmedizin Berlin, Germany*

26/02/16 **Dissecting the functions of inhibitory dorsal horn neurons**
Dr. Hanns Ulrich Zeilhofer *University of Zurich, Switzerland*

04/03/16 **From molecular and cellular mechanisms underlying cortical-dependent memories to cognitive enhancers**
Dr. Kobi Rosenblum *University of Haifa, Israel*

11/03/16 **Tell me how you fire and I'll tell you how you wire**
Dra. Marta Nieto *CNB-CSIC, Madrid*

23/03/16 **Ensuring 'just-right' Wnt signalling during development**
Dr. Jean Paul Vincent *The Crick Institute, London, UK*

15/04/16 **Mechanisms of Axon Growth and Regeneration**
Dr. Frank Bradke *German Center For Neurodegenerative Diseases (DZNE), Bonn, Germany*

22/04/16 **The Arc of synaptic memory**
Dr. Clive Bramham *University of Bergen, Norway*

29/04/16 **Novel mechanisms regulating axonal branching and synaptic specificity in the CNS**
Dr. Dietmar Schmucker *VIB Vesalius Research Center, Leuven, Belgium*

06/05/16 **The role of spontaneous activity in cortical development**
Dr. Matthias Kaschube *Frankfurt Institute for Advanced Studies, Goethe University, Frankfurt - Germany*

13/05/16 **From actions to habits to compulsions in cocaine addiction: neural systems and emerging endophenotypes**
Dr. Barry Everitt *University of Cambridge, UK*

20/05/16 **A novel class of RNAPIII-regulated neuronal enhancers in developing neurons**
Dra. Antonella Riccio *UCL, London, UK*

27/05/16 **Cognitive processing by metastable states**
Dr. Emili Balaguer *Bournemouth University, UK*

30/05/16 **Detoxified botulinum molecules for chronic pain relief.**
Dr. Bazbek Davletov *University of Sheffield, UK*

02/06/16 **Stability and plasticity of inhibitory synapses beyond super-resolution**
Dr. Antoine Triller *Institut de Biologie de l'École Normale Supérieure, Paris, France*

03/06/16 **How Spontaneous Activity Wires the Developing Brain prior to Experience**
Dr. Christian Lohmann *Netherlands Instiute for Neuroscience*

06/06/16 **Mesa Redonda con los Premios Nobel de Medicina, Dres. Hamilton Smith y Erwin Neher.**
Dr. Hamilton Smith y Dr. Erwin Neher *Instituto de Neurociencias*

09/06/16 **BSC at a Glance**
Dr. Mateo Valero *Barcelona Supercomputing Center, Barcelona*

15/07/16 **Cell Fate Decisions during Somatic Cell Reprogramming**
Dr. Duanging Pei *Guangzhou Institutes of Biomedicine and Health, China*

20/07/16 **Brain substrates for human motor learning.**
Dr. Jerome Sanes *Brown University, Providence, USA*

16/09/16 **Basal Ganglia neural circuits underlying sensorimotor functions**
Dr. Gilad Silberberg *Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden*

23/09/16 **Imaging and treating pre-metastatic niches in melanoma**
Dra. Marisol Soengas *CNIO, Madrid*

29/09/16 **Microglial proliferation in health and disease**
Dr. Diego Gomez-Nicola *University of Southampton, UK.*

30/09/16 **Genetic Dissection of Neuron and Glia Genesis using Mosaic Analysis with Double Markers (MADM)**
Dr. Simon Hippenmeyer *IST, Klosterneuburg, Austria*

06/10/16 **Self and non-self as a fundamental distinction in learning**
Dr. Björn Brembs *Universität Regensburg*

07/10/16 **What can neuroscience learn from the visual arts? Perception of three-dimensional space**
Dr. Colin Blakemore *University of Oxford, UK*

21/10/16 **Roles of T-type calcium channels in chronic pain: from sensory afferences to spinal networks**
Dr. Emmanuel Bourinet *Institut de Génomique Fonctionnelle, Montpellier, France*

28/10/16 **Optical probing and optogenetic of TREK channels physiology**
Dr. Guillaume Sandoz *Insitut Valrose de Biologie, Nice, France*

04/11/16 **Studying Neural Circuit Computations in Zebrafish Brain**
Dr. Emre Yaksi *Kavli Institute for Systems Neuroscience /Centre for Neural Computation, Trondheim, Norway*

18/11/16 **Cell polarity and tissue morphogenesis**
Dr Barry Thompson *The Francis Crick Institute, London, UK*

25/11/16 **The small G protein Arl8B controls the number and position of chick retinal ganglion cell axon branches**
Dr. Uwe Drescher *King's College, London, UK*

02/12/16 **How oligodendrocytes form myelin and support axons**
Dr. Mikael Simons *Max Planck Institute for Experimental Medicine*

13/12/16 **Sensorimotor control of Drosophila larval chemotaxis**
Dr. Ibrahim Taştekin *EMBL-CRG Center for Genomic Regulation*

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26/01/16 **¿Cómo se forman los circuitos que permiten coordinar nuestros movimientos?**
Dra. Eloísa Herrera González de Molina *Instituto de Neurociencias*

25/02/16 **La genética y el lenguaje de las células**
Dr. Luis García Alonso *Instituto de Neurociencias*

12/04/16 **Cómo la herencia y el entorno moldean nuestro cerebro.**
Dr. Angel Barco Guerrero *Instituto de Neurociencias*

26/04/16 **Divide (Bien) y Vencerás: Relevancia del Modo de División Celular en el Desarrollo y en Tumorogénesis**
Dra. Ana Carmena *Instituto de Neurociencias*

31/05/16 **No me chilles que no te veo: Función del tálamo en los circuitos neuronales**
Dra. Guillermina López Bendito *Instituto de Neurociencias*

29/06/16 **Música y Neurociencia.**
Dr. Miguel Valdeolmillos *Instituto de Neurociencias*

03/11/16 **¿Cómo se genera la diversidad celular en nuestro cerebro?**
Dr. Javier Morante *Instituto de Neurociencias*

29/11/16 **"¿Mejor solo que mal acompañado?"**
Dra. Cristina Márquez Vega *Instituto de Neurociencias*

PhD Thesis

Bartolini , Giorgia **Molecular Mechanims Regulating the Intracortical Migration of Interneurons.**
Dr. Oscar Marín Parra 03-06-2016

Cárdenas Castelló , Adrián **Robo Receptors Regulate Neurogenesis along Vertebrate Brain Evolution.**
Dr. Víctor Borrell Franco 21-11-2016

Florez Paz , Danny Mauricio **Caracterización Biofísica y Mecánica de Neuronas Propioceptoras en Ratón.**
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Gomis Pont , Alexandra **The Eyes of the Moral Mind: Affect Based-gain Control & Contextual Modulation of Moral Decisions.**
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Murillo Rodríguez , Blanca **Papel del Factor de Transcripción ZIC2 en la Migración de Diferentes Poblaciones Prosencefálicas Durante el Desarrollo del SNC.**
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Rives Quinto , Noemi **Analysis of the Drosophila asymmetric cell division regulator Canoe/Afadin in tumorigenesis.**
Dra. Ana Carmena de la Cruz 10-03-2016

Ruiz Reig , Nuria **Characterization & fate mapping of the thalamic eminence & the caudoventral pallium in mice.**
Dr. Alfonso Fairén Carrión y Dra. Eloísa Herrera González de Molina 01-03-2016

Sempere Ferrández , Alejandro **The callosal contribution to cortical circuits.**
Dr. Emilio Geijo Barrientos 15-12-2016

Events

13th Christmas Meeting of the Instituto de Neurociencias

8th Congress of 5P Syndrome and rare diseases

11th IN Progress Report Workshop.

"Brain Awareness Week 2016" Neuroscience Institute Open Days

“Brain Awareness Week 2016” Brain and society series: “Neuroscience & Violence”

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Press Cuttings