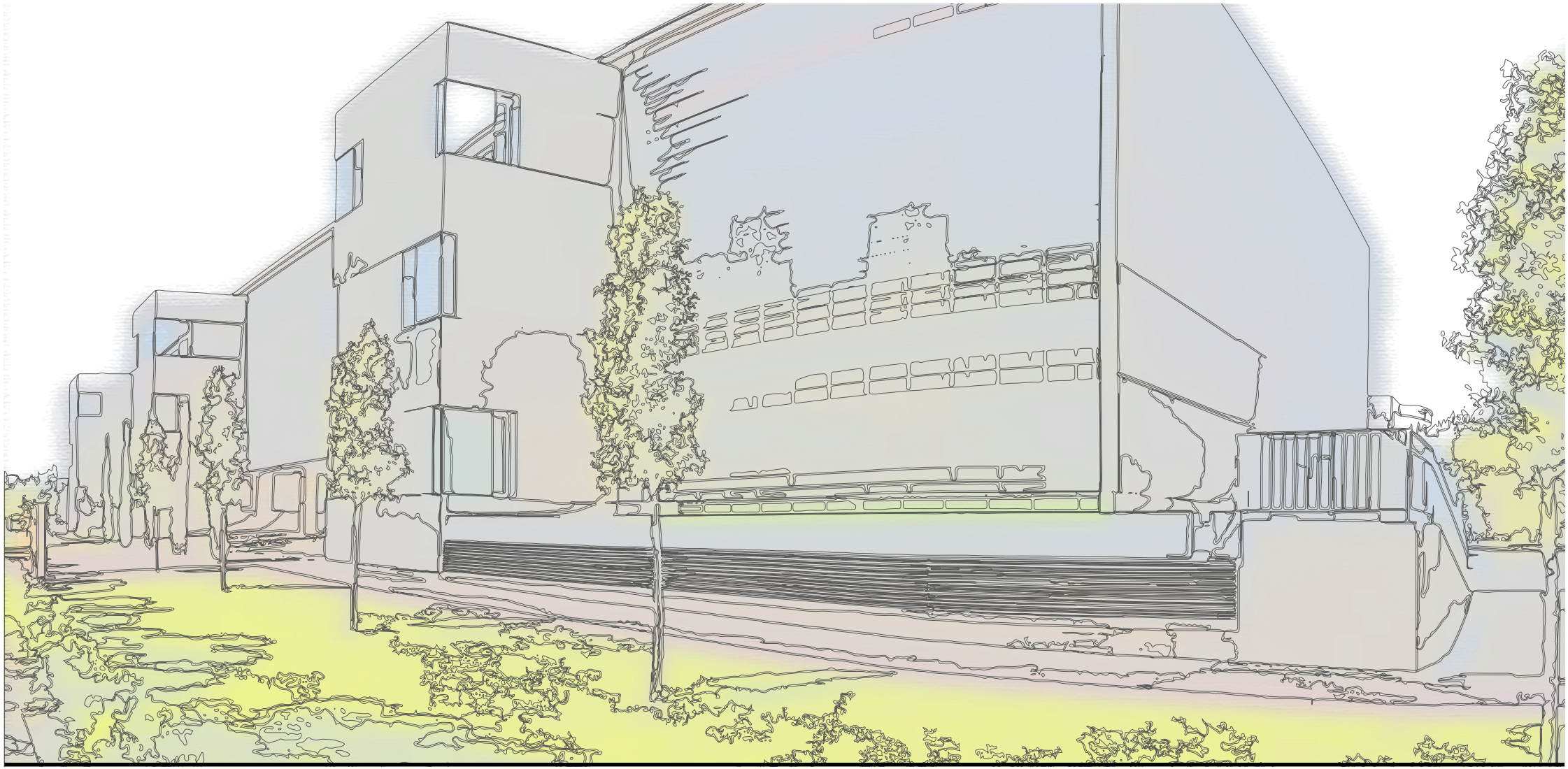
INSTITUTO DE NEUROCIENCIAS

ANNUAL REPORT 2014



EXCELENCIA
SEVERO
OCHOA

ANNUAL REPORT 2014

CSIC
Consejo Superior de Investigaciones Científicas

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

EXCELENCIA SEVERO OCHOA

Salutation

Juan Lerma : Director

In the year 2014 and despite country's sustained cuts in investment in R+D, the IN has navigated this situation keeping the level of revenues for competitive projects and providing a series of important scientific milestones. All this has been endorsed by the accreditation as a "Center of Excellence Severo Ochoa", which was officially awarded in the month of June. This recognition fills us with pride and gives us new impetus for the future.

It must be emphasized that, at the end of 2014, two extraordinary colleagues left the IN after accepting tempting offers from abroad. Oscar Marín, who will head the MRC Center of Developmental Neurobiology at King's College in London, and Beatriz Rico, who joined that same Center as a professor and researcher. In the official farewell by the entire Institute, both presented the achievements obtained in their stay amongst us after returning from their postdoctoral stay in USA. Both received a plate offered by all of us as a sign of remembrance. Some may think that this case is a natural outcome from the scientific and economic crisis that Spain is experiencing. More on the contrary, this is not other thing but a confirmation of the Institute success, having positioned itself as a hothouse of significant international figures in neuroscience. Mobility is something inherent to scientific activity. Our problem is the lack of the necessary capabilities for people replacement, which rules are entirely imposed by the system in which we are immersed.

Another colleague, Alfonso Fairén, reached the age of retirement after belonging to our Institute since its inception as a joint center. We will always remember him and wish him a blissful retirement. We hope that now he can do what he never had time to do.

In 2013 we maintained a stable ca. 60% women and 40% men proportion, and about 20% of our staff comes from other countries. Indeed, more than 30% of our contracted researchers are not Spanish in origin, which indicates on the degree of internationalization of our Centre.

Fulfilling the mission of the IN to generate knowledge about the brain and its mechanisms, this year has been full of relevant findings. We are confident that the selection of this year's milestones, covered in a specific section, will be of interest to the reader of this memory.

This year, we have gained a kind of stability in the number of articles published with respect to previous years; we have also reach to a stable averaged impact factor of our paper, as well as the number of citations to the latest period runs constant.

In the past year, the IN has been subject of a number of relevant actions. For example, the Institute was awarded with the "Important of the Year" prize awarded by the Información newspaper. This award was presented to us by the President of the Generalitat Valenciana, Albert Fabra on 19th of February, 2015 in a solemn ceremony. Likewise, the Economic and Social Council from the UMH recognized the "Remedios Caro Almela" Chair in Neurobiology with one of its prizes. Several members of the IN achieved significant recognition for his research. On the one hand, Angel Barco and Eloisa Herrera were appointed members of the Editorial Board of the journal Molecular Brain, and the latter got the 15th "Alberto Sols" award to the best scientific work. Carlos Belmonte was awarded with the prize "Luis Federico Leloir" by the Ministry of Science, Technology and Innovation from Argentina and Juana Gallar was distinguished by the Faculty of Medicine of the University of the State of Louisiana with the Dean's Award Lecture in Neuroscience. Juan Lerma was elected Secretary General-Elect of the Federation of European Neuroscience Societies (FENS) and member of the Board of the European Brain Council. Finally, Guillermina López-Bendito was chosen among the first 20 members of the Young Investigator Network of Excellence sponsored by FENS and the Kavli Foundation. Thus the IN and its members continue reinforcing its presence at national and international levels.

In 2014, the IN groups continued with a certain degree of expenditure containment. This undoubtedly is due to the still unforeseen improvement in financial support of scientific research in Spain. Logically, it is necessary to search for strategies preventing threatening of the most fundamental structures of the Institute by the continuous crisis of funding for Science in Spain. Successful applications by various researchers to the calls of the European Research Council and other programs of the Horizon 2020, is a natural way to overcome the Spanish crisis. We remain committed to incorporating the latest technology to allow our researchers perform experiments and advance in the knowledge of the brain in equal conditions to our European and American colleagues.

Also it should be noted, that the master taught by staff of our Institute: "Master in Neuroscience: from research to clinics" continues to increase significantly the number of pre-registrations, while and as in previous years, in the 2014 we admitted only 14 students.

Salutation

In 2014 we continue our collaboration in the celebration of the World Brain Awareness Week, organizing several round tables and demonstrations towards diffusion and advocacy of neuroscience. Our open doors journeys, for instance, allowed almost 900 people to visit the Institute and attend lectures on our brain and demonstrations on how through animal models we could get insights into the functioning of the human brain. On this occasion we insisted that neuroscientific knowledge will change the way of thinking and behaving of our society in the future and Neuroscience is called upon to change attitudes and human customs in a radical way. In this task, I would like to thank all those who in one or another position have contributed this year to the Mission of the IN contributing to situate it at the scientific level it has. Also I warmly acknowledge the institutions to which the IN belongs, CSIC and UMH, for the continuous support of our research activity. For the years to come, we are looking forward to developing our program under the auspices of the Severo Ochoa Center of Excellence Award.

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 (See graphic Surface Distribution).

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 units: Developmental Neurobiology, Molecular Neurobiology, and Cellular and Systems Neurobiology. Each unit 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.

What We Do

During the Academic Year 2012-2013 we started the 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.

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 38 tenured researchers (20 from the UMH and 18 from the CSIC), 6 non-tenure scientists, 172 doctoral and postdoctoral researchers and 96 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 2011-2014 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, reaffirms the IN's pursuit of excellence, and its intention to strengthen and specify some of the current lines of research aimed at studying the nervous system. We wish to move 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.

Most Relevant Scientific Milestones

- Determined for the first time the impact of changes in the tridimensional structure of the neuronal chromatin in neuronal function and animal behavior. Our study also identifies genes associated with neuropsychiatric diseases that are particularly sensitive to epigenetic regulation through changes in chromatin architecture.

- Discovered a novel mechanism by which interactions between a limited numbers of axon guidance cues can multiply the responses in developing axons, which is crucial for the formation of brain connectivity.

- Found new clues of neuronal connectivity that underlay the surprising stability and resistance to cascading failures observed in brain networks. The brain compensates the characteristic instability found in interconnected systems and that affects numerous manmade infrastructure networks by following some simple connectivity rules that have now been unveiled. The finding has important technological implications.

- Development of a new method for MRI imaging of the mouse central nervous system that provides unprecedented anatomical detail in young embryos. The extremely high resolution of this fast and reliable method enables identifying most of transient structures and fiber tracts of the embryonic mouse forebrain, as well as subtle anatomical defects in mouse mutants.

- Discovered the neural circuits and the computational mechanisms that allow the brain to improve the quality of the low-resolution images captured by the eye.

- Revealed the requirements for the targeting of Kainate receptors to the synapse and uncovered the fundamental role of high affinity subunits in this process.

- Identification of Eml1 as a novel gene mutated in human malformations of the cerebral cortex, and the role of this gene in regulating cortical progenitor cell position in mouse. This study demonstrates the relevance of embryonic progenitor cells in the pathogenesis of severe human brain malformations and epilepsy.

- Described how tear osmolality increases equivalent to that seen in evaporative dry eye primarily increases background activity of corneal cold thermoreceptors, and maybe underlying discomfort sensations developed during dry eye disease.

- Identification of abnormal expression pattern of Notch receptors, ligands, and downstream effectors in the dorsolateral prefrontal cortex and amygdala of suicidal victims.

- Demonstration that social defeat in adolescent mice increases vulnerability to alcohol consumption.

Patents

- Pharmaceutical Composition for the Treatment of the Epiphora.
  Patent No. ES2408132. Grant date: 28-03-2014. UMH and CSIC.

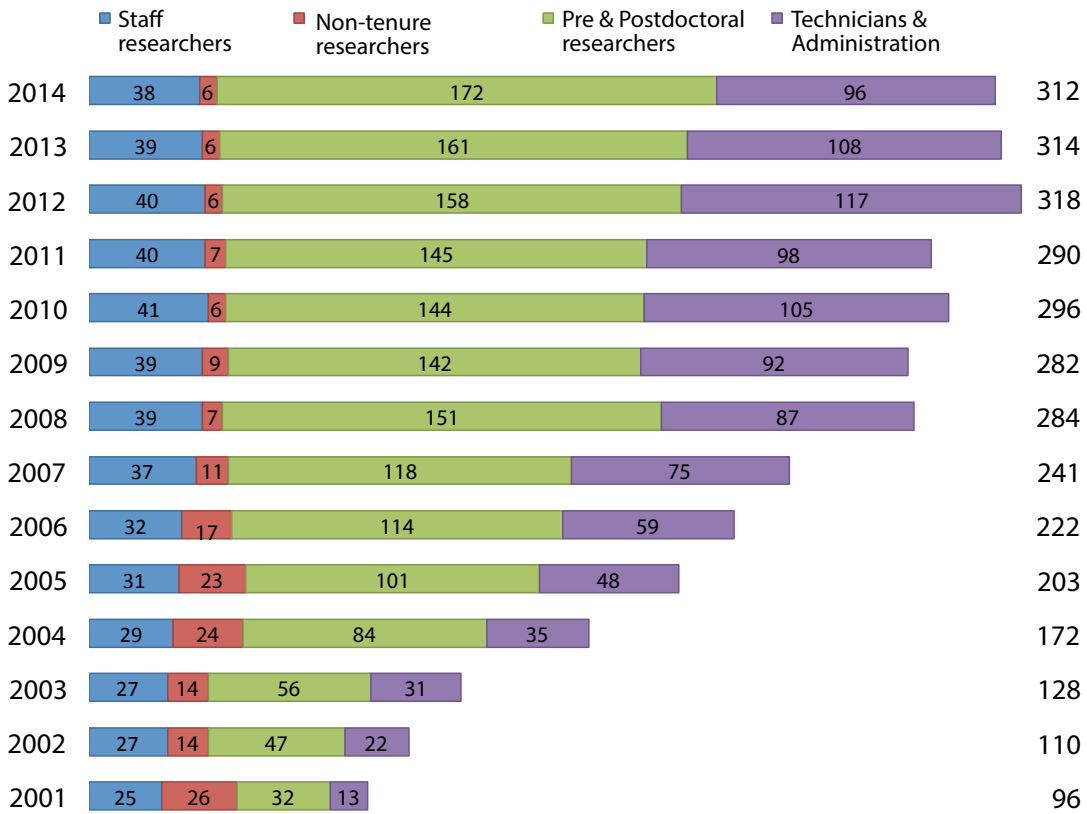
- Method for Determining Alzheimer's Disease by Detection of Glycoproteins Carrying the HNK-1 Glicoepitopo.
  Patent No. P201130290. Award date: 31-01-2014. UMH

- Use of Antagonists of the TRPA1 Receptor for the Treatment of Diseases Associated with Bacterial Infections.
  Patent No. P201131503. Award date: 30-05-2014. UMH and CSIC

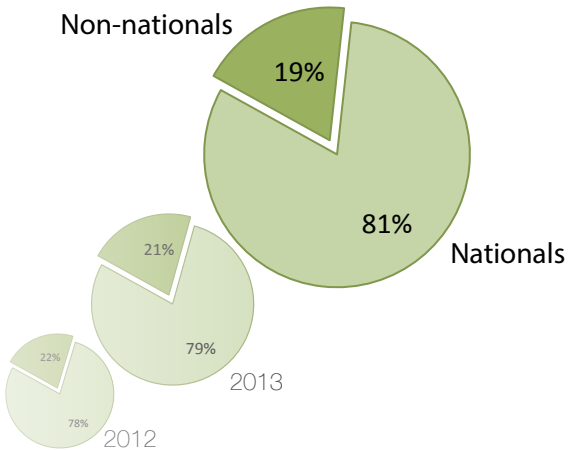
- Non-human Animal Model for Autism Spectrum Disorders, Anxiety and/or Depression.
  Patent No. P201431268. Presentation date: 29-08-2014. CSIC

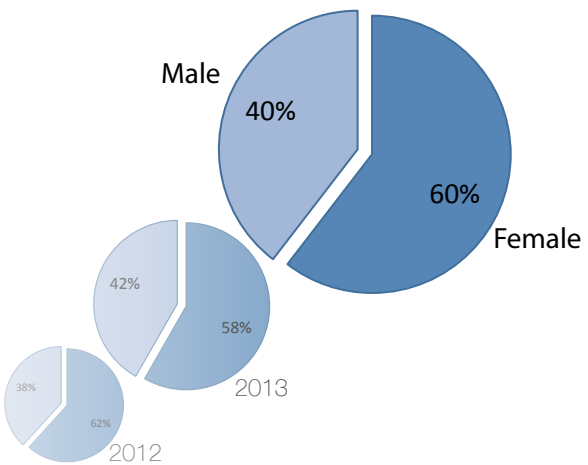
The Institute in Numbers

Personnel by Category

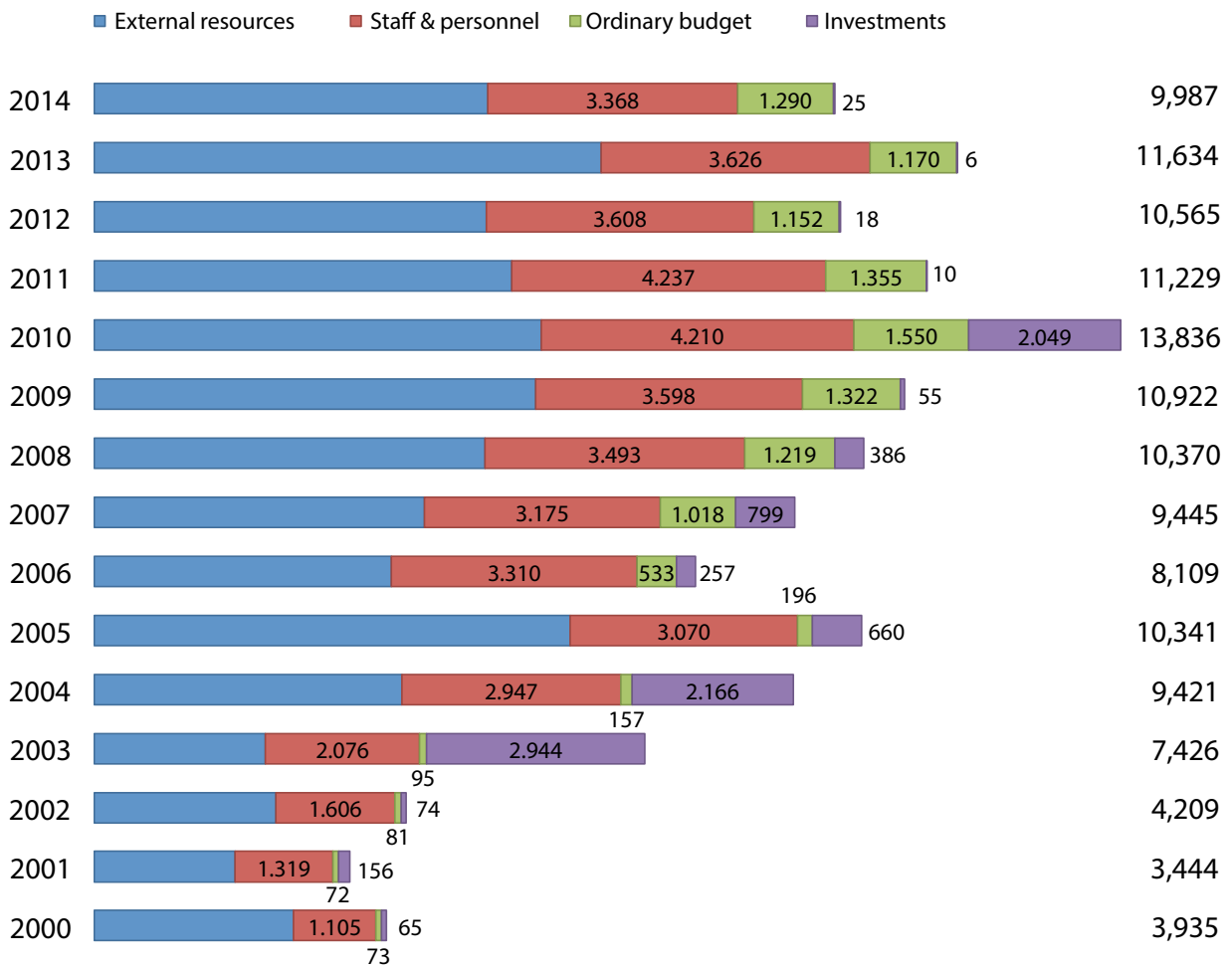


Personnel by Origin & Gender

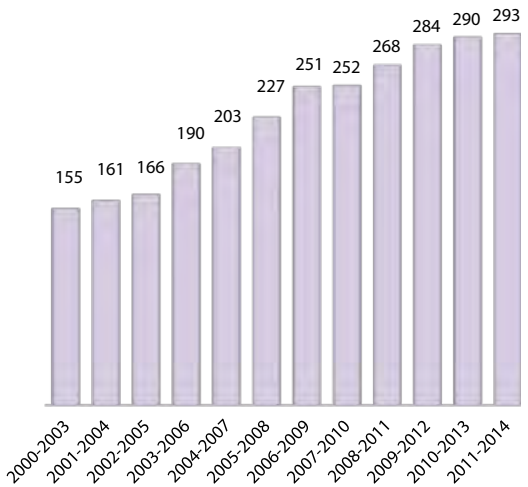




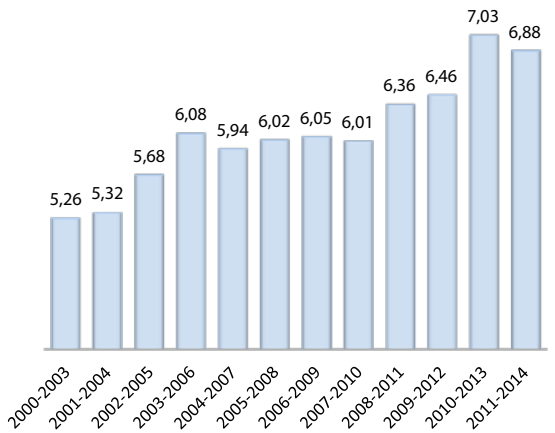
Budget Growth in Thousands of Euros



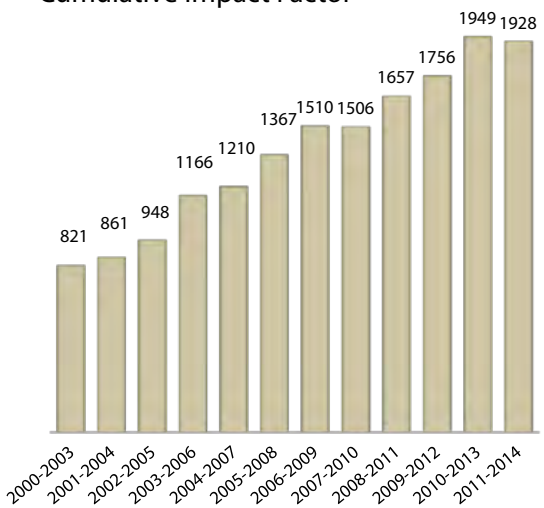
Number of Papers



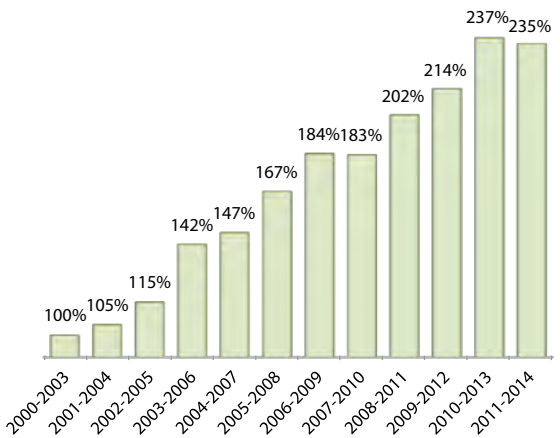
Mean Impact Factor



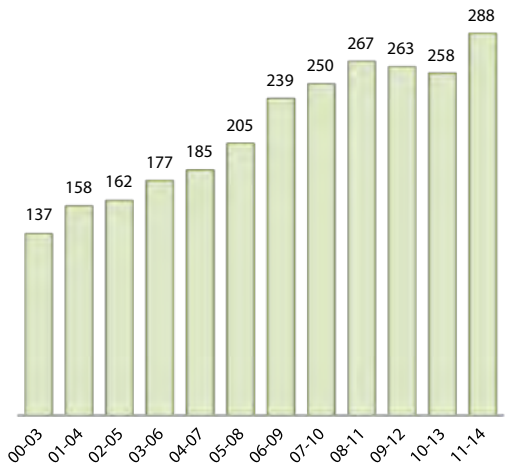
Cumulative Impact Factor



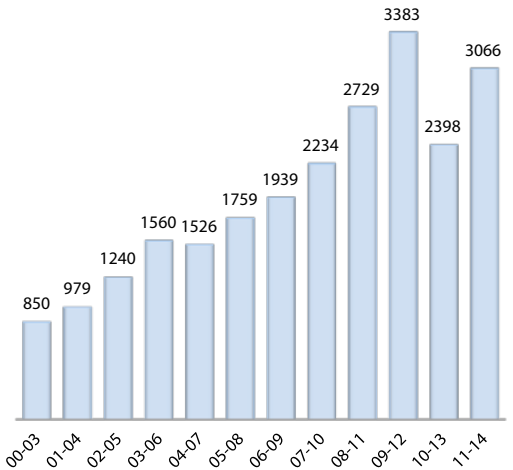
Cumulative Impact Factor Increase



Number of Papers



Citations to the Periods Papers



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Research Units

Cellular & Systems Neurobiology

Director: M. Maravall

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

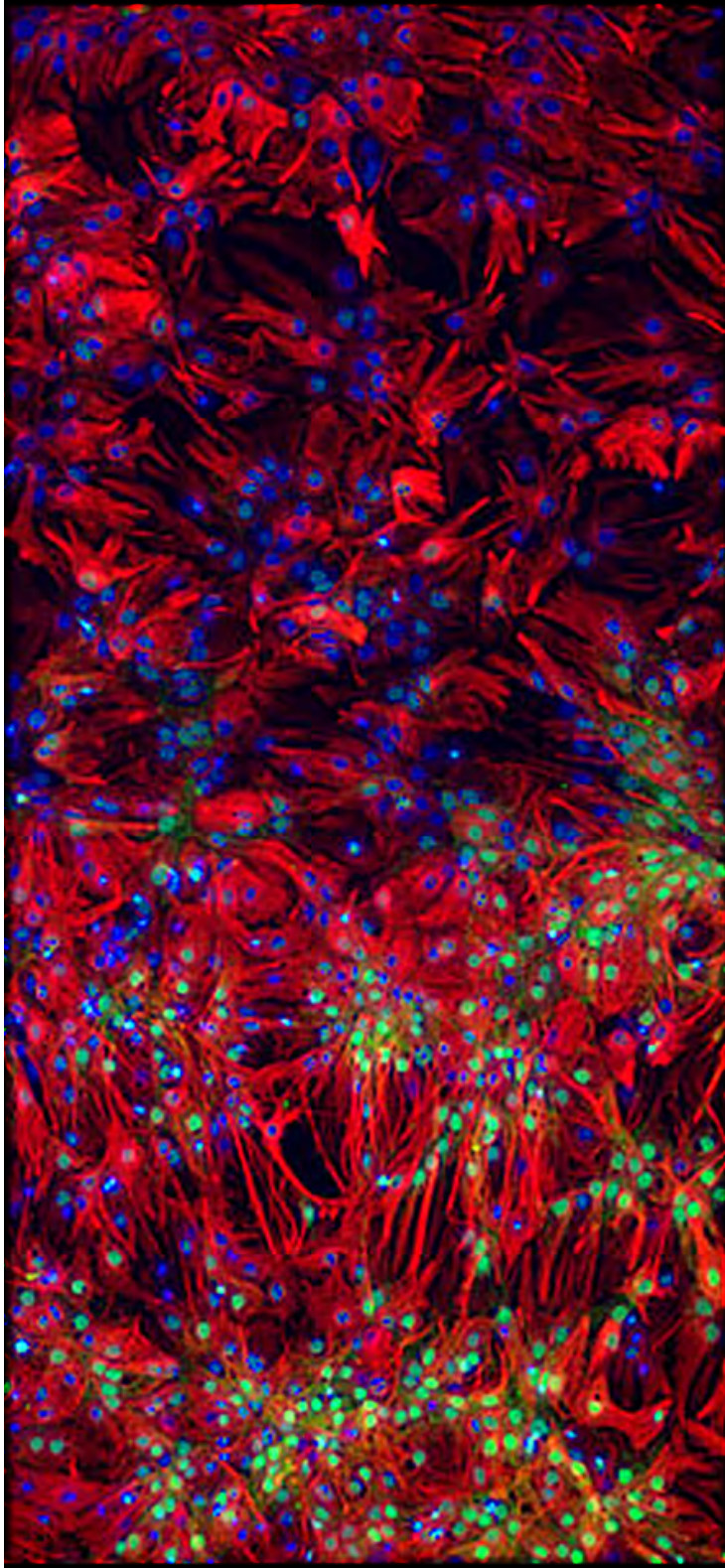
Director: A. Nieto

The Developmental Neurobiology Unit consists of thirteen 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

Director: L. M. Gutiérrez

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 Coord: M.A. Nieto

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 Coord: J. Lerma

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 Coord: F. Viana

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

Coord: O. Marín

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

Coord: S. Martínez

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

Coord: M. Maravall

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

Sensory transduction and nociception

Félix Viana CSIC
Roberto Gallego UMH
Carlos Belmonte 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

PDZ proteins & signaling networks during the specification of neuronal identities

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

Maria Domínguez CSIC

Cortical development

Alfonso Fairén 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

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 & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

Dynamics & plasticity of cortical sensory responses

Miguel Maravall CSIC

Neuronal migration & circuit assembly in the cerebral cortex

Oscar Marín CSIC

Visual Neuroscience Laboratory

Luis M. Martínez CSIC

Experimental Embryology

Salvador Martínez UMH
Constantino Sotelo UMH

Cell movements in development & disease

M. Angela Nieto CSIC

Neural circuit formation & remodeling

Beatriz Rico CSIC

Altered molecular mechanism in Alzheimer's disease & dementia

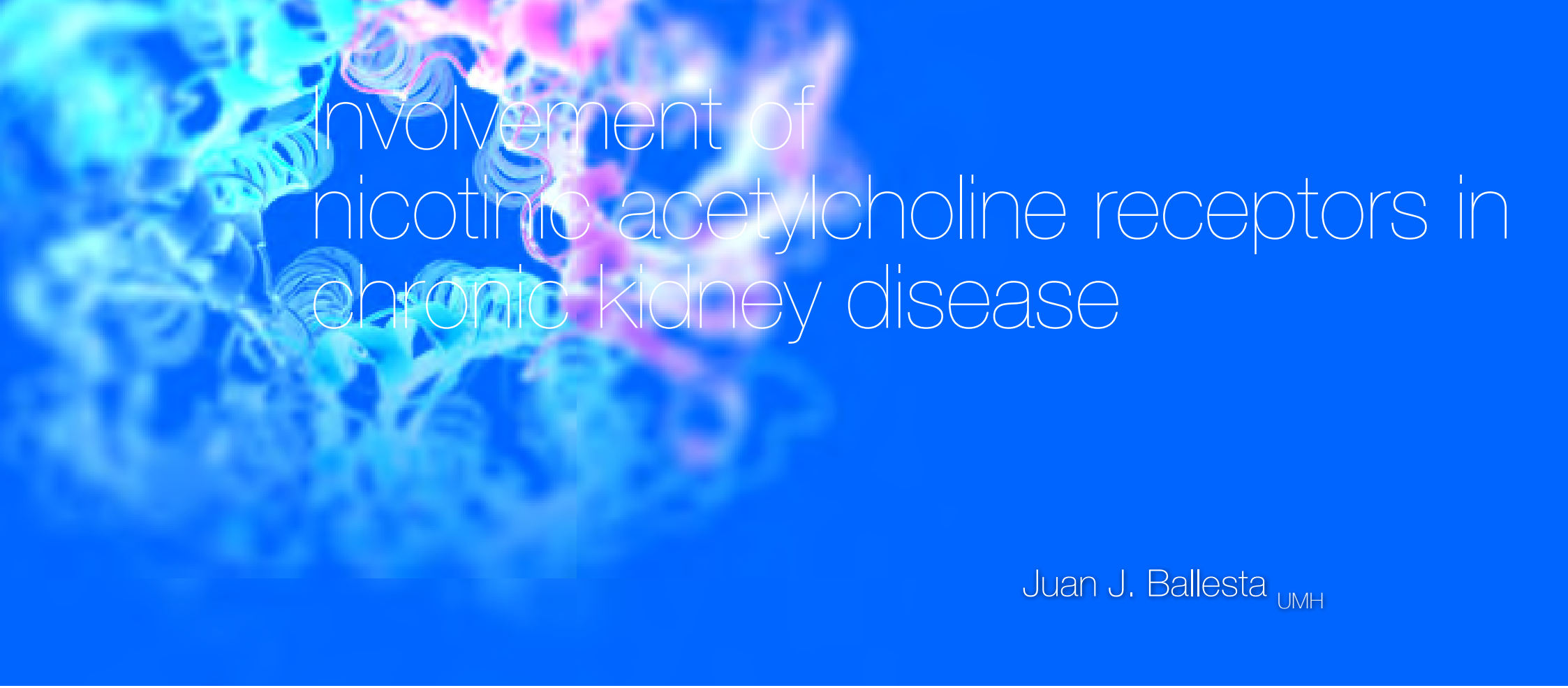
Javier Sáez Valero UMH

Biophysics & pharmacology of ionic channels

Francisco Sala UMH
Salvador Sala UMH

Molecular neurogenetics

Francisco Tejedor CSIC



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*

Ballesta, J.J., del Pozo, C., Castello-Banyuls, J., Faura, C.C.(2012) **Selective down-regulation of α4β2 neuronal nicotinic acetylcholine receptors in the brain of uremic rats with cognitive impairment** **Exp Neurol** *236: 28-33*

Alves DS, Castello-Banyuls J, Faura CC , Ballesta, J.J. (2011). **An extracellular RRR motifflankingthe M1 transmembranedomaingovernsthebiogenesis of homomeric neuronal nicotinicreceptors** **FEBS Letters** *585: 1169-1174*

Vicente-Agullo, F. Rovira, JC. Sala, S. Sala, F. Rodriguez-Ferrer, C. Campos-Caro, A. Criado, M. Ballesta, JJ. (2001). **Multiple roles of theconservedresiduearginine 209 in neuronal nicotinicreceptors.** **Biochemistry** *40:8300-8306.*

Críado, M. Domínguez del Toro, E. Carrasco-Serrano, C. Smillie, Fl. Juíz, JM. Viniegra, S. Ballesta, JJ. (1997). **Differentialexpression of a-bungarotoxin neuronal nicotinicreceptors in adrenergicchromaffincells: a role fortranscription factor Egr-1.** **TheJournal of Neuroscience** *17: 6554-6564.*

Sensory transduction and nociception

Félix Viana CSIC
Roberto Gallego UMH
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 relationshiWps 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 pWrocess 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.

Principal Investigators
Félix Viana
Roberto Gallego
Carlos Belmonte

Associated Investigators
Laura Almaraz (with Ana Gomis)
Elvira de la Peña (with Ana Gomis)

PhD Investigator
Baldemar Santiago

PhD Students
Rebeca Caires
Bristol Denlinger
Carlos Fernández-Peña
Enoch Luis Baltazar
Jan-Albert Manenschijn
Purificación Ordás
Susana Quirce (with Ocular Neurobiology)

Technical Staff
Eva Quintero
Ana Miralles

Administration
Ángeles Gallar

Sensory transduction and nociception

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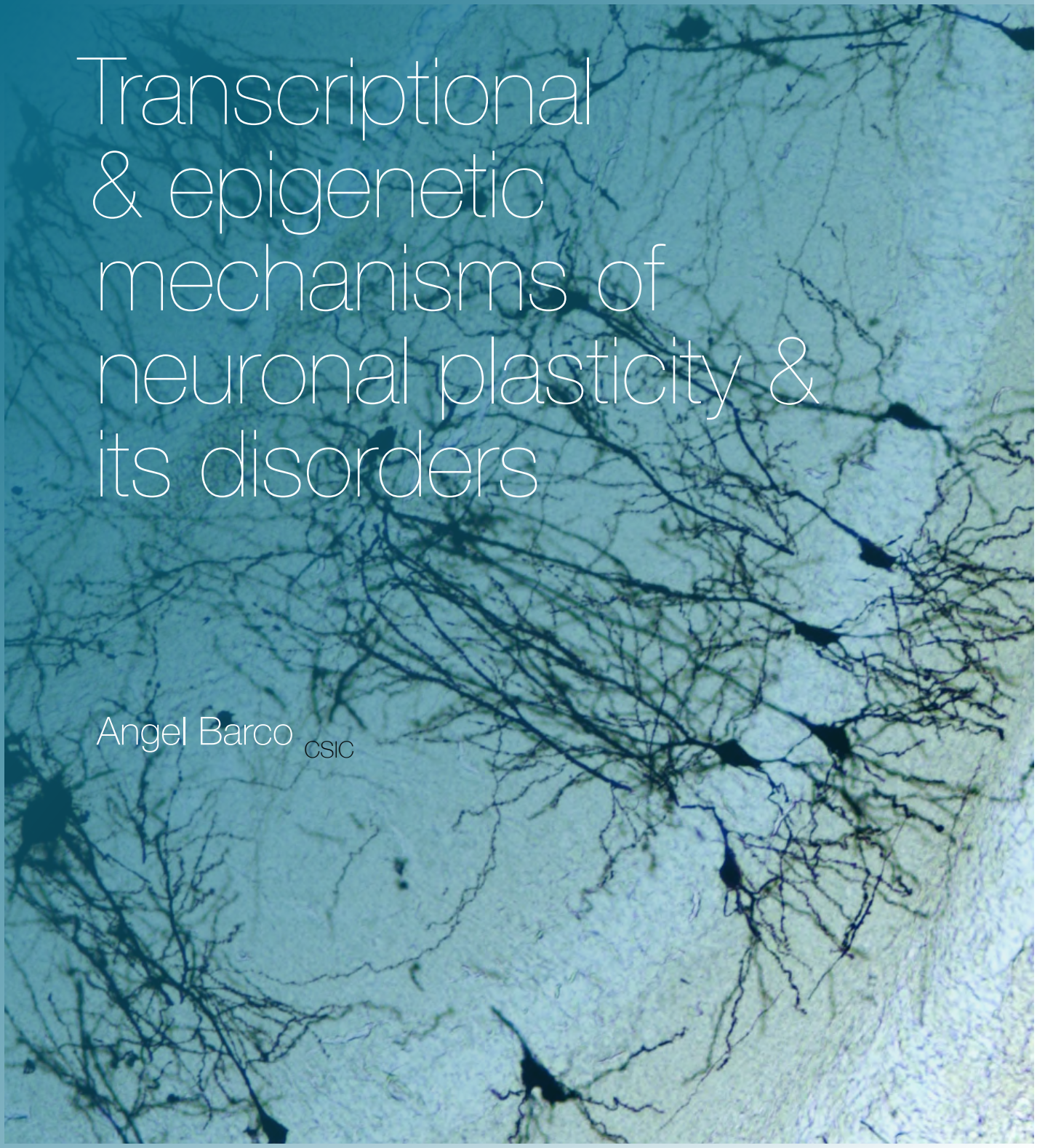

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Angel Barco CSIC

We are interested in molecular mechanisms underlying learning and memory storage, more precisely in the role of transcriptional and epigenetic processes in neuronal plasticity. We also investigate how the malfunction of these mechanisms may lead to pathological situations in the nervous system. Our research focuses on the following two areas:

- Role of activity-dependent gene expression in neuronal plasticity: Alterations in patterns of gene expression are thought to underlie the long-lasting changes in the strength of synaptic connections between neurons responsible for the

encoding of memories in the nervous system. We are investigating the details of the participation of the CREB family of transcription factors, as well as other activity-regulated transcription factors, in plasticity and memory using a multidisciplinary approach that combines mouse genetics, molecular and cellular biology, electrophysiology and behaviour.

- Contribution of epigenetic mechanisms in neuronal plasticity and the etiology of neuropsychiatric diseases: We are interested in exploring the contribution of the covalent modification of histones and the methylation of DNA in learning, memory and other long-lasting modification of the animal's behaviour. We also investigate in mouse model for different neurological conditions, such as Huntington disease and some intellectual disability syndromes, how the deficits in these mechanisms contribute to the pathology.

In both lines of research, we use genome-wide analytical approaches, such as genearrays and techniques based on next generation sequencing, for identifying candidate genes important in these processes.

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Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Fiorenza A, Lopez-Atalaya JP, Rovira V, Geijo-Barrientos E and Barco A. (2015) **Blocking miRNA biogenesis in adult forebrain neurons enhances seizure susceptibility, fear memory and food intake by increasing neuronal responsiveness.** **Cereb Cortex** *2015 Jan 16. pii: bhu332. [Epub ahead of print]*

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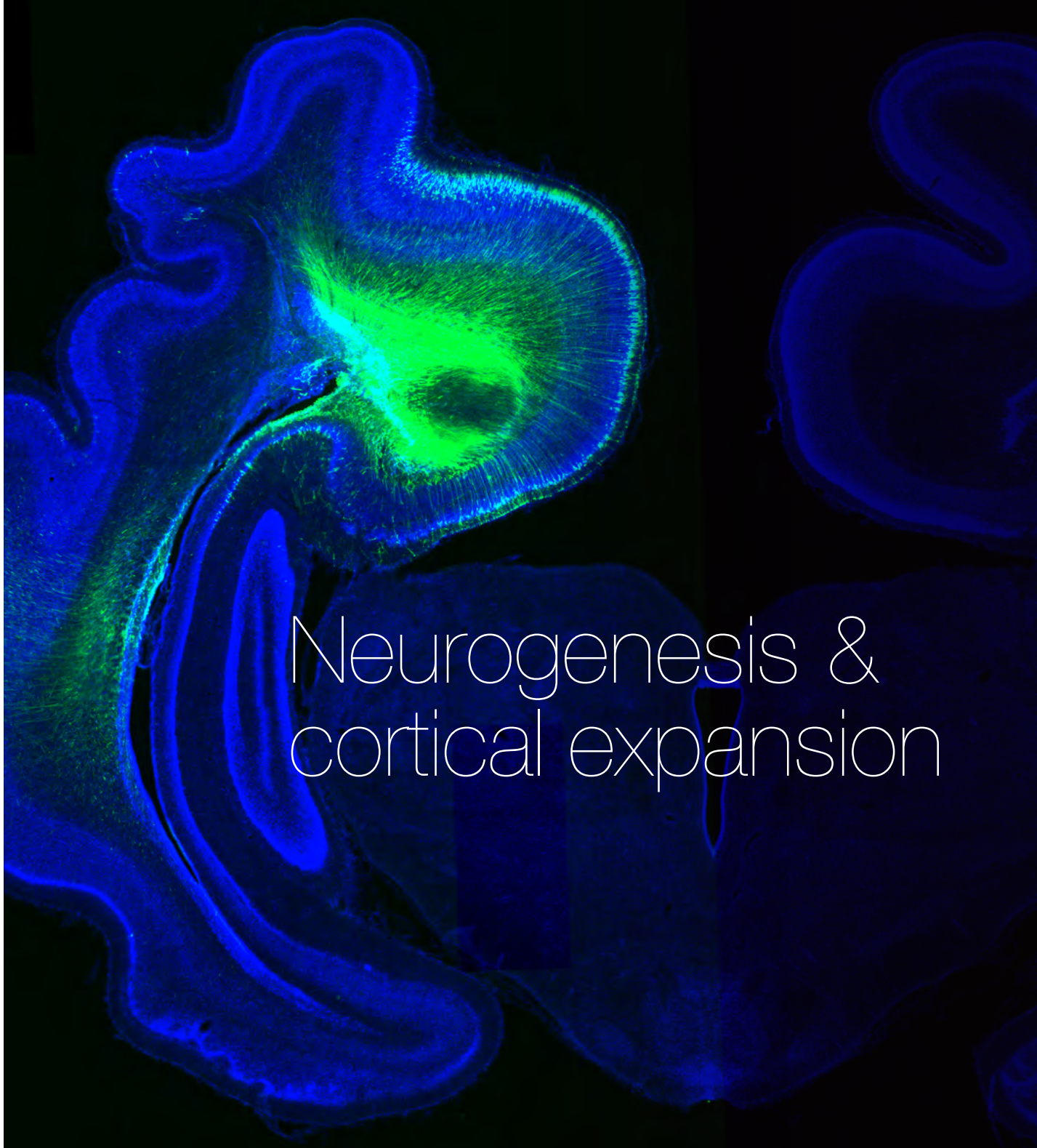
Víctor Borrell CSIC

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

In recent years multiple genetic mutations have been identified as the leading cause for mental retardation or impairment of intellectual capacity in humans. These mutations have been 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 Radial Glia progenitors in the tangential vs. radial expansion of the cerebral cortex, and the molecular mechanisms regulating this process.

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Neurogenesis & cortical expansion

Martínez-Martínez MA‡, Pacheco J‡, Borrell V*, Canals S* (2014) **Phenotyping the central nervous system of the embryonic mouse by Magnetic Resonance Microscopy** **Neuroimage** *97:95-106*

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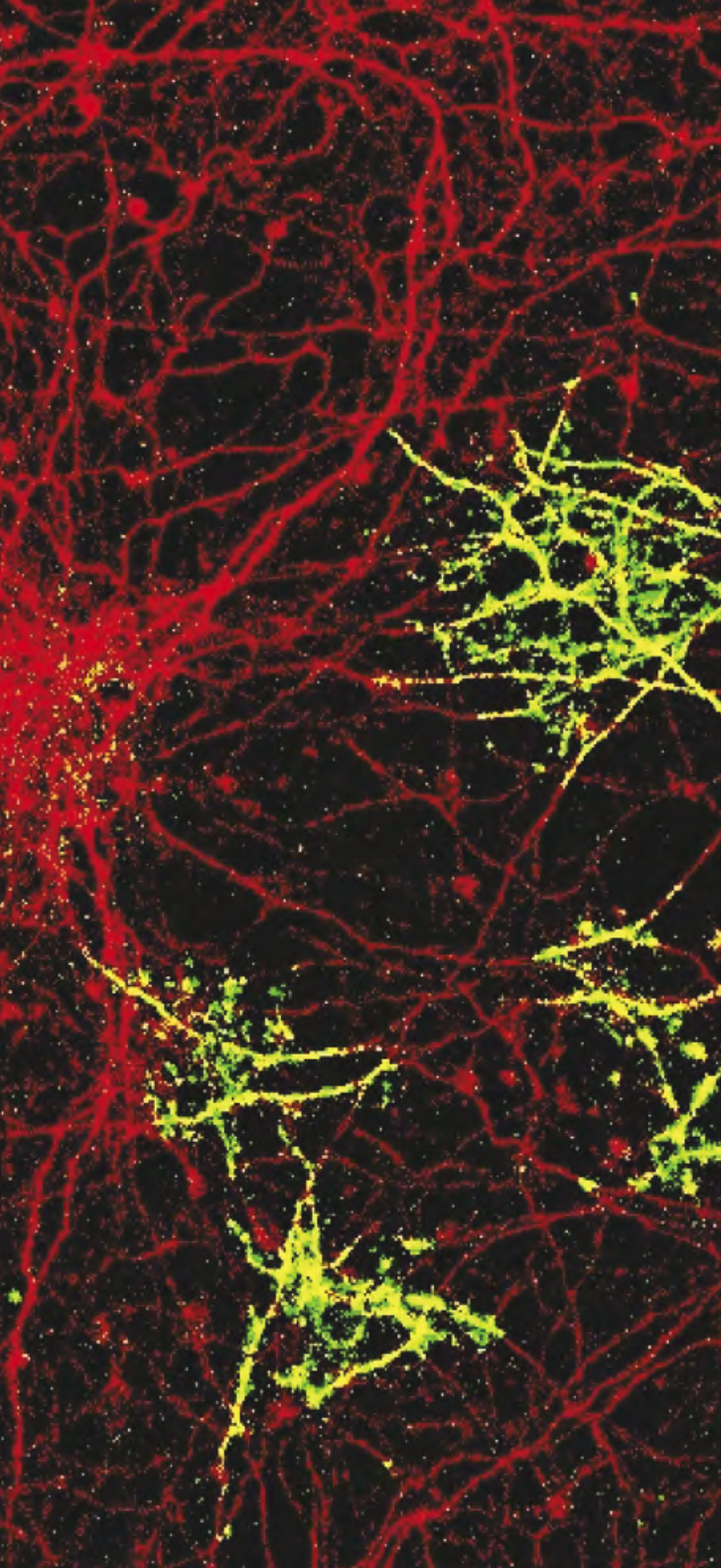

Molecular control of axonal myelination

Hugo Cabedo UMH

Myelination of the peripheral nervous system depends on the appropriate signalling between neurons and Schwann cells. By exposing proteins on the axon surface, neurons control the proliferation, survival and myelination capability of Schwann cell precursors in the peripheral nerves. The most relevant of these factors belong to the neuregulin family of proteins, encoded by NRG1. Axon surface exposed neuregulin activates erbB2 and erbB3 receptors in Schwann cell plasma membrane and elicit intracellular signaling pathways. More than fifteen splicing forms of NRG1 have been described. However, only the neuregulins with a cystein rich region (type III neuregulins) seem to have a promyelinating effect. It is probably because, in contrast to the rest of proteins of this family, type III neuregulins are retained on the axon membrane acting in a juxtacrine way on the neighbouring glial cells. To get further insight in the role of the different splicing forms of NRG1 in vivo we have recently developed transgenic mice expressing the sensory and motor-neuron derived factor (SMDF, a type III neuregulin) under the control of rat neuronal enolase promoter (NSE-SMDF mice). A

preliminary examination shows that the transgen has profound effects on the PNS of these mice. The thickness of the peripheral nerves is notably increased, resembling the nerves from patients affected by neurofibromatosis (a human genetic disease with a high prevalence). In addition the microscopic structure of these nerves is also severely altered. Surprisingly (and again recapitulating neurofibromatosis) approximately 15% of these mice develop big peripheral nervous system tumours, which finally produce paralysis and other neurological symptoms.

Our main goal is to unveil the role of the NRG1-erbB pathway in development and myelination capability of Schwann cells. We'll also explore the role of this signalling pathway in the physiopathology of neurofibroamtosis and in the development of peripheral nervous system tumours. Finally we will test the possibility of using erbB blockers (like lapatinib and tratuzumab) in the treatment of neurofibromatosis and the associated peripheral nervous system tumours. Because the blocking of the NRG1-erbB pathway is already being clinically used for the treatment of a group of breast cancers, it will result easily adaptable for the treatment of peripheral nervous system tumours.

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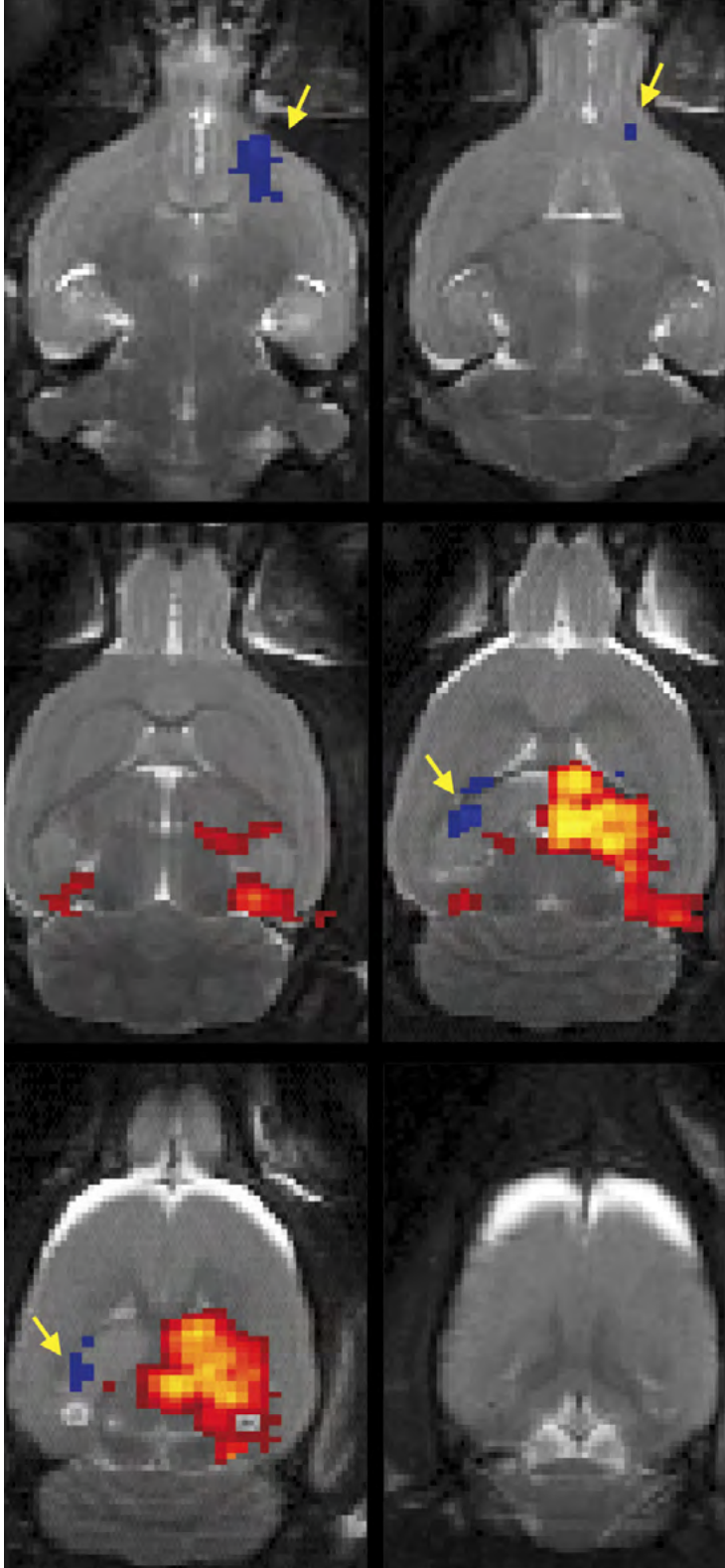
Plasticity of brain networks

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

Reis S, Hu Y, Babino A, Andrade JA, Canals S, Sigman M, Makse H (2014) **Avoiding catastrophic failure in correlated networks of networks.** **Nature Physics.** *10, 762 doi:10.1038/nphys3081*

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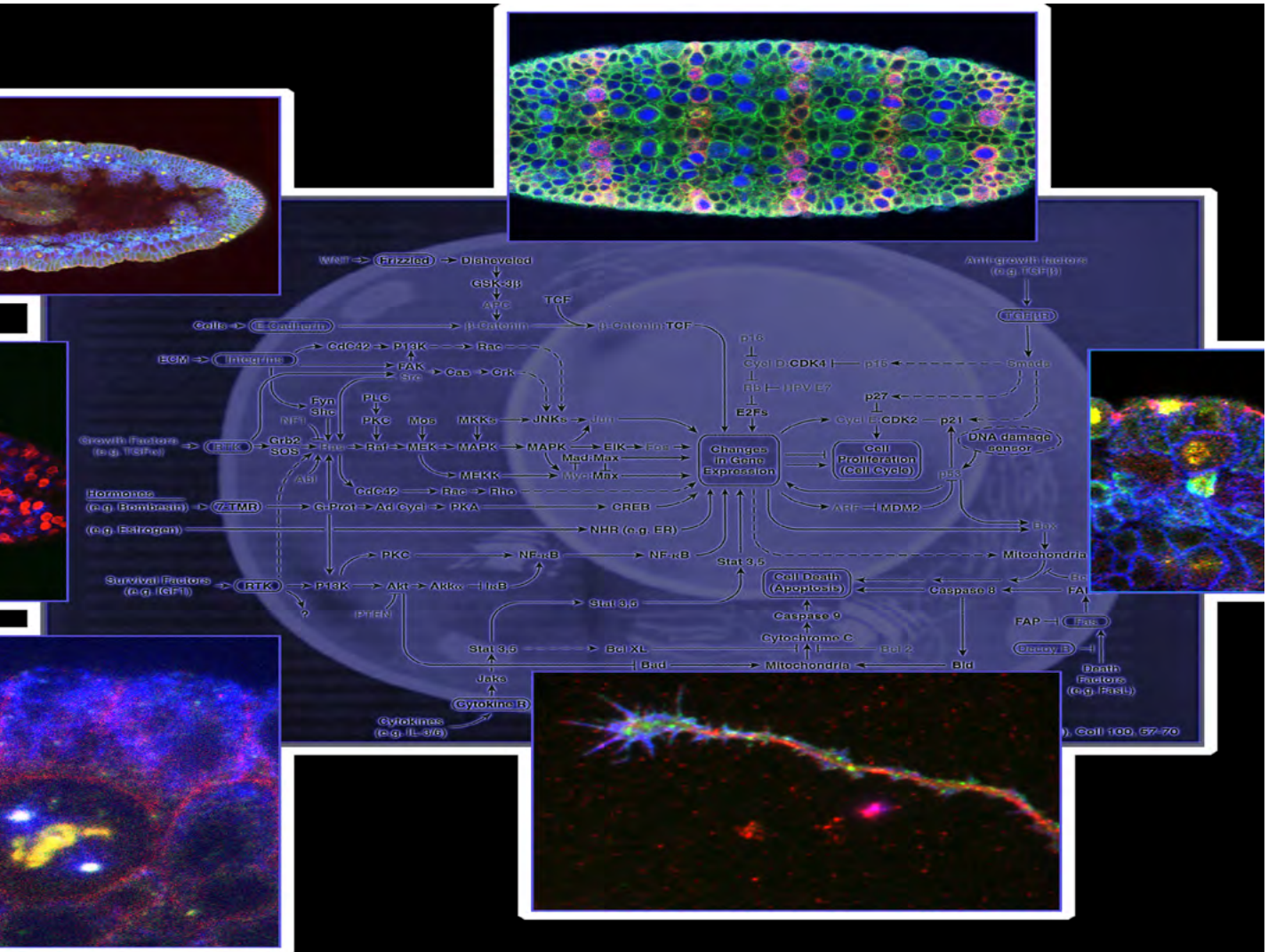
PDZ proteins & signaling networks during the specification of neuronal identities



Ana Carmena CSIC

During the development of the nervous system a great diversity of neuronal types is generated. In fact, the human brain has more than 100,000 millions of neurons, most of them specified during the embryonic development. Unravelling the molecular mechanisms that underlie the acquisition of neuronal identities is the main objective of our group.

PDZ proteins & signaling networks during the specification of neuronal identities

Specifically, we are interested in analyzing in vivo the mechanisms of cross talk between the signal transduction pathways involved in the generation of neural diversity. This will allow us to discover the functional signaling networks established within the cell and the key nodes within the networks required for their formation and regulation. In this context, PDZ (PSD-95, Dlg, ZO-1) domain-containing proteins have a special interest for us. PDZ proteins are usually associated to the cell membrane at particular sub membrane locations, such as cellular junctions and synapses. It is frequent the formation of supramolecular complexes around PDZ-based scaffolds. Indeed, numerous PDZ proteins contribute to the anchoring of proteins to the membrane, to the clustering of receptor and channels, and also to increase the efficacy and fidelity of signal transduction pathways. Thus, PDZ proteins are excellent candidates as hubs of cross-communication between signalling pathways.

Our group analyzes the function of PDZ proteins, including the PDZ protein Canoe/AF-6, during fundamental biological processes for the generation of neural identities, such as asymmetric cell division and neural differentiation. To implement this project, we use a multidisciplinary approach that combines different techniques of Genetics, Cellular Biology, Biochemistry and Molecular Biology. The embryonic/larva development of Drosophila melanogaster is our model system.

Malfunction of PDZ proteins has been associated to cancer and numerous neuropathologies, including schizophrenia, deafness, Parkinson and Alzheimer. Thus, the results of our analysis could contribute to clarify the failures that underlie such diseases, as well as to improve the design of therapeutic agents directed to correct those pathologies.

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Pérez-Gómez, R., Slováková, J., Rives-Quinto, N., Krejci, A. and Carmena, A. (2013) **A Serrate-Notch-Canoe complex mediates glial-neuroepithelial cell interactions essential during Drosophila optic lobe development** **J Cell Sci.** *126, 4873-4884*

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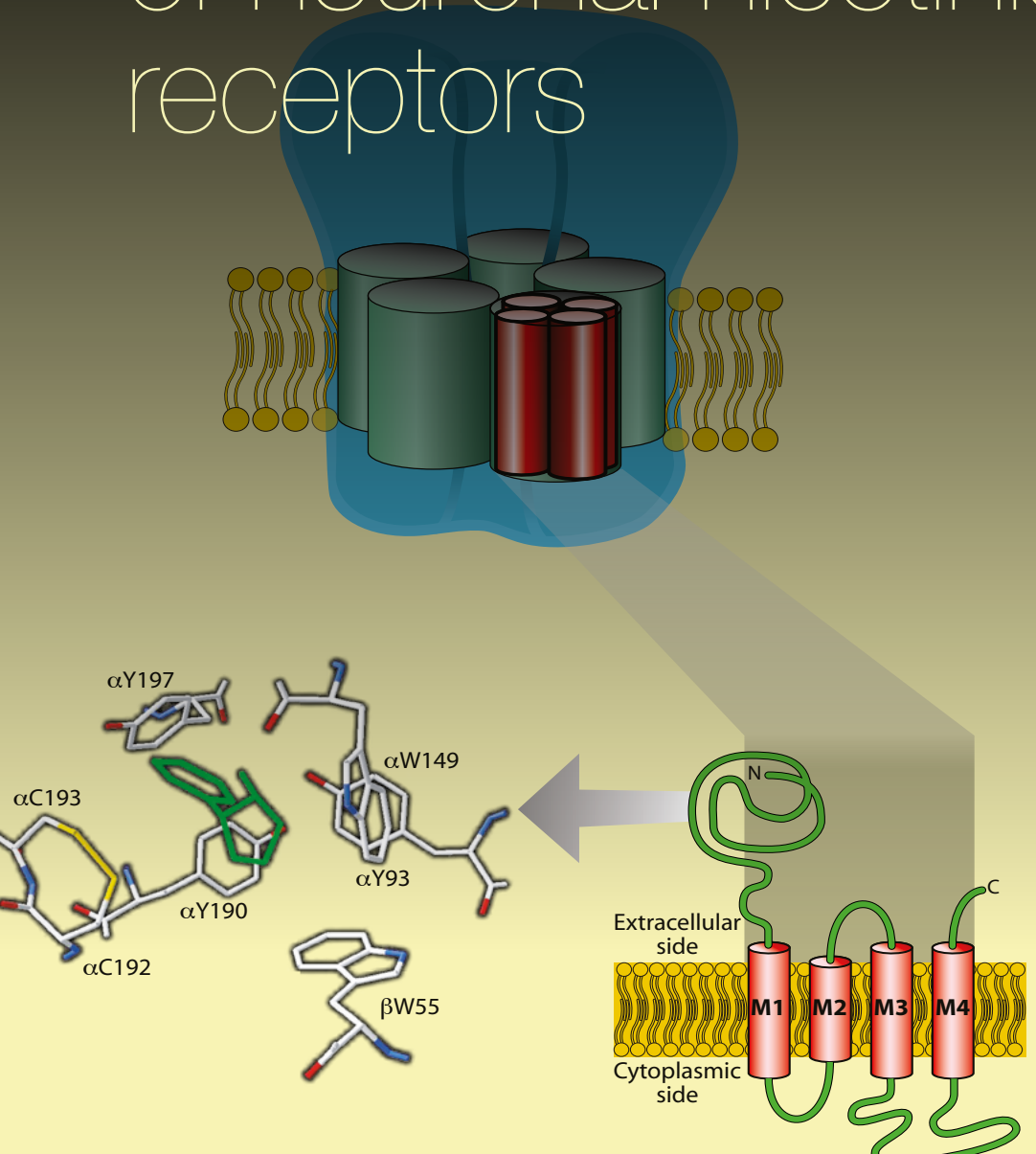
Molecular neurobiology of neuronal nicotinic receptors



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.

Principal Investigator

Manuel Criado

Technical Staff

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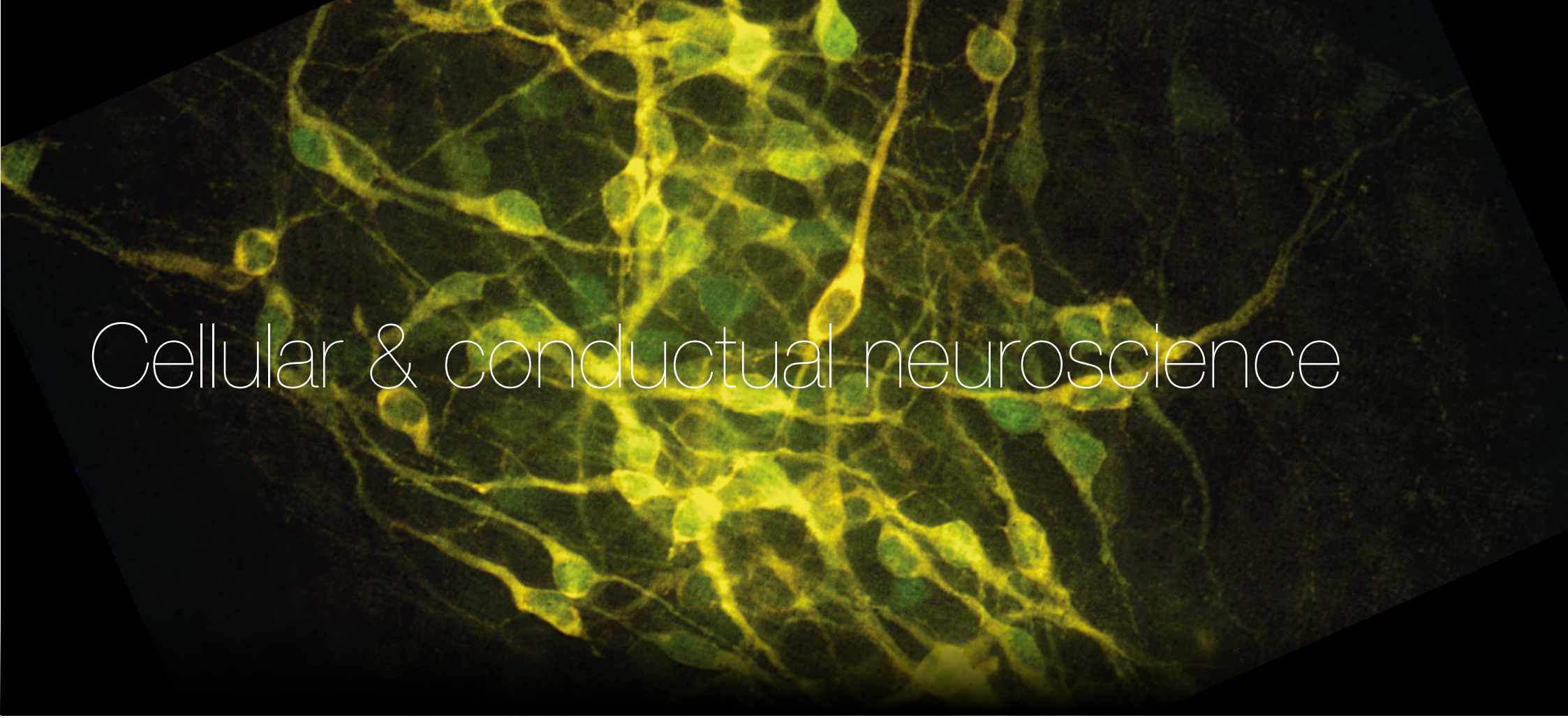

Cellular & conductual neuroscience

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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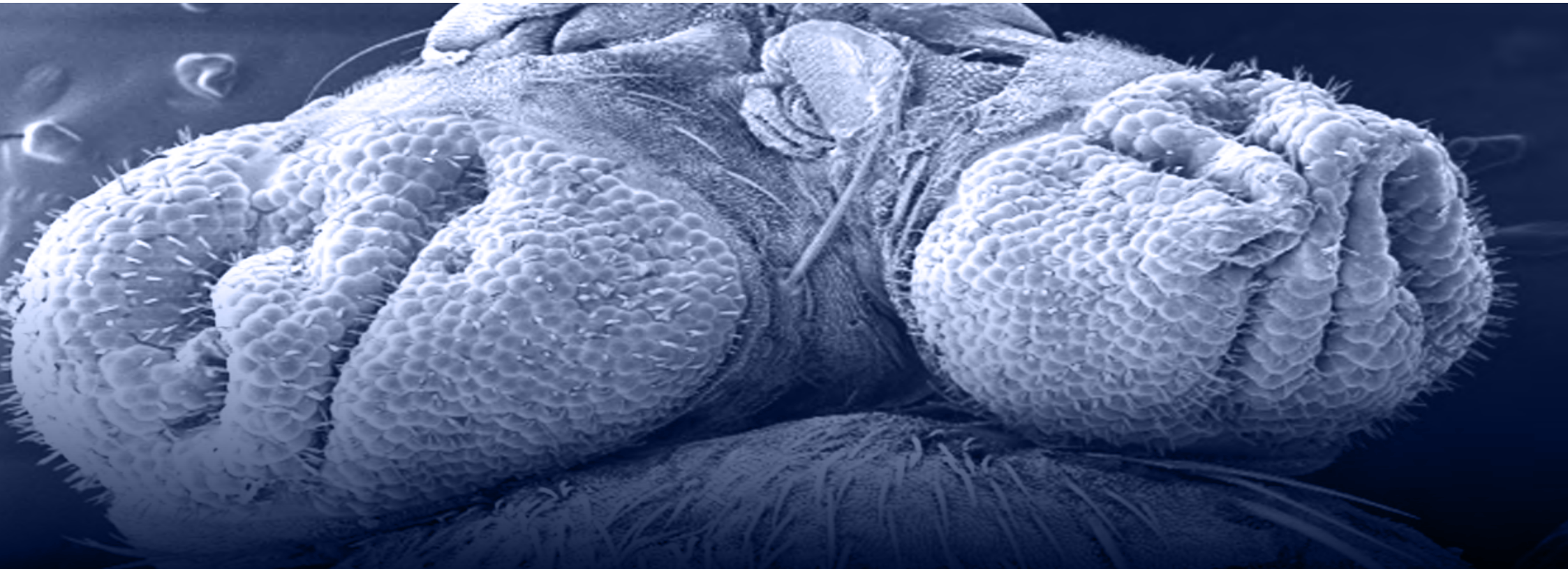
Mechanisms of growth control & cancer in Drosophila

Maria Domínguez CSIC

Our studies are focused on three research projects:

- Systemic and local control of organ growth: Animal size is remarkably constant within species and this constancy is even more striking when we consider the coincidence in size of the left and right sides of bilaterian organisms. To attain such precision, growing organs must be capable to sense and communicate their



growth to other organs in the organism and to have flexibility to adjust their growth programmes and maturation to repair any disturbances occurring during ontogeny. How they do so have remained a mystery over the past decades. We are addressing this long-standing unresolved question in the imaginal discs of the fruit fly Drosophila melanogaster, which are known to have a remarkable flexibility to regulate their size, particularly when they suffer lesions. This year, we reported the identification of a novel insulin-like peptide (Drosophila insulin-like peptide 8, DILP8) that appears to mediate the plasticity of growth and maturation time that ensures the proper final size, proportions, and the symmetry in Drosophila melanogaster.

- 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. Intriguingly, similar organizing signals are used repeatedly to promote growth and patterning in widely different organs (e.g. the neural tube, somites, limbs, eyes, etc.). This raises the question of how organ specificity is achieved. Moreover, dorsal-ventral and anterior-posterior organizers promote growth non-redundantly within an organ; yet hoe the distinct organizing signals are integrated to ensure proper final growth remains unknown. Using the powerful genetic tools available in Drosophila melanogaster, we have shown that specificity is achieved through the activation of the organ-specific transcription factor, Eyegone [homologue of human PAX6(5a)] and the secreted factor Four-jointed [Fjx in vertebrates]. We have shown that Eyegone is necessary and sufficient to mediate the specific growth response of Notch in the eye. Eyegone encodes a member of the PAX-family of oncogenes, but it differs from the canonical members in that Eyegone protein has a truncated paired domain —a conserved DNA-binding domain that is presumed to be essential for PAX-associated oncogenic activity. Strikingly, we found that overexpression of human PAX6 (5a), which is structurally related to Eyegone, induces tumours in vivo, whilst the canonical and previously presumed oncogenic PAX6 variant hardly affects growth in vivo. Our findings also redefine the process of organizer formation and function, and they 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.

- Genetic screens for novel tumour-inducing genes: Over eight years ago, we started complementary high-throughput (gain-of- expression and RNA interference-based) screens for genes that facilitate tumorigenesis by the Notch signal transduction pathway. Through these screens, we identified key genes required for tissue growth control and cancer (see publications). These included two novel epigenetic repressors, Pipsqueak and Lola, that when coupled with Notch overactivation, act as decisive factors in promoting tumour growth and metastases through silencing of the Retinoblastoma-family-protein (Rbf) gene. More recently, we have shown that Notch cooperates with the Pten/PI3K/AKT pathway in promoting tumour invasion. Interestingly, the Notch/Pten/Akt axis is conserved during human leukemogenesis. Our collaborators in the Institute for Cancer Genetics in Columbia (USA), Dr Ferrando and Dr. Palomero, have shown that loss of Pten is responsible for resistance of T-cell acute lymphoblastic leukemic cells to inhibitors of the Notch pathway. In colaboration with Dr.

Mechanisms of growth control & cancer in Drosophila

Borggrefe at the Max Planck Institut in Frieburg, we have shown that the histone demethylase Lid/KDM5A is a core component of Notch silencing complex in tissue growth and tumroigenesis and the conserved microRNA miR-200c/miR-8 as a key regulador of Notch pathway activity in development and metastático cancers. More recently, we have shown that downregulation of the histone methyltransferase E(z) facilitates tumorigenesis by the Notch signalling pathway. This mechanism is 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 using genetic, molecular and cellular methods to study the initiating steps and key genes involved in the transformation of normal healthy cells into cancerous cells capable of metastasing in vivo.

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Mechanisms of growth control & cancer in Drosophila

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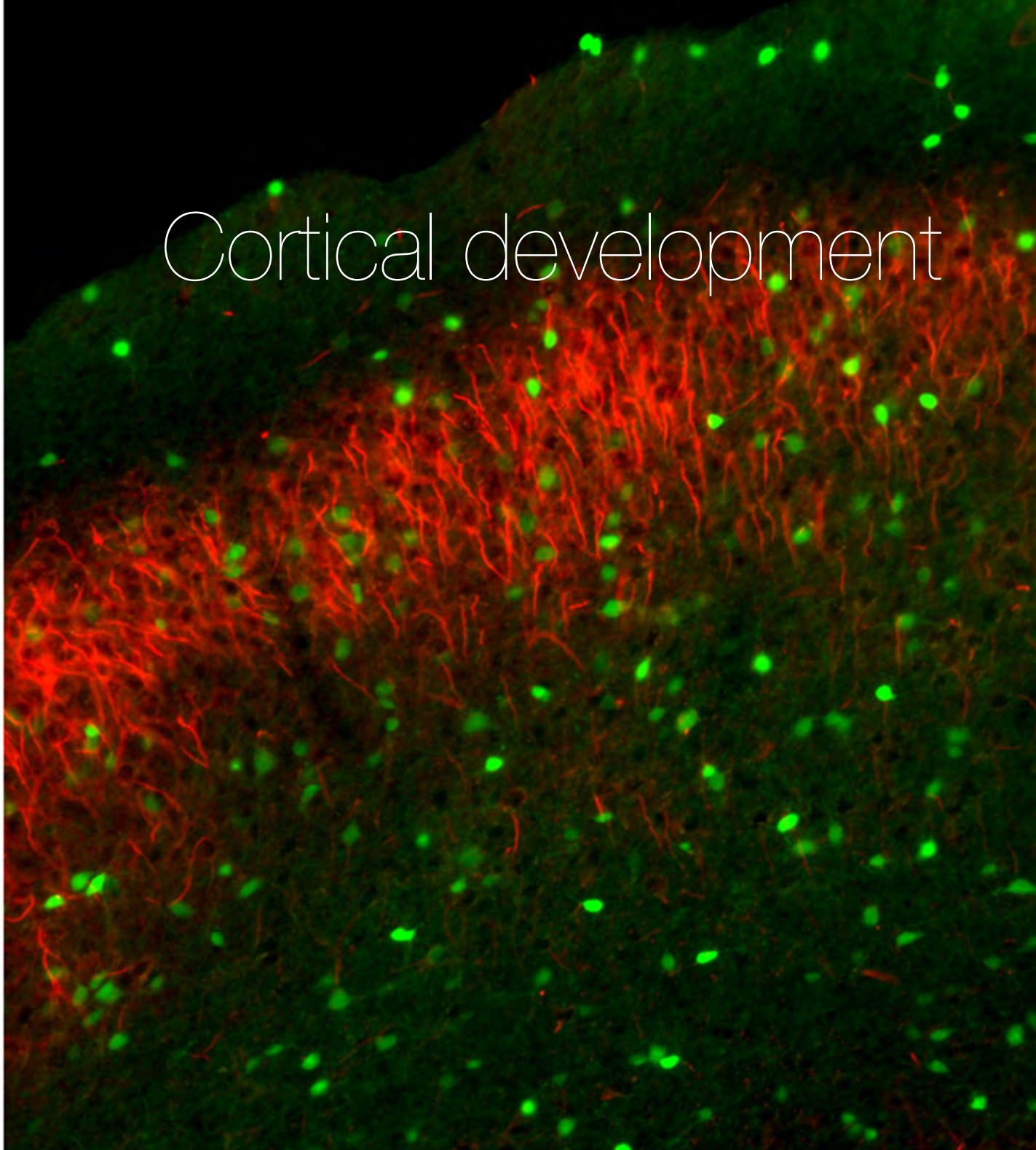
Cortical development

Alfonso Fairén CSIC

Brain function depends on the ordered integration of neurons into microcircuits during development. Our interest has focused on cortical development. First, we are studying the early-differentiating, transient neurons that play functional roles in the development of the cerebral cortex. One of these groups of neurons is formed by Cajal-Retzius cells. These cells synthesize and secrete Reelin, an extracellular matrix molecule that controls the correct laminar organization of the cerebral cortex. We are analyzing the possible roles of second messenger cascades in the control of Reelin processing and secretion by Cajal-Retzius cells. We are also trying



to characterize in molecular terms the Cajal-Retzius cells originated in the thalamic eminence versus those of different embryonic origins. Another group of early neurons is formed by neurons whose axons project to the subpallium. These neurons reside first in the preplate, a transient compartment of the pallial anlage and then in the subplate after preplate partition. However, some of these early projecting neurons never associate with the subplate but remain in the marginal zone of the developing cortex along the prenatal period. We have found that the axonal projections of subclasses of early cortical neurons have diversified anatomical distributions in developing rodent brains. However, such specific topographic projections have not been identified yet in other mammalian species. We aim at a comparative approach to these neuronal populations in other mammalian species including humans.

In a second set of objectives, we are using the entorhinal cortex as a model to analyze synaptogenesis involving subgroups of GABAergic interneurons. This study is relevant since inhibitory microcircuits of the cerebral cortex are implicated in an important spectrum of neurological and neuropsychiatric conditions.

Principal Investigator

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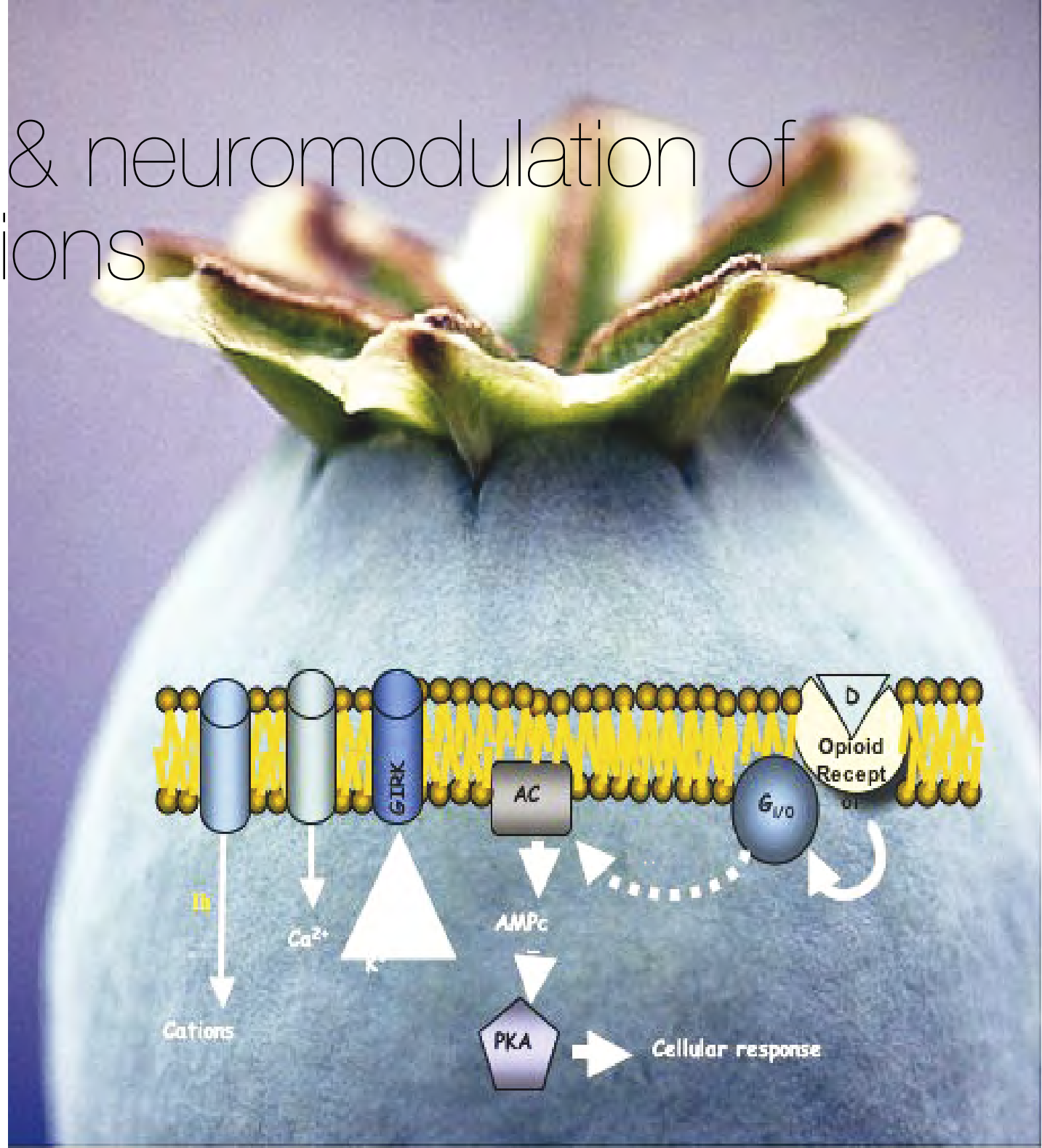
Neurobiology & neuromodulation of the opioid actions

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 MediatedAntinociceptionisDeterminedby Cross–regulationBetween and OpioidReceptors at Supraspinallevel.** **Br J Pharmacol** *DOI: 10.1111/j.1476-5381.2011.01750.x*

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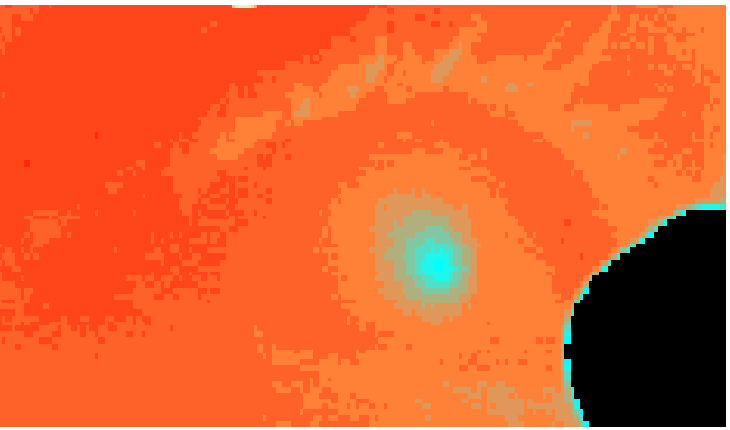
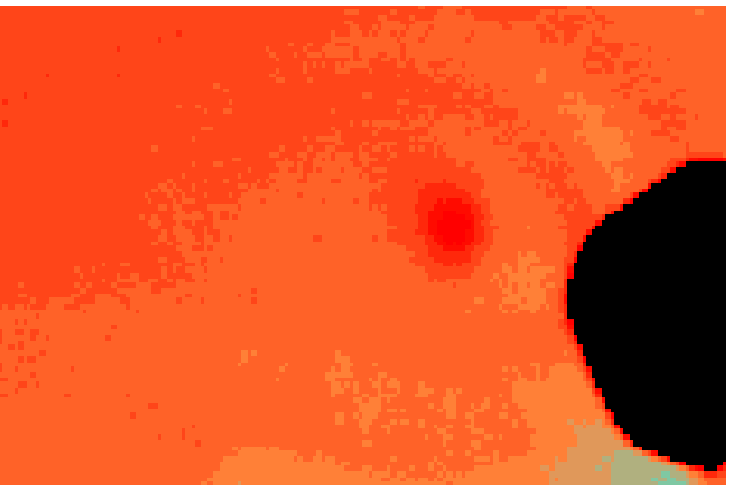
Control

Cold



Heat



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 techniques (recording nerve activity of sensory receptors in nerve endings and axons) and psychophysical studies (analysing the evoked sensations), 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 dryness, discomfort and pain.

Ocular Neurobiology

The ONG has described the sensitivity of the ocular surface to selective stimulation in healthy subjects, as well as the correlation between electrical activity in ocular sensory nerves and sensations evoked in humans; the changes in ocular sensitivity in different pathologies, after ocular refractive surgery or with the use of different ophthalmic drugs; and the role of the ocular surface innervation in blinking and in basal and reflex tearing.

At the present time, the ONG centres on characterizing the temporal course of the electrophysiological activity of corneal sensory nerves after lesion and during several inflammatory processes including dry eye, with special attention to the study of the physiopathology of neuropathic sensations of dryness, discomfort and pain subsequent to nerve lesion.

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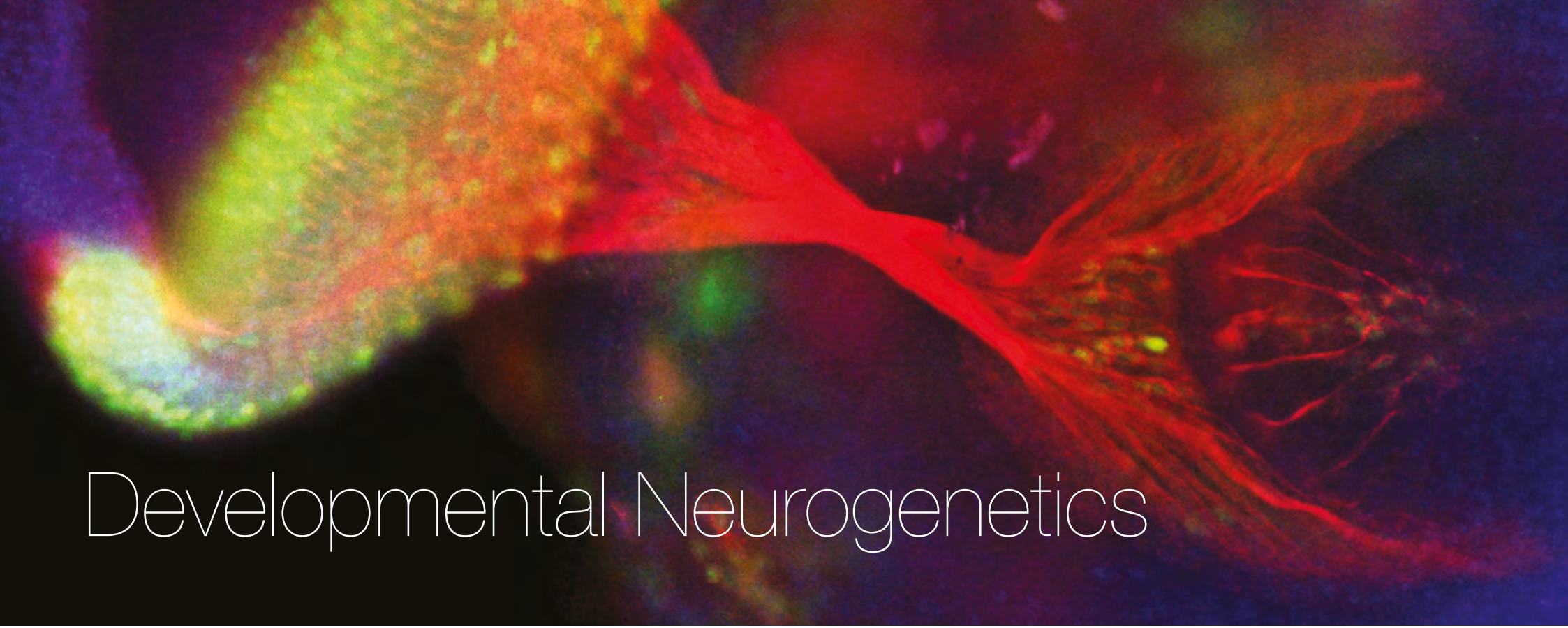

Developmental Neurogenetics

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

Developmental Neurogenetics

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.

Principal Investigator
Luis García-Alonso

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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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Geijo-Barrientos E., González O., Pastore-Olmedo C. (2012). Presence of repeater F-waves in the early stage of Guillain Barre Syndrome. **Journal of the Peripheral Nervous System,** *17(1):128-31. doi: 10.1111/j.1529-8027.2012.00383.x.*

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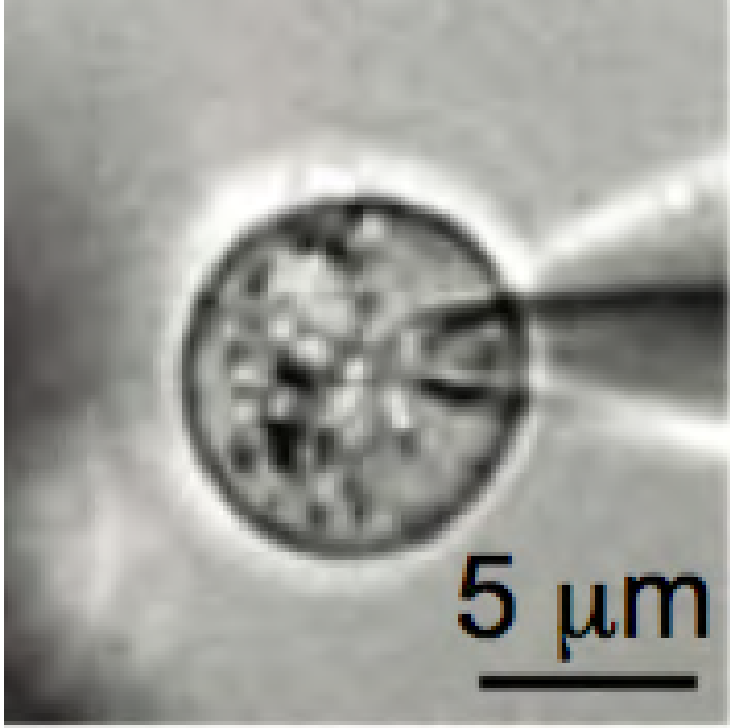
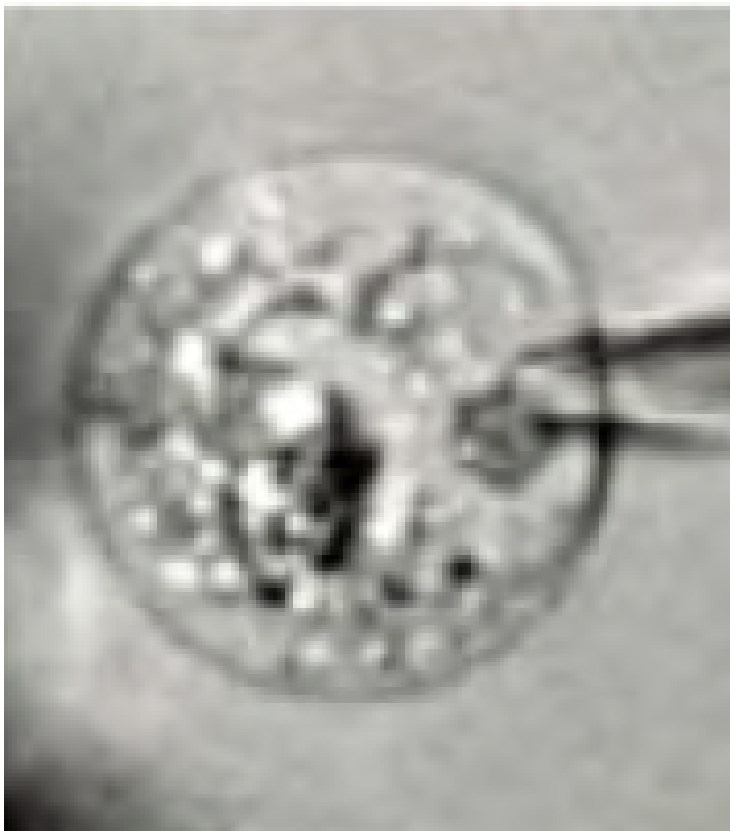
Mechanotransduction in mammals

Ana Gomis CSIC





The first step in pain sensation is the activation by noxious stimuli of a subpopulation of primary sensory neurons named "nociceptive neurons". Based upon the form of energy to which they respond preferentially, nociceptive neurons have been classified as sensitive to mechanical, irritant chemicals and thermal stimuli. The detection of noxious mechanical stimuli is an important element in pain induction, and mechanical alodynia (where normal stimuli become painful) is an important clinical problem.

Mechanotransduction remains less well understood in molecular and functional terms than the detection of thermal and chemical stimuli, where many receptors have been cloned. We also ignore the reasons for threshold differences between low and high threshold mechanoreceptors that encode innocuous and noxious mechanical forces respectively.

This project will focus on the characterisation, in cultured neurons of the trigeminal and dorsal root ganglion, of cells that respond to low and to high

intensity mechanical stimuli. In parallel, we will work on the identification and characterisation of the responses of the TRP channels evoked by mechanical stimulus. Several stretch activated TRP channels have been cloned recently and the TRPs channels are firm candidates to be sensory mechanotransducction channels. We use single cell electrophysiology and Ca2+ imaging at sensory neurones and after transfection of TRP channels in mechanically insensitive HEK293 cells. Moreover, we use molecular biology approaches in collaboration with the sensory transduction and nociception group.

Finally, the effects of drugs and blockers of the identified channels will be tested and validated in low and high threshold sensory afferents of the knee joint recorded in anesthetized rats. This last step is very important in the establishment of new therapies against pain.

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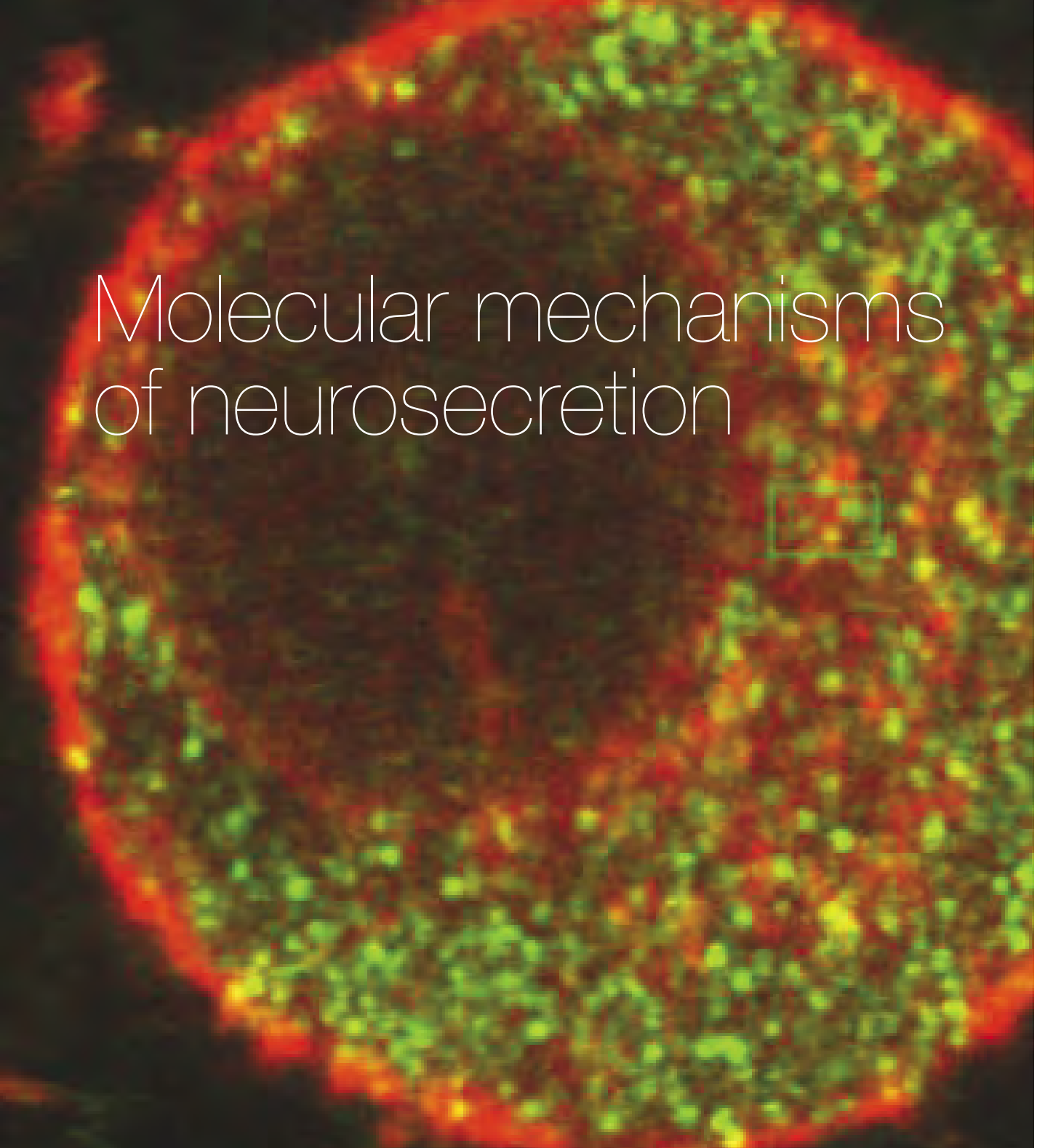

Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH

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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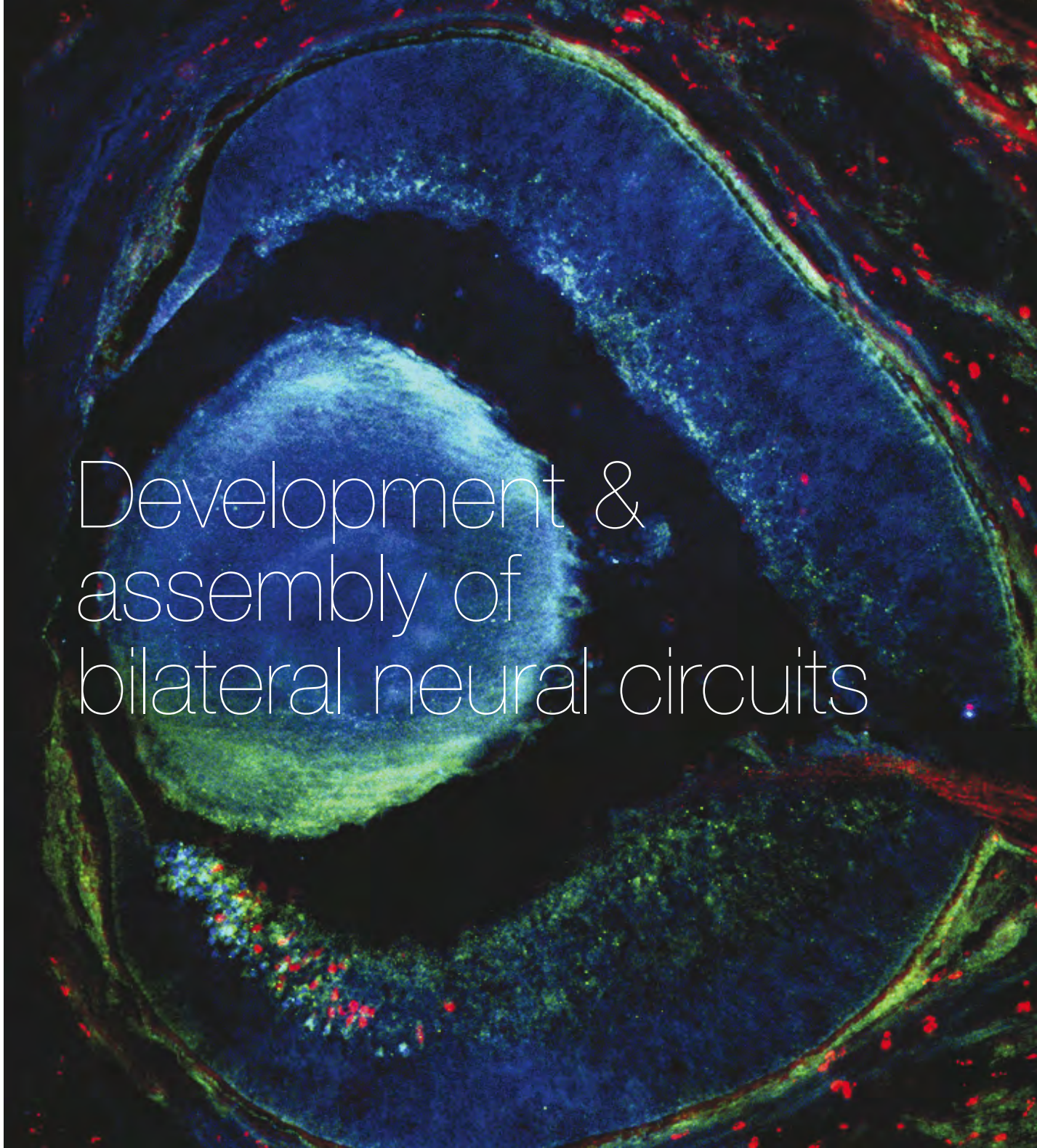
Development & assembly of bilateral neural circuits

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 ofbilateral neural circuits

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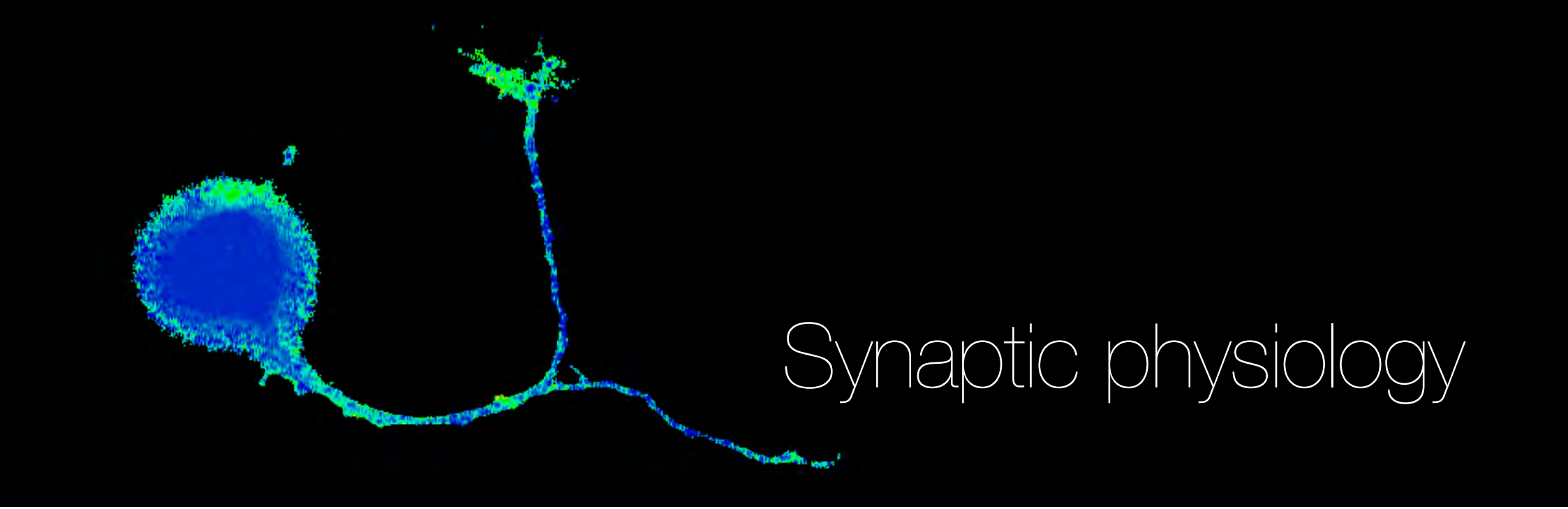

Synaptic physiology

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, the main objective of the lab for the years to come is to identify and to evaluate the role of scaffolding 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. On the other hand, we have 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. We have also identified and analyzed new signalling pathways triggered by these receptors and that through the interaction of identified proteins influence neuronal maturation and neuritic proliferation. 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.

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Synaptic physiology

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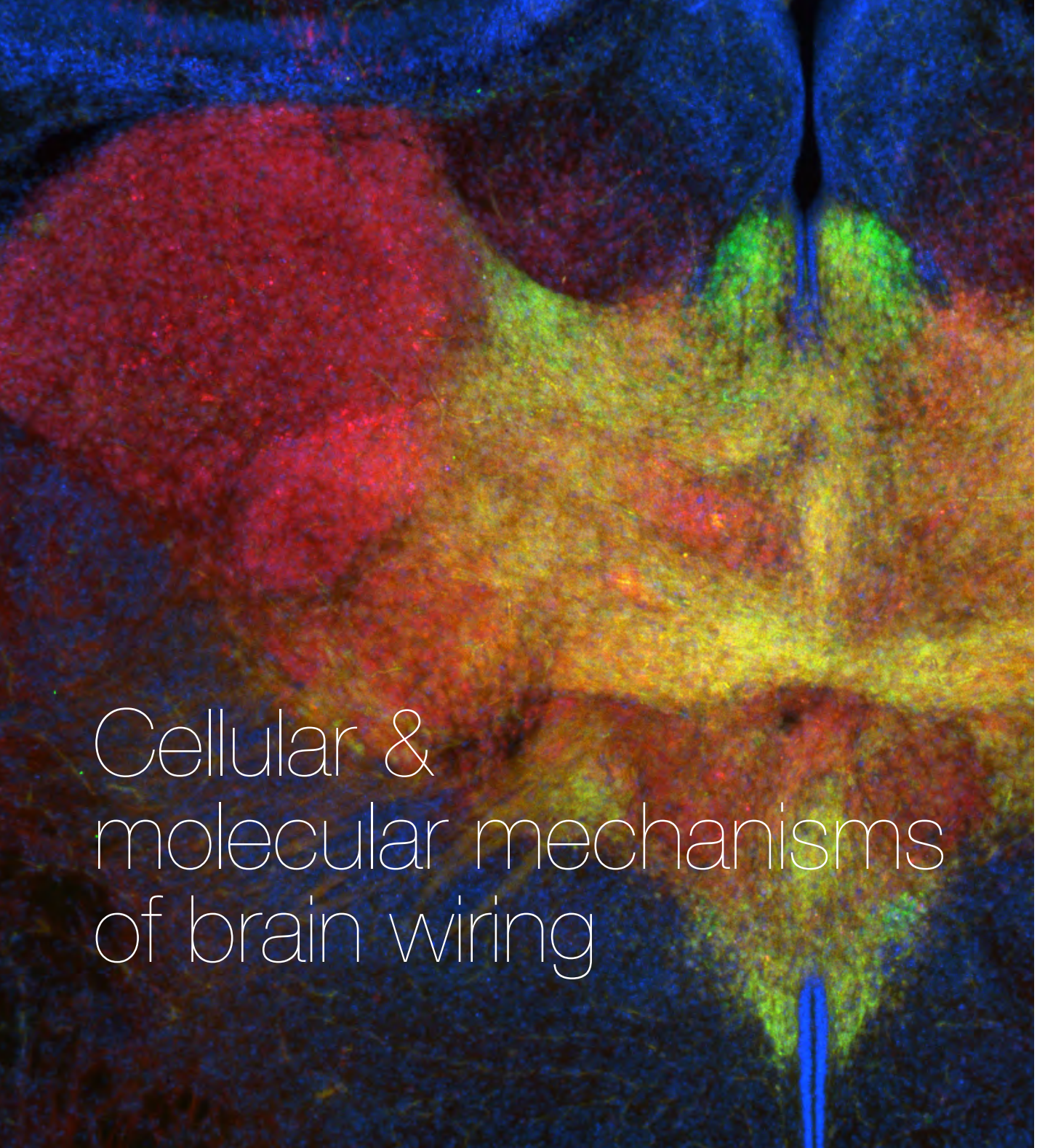

Cellular & molecular mechanisms of brain wiring

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.

Three major questions are been focused in the laboratory: i) the transcriptional control of thalamocortical topography; ii) the activity-dependent mechanisms involved in thalamocortical guidance and wiring, and iii) the role of the thalamus and its connectivity in the neuroplastic cortical changes following sensory deprivation.

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 guidance of this major axonal tract (see Current Biology 24, 494-508 (2014), Nature Neuroscience 15,1134-43 (2012), Journal of Neuroscience 32,4372-85 (2012), Current Biology 25,1478-55(2011), Neuron 24, 1085-98 (2011), PLoS Biology 7, e98 (2009), J Neurosci 27, 3395-407 (2007), Cell 125, 127-42 (2006), Nat Rev Neurosci 4, 276-8 (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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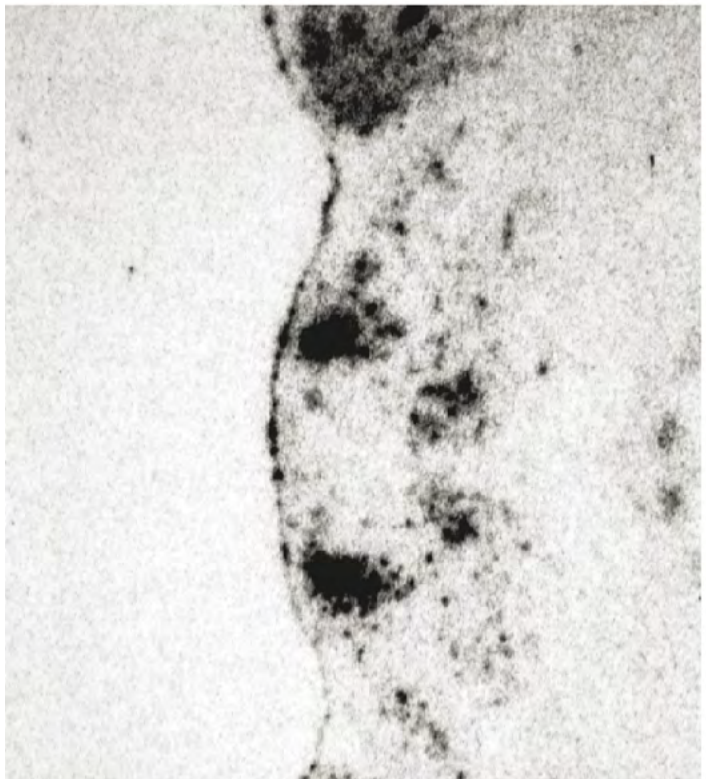
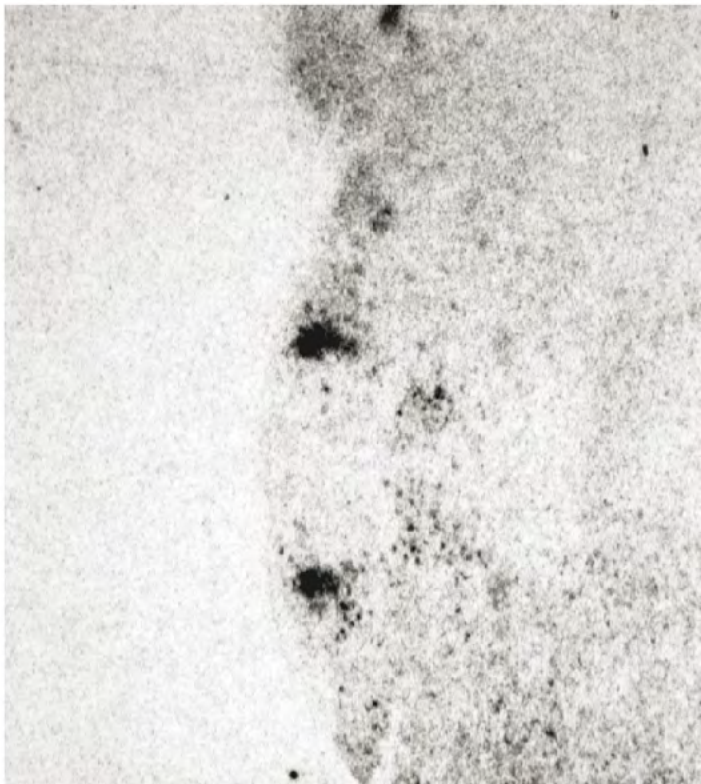
Translational neuropsychopharmacology of neurological and psychiatric diseases

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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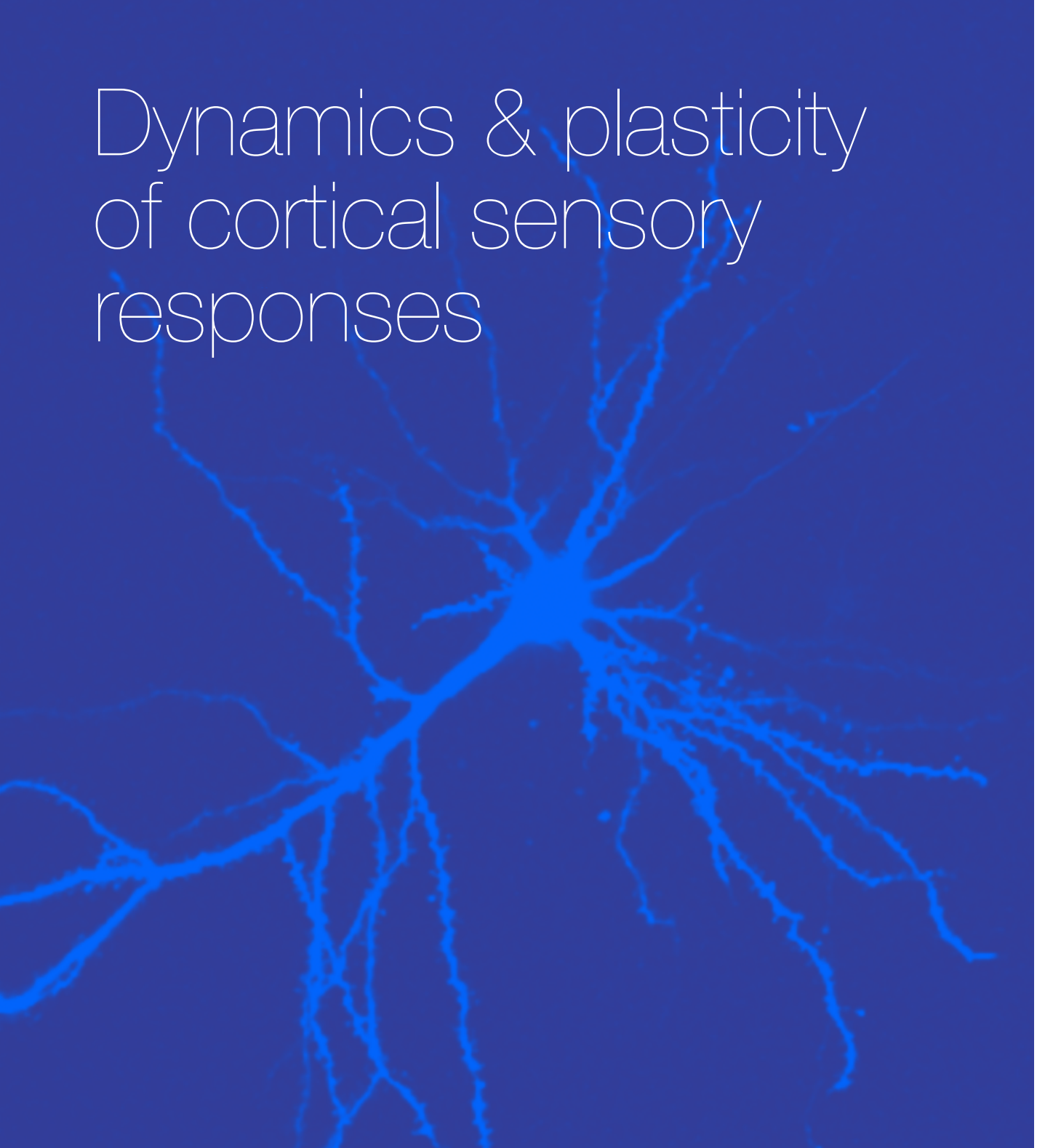
Dynamics & plasticity of cortical sensory responses



Miguel Maravall CSIC

As an animal explores its environment, activity patterns generated by neurons in its cerebral cortex represent the outside world and play a decisive role in its perception. Beyond representing specific stimulus features, neuronal responses of sensory cortical regions change dynamically depending on sensory context, internal brain state and even aspects of stimulus significance (such as novelty or pleasant or noxious associations). The responses themselves regulate modifications in the underlying neuronal circuits, through modulation of synaptic and cellular plasticity.

Dynamics & plasticity of cortical sensory responses

Our group's goal is to analyze this fascinating interplay by identifying neuronal operations or computations whose function can be characterized in terms of sensory performance in the intact animal, and describing the underlying mechanisms at the level of cellular and synaptic interactions. We work on the somatosensory whisker system of rodents. We focus on the dynamics of neuronal responses that occur as an animal explores a given environment. Adapting its responses with rapid forms of plasticity, the whisker system can quickly improve its ability to represent the scene.

To analyze the functional effects of response dynamics and identify the underlying mechanisms we combine a diverse set of techniques: electrophysiology (whole-cell patch clamp and extracellular recordings) and imaging, data analysis using the mathematical tools of information theory, and computer modelling. We record responses to controlled, complex tactile stimuli in the cortex and thalamus (successive stages in the sensory pathway). We use models to formulate hypotheses on how specific cellular and synaptic mechanisms can generate these representations. We characterize the mechanisms in detail within a reduced preparation, the acute thalamocortical slice.

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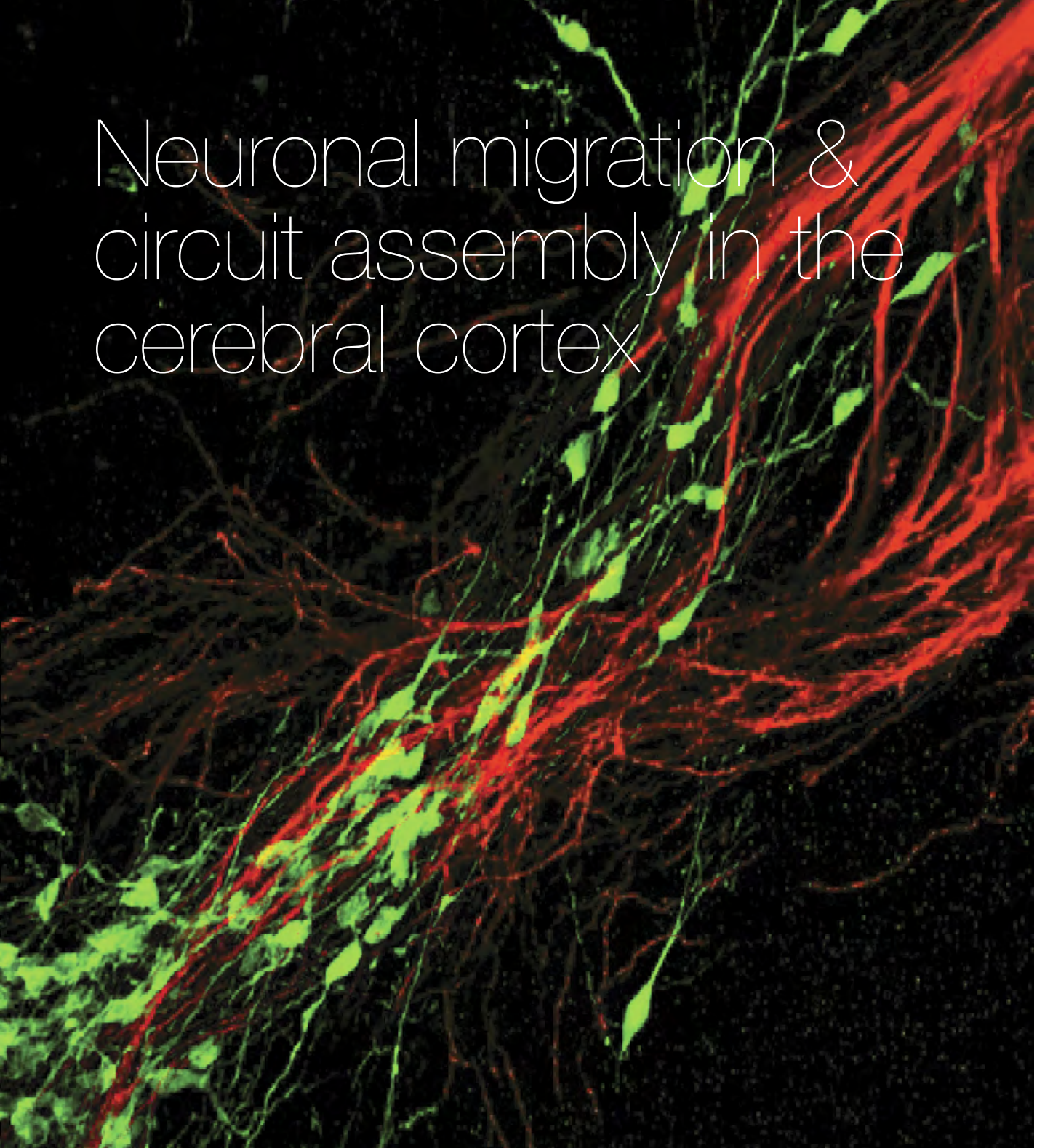

Neuronal migration & circuit assembly in the cerebral cortex

Oscar Marín CSIC

The main aim of our laboratory is to understand the molecular and cellular mechanisms controlling the development of the most anterior region of the brain, the telencephalon. The telencephalon contains key structures for the function of the mammalian brain, such as the basal ganglia and the cerebral cortex. The cerebral cortex, for example, is the larger structure of central nervous system and is essential for the intellectual functions that distinguish us as humans.

Neuronal migration & circuit assembly in the cerebral cortex

As in other regions of the central nervous system, most telencephalic neurons are generated during development from precursor cells located in very specific areas, named proliferative zones. In most cases, the place and time of birth of a neuron highly influence its fundamental characteristics (such as its neurotransmitter content, for example). However, we still have a very limited knowledge of the factors that control this process, called neuronal specification. Our group is interested in understanding the molecular mechanisms controlling the specification of different neuronal populations in the telencephalon. In other words, we want to discern what factors determine how the different types of neuronal precursors decide their fate.

In addition, since proliferative regions are normally located at a distance from the place where neurons finally reside and function, new neurons have to move to reach their final position in the telencephalon. The process of neuronal migration is particularly complex in the cerebral cortex, where neurons have to migrate very long distances to reach their destination. One of the main research interests of our laboratory is to understand the cellular and molecular mechanisms controlling the migration of cortical neurons. We are combining multiple experimental methods, such as experimental embryology, time-lapse microscopy or in vivo analysis of transgenic and knockout mice to identify the molecules that mediate this process. Using these methods, we have just begun to discover some of the molecules controlling neuronal migration in the telencephalon.

Understanding the mechanisms that control the wiring of interneurons in the cerebral cortex may shed light into the etiology of psychiatric disorders. In this context, our group focuses most of its efforts in the identification of novel genes controlling the development of cortical inter-neurons, a type of cortical cell which dysfunction underlies the etiology of neurological and psychiatric disorders such as epilepsy or schizophrenia. For example, in collaboration with the lab of Beatriz Rico we have recently found that the schizophrenia susceptibility gene Nrg1 and its ErbB4 receptor are required for the wiring of some cortical interneurons. Our laboratory is currently exploring the role of other disease specific genes in the wiring of cortical interneurons.

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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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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*

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Experimental Embryology

Salvador Martínez UMH
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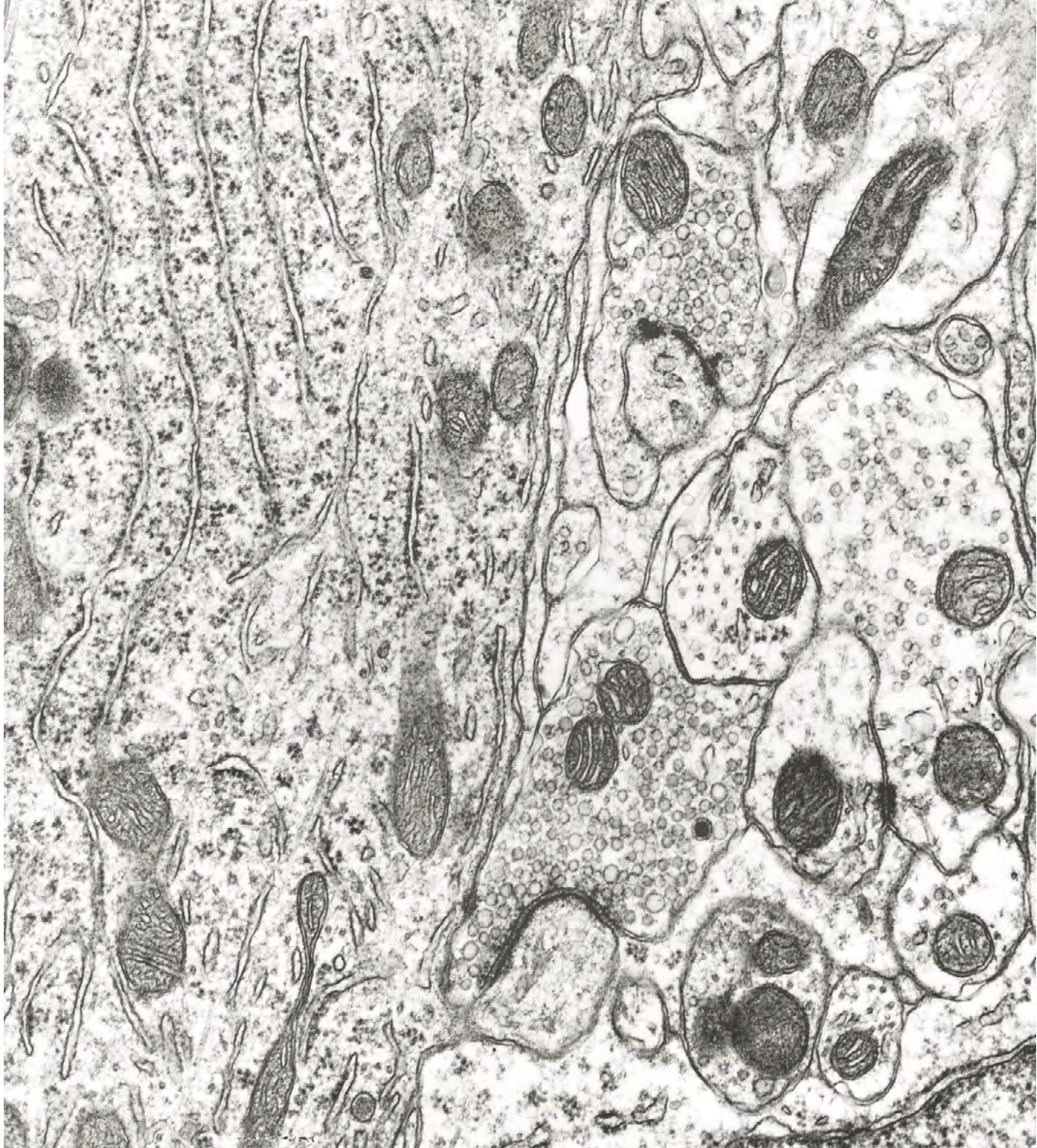
Our studies are focused on four research projects:

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



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

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

Neurogenetics: We are studying expression patterns of important genes related to the structural organization of the brain through its development. This research line is part of the Allen Institute Brain Development project in which we pretend in a large-scale manner to analyse the expression pattern genes at several embryonic stages of mice (www.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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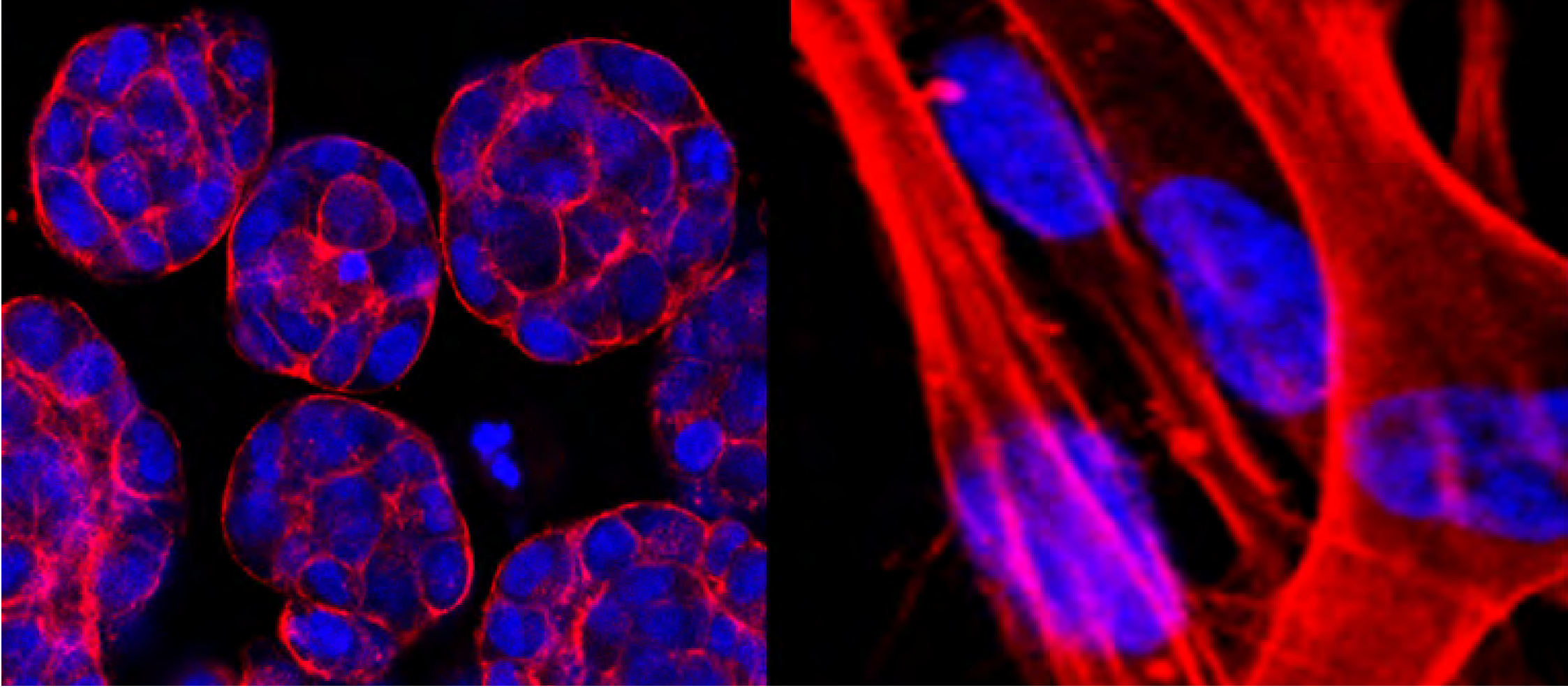

Cell movements in development & disease

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), while its activation in the adult kidney leads to renal fibrosis (2006). 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) determines embryonic territories at gastrulation, ensuring the formation of the nervous system (2011).

Snail activity is regulated by multiple mechanisms, from the gene transcriptional control to protein availability in the nucleus or postranslational modifications. We had previously characterized the nuclear import pathways (2009) and participated in a study that defines a novel phosphorylation of the Snail protein, promoting its nuclear retention and therefore, its activity (2012). Now we have described a novel nuclear export pathway for Snail and other transcription factors (TFs) that involves the protein elongation factor eF1A. This is a new mechanism to attenuate the function of TFs and unveils a nuclear function for EF1A (2013).

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 traced back the origin of the superfamily to a protoSnail gene that underwent tandem duplication in the last common ancestor of the Diploblasts and Bilateria (2009). These studies favour the analyses of ancestral and acquired functions. 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 .

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 recently 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 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.

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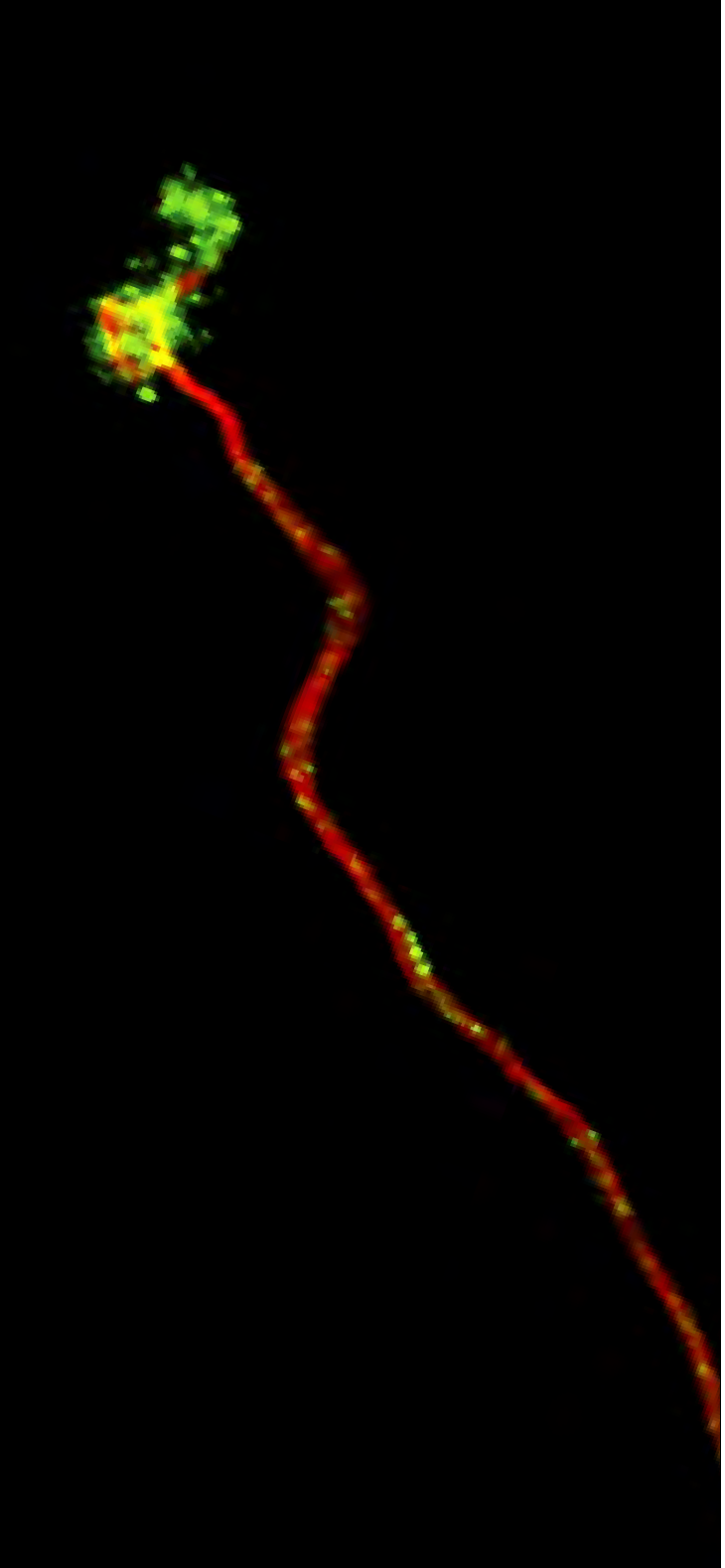

Neural circuit formation & remodeling

Beatriz Rico CSIC

Our research focuses on the study of the cellular and molecular mechanisms controlling the development of neural networks. Brain wiring is a tightly regulated process involving a number of consecutive steps. Once immature neurons have reached their final destination, they extend axons to different regions. Subsequently, the initial axons generate additional branches to form a terminal field. Finally, undifferentiated contacts with targeted neurons will develop into mature synapses, whereas unused terminals will be eliminated. To investigate the involvement of particular genes in the regulation of these events, we utilize tissue and cell specific conditional mutant mice, using histology, biochemical, molecular and cellular biology techniques. Currently, our studies focus in studying the role of different families of molecules in controlling the axonal development and synapse formation. In particular, our laboratory investigates the role of focal adhesion kinase, FAK, in axonal arborisation. In addition, we study the involvement of neurotrophins and neuregulins in axonal development and synapse formation. Following

these investigations, we are also interested in how these molecules interact among them to participate in the same or opposite mechanisms in the neuron. Finally, our last aim is to search for known and unknown molecules that might be involved in the assembly of neural circuits.

There are increasing evidences suggesting that impaired neuronal circuit development might be behind some human disorders, from learning disabilities to major psychiatric and neurological illnesses such as autism, schizophrenia or Alzheimer. Thus, to understand which are the mechanisms regulating these processes is a challenge for the neuroscientist in the next coming years.

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Altered molecular mechanism in Alzheimer's disease & dementia

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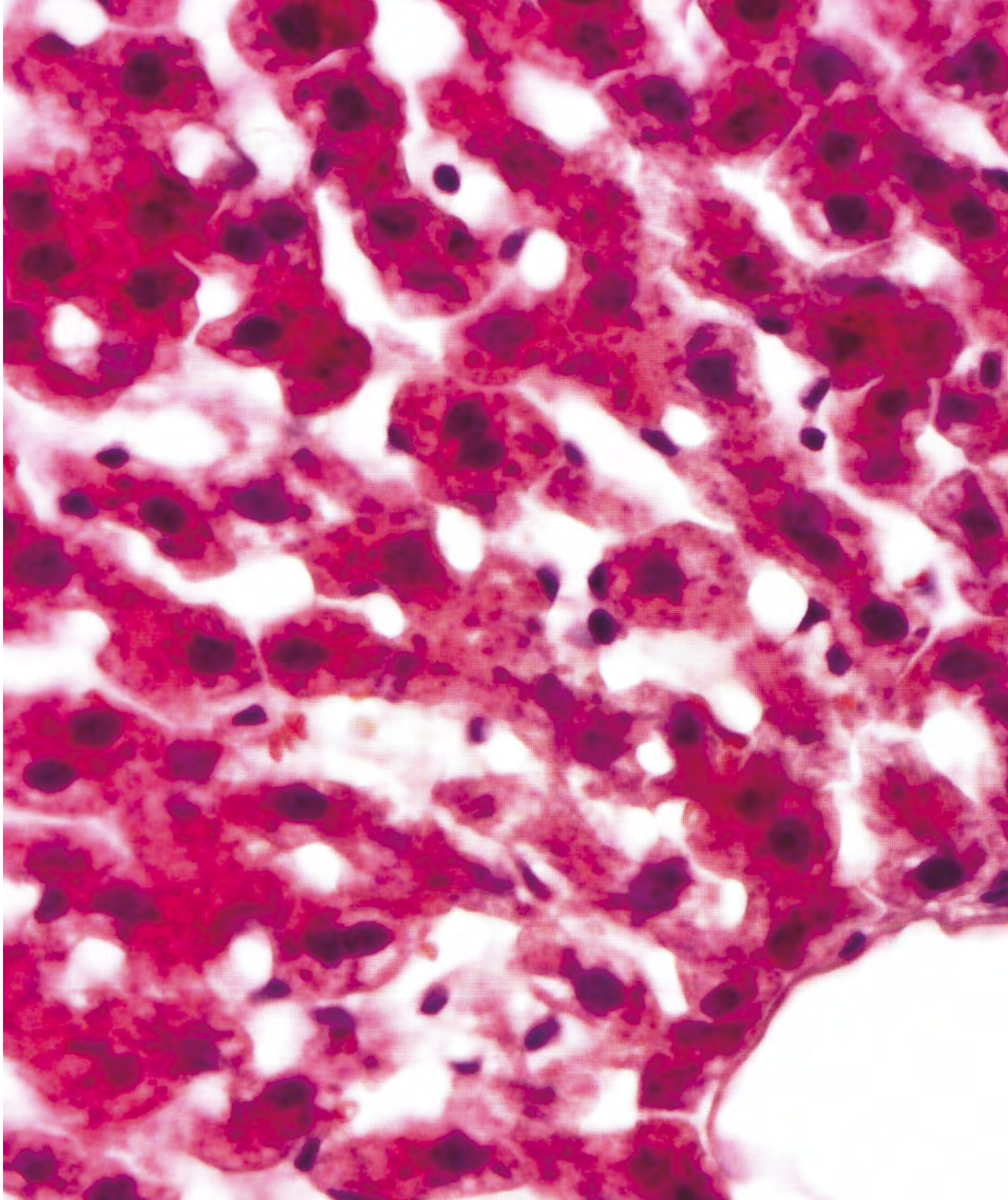
Our aim at the IN is to introduce a line of research into Alzheimer's disease (AD) and dementia that originated from a basic point of view but that was relevant to the development of clinical-diagnostic applications. Therefore, the translational benefits of our research lie



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.

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 proteolitic processing of amyloid protein precursor) and AChE, which may be relevant for the pathological progress of dementia and the design of therapeutic strategies.

In the last few years, we have described 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 indentify secretase-related proteins, related with β-amyloid metabolism, in the cerebrospinal fluid.

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Altered molecular mechanism in Alzheimer's disease & dementia

García-Ayllón MS, Campanari ML, Montenegro MF, Cuchillo-Ibañez I, Belbin O, Lleó A, Tsim K, Vidal CJ, Sáez-Valero J (2014) **Presenilin-1 influences processing of the acetylcholinesterase membrane anchor PRiMA** **Neurobiol Aging** *35, 1526-1536*

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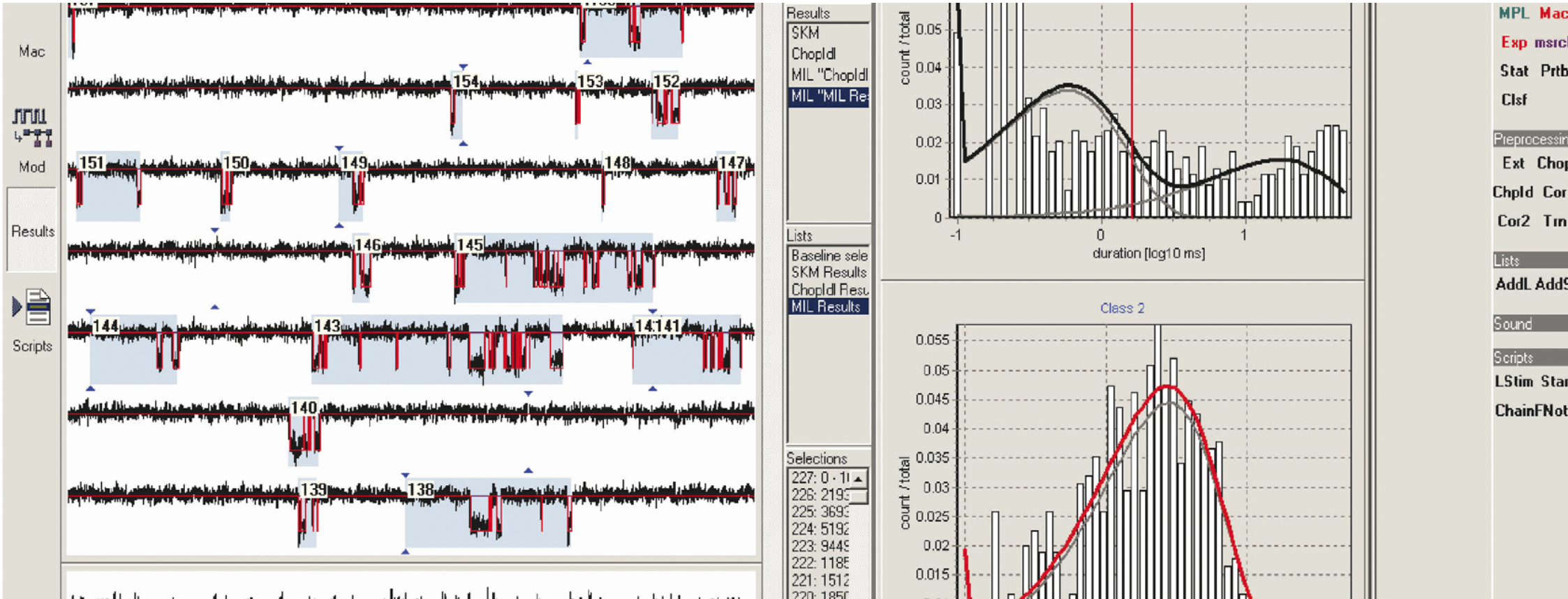
Biophysics & pharmacology of ionic channels

Francisco Sala UMH

Salvador Sala UMH

Our research interests are the functional study of ligand-gated ionic channels, mainly the neuronal nicotinic acetylcholine receptors (NNRs). The two major aspects of these studies are:

The relationship between molecular structure and function. By combining heterologous expression



of receptor subunits, wild type or mutated, and electrophysiological techniques (recordings of macroscopic and single channel currents), we study the structural components involved in different functional characteristics of NNRs, principally the structures involved in the transmission of the signal produced at the binding site towards the gate of the ionic pore. The results are analyzed in the theoretical framework of different kinetic models.

Pharmacological properties of several substances with potential therapeutic interest. NRRs are involved in the etiopathogenesis of several neurodegenerative diseases (Alzheimer, Parkinson, etc.) and in some socio-pathological behaviors (nicotine addiction). We study different drugs that could be useful in the therapy of these diseases. The primary objectives are establishing their pharmacological selectivity for different subtypes of NNRs and the study of the mechanism of action at the molecular level. For this we use both the heterologous expression of different subunit combinations of NNRs and the study of the native receptors in chromaffin cells, by using the electro-physiological techniques described above.

Principal Investigators

Francisco Sala

Salvador Sala

Technical Staff

José Mulet

Manuel Criado*, Luis M. Valor, José Mulet, Susana Gerber, Salvador Sala, Francisco Sala (2012) **Expression and functional properties of α7 acetylcholine nicotinic receptors are modified in the presence of other receptor subunits** **J Neurochem.** *123, 504–514*

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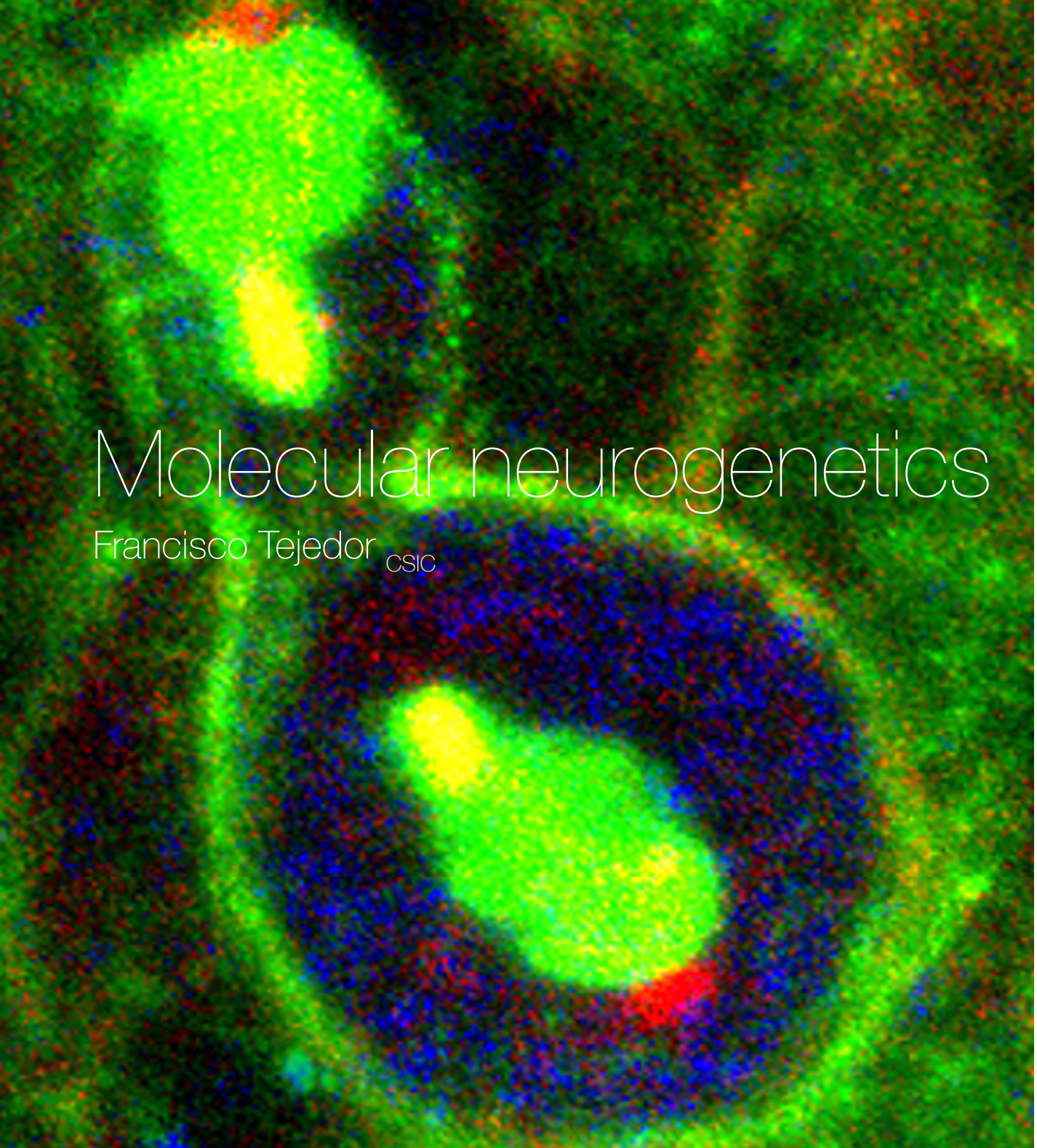

Molecular neurogenetics

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 role in neural proliferation, neurogenesis, and neuronal differentiation. 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. Since DS is originated by the triplication of chromosome 21, we are using experimental models to determine how an excess of Mnb function can 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.

Principal Investigator
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PhD Investigator
Francisco Gutierrez-Aviño

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Victoria Florencio
Veronica Hernando

Master Student
Rui Joao Da Silva Loureiro
(Leonardo da Vinci Program
Universidade Aveiro, Portugal)

Technical Staff
Sofia Jimenez Garcia

Ulf Soppa, Julian Schumacher, Victoria Florencio Ortiz, Francisco J. Tejedor and Walter Becker (2014) **The Down syndrome related protein kinase DYRK1A phosphorylates p27Kip1 and Cyclin D1 and induces cell cycle exit and neuronal differentiation** **Cell Cycle** *13:13, 1–17*

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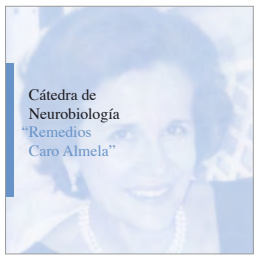
Collaborations & Agreements

Public and Private Institutions

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



Cátedra de Neurobiología Remedios Caro Almela

Cátedra para el Estudio de la Esclerosis Lateral Amiotrófica: Ciudad de Elche y Fundación Diógenes.

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

FUNDACIÓN DUQUES DE SORIA

GENERALITAT VALENCIANA
CONSELLERIA DE SANITAT
Unidad Asociada del Hospital de Sant Joan

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Fundación Marcelino Botín

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ALLEN INSTITUTE for BRAIN RESEARCH
Fueling Discovery

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.

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) and Magdalena Götz (2013).

The latest Prize Ceremony was held on October 25th, 2013 at the Instituto de Neurociencias. The previous prize winner Dr. Christine Holt, 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

The Remedios Caro Almela Prize for Research in Developmental Neurobiology 2013

The jury of the 6th Edition of the "Remedios Caro Almela" Prize in Developmental Neurobiology met on June 19th of 2013 and was integrated by Josep Xavier Barber, Adjunt Vice-Rector of Research and Innovation of the UMH; Juan Lerma, Director of the Instituto de Neurociencias, Christine Holt, winner of the fifth edition of the award, Paola Bovolenta, from the Center of Molecular Biology Severo Ochoa, Patrick Charnay, de l' École Normale Supérieure of Paris and the previous Remedios Caro Almela Chairman, Constantino Sotelo. The jury unanimously decided to award the prize "Remedios Caro Almela in Development Neurobiology to Professor Magdalena Götz, Chair of the Department of Physiological Genomics of the Ludwig-Maximilians- University, and Director of the Stem Cell Institute of the Centre Helmholtz, both in Munich, Germany for her contributions to the understanding of the cellular and molecular mechanisms that govern the formation of the cerebral cortex. Dr. Götz has discovered that radial glial cells are not only guidance structures for migrating neurons, but also generate neurons as well as glial cells in the developing forebrain. Among other important findings, she demonstrated that glial cells can

be reprogrammed to functional nerve cells by transfection with some determinants of neuronal specification. Newly formed neurons are able to functionally integrate in adult cortical circuits. This cellular reprogramming opens new avenues for the repair of the brain after traumatic injuries or in neurodegenerative diseases.
Her work has received a unanimous international recognition, being in recent years invited lecturer in major World Congress devoted to the study of the development of the nervous system. The jury highlighted the novelty and quality of their contributions and the high productivity of his research group.

Professor Götz was born in Germany, in 1962, studied biology at the universities of Tübingen and Zürich. She did his doctorate at the Institute Friedrich-Miescher of the Max-Planck Society, Tübingen. After several postdoctoral stays in Germany and United Kingdom, she continued her work as a group leader at the Max Planck Institute of Neurobiology in Martinsried, until being appointed Chair of Genomic Physiology and Director of the Stem Cell Institute of the Helmholtz Center.
Magdalena Götz is Editor of Development, Associate Editor of Journal of Neuroscience and member of the editorial board of Cell Stem Cell, Development, EMBO Journal, Genes and Development, Journal of Neuroscience, Glia, BMC Developmental Biology, Cell Adhesion and Migration, Frontiers in Neurogenesis, and Current Opinion in Genetics and Development

She has also received numerous important awards, including the Federal Cross of Merit on Ribbon, EMBO Member, and Member of Academia Europaea and Leopoldina.

The next Remedios Caro Almela Prize will be awarded in 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.

Services & Facilities

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. Where washing, preparation and sterilization of all materials used in the animal house are centralized. It has 3 autoclaves, two spraying SAS, rackwasher, etc .

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).

Administrative & Service Staff

Manager

Mª Teresa García Hedo

Administration

Mª Luz Arce Fernández
Mª Jesús Arencibia Rojas
Helena Campos Martín
Mª Auxiliadora Casanova Javaloyes
Gisele Díaz Pérez
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Beatriz Yunta Arce

Purchase & Storage

Isabel Ortega Castillo

Maintenance

Jesús Campos Roldán

Electronic Workshop

Víctor Rodríguez Milán

Administrative & Service Staff

Imaging
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Computing
Mª Isabel Sánchez Febrero

Radioactivity Control
Emilio Gutiérrez Flores

Scientific Illustration
Stuart Bailey Ingham

Cell Culture
Sara Carratalá Gosálbez
Rosa García Velasco

Glassware & Autoclaving
Trinidad Guillén Carrillo

Brain Imaging Service
Jesús Pacheco Torres

Administrative & Service Staff

Veterinary Staff

Mª Jesús Molina Cimadevilla
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Animal House

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Ana Lorena Marín Sánchez
Patricia Muñoz Robledano
Rebeca Ortiz Méndez
Raúl Pardo Mérida
Eva María Sabater Sánchez
Sonia Segura Llobregat
Mª Ángeles Soler Ripoll
Lucía Yuste Jiménez

Drosophila Service

Alicia Sánchez Rincón

Zebrafish Facility

Diana Abad Bataller
Teresa Martín Rey

Publications

Article

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Seminars

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Dr. Salvador Soto-Faraco Universidad Pompeu Fabra

24/01 **Epileptogenic cortical malformations: exploring genotype-phenotype links and pathophysiological mechanisms**
Dr. Alfonso Represa Institut de Neurobiologie de la méditerranée, Marsella, Francia

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Dr. Simone Calzolari Barcelona Science Park (PCB)

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Dr. Pierre Leopold Institute of Biology Valrose, Universite Sophia. Antipolis, Nice, France.

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Dr. Peter Ulhaas University of Glasgow, Scotland

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Dr. Klaus-Armin Nave Max Planck Institute of Experimental Medicine, Goettingen. Germany.

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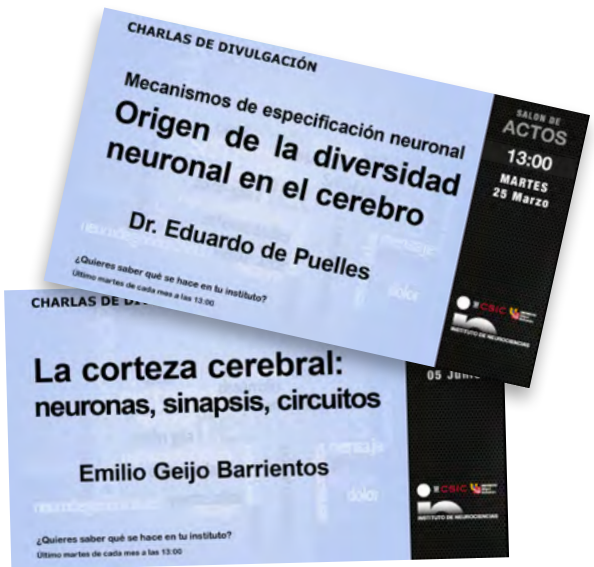

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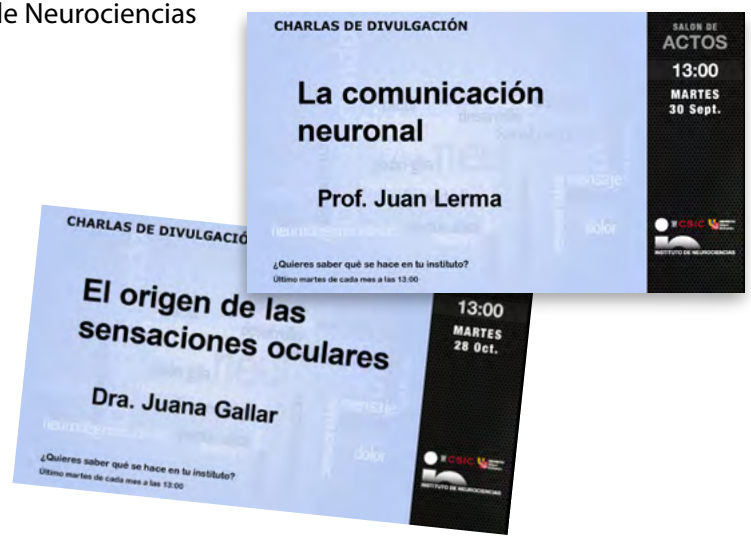

PhD Thesis

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Gomis Coloma , Clara **New Insights into Mechanisms Controlling the Schwann Cell Phenotype During Tumourigenesis and After Injury.** *Hugo Cabedo Mart (Director)*

Ciceri , Gabriele **Development of Neuronal Lineages in the Mammalian Cerebral Cortex** *Oscar Mar n Parra (Director)*

Miguela Fernndez , Veronica **Molecular Mechanisms of oncogenesis mediated by the BTB transcription factor pipsqueak: impact of sumoylation & proteolytic processing.** *Mar a Dom nguez Castellano (Directora)*

Luis Baltazar , Enoch **Participacin del Canal Inico de Potasio Task-3 en la Sensibilidad a Fr o: Estudio de su Expresin y Funcin en Neuronas Sensoriales Primarias que Expresan el Canal Inico TRMP8.** *Flix Viana de la Iglesia (Director)*

Mart nez Lpez , Jess Eduardo **Mecanismos Genticos Implicados en la Diferenciacin de las Poblaciones Neuronales del Mesencfalo y Cerebelo** *Eduardo de Puelles Mart nez de la Torre (Director)*

Other Activities

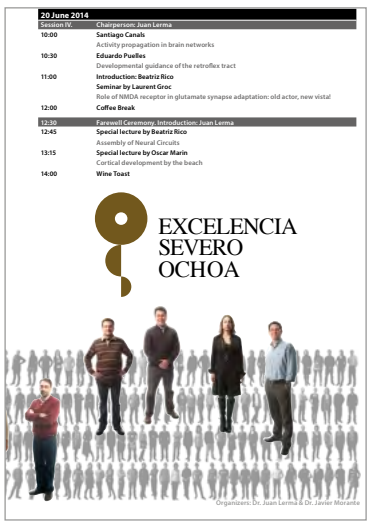
11th Christmas Meeting of the Instituto de Neurociencias (joint with the 4th Prometeo KARTACO meeting)

6th Congress of 5P Sindrome and rare diseases

V Simposium PROMETEO NEC_2. Anomalías genéticas del desarrollo cortical y disfunción cerebral

10th IN Progress Report Workshop.

"Brain Awarenes Week 2014" activities.



Press Cuttings

Dos investigadores del Instituto de Neurociencias de la UMH, entre los 25 más influyentes del panorama científico del diario El Mundo

El diario El Mundo incluye a los investigadores del Instituto de Neurociencias, centro mixto de la Universidad Miguel Hernández (UMH) de Elche y el Consejo Superior de Investigaciones Científicas (CSIC), Carlos Belmonte y Ángela Nieto dentro de la lista de los 25 científicos más influyentes para 2014. **Leer más**