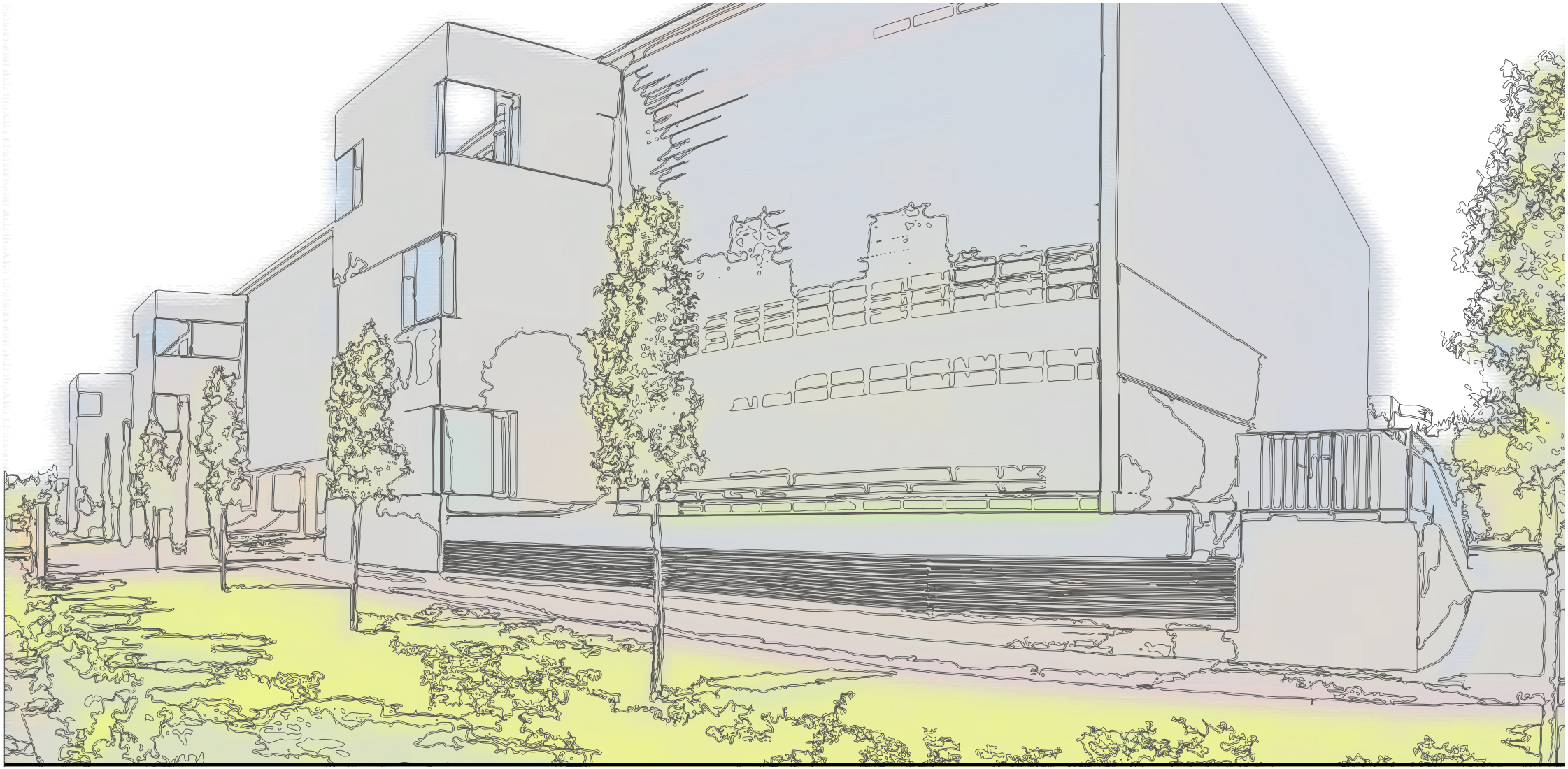
INSTITUTO DE NEUROCIENCIAS

ANNUAL REPORT 2015



EXCELENCIA
SEVERO
OCHOA

ANNUAL REPORT 2015

Salutation

Juan Lerma : Director

The year 2015 has been a year of continuity and stabilization for the Instituto de Neurociencias, which continues to maintain a good level of income for projects, published works and scientific achievements. All likely favored by the accreditation as a "Center of Excellence Severo Ochoa", which officially started in July, 2014 and that is allowing us to undertake new initiatives, as reported later.

This year, one more colleague left the Institute, tempted by extraordinary offers from abroad. Miguel Maravall joined the University of Sussex in mid-2015 as Professor of Neuroscience. In the official farewell by the entire Institute, Miguel presented the achievements obtained in their stay amongst us after returning from his postdoctoral stay in USA and Italy. Miguel was presented with a plate as a sign of remembrance. It is still noting the role of the Institute as a hotbed of important international figures in neuroscience. Mobility is something inherent in scientific activity. Our problem is the lack of the capabilities for people replacement, imposed by the system in which we are immersed.

Two other members of the Institute, Fernando Moya and Roberto Gallego, reached the age of retirement in 2015 after belonging to our Institute since its inception. In particular, the retirement of Roberto represents, perhaps, a turning point in the history of our Institute because he was one of its founders. We will always remember him and wish them both a blissful retirement enabling them to perform what they never had time to do for their great dedication to the Institute and the University.

The Institute, however, has taken the initiative to incorporate young scientists with the tools we have at hand. Thus, Ramón Reig, from the Karolinska Institute, and Alex Gómez-Marín and Cristina Márquez, from the prestigious Champalimaud Center, joined our Institute. All three are setting their research groups and join José López-Atalaya and Berta Lopez Sanchez-Laorden, who got a project for young researchers (JIN) and Ramón y Cajal contract, respectively.

But they are not the only additions. The prestigious British researcher Richard Morris, has decided to also join the IN and Julio Barbas, a CSIC Investigator moved from Madrid to collaborate with

internationalization actions, both in the framework of the Severo Ochoa Program. Without a doubt, these are significant additions, which have to be very positive for the coming years.

In 2015 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 speaks 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 reach to a stable averaged impact factor of our papers (7.21 in 2015), as well as the number of citations to the latest period runs fair enough.

In the past year, the IN has been subject of a number of relevant actions. For example, the Institute received in a solemn ceremony the "Important of the Year" prize, awarded by the newspaper Información, from the hands of the President of the Generalitat Valenciana, Alberto Fabra on February 19, 2015. Several members of the IN have achieved significant recognition to his research work. For example, Ángela Nieto received the Distinction to the Scientific Merit of the Generalitat Valenciana; Juana Gallar was elected Vice President of the European division of the International Society for Eye Research; Carlos Belmonte received the prize of the Spanish Society of Pain to the best research group on neuropathic pain and Eloisa Herrera was presented in April with the "Alberto Sols Prize" to the best scientific paper. Finally, Santiago Canals was featured by Scientific American magazine as one of the "10 World Innovators" in the field of memory, along with personalities such as Hermann Ebbinghaus, Sigmund Freud, Donald Hebb and Eric Kandel. Congratulations to all. The IN and its members continue reinforcing its presence at national and international levels.

In 2015, the IN groups have continued with a certain degree of expenditure containment. This is undoubtedly due to the erratic schedule for calls for projects 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. IN members are committed to this endeavour because we continue to incorporate to the Center the latest techniques to allow our researchers perform experiments and advance in the knowledge of the brain in equal conditions to our European and American colleagues.

Salutation

A remarkable event in 2015 has been the celebration of the 15th anniversary of the establishment of the Remedios Caro Almela Chair of Neurobiology. For its commemoration, we organized a symposium with the participation of scientists awarded in previous editions with the Prize in Developmental Neurobiology Remedios Caro Almela, who kindly agreed to take part in it joined by some young scientists of the IN. In this event, Magdalena Götz (Remedios Caro Almela Prize 2013) gave the VI Remedios Caro Almela Lecture.

On the next day, the award ceremony of the 7th Remedios Caro Almela Award on Developmental Neurobiology took place. This year the Swiss researcher Silvia Arber was awarded, and before the ceremony, she delivered the VII Caro Almela Lecture with the title "Disentangling neuronal circuits for motor control".

In 2015 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 more that 1000 people, mainly kids, 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 an excellent scientific level. Also I warmly acknowledge the institutions to which the IN belongs, CSIC and UMH, for the continuous support of our research activity.

Worth mention is that in 2016 my replacement in the Institute's Direction will take place, after more than 8 years of service. From here I wish the person taking this responsibility all the possible luck, at the same time committing my support in the task of developing research programs in the coming years.

Juan Lerma, Director.

A Bit of History

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

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

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

Where We Are

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

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

What We Do

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

The IN is a publicly funded centre dedicated to brain research in both normal and pathological conditions. This is achieved through a multidisciplinary approach towards the study of the structure, function and development of the nervous system at the molecular, cellular, and integrative levels.

The Institute is organised into three research 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.

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 37 tenured researchers (20 from the UMH and 17 from the CSIC), 6 non-tenure scientists, 192 doctoral and postdoctoral researchers and 83 technical and administrative staff (See graphic IN in Numbers: Personnel).

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

Where We Are Going

In 2010, the IN implemented its second Strategic Plan, which at the request of the CSIC was elaborated in 2009. The previous Plan shaped the IN along the last five years (2005-2009). The second outlines the guidelines for consolidation, with the clear goal of becoming a center of excellence in the European Research Area. The 3rd Action Plan, started in 2014, 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

- Demonstrated that a single gene variation in the glutamatergic system results in behavioral symptomatology consistent with autism spectrum disorders as well as in alterations in synaptic function in regions involved in social activity. (Aller et al., **J. Neurosci.** 35(40):13619 –13628 . 2015 (Journal cover; commented on "This week in the Journal")

- Demonstration that the nociceptive channel TRPV1 is a molecular target of hyaluronan (HA), the main component of the extracellular matrix. HA reduces the excitability of TRPV1 channels thereby lowering impulse activity in the peripheral nociceptor endings underlying pain (Caires et al.. **Nature Comm.** 10.1038/ncomms9095 (2015)

- We have described a novel role for the transcription factor Zic2 in the migration of certain types of neurons that contribute to the formation of the telencephalon. This new role for Zic2 help us to understand the devastating phenotypes showed by mammals with mutations in this gene, such as holoprosencephaly, spina bifida or schizophrenia. (Murillo et al., **J Neuroscience** 35(32): 11266-11280)

- Demonstrated that the transcription factor SRF plays an important function in controlling asymmetric neuronal outgrowth, which has profound implications in the formation of the nervous system. (Scandaglia et al., **Scientific Reports** 7;5:17470. 2015)

- Demonstrated that interfering with the biogénesis microRNAs disrupts the homeostatic mechanisms protecting neurons from overactivation, unveiling a new role microRNAs system in the regulation of neuronal firing threshold (Fiorenza et al., **Cereb Cortex** 2015 Jan 16 [Epub ahead of print])

- Demonstrated that mice models of Rubinstein-Taybi syndrome, a genetic disease associated with intellectual disability, recapitulate the microcephaly observed in patients, and demonstrated that the haploinsufficiency that causes the disease has a differential impact on the forebrain development (Ateca-Cabarga et al. **Sci Reports** 2015)

- Discovered the role of the DCC Netrin-1 receptor in the process of axon growth. DCC acts as an accelerator for axonal outgrowth in thalamocortical axons and its expression is regulated by activity-dependent mechanisms. (Castillo-Paterna M et al. **EMBO Rep** 2015)

- Revealed a cycle of proteolytic activity underlying growth cone collapse and restoration used by axons to find their correct trajectory in the brain. BACE1 and γ-secretase inhibition have physiologically opposite effects in this process. (Barão et al. **Cell Reports** 2015).

- Discovered the implication of the Wnt binding receptor Frizzled3 in the embryonic ontogeny of the two main striatal pathways (striatonigral and striatopallidal) and identify novel (non)cell-autonomous roles for Frizzled3 in the striatal pathway formation. (Morello F et al. **J of Neurosci** 2015.)

- Demonstrated the existence of a genetic protomap of cerebral cortex folding in ferret and human. Variations in intensity of expression of thousands of genes anticipate and predict the pattern of formation of folds in the cerebral cortex. Among the genes that define the protomap there are 80% of those whose mutation causes brain malformations during human embryonic development. This protomap does not exist in mice, where the cerebral cortex does not fold. (**EMBO J** 34:1859-1874. Cover caption, Comment in EMBO J (Have you seen?))

- Shown that the development of renal fibrosis requires the activation of an epithelial to mesenchymal transition (EMT) in the renal epithelial cells and that systemic treatment with EMT inhibitors attenuates the established disease in mouse models of fibrosis. These results solve a long debate on the origin of myofibroblasts and open new avenues for the design of antifibrotic therapies. (Grande et al., **Nature Medicine** 21, 989-997.)

- Found that the Hippo signaling pathway, a tumor suppressor pathway, regulates asymmetric cell división (Keder et al., **Current Biology** 25, 2739-2750)

- Discovered a fundamental role of short-term synaptic plasticity in the establishment of polysynaptic communication channels between the hippocampus and neocortex to transmit information multiplexed in the frequency domain. (Moreno et al. **Cereb Cortex** 2015 pii: bhv033)

- Whole-brain activity maps uncover a widespread contribution of vestibular signaling to a self-centered framework for multimodal sensorimotor integration in support of movement planning, execution, and spatial navigation. (Rancz et al. J. **Neurosci** 2015 35(15):5926-34)

- Revealed components of the KAR interactome, and they show that GluK1 and Go proteins are natural partners, accounting for the metabotropic effects of KARs. (Rutkowska-Wlodarczyk et al., **J Neurosci.** 5(13):5171–5179, 2015) (commented in "This week in the Journal")

Patents

- Pharmaceutical composition for the treatment of dry eye. US9095609 (B2; August/04/2015, UMH).
- Non-human Animal Model for Autism Spectrum Disorders, Anxiety and/or Depression. PCT 1641.993. (13-08-2015, CSIC)

The Institute in Numbers

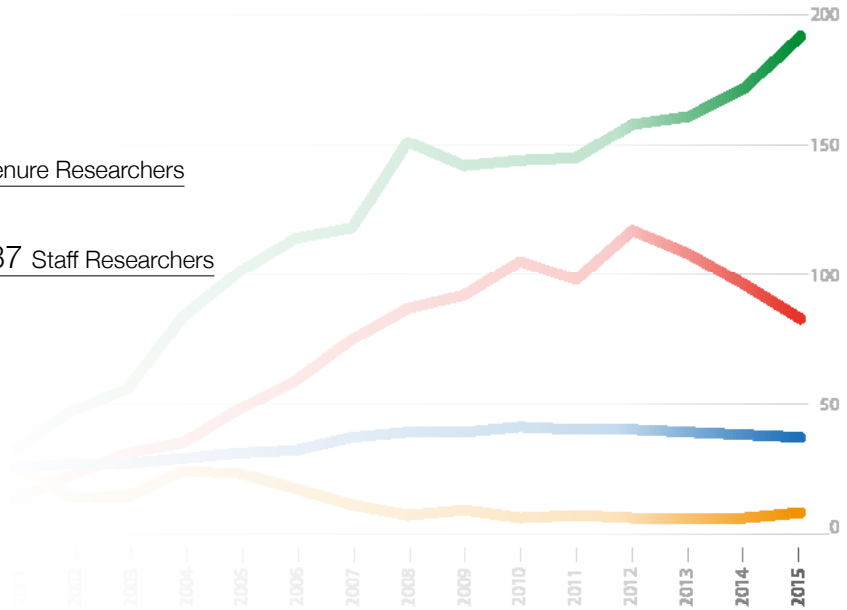
192 Pre & I

Personnel by Category

8 Non-tenure Researchers

37 Staff Researchers

83 Technicians & Administration

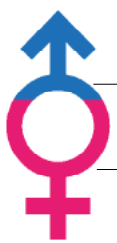


by Origin

Non-nationals

% Nationals

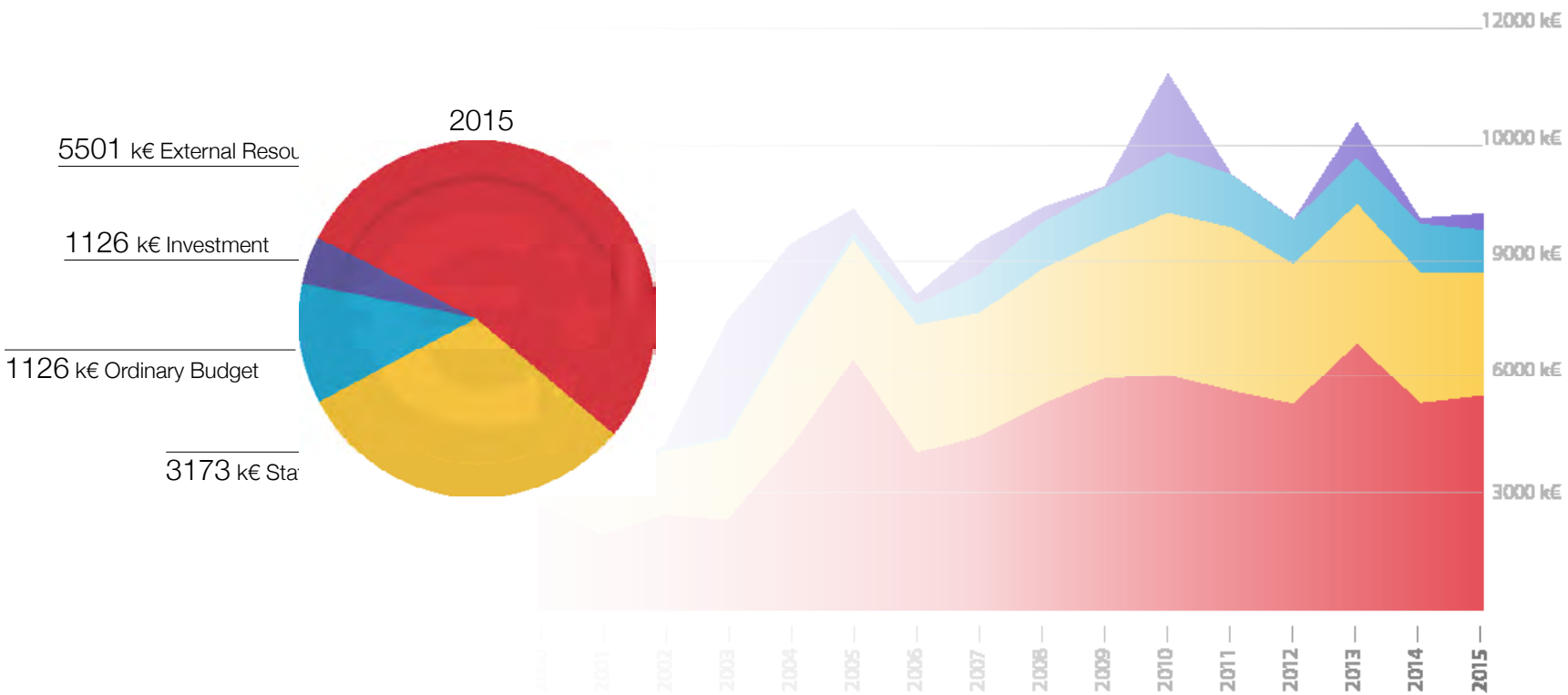
by Gender

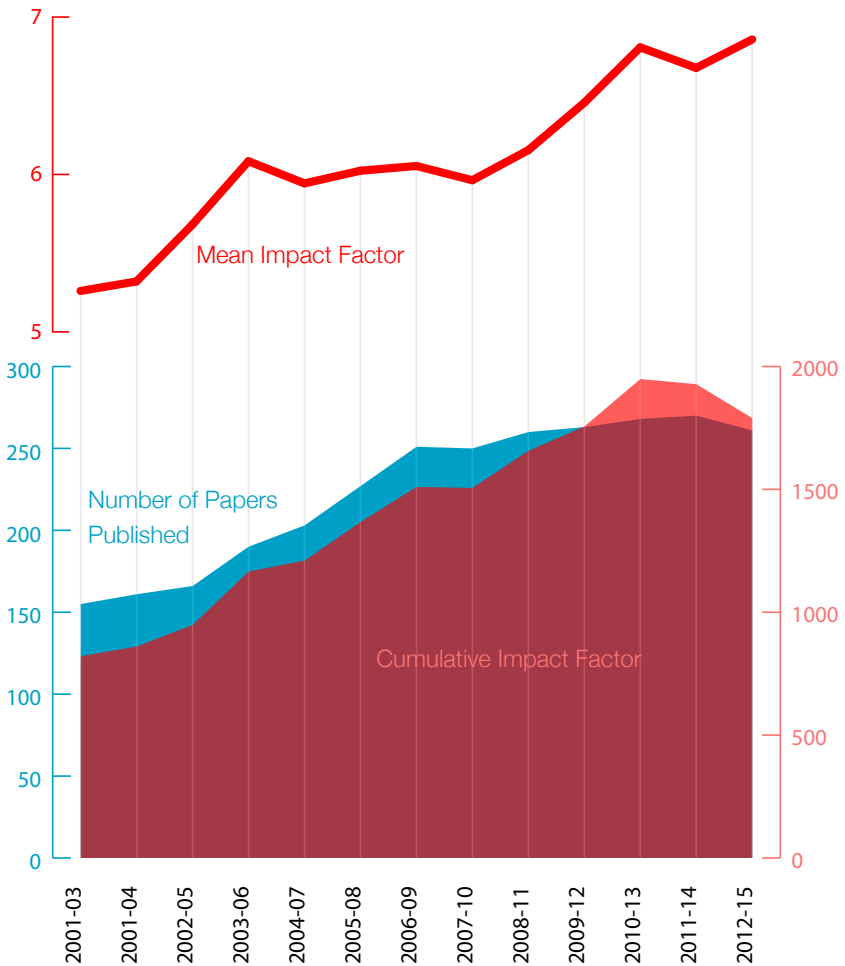


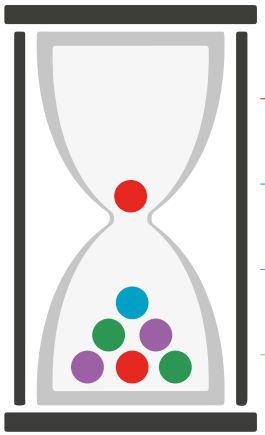
39% Men

61% Women

Budget Growth in Thousands of Euros







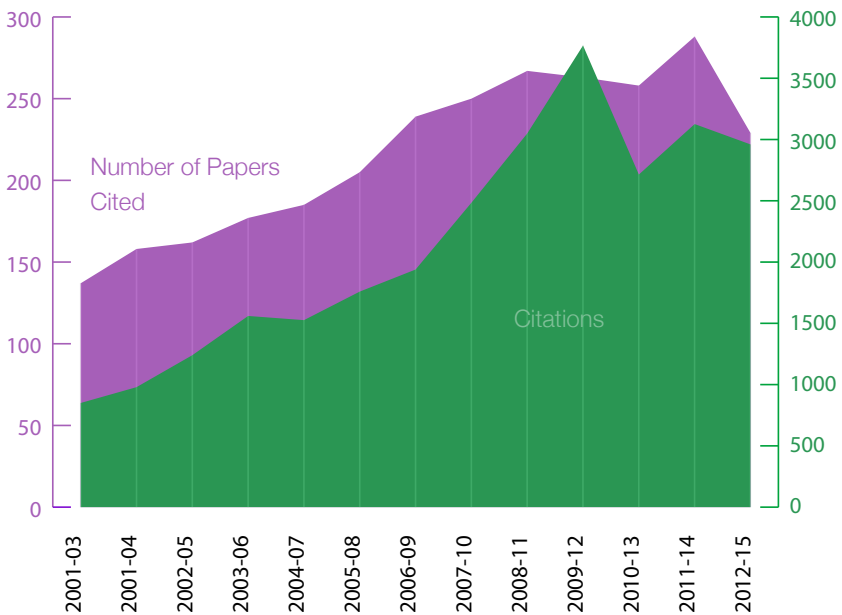
6,85 Mean Impact Factor

261 Papers Published

229 Papers Cited

2960 Citations

for the period 2012-2015



Research Units

Cellular & Systems Neurobiology

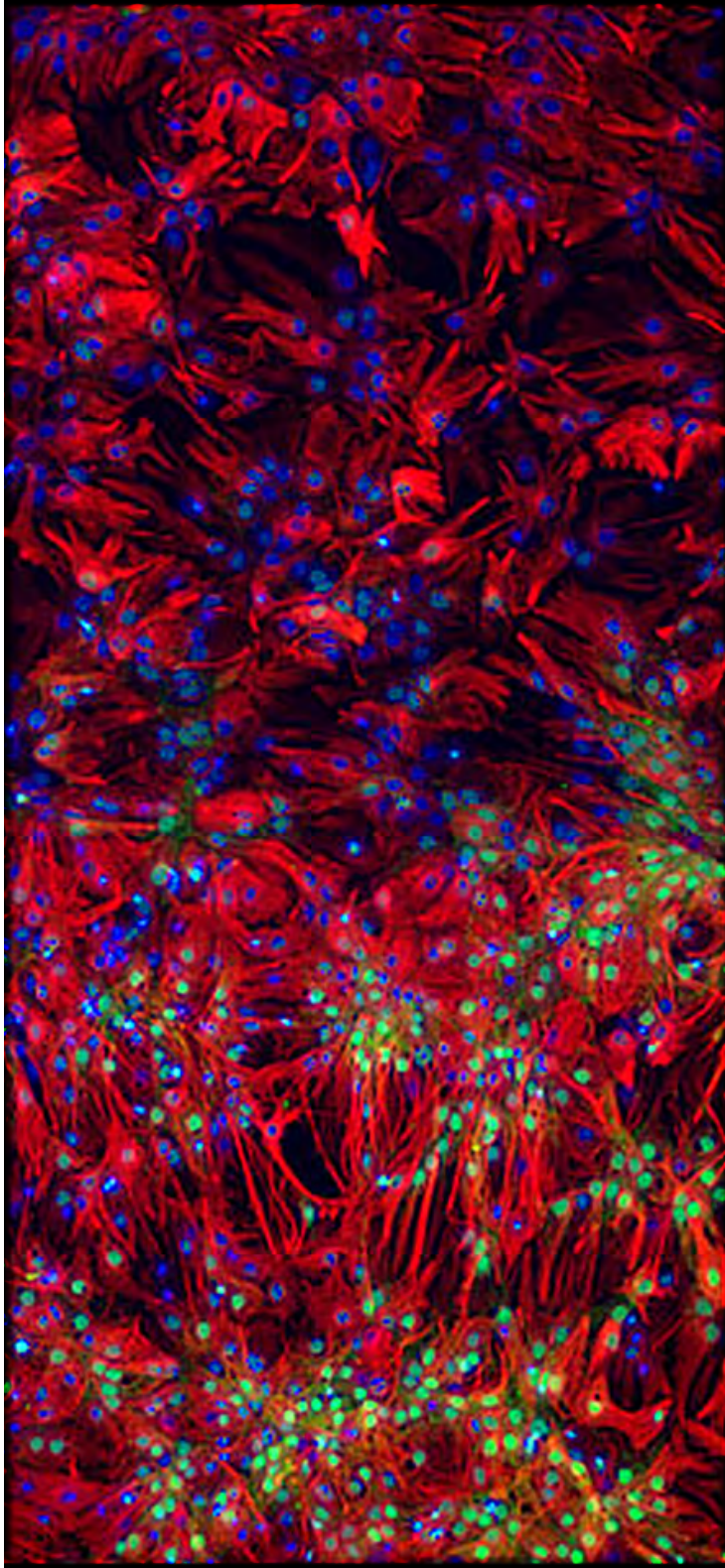
The Cellular and Systems Neurobiology Unit consists of nine groups whose research focuses on the function of the cerebral cortex and several sensory systems, primarily using electrophysiological, computational and imaging approaches.

Developmental Neurobiology

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

Molecular Neurobiology

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



Research Lines

Morphogenesis

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

Synaptic Transmission & Plasticity

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

Sensory Transduction

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

Neuronal Migration & Circuit Assembly in the Cerebral Cortex

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

Nervous System Pathology

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

Systems Neurobiology

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

Research Groups

Involvement of nicotinic acetylcholine receptors in chronic kidney disease

Juan J. Ballesta UMH

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Angel Barco CSIC

Neurogenesis & cortical expansion

Víctor Borrell CSIC

Molecular control of axonal myelination

Hugo Cabedo UMH

Plasticity of brain networks

Santiago Canals Gamoneda CSIC

Signaling networks underlying asymmetric cell division

Ana Carmena CSIC

Molecular neurobiology of neuronal nicotinic receptors

Manuel Criado UMH

Cellular & conductual neuroscience

Carmen de Felipe UMH

Mechanisms of growth control & cancer in *Drosophila*

María Domínguez CSIC

Neurobiology & neuromodulation of the opioid actions

Clara C. Faura Giner UMH

Ocular Neurobiology

Juana Gallar UMH

Mª Carmen Acosta UMH

Developmental Neurogenetics

Luis García-Alonso CSIC

Physiology of the cerebral cortex

Emilio Geijo UMH

Mechanotransduction in mammals

Ana Gomis CSIC

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

Integrative Neurogenomics
José López-Atalaya 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

Visual Neuroscience Laboratory
Luis M. Martínez CSIC

Cell movements in development & disease
M. Angela Nieto CSIC

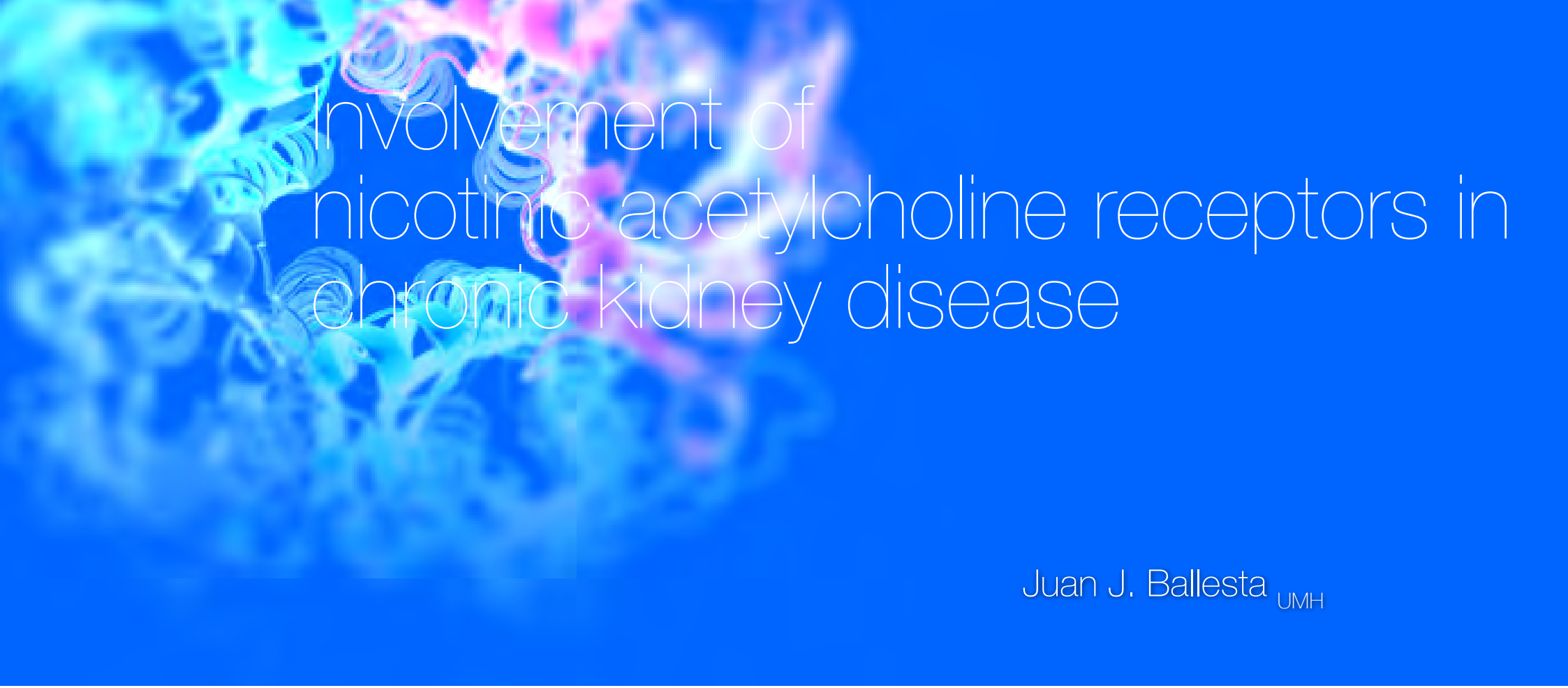
Sensory-motor processing by subcortical areas
Ramón Reig García CSIC

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

Biophysics & pharmacology of ionic channels
Francisco Sala UMH
Salvador Sala UMH

Molecular neurogenetics
Francisco Tejedor CSIC

Sensory transduction and nociception
Félix Viana CSIC
Roberto Gallego UMH
Carlos Belmonte UMH



Involvement of nicotinic acetylcholine receptors in chronic kidney disease

Juan J. Ballesta UMH

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

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

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

Principal Investigator
Juan J. Ballesta

Clinical Collaborator
Carlos del Pozo

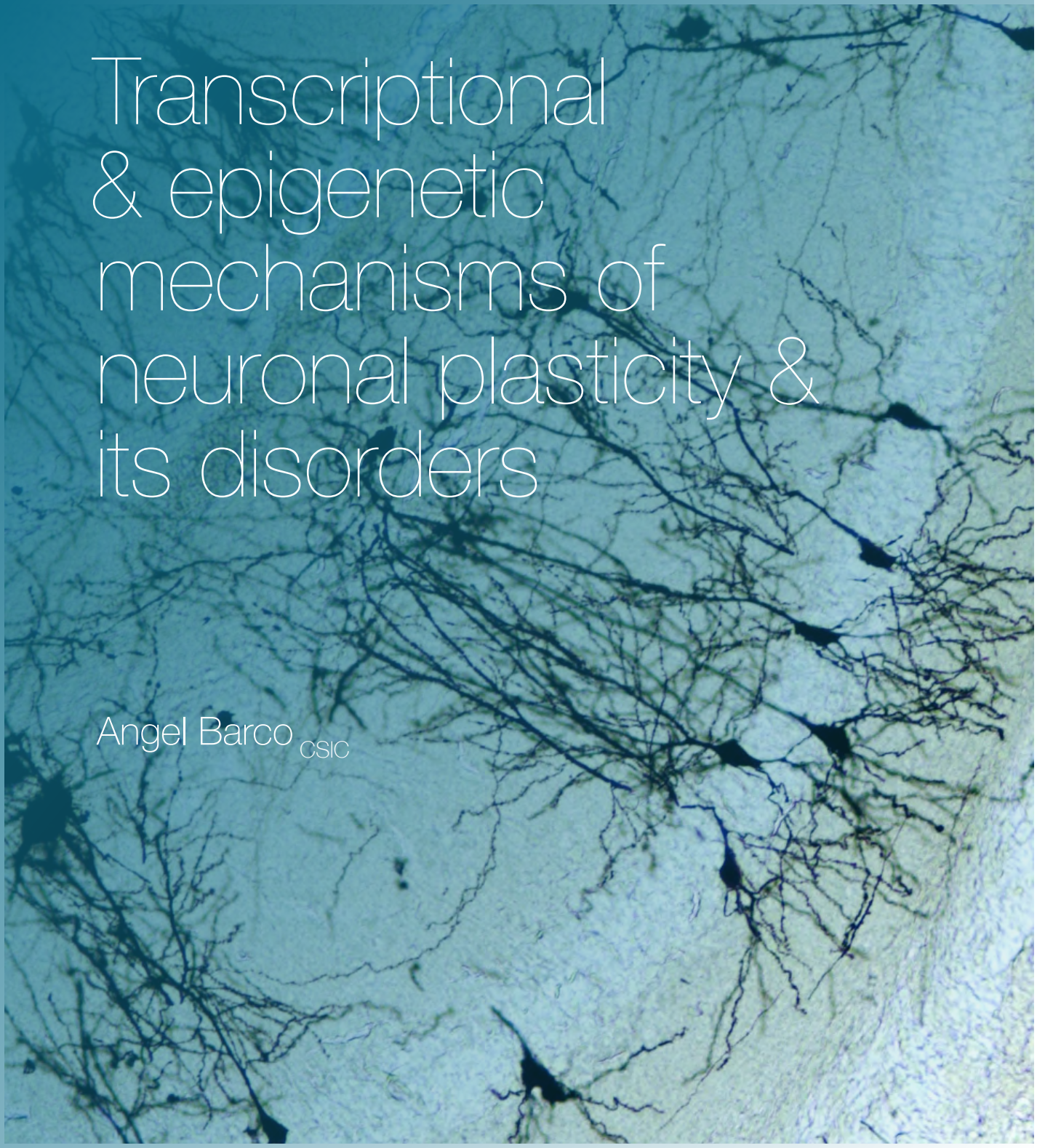
Ballesta, J.J., Cremades, J., Rodriguez-Muñoz, M., Garzón, J., Faura, C.C. (2012) **Sensitivity to μ Opioid Receptor Mediated Antinociception is Determined by Cross–regulation Between μ and δ Opioid Receptors at Supraspinal level** **British Journal of Pharmacology** *166: 309-326*

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 theconservedresidueарginine 209 in neuronal nicotinicreceptors.** **Biochemistry** *40:8300-8306.*

Críado, M. Domínguez del Toro, E. Carrasco-Serrano, C. Smillie, FI. 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.*



Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Angel Barco CSIC

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

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

We currently work on two main lines of research:

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

- Contribution of epigenetic mechanisms to brain diseases: We investigatethe contribution of epigenetic mechanisms, such as histone acetylation and methylation, to the pathoetiology of different neurological conditions, including Huntington's disease, Rubinstein-Taybi syndrome and X-linked intellectual disability. Towards this end, we generate and characterize mouse models for these conditions, explore the molecular causes of the disease and tackle new therapies.

Principal Investigator
Angel Barco

Associate Investigator
Luis M. Valor
José P. López-Atalaya

PhD Investigators
Beatriz del Blanco
Romana Tomasoni

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

Technical Staff
Román Olivares

Transcriptional & epigenetic mechanisms of neuronal plasticity & its disorders

Scandaglia M, Benito E, Morenilla-Palao C, Fiorenza F, del Blanco B, Coca Y, Herrera E, Barco A (2015) **Fine-tuned SRF activity controls asymmetrical neuronal outgrowth: implications for cortical migration, neural tissue lamination and circuit assembly.** **Sci Reports** *5:17470.*

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]*

Lopez-Atalaya J, and Barco A (2014) **Can changes in histone acetylation contribute to memory formation?** **Trends Genet** *30(12):529-39.*

Ito S, Magalska A, Alcaraz-Iborra M, Lopez-Atalaya JP, Rovira V, Contreras-Moreira B, Lipinski M, Olivares R, Martinez-Hernandez J, Ruszczycki B, Lujan R, Geijo-Barrientos E, Wilczynski GM and Barco A. (2014) **Loss of neuronal 3D chromatin organization causes transcriptional and behavioural deficits related to serotonergic dysfunction.** **Nat Commun** *5:4450.*

Lopez-Atalaya JP, Ito S, Valor LM, Benito E and Barco A. (2013) **Genomic targets, and histone acetylation and gene expression profiling of neural HDAC inhibition.** **Nucleic Acids Res** *41(17): 8072-84.*

Valor LM, Guiretti D, Lopez-Atalaya JP and Barco A (2013) **Genomic landscape of transcriptional and epigenetic dysregulation in early-onset polyglutamine disease** **J Neurosci** *33(25): 10471-82*

Benito E, Valor LM, Jimenez-Minchan M, Huber W and Barco A. (2011) **Comparative transcriptomics identifies CREB as a primary hub of activity-driven neuronal gene expression.** **J Neurosci** *31(50): 18237-50.*

Lopez-Atalaya JP, Ciccarelli A, Viosca J, Valor LM, Jimenez-Minchan M, Canals S, Giustteto M and Barco A. (2011) **CBP is required for environmental enrichment-induced neurogenesis and cognitive enhancement.** **EMBO J** *30(20): 4287-98.*

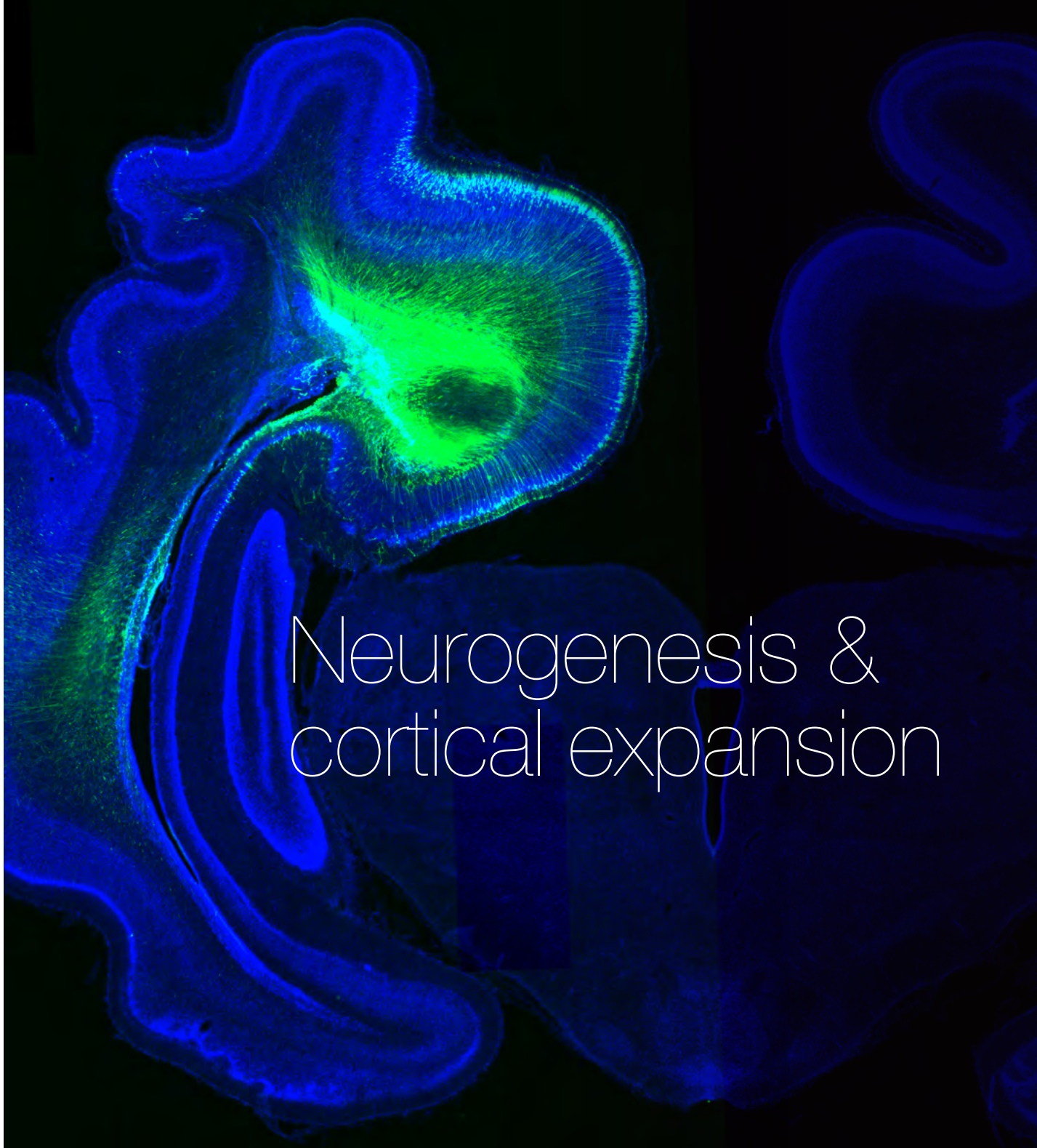
Benito E and Barco A. (2010) **CREB's control of intrinsic and synaptic plasticity: Implications for CREB-dependent memory models.** **Trends Neurosci** *33(5): 230-40.*

Barco A, Patterson S, Alarcon JM, Gromova P, Mata-Roig M, Morozov A and Kandel ER. (2005) **Gene expression profiling of facilitated L-LTP in VP16-CREB mice reveals that BDNF is critical for both the maintenance of LTP and for synaptic capture.** **Neuron** *48(1): 123-137.*

Alarcon JM, Malleret G, Touzani K, Vronskaya S, Ishii S, Kandel ER and Barco A. (2004) **Chromatin acetylation, memory, and LTP are impaired in CBP+/- mice: a model for the cognitive deficit in Rubinstein-Taybi syndrome and its amelioration.** **Neuron** *42(6): 947-959.*

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

De Juan Romero C, Bruder C, Martínez-Martínez M, Tomasello U, Sanz-Anquela JM, Borrell V (2015) **Discrete domains of gene expression in germinal layers distinguish the development of gyrencephaly** **EMBO Journal** *34:1859-1874*

De Juan Romero C, Borrell V (2015) **Coevolution of Radial Glial Cells and the Cerebral Cortex** **Glia** *63:1303-1319*

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*

Borrell V*, Calegari F* (2014) **Considerations on Cortical Development, Evolution and Cell Cycle Length of Neural Stem Cells.** **Neurosci Res** *86C:14-24*

Kielar M, Tuy FPD, Lebrand C, Bizzotto S, De Juan C, Poirier K, Oegama R, Mancini G, Bahi-Buisson N, Olaso R, Le Moing AG, Boutourlinsky K, Boucher D, Carpentier W, Berquin P, Deleuze JF, Belvindrah R, Borrell V, Welker E, Chelly J, Croquelois A, Francis F (2014) **"Mutations in the microtubule-associated protein Eml1 lead to ectopic progenitors and heterotopia formation during cortical development in mouse and human"** **Nat Neurosci** *17:923-933.*

Borrell V, Gotz M (2014) **"Role of Radial Glia cells in cerebral cortex folding"** **Curr Opin Neurobiol** *27:39-46.*

Pilz GA, Shitamukai A, Reillo I, Pacary E, Schwausch J, Stahl R, Ninkovic J, Snippert HJ, Clevers H, Godinho L, Guillemot F, Borrell V, Matsuzaki F, Götz M (2013) **"Amplification of progenitors in the mammalian telencephalon includes a novel radial glia cell type".** **Nat Comm** *4:2125.*

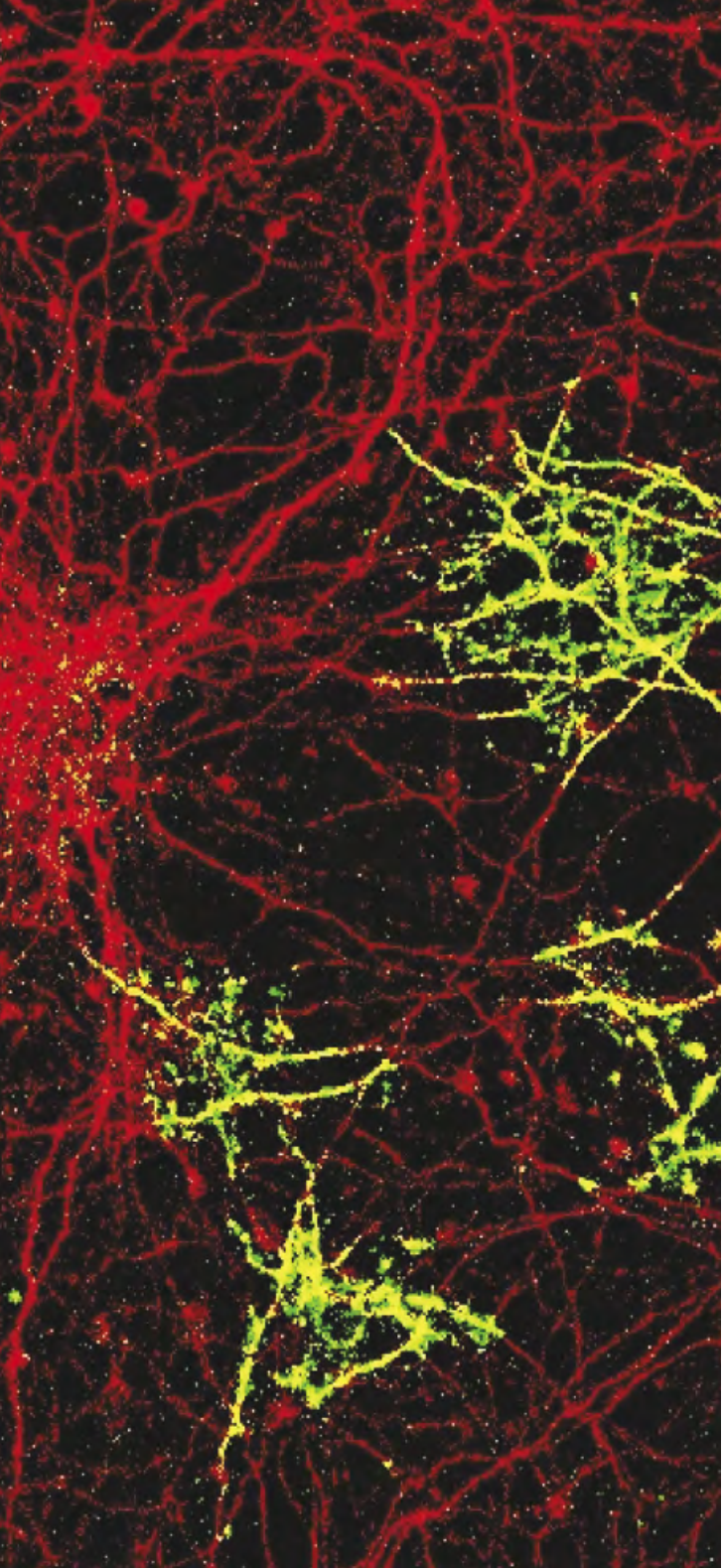
Nonaka-Kinoshita M, Reillo I, Artegiani B, Martínez-Martínez MA, Nelson M, Borrell V*, Calegari F* (2013) **"Regulation of Cerebral Cortex Size and Folding by Expansion of Basal Progenitors".** **EMBO** *32:1817-1828.*

Stahl R, Walcher T, De Juan C, Pilz GA, Capello S, Irmler M, Sanz-Anquela JM, Beckers J, Blum R, Borrell V, Götz M (2013) **"TRNP1 regulates expansion and folding of the mammalian cerebral cortex by control of radial glial fate".** **Cell** *153:535-549.*

Kelava I, Reillo I*, Murayama A*, Kalinka AT, Stenzel D, Tomancak P, Matsuzaki F, Lebrand C, Sasaki E, Schwamborn J, Okano H, Huttner WB†, Borrell V† (2012) **"Abundant occurrence of basal radial glia in the subventricular zone of embryonic neocortex of a lissencephalic primate, the common marmoset Callithrix jacchus".** **Cerebral Cortex** *22:469-481.*

Reillo I, Borrell V (2012) **"Germinal zones in the developing cerebral cortex of ferret: ontogeny, cell cycle kinetics and diversity of progenitors".** **Cerebral Cortex** *22:2039-2054.*

Borrell V, Reillo I (2012) **"Emerging roles of neural stem cells in cerebral cortex development and evolution".** **Developmental Neurobiology** *72:955-971.*



Molecular control of axonal myelination

Hugo Cabedo UMH

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

Molecular control of axonal myelination

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

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Gomez-Sanchez JA, Gomis-Coloma C, Morenilla-Palao C, Peiro G, Serra E, Serrano M, Cabedo H (2013) **Epigenetic induction of the Ink4a/Arf locus prevents Schwann cell overproliferation during nerve regeneration and after tumorigenic challenge.** **Brain** *Brain. 2013 Jul;136(Pt 7):2262-78. doi: 10.1093/brain/awt130. Epub 2013 Jun 6.*

Donier E, Gomez-Sanchez JA, Grijota-Martinez C, Lakomá J, Baars S, Garcia-Alonso L, Cabedo H. (2012) **L1CAM binds ErbB receptors through Ig-like domains coupling cell adhesion and neuregulin signalling.** **PLoS One** *2012;7(7):e40674*

Morenilla-Palao C, Pertusa M, Meseguer V, Cabedo H, Viana F. (2009) **Lipid raft segregation modulates TRPM8 channel activity.** **J Biol Chem.** *3;284(14):9215-24.*

Gomez-Sanchez JA, , Lopez de Armentia M, Lujan R, Kessaris N, Richardson WD, Cabedo H. 2009) **Sustained axon-glial signaling induces Schwann cell hyperproliferation, Remak bundle myelination, and tumorigenesis.** **J Neurosci.** *29(36) , 11304 – 11315.*

Pertusa M*, Morenilla-Palao C*, Carteron C, Viana F, Cabedo H. (2007) **Transcriptional control of cholesterol of biosynthesis in Schwann cells by axonal neuregulin 1.** **J. Biol. Chem.** *282(39):28768-78.*

Carteron C, Ferrer-Montiel A, Cabedo H. (2006) **Characterization of a neural-specific splicing form of the human neuregulin 3 gene involved in oligodendrocyte survival.** **J Cell Sci.** *119(Pt 5):898-909.*

Cabedo,H*.,Carteron,C.,Ferrer-Montiel,A. (2004). **Oligomerization of the sensory and motor neuron-derived factor prevents protein O-glycosylation.** **J. Biol Chem.** *279(32): 33623- 33629 (* corresponding author).*

Caprini, M., Gomis, A., Cabedo, H., Planells-Cases, R., Belmonte, C., Viana, F., Ferrer-Montiel, A. (2003). **GAP43 stimulates inositol trisphosphate-mediated calcium release in response to hypotonicity.** **EMBO J.** *22(12): 3004- 3014.*

Cabedo, H., Luna, C., Fernández, AM., Gallar, J., Ferrer-Montiel, A. (2002). **Molecular determinants of the sensory and motor-neuron derived factor insertion into plasma membrane.** **J. Biol Chem.** *277(22): 19905- 19912.*

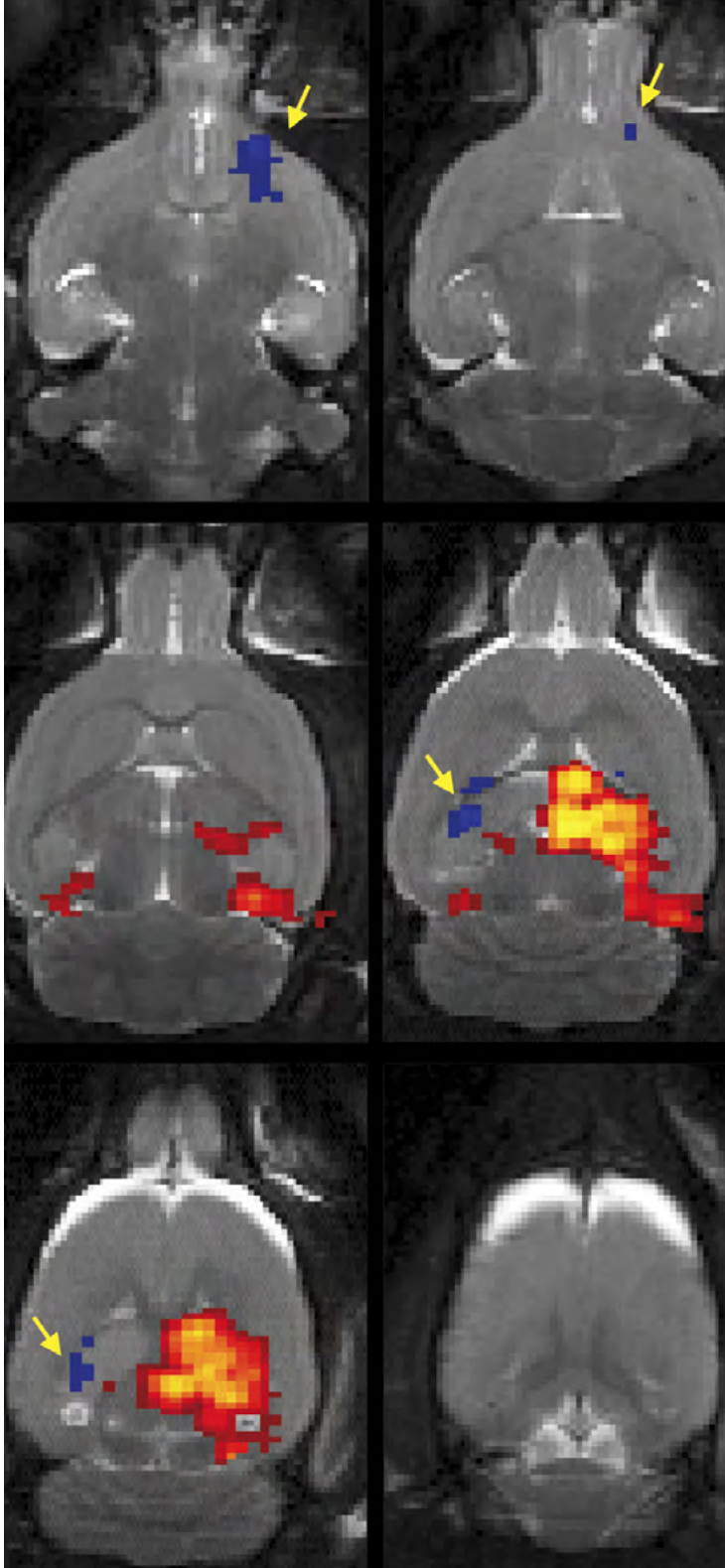
Plasticity of brain networks

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

Moreno A, Morris RG, Canals S* (2015) **Frequency-dependent gating of hippocampal-neocortical interactions.** **Cereb. Cortex** *pii: bhv033 10.1093/cercor/bhv033*

Rancz EA, Moya J, Drawitsch F, Brichta AM, Canals S*, Margrie TW* (2015) **Widespread Vestibular Activation of the Rodent Cortex.** **J. Neurosci.** *In Press*

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*

Dudek M, Abo-Ramadan U, Hermann D, Brown M, Canals S, Sommer WH, Hyytiä P. (2014) **Brain activation induced by voluntary alcohol and saccharin drinking in rats assessed with manganese-enhanced magnetic resonance imaging.** **Addict. Biol.** *In Press doi: 10.1111/adb.12179*

Jego, P., Pacheco-Torres, J., Araque, A., Canals, S* (2014) **Functional MRI in mice lacking IP3-dependent calcium signalling in astrocytes.** **J. Cereb. Blood Flow Metab.** *34(10):1599-603*

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

Álvarez-Salvado, E., Pallarés, V., Moreno, A., Canals, S* (2013) **Functional MRI of long-term potentiation: imaging network plasticity.** **Philos. Trans. R. Soc. Lond. B.** *369:1152-68.*

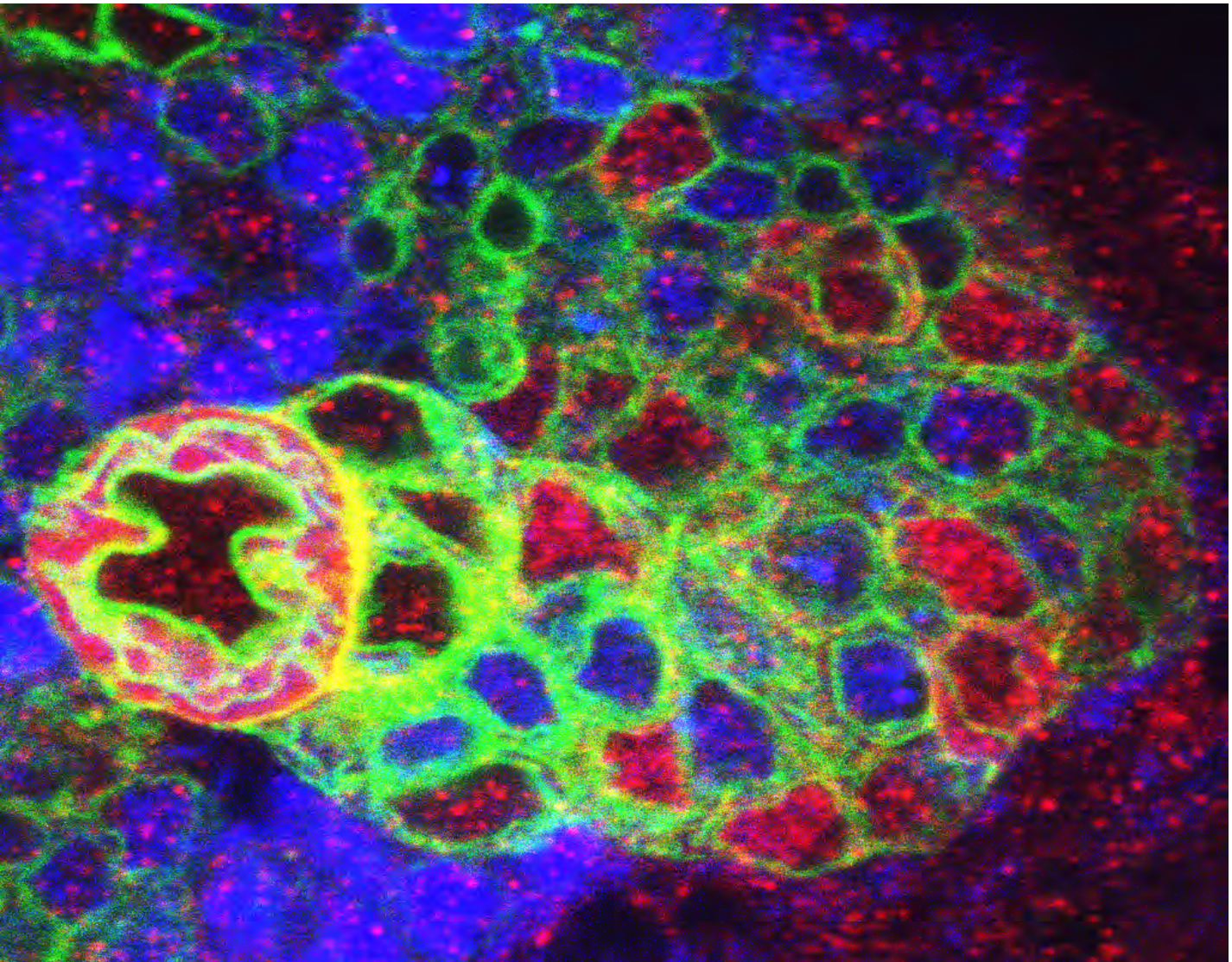
Moreno A, Jego P, de la Cruz F, Canals S.* (2013) **Neurophysiological, metabolic and cellular compartments that drive neurovascular coupling and neuroimaging signals.** **Front Neuroenergetics** *5:3 doi: 10.3389/fnene.2013.00003*

Canals, S.*, Beyerlein, M. and Logothetis, N.K. (2009). **Functional MRI evidencefor LTP-induced neural networkreorganization.** **Curr. Biol.** *19(5):398-403. (* Correspondingauthor)*

Canals, S.*, Beyerlein, M., Keller, A.L., Murayama Y. and Logothetis N.K*. (2008) **MagneticResonanceImaging of cortical connectivity in vivo.** **Neuroimage** *40(2):458-72. (* Correspondingauthor)*

Signaling networks underlying asymmetric cell division

Ana Carmena CSIC



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

answering three fundamental questions in the field:

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

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

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

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

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Signaling networks underlying asymmetric cell division

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

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-å4884*

Keder, A.and Carmena, A. (2013) Cytoplasmic protein motility and polarized sorting during asymmetric cell division **WIREs Dev Biol.** *Doi: 10.1002/wdev.116*

Carmena, A. (2012) A big new job for small GTPases. **Small GTPases** *3 (3): 1-4*

Slováková, J., Speicher, S., Sánchez-Soriano, N., Prokop, A. and Carmena, A. (2012) The Actin-Binding Protein Canoe/AF-6 Forms a Complex with Robo and Is Required for Slit-Robo Signaling During Axon Pathfinding at the CNS Midline **J Neurosci** *32 (29): 10035-10044.*

Slováková, J. and Carmena, A. (2011) Canoe/AF-6 functions at the CNS midline glia in a complex with Shotgun and Wrapper-Nrx-IV during neuron-glia interactions. **Development,** *138: 1563-1571.*

Carmena, A*., Makarova, A. and Speicher, S. (2011) The Rap1-Rgl-Ral signaling network regulates neuroblast cortical polarity and spindle orientation. **J Cell Biol,** *195: 553-562. (*corresponding author)*

Carmena, A. (2009) Aproaching Drosophila development through proteomic tools and databases: At the hub of the post-genomic era. **Mech. Dev.** *126: 761-770.*

Speicher, S., Fischer, A., Knoblich, J and Carmena, A. (2008). The Drosophila PDZ Protein Canoe Regulates the Asymmetric Division of Neural and Muscle Progenitors. **Current Biology,** *18: 831-838.*

Carmena, A. (2008) Signaling networks during development: the case of asymmetric cell division in the Drosophila nervous system. **Dev. Biol.** *321: 1-17.*

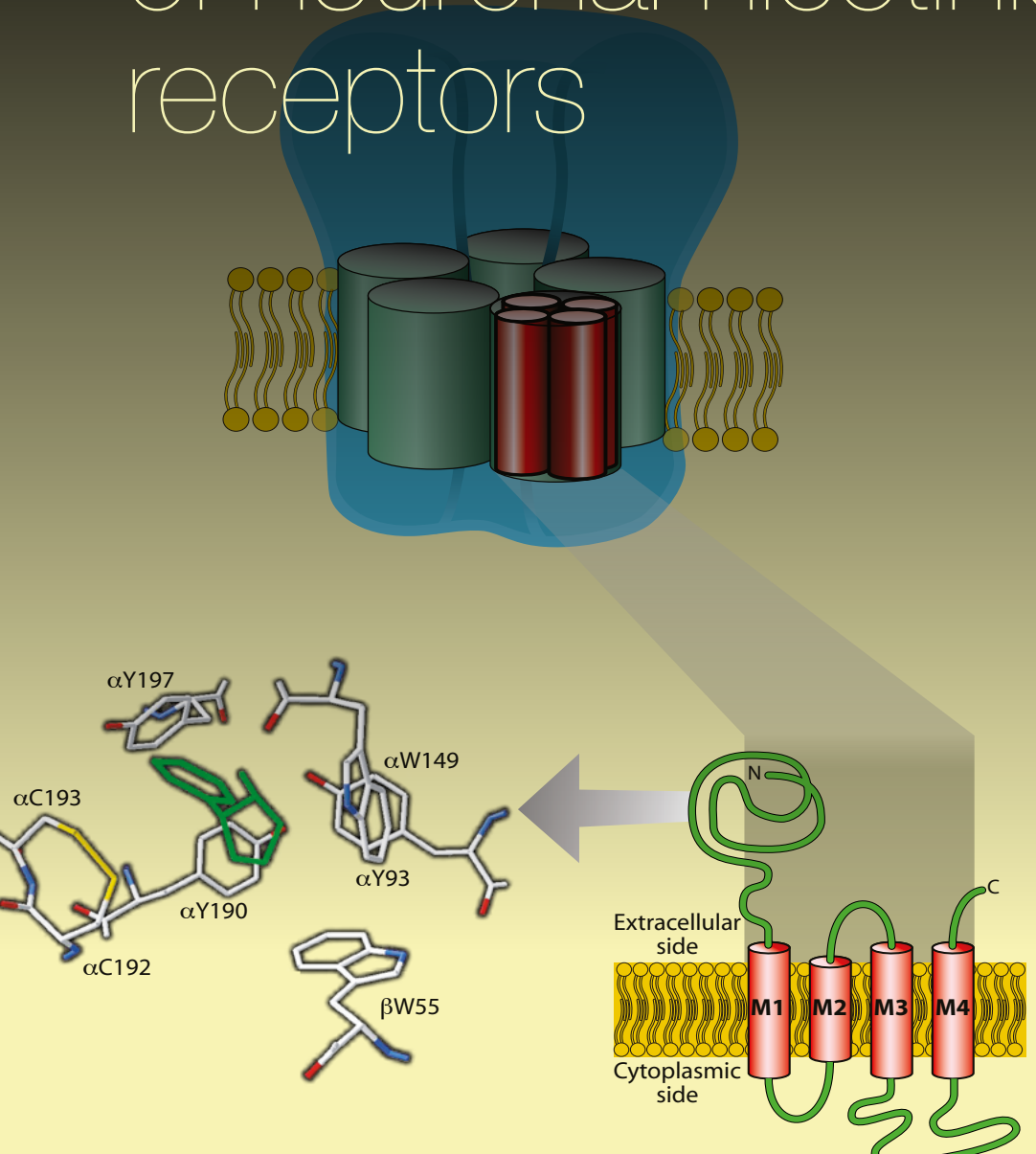
Carmena, A*, Speicher, S and Balylies, M. (2006) The PDZ protein Canoe/AF-6 Links Ras-MAPK, Notch and Wingless/Wnt Signaling Pathways by Directly Interacting with Ras, Notch and Dishevelled. **PLoS ONE** *1(1): e66. doi:10.1371/journal.pone.0000066 (*corresponding author)*

Carmena, A. and Baylies, M.K.

(2005) Development of the Larval Somatic Musculature **In "Muscle Development in Drosophila** *Landes Bioscience. H. Sink editor*

Carmena, A., Buff, E., Halfon, MS., Gisselbrecht, S., Jiménez, F., Baylies, MK., Michelson, AM. (2002). Reciprocal regulatory interactions between the Notch and Ras signaling pathways in the Drosophila embryonic mesoderm. **Dev. Biol.** *244: 226-242.*

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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Criado, M., Valor, L.M., Mulet, J., Gerber, S., Sala, S., Sala, F (2012) Expression and functional properties of alpha7 acetylcholine nicotinic receptors are modified in the presence of other receptor subunits **J. Neurochem.** *123, 504-514*

Criado, M., Mulet, J., Gerber, S., Sala, S., Sala, F. (2011) A small cytoplasmic region adjacent to the fourth transmembrane segment of the alpha7 nicotinic receptor is essential for its biogenesis. **FEBS Lett.** *585, 2477-2480.*

Criado, M., Mulet, J., Gerber, S., Sala, S., Sala, F. (2011) Mutants of beta-strand beta3 and theloop B in the interface between alpha7 subunits of a homomeric acetylcholine receptor show functional and pharmacological alterations. **J. Neurochem.** *118, 968-978.*

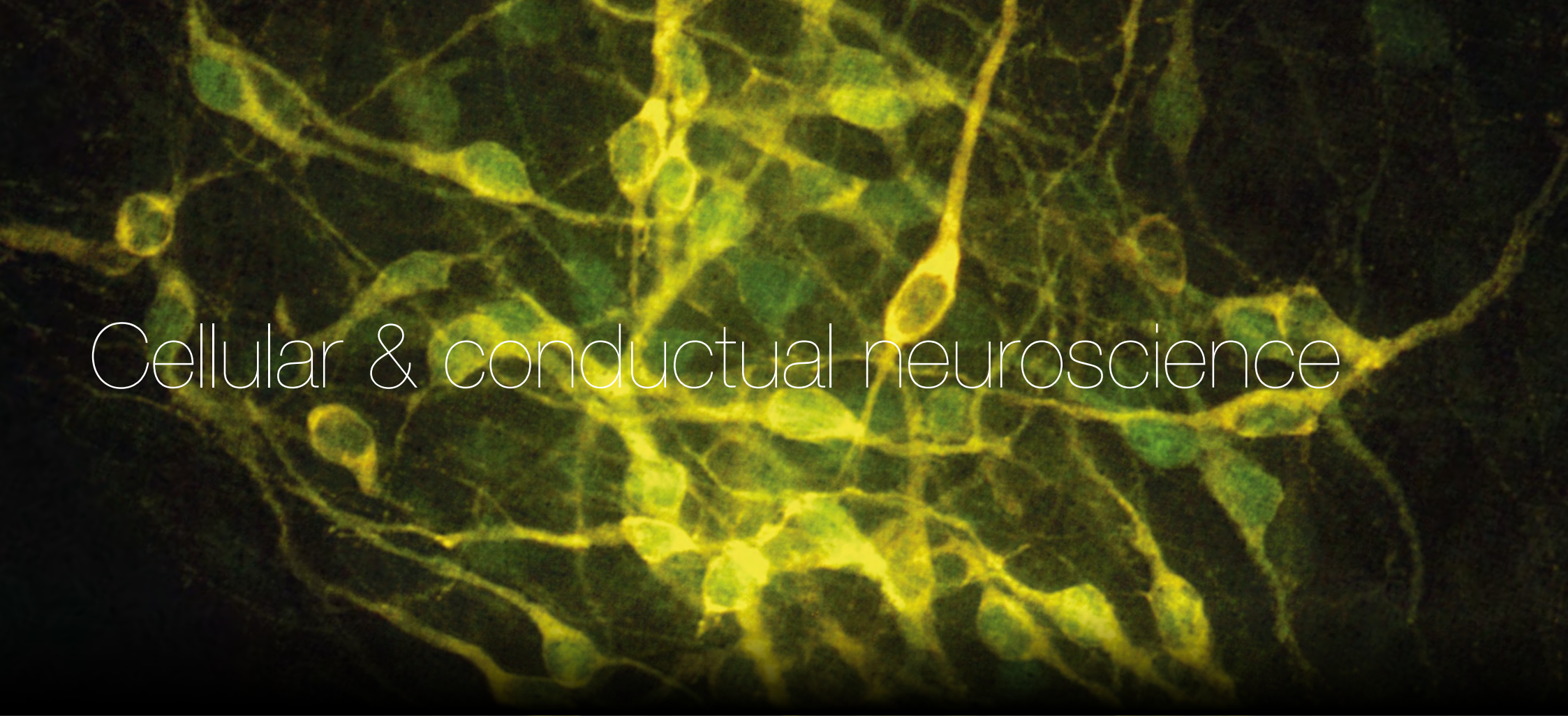
Criado, M., Svobodová, L., Mulet, J., Sala, F., Sala, S. (2011) Substitutions of amino acids in the pore domain of homomeric alpha7 nicotinic receptors for analogous residues present in heteromericr eceptors modify gating, rectification and binding properties. **J. Neurochem.** *119, 40-49.*

Criado, M., Mulet, J., Castillo, M., Gerber, S., Sala, S., Sala, F. (2010) The loop between beta-strands beta2 and beta3 and its interactionwiththe N-terminal alpha-helix is essential for biogenesis of alpha7 nicotinicreceptors. **J. Neurochem.** *112, 103-111.*

Criado, M., Castillo, M., Mulet, J., Sala, F., Sala, S. (2010) Role of loop 9 on the function of neuronal nicotinic receptors. **Biochim. Biophys. Acta Biomembranes** *1798, 654-659.*

Aldea, M., Castillo, M., Mulet, J., Sala, S., Criado, M., Sala, F. (2010) Role of the extracellular transmembrane domain interface in gating and pharmacology of a heteromeric neuronal nicotinic receptor **J. Neurochem.** *113, 1036-1045*

Alexander, J., Sagher, D., Krivoshein, A., Criado, M., Jefford, G., Green, W. (2010) Ric-3 promotes alpha7 nicotinic receptor assembly and trafficking through the ER sub-compartment of dendrites. **J. Neurosci.** *30, 10112-10126*



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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Eva del Rio

Delgado-Morales R; del Rio, E; Gomez-Roman, A ; Bisagno, V ; Nadal, R ; de Felipe, C; Armario, A (2012) **Adrenocortical and behavioural response to chronic restraint stress in neurokinin-1 receptor knockout mice.** **Physiology & Behavior** *105 (3): 669-675*

Gad, Monika, Pedersen, Anders Elm, Kristensen, Nanna Ny, de Felipe, Carmen, Claesson, Mogens H. (2009) **Blockage of the Neurokinin 1 Receptor and Capsaicin-Induced Ablation of the Enteric Afferent Nerves Protect SCID Mice Against T-Cell-Induced Chronic Colitis,** **Inflammatory Bowel Diseases,** *15 (8): 1174-1182*

Tebar, LA et al (2008) **Deletion of the mouse RegIIIbeta (Reg2) gene disrupts ciliary neurotrophic factor signaling and delays myelination of mouse cranial motor neurons.** **PNAS,** *105(32):11400-5,*

Zhao, S.L.; Maxwell, S.; Jiménez-Beristain, A.; Vives, J.; Kuehner, E.; Zhao, J.X.; O'Brien, C.; De Felipe, C.; Semina, E.; Li, M. (2004) **Generation of embryonic stem cells and transgenic mice expressing green fluorescence protein in midbrain dopaminergic neurons.** **Eur. J. Neurosci.,** *19 (5): 1133-1140,*

Gadd, CA; Murtra, P; De Felipe, C; Hunt, SP. (2003) **Neurokinin-1 receptor-expressing neurons in the amygdala modulate morphine reward and anxiety behaviors in the mouse.** **J.Neurosci.,** *23 (23): 8271-8280.*

Morcuende, S; Gadd, C.A.; Peters, M.; Moss, A.; Harris, E.A.; Sheasby, A.; Fisher, A.S.; De Felipe, C.; Mantyh, P.W.; Rupniak, N.M.J.; Giese, K.P.; Hunt, S.P. (2003) **Increased neurogenesis and brain-derived neurotrophic factor in neurokinin-1 receptor gene knockout mice.** **EurJ. Neurosci.,** *18 (7): 1828-1836,*

Froger, N; Gardier, AM; Moratalla, R; Alberti, I; Lena, I; Boni, C; De Felipe, C; Rupniak, NM; Hunt, SP; Jacquot, C; Hamon, M; Lanfumey, L. (2001) **5-hydroxytryptamine (5-HT)1A autoreceptor adaptive changes in substance P (neurokinin 1) receptor knock-out mice mimic antidepressant-induced desensitization.** **J Neurosci.,** *25: 8188-8197.*

Murtra, P; Sheasby, AM; Hunt, SP; De Felipe, C. (2000) **Rewarding effects of opiates are absent in mice lacking the receptor for substance P.** **Nature,** *405 (6783): 180-183.*

Bester, H; De Felipe, C; Hunt, SP. (2000) **The NK1 receptor is essential for the full expression of noxious inhibitory controls in the mouse.** **Journal of Neuroscience,** *21:1039-1046.*

Doyle, CA; De Felipe, C; O´Brien, JA; Palmer, JA; Hunt, SP. (2000) **The role of substance P in nociception, analgesia and aggression: The molecular Basis of Pain.** **Ed J.Wiley, New York,** *1:1-1*

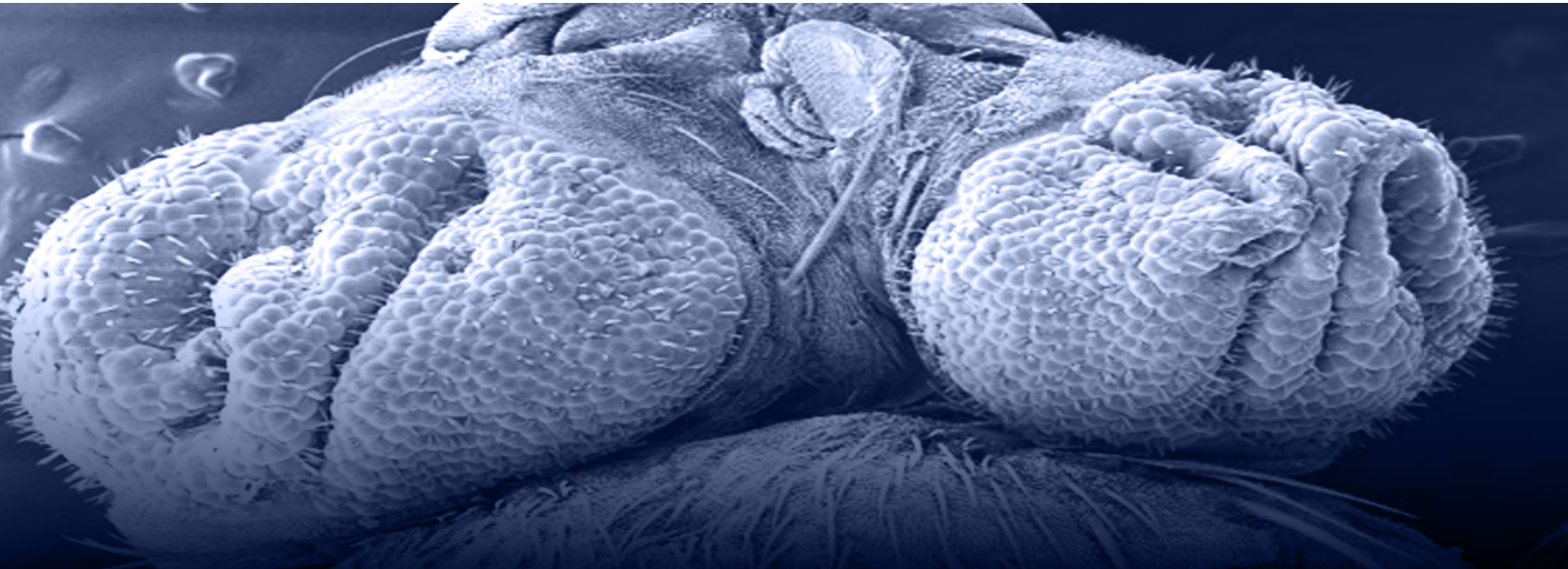
De Felipe, C; Herrero, JF; O´Brien, JA; Palmer, JA; Doyle, CA; Smith, AJH; Laird, JM; Belmonte, C; Cervero, F; Hunt, SP. (1998) **Altered nociception, analgesia and aggression in mice lacking the receptor for substance P.** **Nature,** *392:394-397.*

Mechanisms of growth control & cancer in Drosophila

María Domínguez CSIC

Our studies are focused on three complementary research projects:

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



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

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

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

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

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

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Mechanisms of growth control & cancer in Drosophila

Vallejo DM#, Juarez S#, Bolivar J, Morante J*, Dominguez M* (2015) **A brain circuit that synchronizes growth and maturation revealed through Dilp8 binding to Lgr3.** **Science** *2015 13;350(6262):aac6767. doi: 10.1126/science.aac6767.*

Reiff T#, Jacobson J#, Cognigni P#, Antonello Z#, Ballesta-Illan E, Tan KT, Yew JY, Dominguez M*, Miguel-Aliaga I* (2015) **Endocrine remodelling of the adult intestine sustains reproduction in Drosophila.** **eLife** *2015 Jul. 28;4:e06930. doi: 10.7554/eLife.06930.00).*

Antonello, ZA, Reiff, T, Ballesta-Illan, E, M. Dominguez (2015) **Robust intestinal homeostasis relies on cellular plasticity in enteroblasts mediated by miR-8-Escargot switch.** **EMBO J** *2015 34(15):2025-41. doi: 10.15252/embj.20159151*

Ríos-Barrera LD, Gutiérrez-Pérez I, Dominguez M, Riesgo-Escovar JR (2015) **acal is a Long Non-coding RNA in JNK Signaling in Epithelial Shape Changes during Drosophila Dorsal Closure.** **PLoS Genet** *2015 11(2): e1004927. doi:10.1371/journal.pgen.1004927*

Dominguez M. (2014) **Editorial. Cancer models in Drosophila.** **Semin Cell Dev Biol** *2014 Apr;28:62. doi: 10.1016/j.semcdb.2014.04.022. Epub 2014 Apr 19.*

Dominguez M. (2014) **Oncogenic programmes and Notch activity: an 'organized crime'? Semin Cell Dev Biol** **Semin Cell Dev Biol** *2014A pr;28:78-85. doi: 10.1016/j.semcdb.2014.04.012. Epub 2014 Apr 26.*

MoranteJ*,VallejoDM,DesplanC.&DominguezM. (2013) **Conserved miR-8/miR-200 Defines a Glial Niche that Controls Neuroepithelial Expansion and Neuroblast Transition.** **Dev Cell** *2013 Oct 28;27(2):174-87. doi: 10.1016/j.devcel.2013.09.018. Epub 2013 Oct 17*

Mulero MC, Ferres-Marco D, Pecoraro M, Islam K, Charneco C, Bellora N, Toll A, Gallardo F, Asensio E, López-Arribillaga E, Rodilla V, Iglesias M, Shih V, Alba M, Di Croce L, Hoffmann A, Villa-Freixa J, Lopez-Bigas N, Keyes B, Dominguez M, Bigas A, and Espinosa L. (2013) **Chromatin-bound IkBa is a modulator of PRC2-dependent repression in development and cancer.** **Cancer Cell** *2013 Aug 12;24(2):151-66. doi: 10.1016/j.ccr.2013.06.003. Epub 2013 Jul 11.*

Da Ros V, Gutierrez-Pérez I, Ferres-Marco D, Dominguez M. (2013) **Dampening the signals transduced through hedgehog signal via microRNA miR-7 facilitates Notch-induced tumourigenesis.** **PLOS Biol** *2013 May; 11(5):e1001554. doi: 10.1371/journal.pbio.1001554. Epub 2013 May 7.*

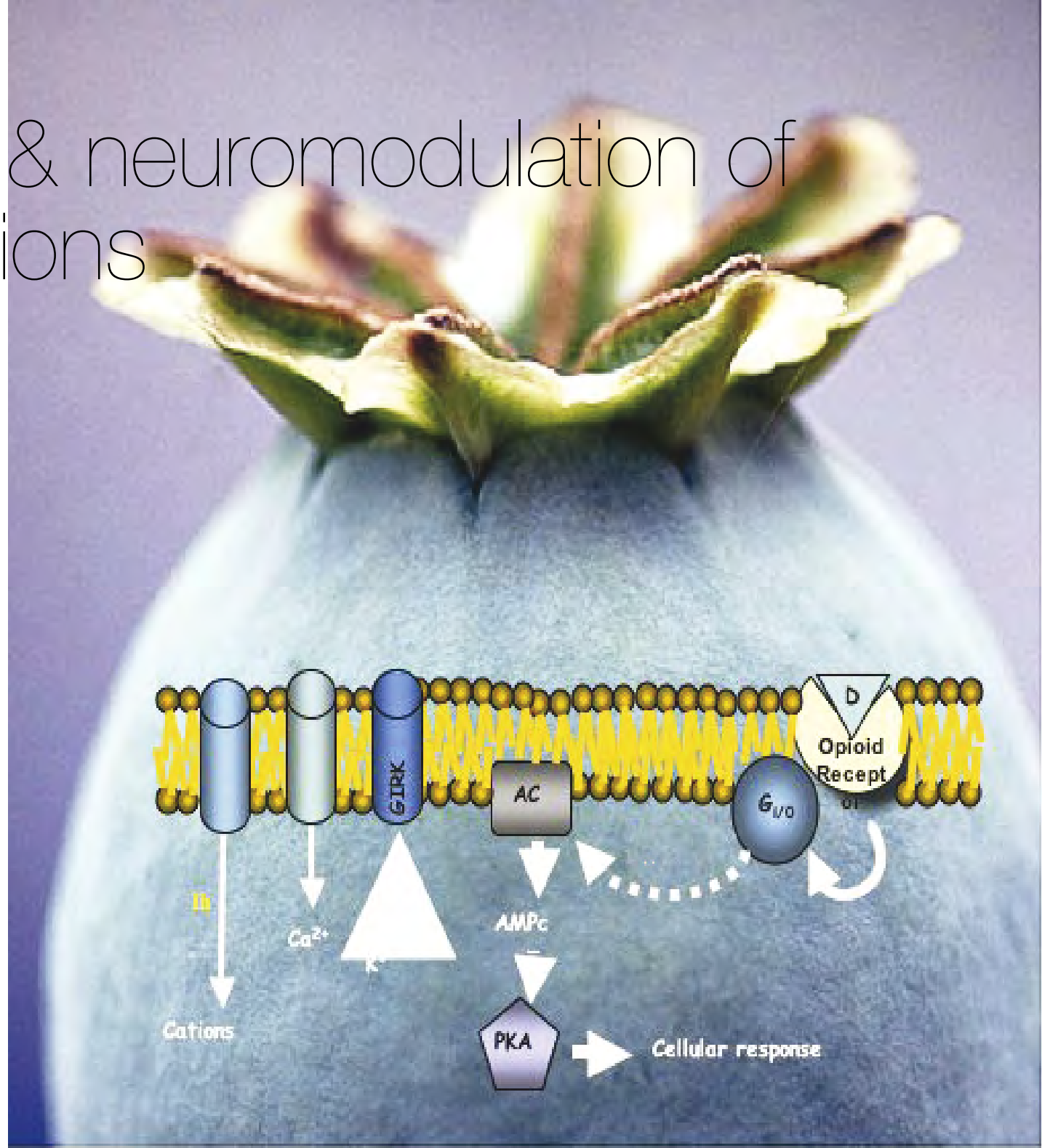
Ntziachristos P, Tsirigos A, Van Vlierberghe P, Nedjic J, Trimarchi T, Flaherty MS, Ferres-Marco D, Da Ros V, et al. (2012) **Genetic inactivation of the PRC2 complex in T-cell Acute Lymphoblastic Leukemia.** **Nature Medicine** *2012 18 (2), 98–301 doi:10.1038/nm.2651*

Garelli A, Gontijo A, Miguela V, Caparros E, Dominguez M (2012) **Imaginal discs secrete insulin-like peptide 8 to mediate plasticity of growth and maturation time.** **Science** *2012 336 (6081): 579-582 doi: 10.1126/science.1216735.*

Neurobiology & neuromodulation of the opioid actions

Clara C. Faura Giner UMH

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



Neurobiology & neuromodulation of the opioid actions

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

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

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

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

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

Ballesta, JJ, del Pozo, C, Castelló-Banyuls, J, Faura, CC, (2012) **Selective down-regulation of a4b2 neuronal nicotinic acetylcholine receptors in the brain of uremia rats with cognitive impairment.** **Exp Neurol** *236: 28-33.*

Daiane S. Alves1, Juan Castello-Banyuls, Clara C. Faura, Juan J. Ballesta (2011) **An extracellular RRR motif flanking the M1 transmembrane domain governs the biogenesis of homomeric neuronal nicotinic acetylcholine receptors.** **FEBS Lett.** *585(8):1169-74.*

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S. (2010) **Single dose dipyrone for acute postoperative pain. Cochrane** **DatabaseSyst Rev.** *(9):CD003227.*

Berbel P, Navarro D, Ausó E, Varea E, Rodríguez AE, Ballesta JJ, Salinas M, Flores E, Faura CC, de Escobar GM. (2010) **Role of late maternal thyroid hormones in cerebral cortex development: an experimental model for human prematurity.** **CerebCortex.** *20(6):146 2-75*

E. Kalso, L. Allan, P.L.I. Dellemijn, C.C. Faura, W.I. Ilias, T.S. Jensen, S. Perrot, L.H. Plaghki y M. Zenz. (2007) **Recommendations for using opioids in chronic non cancer pain.** **Pain. Best Practice & Research Compendium. Breivik and Shipley, Eds. Elsevier, Oxford,** *323-327.*

C. Gouarderes, C. C. Faura and JM. Zajac (2004). **Rodent strain differences in the NPFF1 and NPFF2 receptor distribution and density in the central nervous system.** **Brain Res.** *1014: 61-70, 2004*

Mas, M., Sabater, E., Olaso, MJ., Horga, JF ., Faura, CC. (2000). **Genetic variability in morphine sensitivity and tolerance between different strains of rats.** **Brain Res.** *866: 109-115.*

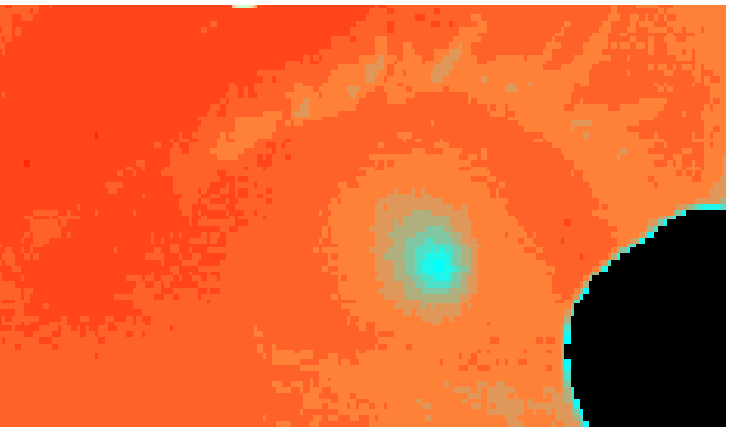
Faura,CC.,Collins,SL.,Moore,RA.,McQuay,HJ. (1998). **Systematic review of factorsaffecting the ratios of morphine and its major metabolites.** **Pain,** *74: 43-53.*

Faura, CC., Olaso, MJ., Horga, JF. (1996). **Morphine-3-glucuronide behaves as a functional antagonist of morphine-6-glucuronide, butnot of morphine analgesia in tolerant and non tolerantmice.** **Pain,** *65: 25-30.*

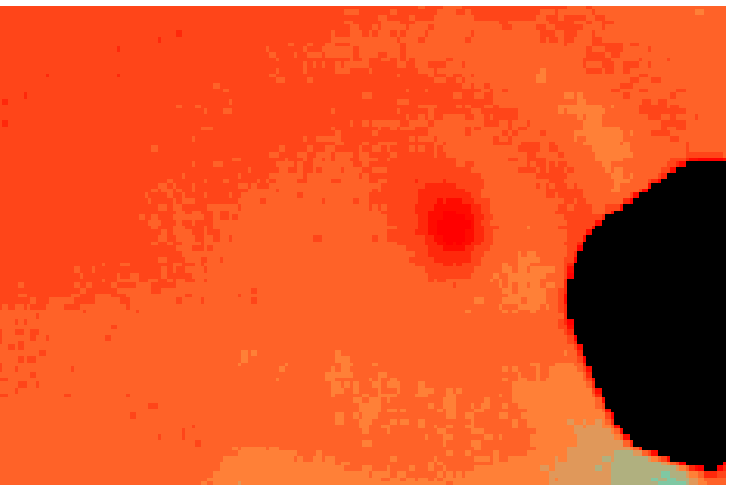
McQuay, HJ., Carroll, D., Faura, CC., Gavaghan, DJ., Hand, CW., Moore, RA. (1990). **Oral morphine in cancerpain: Influences on morphine and metabolite concentration.** **Clin Pharmacol Ther,** *48: 236-244.*

Control

Cold



Heat



Ocular Neurobiology

Juana Gallar UMH

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The main interest of the Ocular Neurobiology Group (ONG) is to study the functional activity of sensory nerves from the ocular surface, responsible for the genesis of sensations evoked by stimulation of ocular tissues as well as for the trophic maintenance and correct moisturizing of the ocular surface. Using both, electrophysiological 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 studies the neural mechanisms responsible for the neural regulation of ocular surface wetness, studying the molecular and cellular mechanisms underlying sensory transduction, and the role of sensory input in the reflex regulation of tear production and blinking, as well as their changes with aging.

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Dienes L, Kiss HJ, Perényi K, Szepessy Z, Nagy ZZ, Barsi Á, Acosta MC, Gallar J, Kovács I. (2015) **The Effect of Tear Supplementation on Ocular Surface Sensations during the Interblink Interval in Patients with Dry Eye.** **PLoS One** *10(8):e0135629*

Acosta MC, Luna C, Quirce S, Belmonte C, Gallar J. (2014) **Corneal sensory nerve activity in an experimental model of UV keratitis.** **Invest Ophthalmol Vis Sci.** *55: 3403-3412*

Parra A, Gonzalez-Gonzalez O, Gallar J, Belmonte C. (2014) **Tear fluid hyperosmolality increases nerve impulse activity of cold thermoreceptor endings of the cornea.** **Pain** *155: 1481-1491*

Acosta MC, Luna C, Quirce S, Belmonte C, Gallar J (2013) **Changes in sensory activity of ocular sensory nerves during allergic keratoconjuctivitis.** **Pain** *154: 2353-2362*

Belmonte C, Gallar J. (2011) **Cold Thermoreceptors, Un expected Players in Ocular Dryness.** **Invest Ophthalmol Vis Sci.** *52: 3888-3892.*

McLaughlin CR, Acosta MC, Luna C, Liu W, Belmonte C, Griffith M, Gallar J (2010). **Regeneration of functional nerves within full thickness collagen-phosphorylcholine corneal substitute implants in guinea pigs.** **Biomaterials** *31: 2770-2778.*

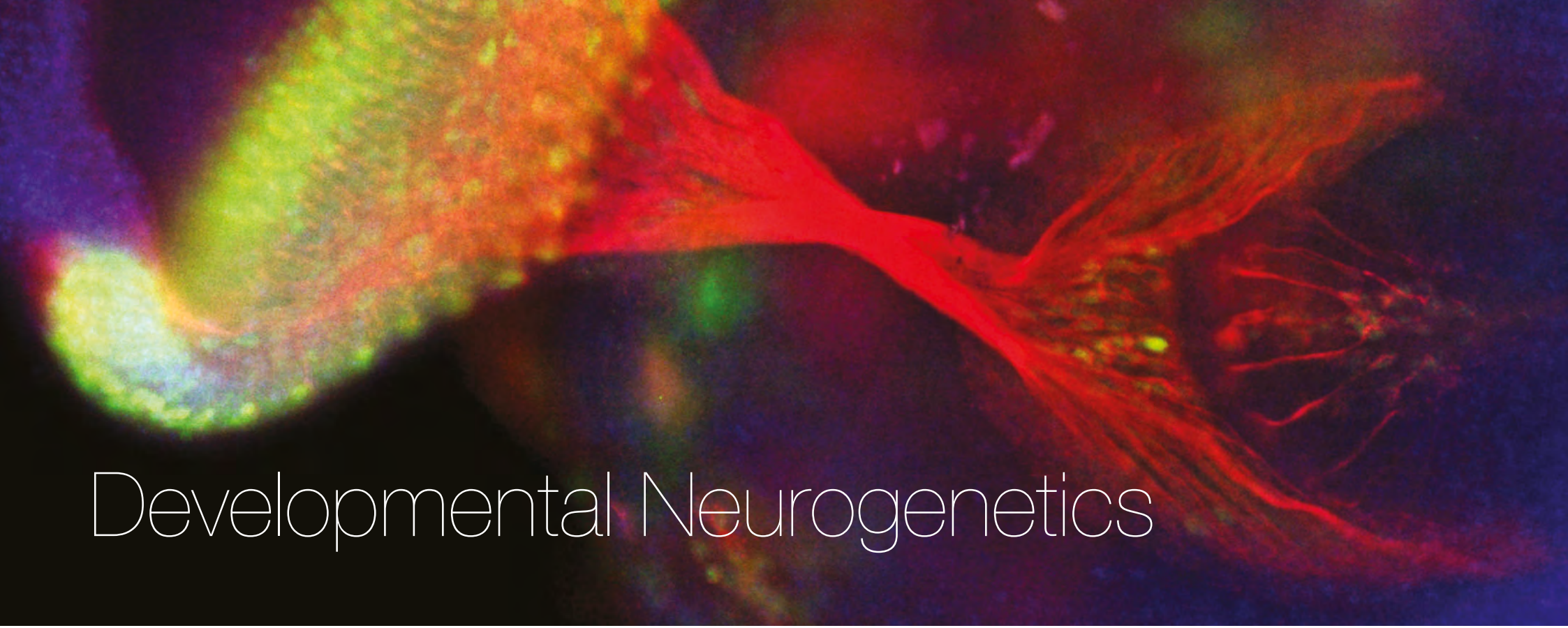
Parra A, Madrid R, Echevarria D, Del Olmo S, Morenilla-Palao C, Acosta MC, Gallar J, Dhaka A, Viana F, Belmonte C (2010). **Ocular surface wetness is regulated by TRPM8-dependent cold thermoreceptors of the cornea.** **Nat Med** *16: 1396-1399.*

Acosta, MC., Alfaro, ML., Borras, F., Belmonte, C., Gallar, J. (2006) **Influence of age, gender and iris color on mechanical and chemical sensitivity of the cornea and conjunctiva.** **Exp. Eye Res.** *83: 932-938.*

Acosta MC, Peral A, Luna C, Pintor J, Belmonte C, Gallar J. (2004). **Tear secretion induced by selective stimulation of corneal and conjunctival sensory nerve fibers.** **Invest. Ophthalmol. Vis. Sci.** *45: 2333-2336.*

Belmonte, C., Acosta, MC., Gallar, J. (2004). **Neural basis of sensation in intact and injured corneas.** **Exp. Eye Res.** *78: 513-25.*

Acosta, MC., Belmonte, C., Gallar, J. (2001). **Sensory experiences in humans and single unit activity in cats evoked by polymodal stimulation of the cornea.** **J. Physiol.** *534 (2): 511-525.*



Developmental Neurogenetics

Luis García-Alonso CSIC

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

Developmental Neurogenetics

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

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

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Donier, E., Gomez-Sanchez, J.A., Grijota-Martinez, C., Lakomá, J., Baars, S., Garcia-Alonso, L., Cabedo, H. (2012) **L1CAM binds ErbB receptors through Ig-like domains coupling cell adhesión and neuregulin signalling.** **PlosONE** *7: e40647*

Lakomá, J., Garcia-Alonso, L., Luque, J. (2011). **Reelin sets the pace of neocortical neurogenesis.** **Development,** *138: 5223-5234.*

Nagaraj, K., Kristiansen, L., Skrzynski, A., Castiella, C., Garcia-Alonso, L., Hortsch, M. (2009). **Pathogenic human L1-CAM mutations reduce the adhesion-dependent activation of EGFR.** **Hum. Mol. Genet.,** *18: 3822-3831.*

Kristiansen, L., Velasquez, E., Romani, S., Baars, S., Berezin, V., Bock, E., Hortsch, M., Garcia-Alonso, L. (2005). **Genetic analysis of an overlapping functional requirement for L1- and NCAM-type proteins during sensory axon guidance in Drosophila.** **Mol. Cell. Neurosci.,** *28: 141-152.*

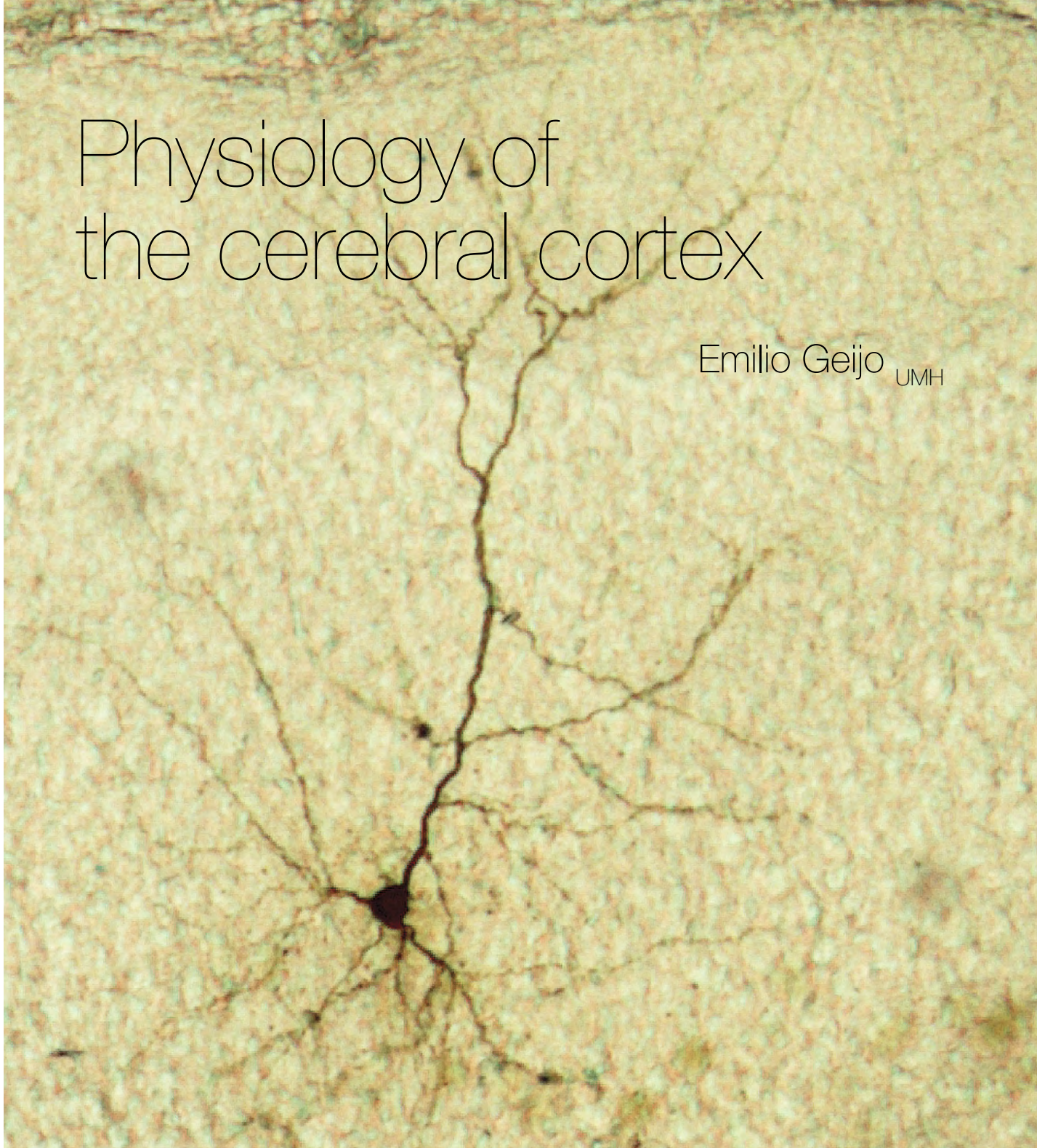
Garcia-Alonso, L., Romani, S., Jimenez, F. (2000). **The EGF and FGF receptors mediate Neuroglian function to control growth cone decisions during sensory axon guidance in Drosophila.** **Neuron,** *28:741-752.*

Garcia-Alonso, L. (1999). **Postembryonic sensory axon guidance in Drosophila.** **Cell. Mol. Life Sci.,** *55: 1386-1398.*

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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Troca-Marín, J; Geijo-Barrientos E. (2010). Inhibition by 5-HT of the synaptic responses evoked by callosal fibers on cortical neurons in the mouse. **Pflugers Archiv European Journal of Physiology.** *Nov;460(6):1073-85. Epub 2010 Sep 14.*

Pastore-Olmedo C, González O, Geijo-Barrientos E (2009). A study of F-waves in patients with unilateral lumbosacral radiculopathy. **European Journal of Neurology** *16(11):1233-9, 2009.*

Valdés-Sánchez L, Escámez T, Echevarria D, Ballesta JJ, Tabarés-Seisdedos R, Reiner O, Martinez S, Geijo-Barrientos E (2007). Postnatal alterations of the inhibitory synaptic responses recorded from cortical pyramidal neurons in the Lis1/sLis1 mutant mouse. **Mol. Cell Neuroscience.** *Jun;35(2):220-9.*

Tabarés-Seisdedos R, Escámez T, Martínez-Giménez JA, Balanzá V, Salazar J, Selva G, Rubio C, Vieta E, Geijo-Barrientos E, Martínez-Aran A, Reiner O, Martínez S. (2006) Variations in genes regulating neuronal migration predict reduced prefrontal cognition in schizophrenia and bipolar subjects from mediterranean Spain: a preliminary study. **Neuroscience.** *139(4):1289-300.*

De la Peña, E, Geijo-Barrientos, E. (2000). Participation of low threshold calcium currents in excitatory synaptic transmission in guinea-pig frontal cortex. **European Journal of Neuroscience,** *12(5): 1679-1686.*

Geijo-Barrientos, E. (2000). Subthreshold inward membrane currents in guinea-pig frontal cortex neurons. **Neuroscience** *95(4): 965-972.*

Mechanotransduction in mammals

Ana Gomis CSIC

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

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

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

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

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

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

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Mechanotransduction in mammals

Caires R, Luis E, Taberner F, Fernández-Ballester G, Ferrer-Montiel A, Balazs E, Gomis A, Belmonte C and de la Peña E. (2015) **Hyaluronan modulates TRPV1 channel opening reducing peripheral nociceptor activity and pain.** **Nature communications** *10.1038/ncomms9095*

Imane Jemal, Sergio Soriano, Anna Lucia Conte, Cruz Morenilla and Ana Gomis (2014) **G protein-coupled receptor signalling potentiates the osmo-mechanical activation of TRPC5 channels** **Pflugers Arch - Eur J Physiol** *466:1635-1646*

Peter M. Zygmunt, Anna Ermund, Pouya Movahed, David A. Andersson, Charlotte Simonsen, Bo A.G. Jönsson, Bryndis Birnir, Stuart Bevan, Alain Eschalier, Christophe Mallet, Ana Gomis and Edward D. Högestätt. (2013) *Monoacylglycerols activate TRPV1 - a link between phospholipase C and TRPV1.* **rnir.** **PLoS One** *8, e81618-32*

Gomis A*, Meini S*, Miralles A, Valenti C, Giuliani S, Belmonte C, Maggi CA (2013) **Blockade of nociceptive sensory afferent activity of the rat knee joint by the bradykinin B2 receptor antagonist fasitibant.** **Osteoarthritis and Cartilage** *21:1346-1354. (*corresponding author)*

Pierluigi Valente, Asia Fernández-Carvajal, María Camprubí-Robles, Ana Gomis, Susana Quirce, Félix Viana, Gregorio Fernández-Ballester, José M. González-Ros, Carlos Belmonte, Rosa Planells-Cases and Antonio Ferrer-Montiel. (2011) **Membrane-tethered peptides patterned alter the TRP domain potently and selectively inhibit TRPV1 channel activity.** **FASEB J** *25:1628-1640.*

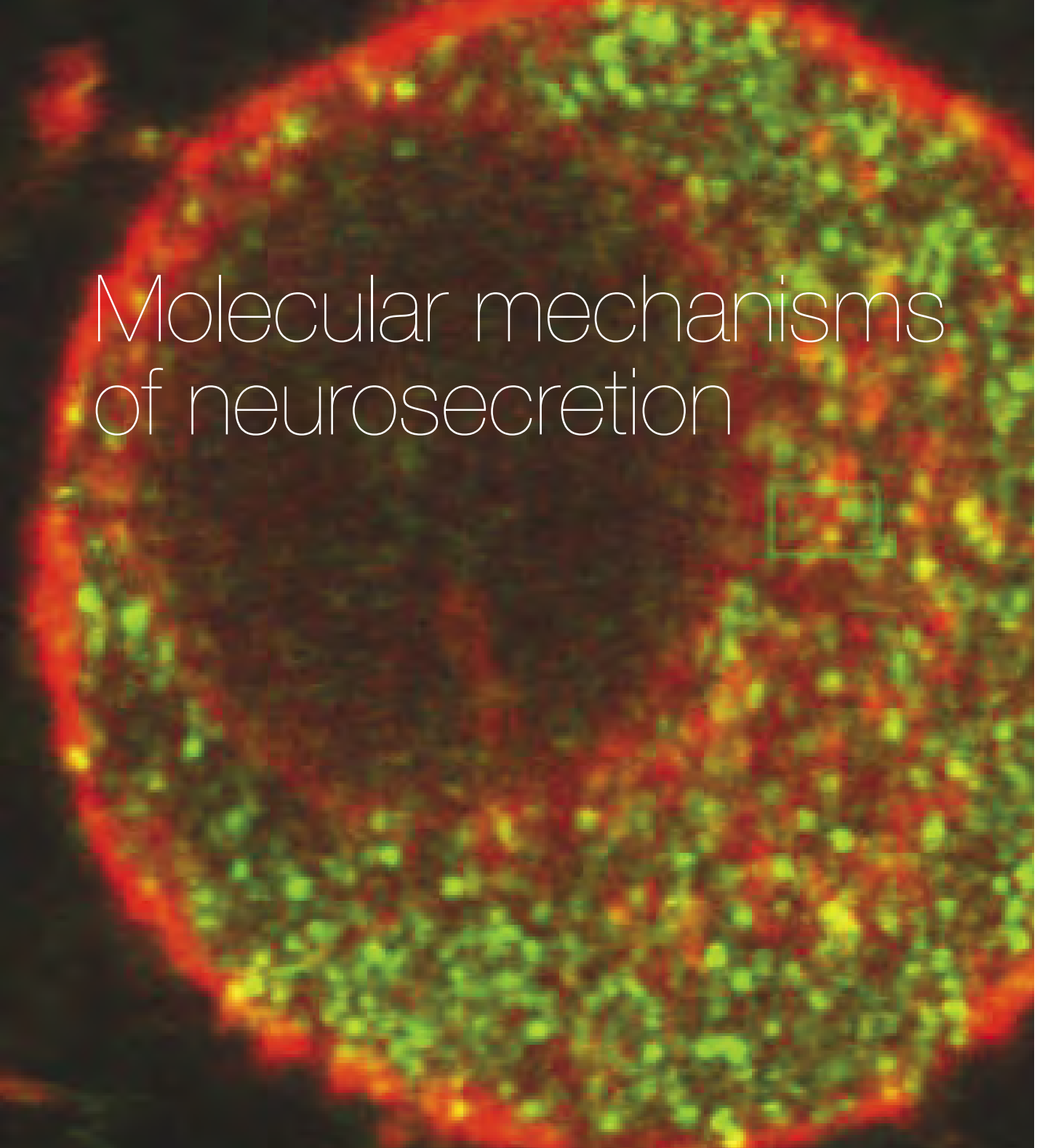
Ana Gomis*, Ana Miralles, Robert F. Schmidt and Carlos Belmonte. (2009) **Intra-articular injections of hyaluronan solutions of different elastoviscosity reduce nociceptive nerve activity in a model of osteoarthritic knee joint of the guinea pig.** **Osteoarthr. Cartilage** *17: 798-804. (*corresponding author)*

Pierluigi Valente,Nuria Garcia-Sanz, Ana Gomis, Asia Fernandez-Carvajal , Gregorio Fernandez-Ballester , Felix Viana , Carlos Belmonte and Antonio Ferrer-Montiel. (2008) **Identification of molecular determinants of channel gating in transient receptor potential box of vanilloid receptor.** **FASEB Journal** *22: 3298-3309.*

Ana Gomis*, Sergio Soriano, Carlos Belmonte and Félix Viana. (2008) **Hypoosmotic-and pressure-induced membrane stretch activate TRPC5 channels.** **J. Physiology** *586: 5633-5649.) (*corresponding author)*

Nuria García-Sanz, Pierluigi Valente, Ana Gomis, Asia Fernández-Carvajal, Gregorio Fernandez-Ballester, Félix Viana, Carlos Belmonte and Antonio Ferrer-Montiel (2007) **The TRP domain of the vanilloid receptor I is a molecular determinant of channel gating.** **Journal of Neuroscience** *27:11641-11650*

Ana Gomis, Ana Miralles, Robert F. Schmidt and Carlos Belmonte. (2007) **Nociceptive nerve activity in an experimental model of knee joint osteoarthritis of the guinea pig: Effect of intra-articular hyaluronan application.** **Pain** *130:126-136*



Molecular mechanisms of neurosecretion

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

Molecular mechanisms of neurosecretion

Our research interest is focused in two different aspects of the molecular mechanisms of neurotransmission:

Implication of the cytoskeleton in different aspects of neurosecretion and the determination of role and regulation of SNARE proteins in the process of membrane fusion.

Experimental approaches involve strategies using antibodies, sequence peptide design and protein overexpression that demonstrate the participation of specific protein domains in exocytosis. In addition, the role of these proteins on the secretory stages have been studied using amperometry and TIRFM, techniques that resolve single fusion events.

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

García-Martinez, V, Villanueva, J, Torregrosa-Hetland, C, Bittman, R, Higdon, A, Darley-Usmar, V, Bazbetov, B, and Gutiérrez, LM (2013) Lipid metabolites enhance secretion acting on SNARE microdomains and altering the extent and kinetics of singel release events in bovine chromaffin cells **Plos One** *9, e75845*

Gutiérrez, LM. (2012) New insights into the role of the cortical cytoskeleton in exocytosis from neuroendocrine cells. **Int Rev Cell Mol Biol.** *295, 109-135*

Darios, F, Ruiperez, V., López-Font, I., Villanueva, J., Gutiérrez, L.M., and Davletov, B. (2010) -Synuclein sequesters arachidonic acid to modulate SNARE-mediated exocytosis. **EMBO reports.** *11, 528-533.*

Villanueva, J., Torregrosa-Hetland, C-J, Gil A, González-Vélez, V., Segura, J., Viniegra, S., and Gutiérrez, L-M- (2010) The organization of the secretory machinery in chromaffin cells as a major factor in modelling exocytosis. **HFSP Journal.** *4, 85-92.*

López, I., Ortiz, J.A., Villanueva, J., Torres, V., Torregrosa-Hetland, C-J. Francés, M.M, Viniegra, S. and Gutiérrez, L. M. (2009) Vesicle motion and fusion is altered in chromaffin cells with increased SNARE cluster dynamics. **Traffic.** *10; 172-185.*

Darios, F.,Wasser,C,Shakirzyanova,A,Giniatullin, A., Goodman, K. Munoz-Bravo, J.L, Raingo, J., Jorgacevsk, J. Kreft, M.,Zorec, R.,Rosa JM, Gandia, L., Gutiérrez, LM., Binz, T.,Giniatullin, R., Kavalali, E, Davletov, B (2009) Sphingosine facilitates SNARE complex assembly and activates synaptic vesicle exocytosis. **Neuron.** *62, 683-694.*

López, I., Giner, D., Ruiz-Nuño, A.;Fuentealba, J.;Viniegra, S.;Garcia, A.G.;Davletov, B.., Gutiérrez, L.M. (2007) Tight coupling of the t-SNARE and calcium channel microdomains in adrenomedullary slices and not in cultured chormaffin cell. **Cell Calcium,** *41: 547-558.*

Giner, D.., López, I.., Villanueva, J.;Tórres, V.., Viniegra, S.., Gutiérrez, L.M. (2007) Vesicle movements are governed by the size and synamics of f-actin cytoskeletal structures in bovine chromaffin cells. **Neuroscience,** *146: 659-669.*

Giner, D., Ñeco, P., Francés, MM., López, I., Viniegra, S., Gutiérrez, LM. (2005) Chromaffin Cell F-actin cytoskeleton real-time dynamics during secretion studied by Transmitted Light and Fluorescente Microscopy. **J. Cell. Sci.,** *118: 2871-2880.*

Ñeco, P., Giner, D., Viniegra, S., Borges, R., Villarroel, A., Gutierrez, LM. (2004) New roles of myosin II during the vesicle transport and fusion in chromaffin cells. **J. Biol. Chem.,** *279: 27450-27457.*

Development & assembly of bilateral neural circuits

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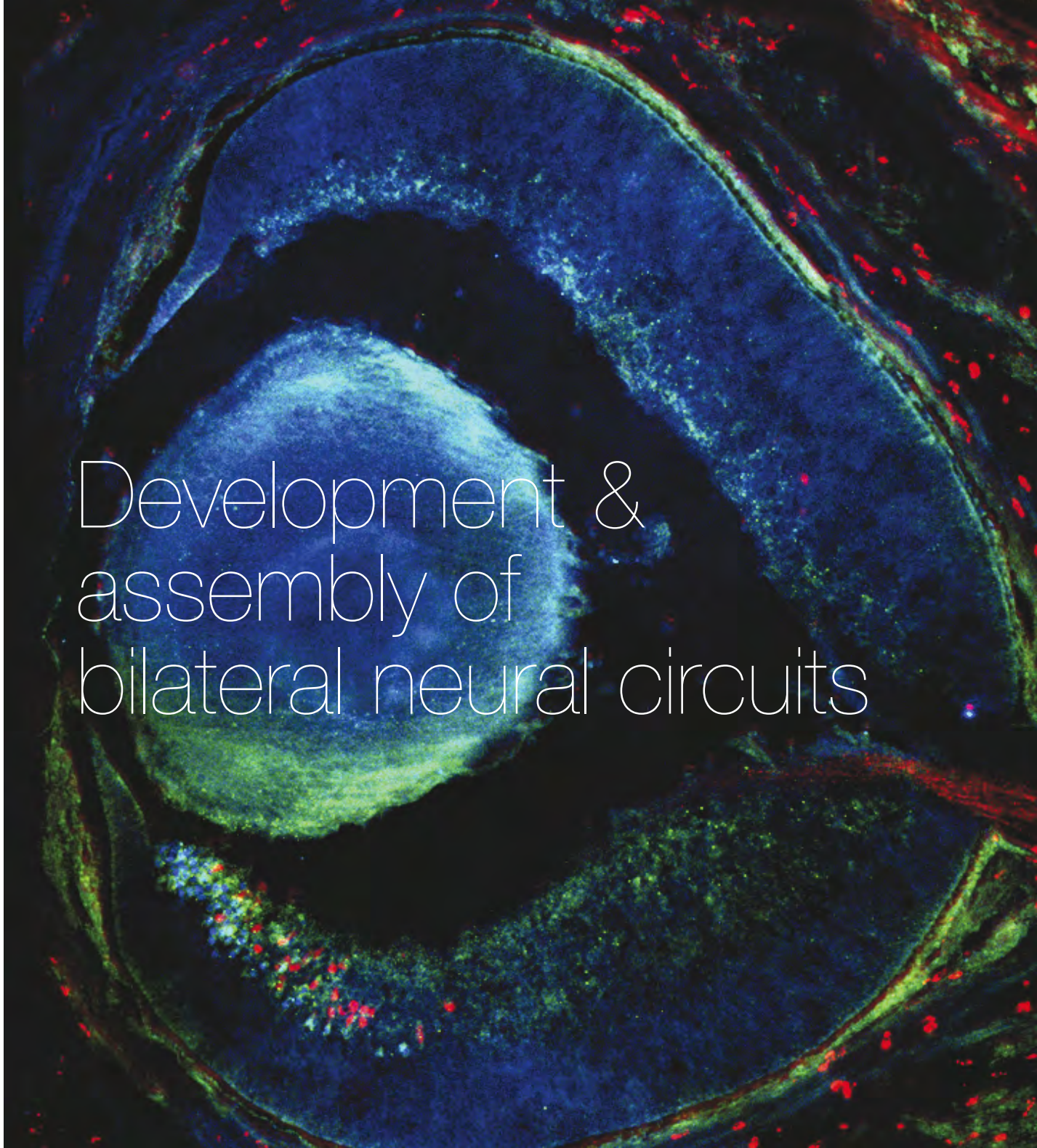
Most metazoans are bilaterally symmetric and many features of mature neural function including the interpretation of sensory information and the coordination of locomotion depend on the coherent communication between the two brain hemispheres. In order to integrate sensory information from both sides



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

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

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Development & assembly of bilateral neural circuits

Murillo B, Ruiz-Reig N, Herrera M, Fairén A and Herrera E. (2015) **Zic2 Controls the Migration of Specific Neuronal Populationsin the Developing Forebrain** **Journal of Neuroscience** *35(32):11266 –11280*

Escalante A, Murillo B, Morenilla-Palao C, Klar A and Herrera E (2013) **Zic2-dependent axon midline avoidance controls the formation of major ipsilateral tracts in the CNS** **Neuron** *80, 1392–1406*

Benjumeda I, Escalante A, Law C, Morales D, Chauvin G, Muca G, Coca Y, López-Bendito G, Kania A, Martínez-Otero L and Herrera E (2013) **Uncoupling of EphA/ephrinA signaling and spontaneous activity in neural circuit wiring** **Journal of Neuroscience** *33(46):18208-18218 (Cover Caption)*

Sanchez-Arrones L, Nieto-López F, Sánchez-Camacho C, Carreres MI, Herrera E, Okada A and Bovolenta P (2013) **Shh/Boc signaling is required for sustained generation of ipsilateral-projecting ganglion cells in the mouse retina** **Journal of Neuroscience** *33(20):8596-607*

Carreres MI, Escalante A, Murillo B, Chauvin G, Gaspar P, Vegar C and Herrera E. (2011) **The transcription factor Foxd1 is required for the specification of the temporal retina in mammals.** **Journal of Neuroscience.** *13;31(15):5673-81. (Cover caption).*

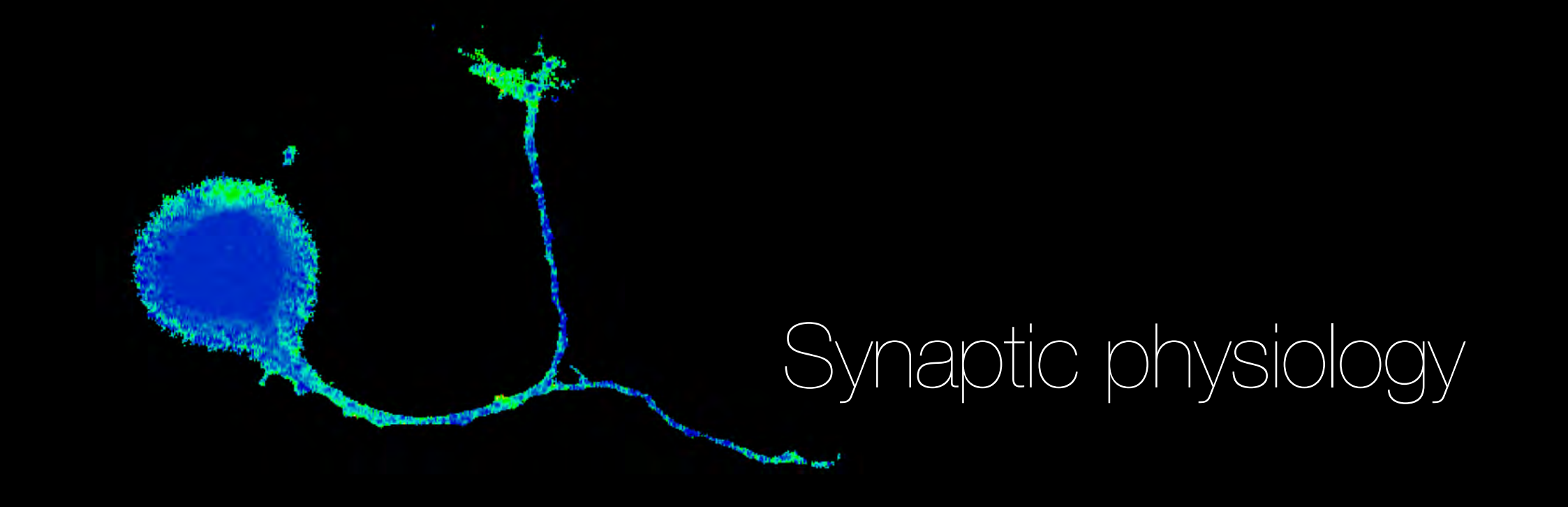
García-Frigola C and Herrera E. (2010) **Zic2 controls eye-specific refinement of retinal fibers by regulating the expression of the serotonin transporter. EMBO Journal, 29(18): 3170-83.** **EMBO Journal** *15;29(18):3037-8.*

García-FrigolaC,CarreresMA,VegarC,MasonCAandHerreraE. (2008) **Zic2 promotes axonal divergence at the optic chiasm midline by EphB1-dependentand–independentmechanisms.** **Development** *135(10):1833-41*

Williams, S., Mason, CA., Herrera, E. (2004) **The optic chiasm as a midline choice point.** **Current Opinion in Neurobiology** *14: 1: 51-60.*

Herrera, E., Marcus, R., Li, S., Williams, SE., Erskine, L., Lai, E., Mason, CA. (2004) **FoxD1 is required for proper formation of the optic chiasm.** **Development** *131: 5727-5739.*

Herrera, E., Brown, L., Aruga, J., Rachel, R., Dolen, G., Mikoshiba, K., Brown, S., Mason, CA. (2003) **Zic2 patterns binocular vision by specifying the uncrossed retinal projection.** **Cell** *114: 545-557. (Cover Caption).*



Synaptic physiology

Juan Lerma CSIC

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

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

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

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

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

Synaptic physiology

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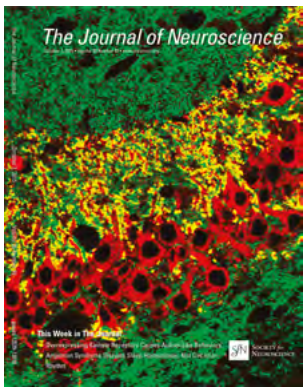


Palacios-Filardo J., Aller M.I., Lerma J. 2016 (Epub 2014 Oct 14) Synaptic targeting of kainate receptors **Cerebral Cortex** 26:1464-1472

Aller MI, Pecoraro V, Paternain AV, Canals S, Lerma J 2015 Increased Dosage of High-Affinity Kainate Receptor Gene *grik4* Alters Synaptic Transmission and Reproduces Autism Spectrum Disorders Features. **Journal of Neuroscience** 35:13619–13628.

Rutkowska-Wlodarczyk I., Aller M.I., Valbuena S., Bologna JC, Prezeau L, Lerma J. 2015 A Proteomic Analysis Reveals the Interaction of GluK1 Ionotropic Kainate receptor Subunits with Go proteins **Journal of Neuroscience** 35:13619–13628

Lerma J, De Carlos J. 2014 Epilogue: Cajal's unique and legitimated school. **Front. Neuroanat.** 02 July 2014. doi: 10.3389

Lerma, J. and Marques JM 2013 Kainate Receptors in Health and Disease **Neuron** *80: 292-311*

Marques JM, Rodrigues RJ, Valbuena S, Rozas JL, Selak S, Marin P, Aller MI, and Lerma J 2013 CRMP2 Tethers Kainate Receptor Activity to Cytoskeleton Dynamics During Neuronal Maturation **Journal of Neuroscience** *33: 18298 18310*

Godino MC, Romera VG, Snchez-Tomero JA, Pacheco J, Canals S, Lerma J, Vivancos J, Moro MA, Torres M, Lizasoain I & Snchez-Prieto J. 2013 Amelioration of ischemic brain damage by peritoneal dialysis, **Journal of Clinical Investigation** *123: 4359-4363.*

Rodrigues RJ, Lerma J 2012 Metabotropic signaling by kainate receptors. **Wiley Interdisciplinary Reviews: Membrane Transport and Signaling** *1: 399–410*

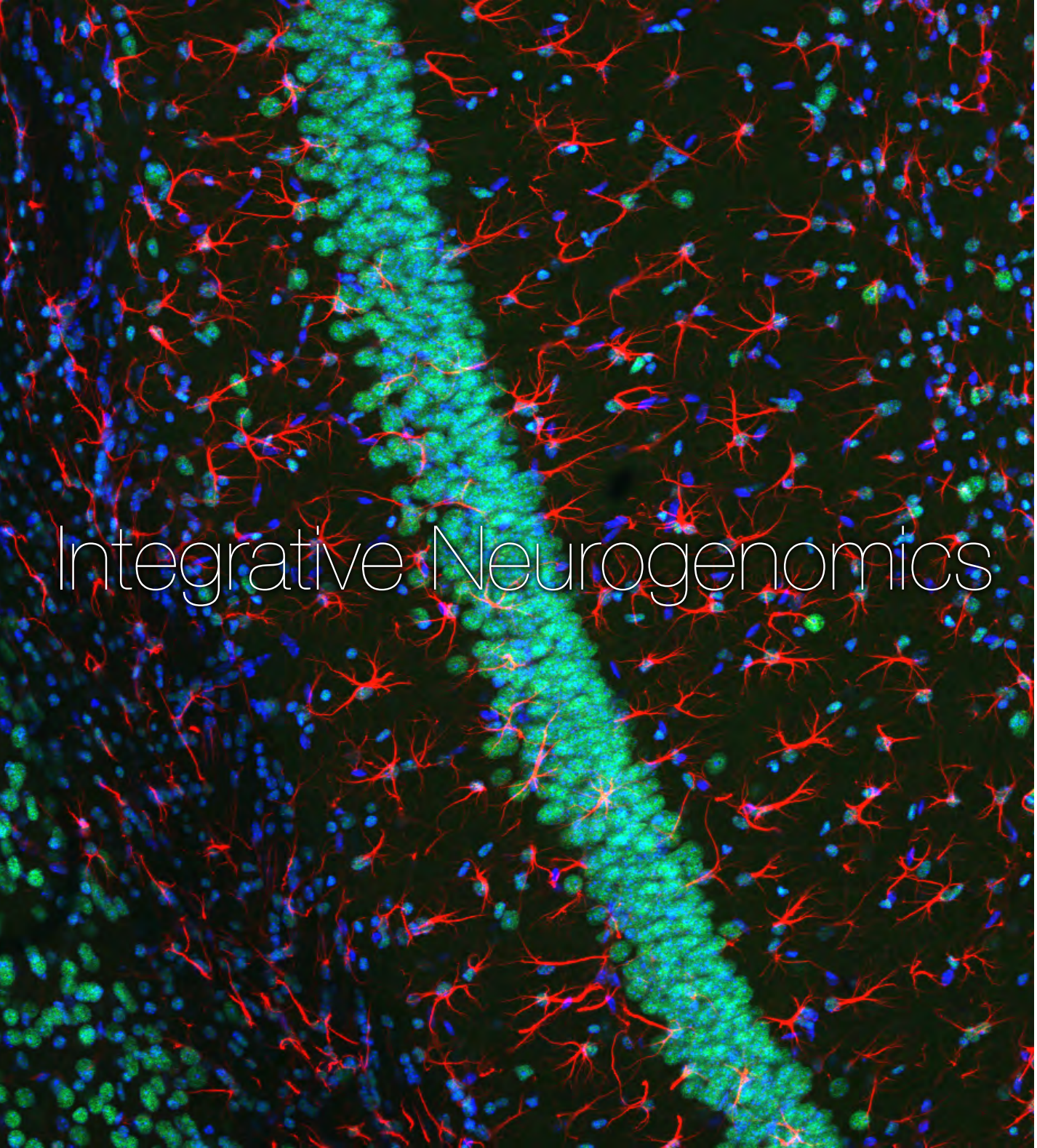
Mire E, Mezzera C, Leyva-Díaz E, Paternain AV, Squarzoni P, Bluy E, Castillo-Paterna M, López MJ, Peregrín S, Tessier-Lavigne M, Garel S, Galcerán J, Lerma J, López-Bendito G 2012 Spontaneous activity mediates a developmental switch in thalamocortical axon growth by regulating Robo1 transcription **Nature Neuroscience** *15:1134–1143*

Lerma J. 2011 Net(o) excitement for Kainate receptors. **Nature Neuroscience.** *14: 808-810*

Fazzari F., Paternain A.V., Valiente M., Pla R., Luján R., Lloyd K., Lerma J., Marín O. and Rico B. 2010 Control of cortical GABA circuitry development by Nrg1/ErbB4 signalling. **Nature** *464,1376-80*

Lau GC, Takayasu Y, Rodenas-Ruano A, Paternain AV, Lerma J, Bennett MVL, and Zukin RS 2010 SNAP-25 is a target of protein kinase C phosphorylation critical to NMDA receptor trafficking. **Journal of Neuroscience,** *30, 242–254*

Selak S, Paternain AV, Aller MI, Picó E, Rivera R, Lerma J. 2009 A role for SNAP25 in internalization of kainate receptors and synaptic plasticity. **Neuron** *63, 357-71.*



Integrative Neurogenomics

José P. López-Atalaya CSIC

Cell identity is a reflection of a cell type-specific gene expression profile, and consequently, cell type-specific transcription factor networks are considered to be at the core of a given cellular phenotype. However, under certain circumstances, differentiated cells have the capability to undergo profound morphological and functional changes in response to specific stimuli. Importantly, this phenotypic plasticity is encompassed by a dramatic gene network rewiring and modification of their epigenetic landscape.

Integrative Neurogenomics

One of the most striking naturally occurring transitions in cellular phenotype is observed in the mammalian brain. In the brain, glial cells play fundamental roles in neuronal physiology including regulation of neurotransmission and synapse formation and maintenance. In addition, neuroglia constitutes the intrinsic brain defence system. Stroke, trauma, infection or chronic neurodegeneration are associated with a pronounced glial response. This dual role is associated to a profound phenotypic switch in response to the environmental conditions, from “quiescent” to “activated” states. Critically, microglia and astrocytes in order to fulfill their functions, must orchestrate complex functional programs in response to a variety of stimuli that dictate the induction of the switch in their phenotype.

We combine mouse genetics, genomics and cell biology approaches to investigate the genetic and epigenetic rewiring underlying the transition between cellular phenotypes, with a particular focus on the interplay between sequence-specific transcription factors, enhancer activity, chromatin organization and nuclear architecture. Our research explores the boundaries of epigenome plasticity in differentiated cells that should prove useful for further understanding transcriptional control of cell state. Investigation of the molecular pathways underlying such processes in glial cells provides direct mechanistic links to neuroinflammatory processes in brain aging and neurodegenerative diseases.

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Lopez-Atalaya JP, Valor LM, and Barco A. (2014) **Epigenetic factors in intellectual disability: the Rubinstein-Taybi syndrome as a paradigm of neurodevelopmental disorder with epigenetic origin** **Prog Mol Biol Transl Sci.** *128:139-76.*

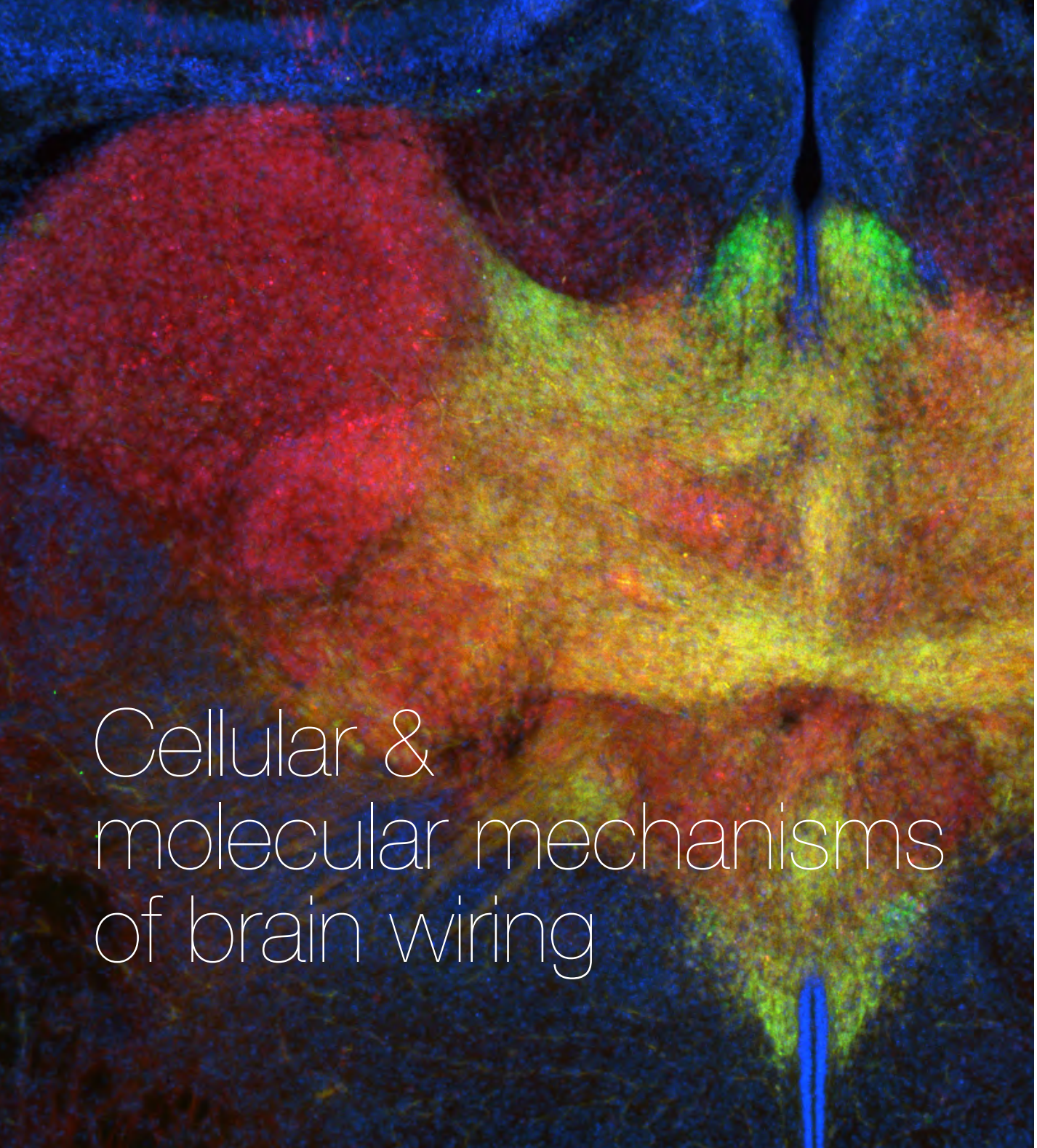
Lopez-Atalaya J, and Barco A (2014) **Can changes in histone acetylation contribute to memory formation?** **Trends Genet** *30(12):529-39.*

Lopez-Atalaya JP, Ito S, Valor LM, Benito E and Barco A. (2013) **Genomic targets, and histone acetylation and gene expression profiling of neural HDAC inhibition.** **Nucleic Acids Res** *41(17): 8072-84.*

Valor LM*, Guiretti D*, Lopez-Atalaya JP* and Barco A (2013) **Genomic landscape of transcriptional and epigenetic dysregulation in early-onset polyglutamine disease** **J Neurosci** *33(25): 10471-82*

Lopez-Atalaya JP, Gervasini C, Mottadelli F, Spena S, Piccione M, Scarano G, Selicorni A, Barco A, Larizza L (2012) **Histone acetylation deficits in lymphoblastoid cell lines from patients with Rubinstein-Taybi syndrome** **J Med Genet** *49(1):66-74.*

Lopez-Atalaya JP, Ciccarelli A, Viosca J, Valor LM, Jimenez-Minchan M, Canals S, Giustteto M and Barco A. (2011) **CBP is required for environmental enrichment-induced neurogenesis and cognitive enhancement.** **EMBO J** *30(20): 4287-98.*



Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

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

Cellular & molecular mechanisms of brain wiring

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

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

Within these projects we are using several experimental programmes, these include: optical imaging, manipulation of gene expression in vivo, cell and molecular biology, biochemistry, cell culture and electrophysiology. We have also used gain- and loss-of-function experiments to help unravel new mechanisms involved in the development and rewiring of this major axonal tract (see EMBO Reports 16:851-62 (2015); 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

Morello F, Prasad AA, Rehberg K, Vieira de Sá R, Antón-Bolaños N, Leyva-Diaz E, Adolfs Y, Tissir F, López-Bendito G, Pasterkamp RJ. (2015) **Frizzled3 Controls Axonal Polarity and Intermediate Target Entry during Striatal Pathway Development.** **J Neurosci.** *Oct 21;35(42):14205-19*

Castillo-Paterna M, Moreno-Juan V, Filipchuk A, Rodríguez-Malmierca L, Susín R, López-Bendito G (2015) **DCC functions as an accelerator of thalamocortical axonal growth downstream of spontaneous thalamic activity** **EMBO Rep.** *Jul;16(7):851-62.*

Garel S, López-Bendito G. (2014 **Inputs from the thalamocortical system on axon pathfinding mechanisms** **Curr Opin Neurobiol** *Aug;27:143-50*

Leyva-Díaz E, del Toro D, Menal MJ, Cambray S, Susín R, Tessier-Lavigne M, Klein R, Egea J, López-Bendito G. (2014) **FLRT3 is a Robo1-interacting protein that determines Netrin-1 attraction in developing axons** **Curr Biol.** *Mar 3;24(5):494-508*

Mire E, Mezzera C, Leyva-Díaz E, Paternain AV, Squarzoni P, Bluy L, Castillo-Paterna M, López MJ, Peregrín S, Tessier-Lavigne M, Garel S, Galcerán J, Lerma J, López-Bendito G. (2012) **Spontaneous activity regulates Robo1 transcription to mediate a switch in thalamocortical axon growth.** **Nat. Neurosci** *Jul 8;15(8):1134-43*

Marcos-Mondéjar P, Peregrín S, Li JY, Carlsson L, Tole S, López-Bendito G. (2012) **The lhx2 transcription factor controls thalamocortical axonal guidance by specific regulation of robo1 and robo2 receptors.** **J Neurosci** *Mar 28;32(13):4372-85*

Bielle F, Marcos-Mondéjar P, Leyva-Díaz E, Lokmane L, Mire E, Mailhes C, Keita M, García N, Tessier-Lavigne M, Garel S, López-Bendito G (2011) **Emergent growth cone responses to combinations of slit1 and netrin 1 in thalamocortical axon topography.** **Curr. Biol.** *Oct 25;21(20):1748-55.*

Bielle F, Marcos-Mondejar P, Keita M, Mailhes C, Verney C, Nguyen Ba-Charvet K, Tessier-Lavigne M, López-Bendito G, Garel S (2011) **Slit2 activity on the migration of guidepost neurons shapes thalamic projections during development and evolution.** **Neuron** *69: 1085-1098.*

Sánchez-Alcañiz JA, Haege S, Mueller W, Pla R, Mackay F, Schulz S, López-Bendito G, Stumm R, Marín O (2011) **Cxcr7 controls neuronal migration by regulating chemokine responsivenes.** **Neuron** *69:77-90.*

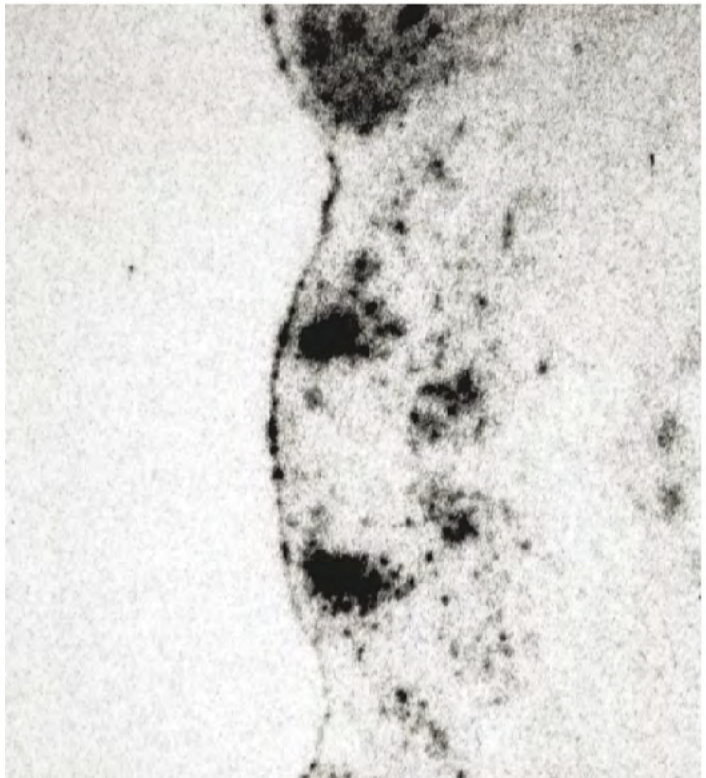
Little GE*, López-Bendito G*, Rünker AE, García N, Piñon MC, Chédotal A, Molnár Z, Mitchell KJ (2009) **Specificity and plasticity of thalamocortical connections in Sema6A mutant mice.** **PLoS Biol.** *28:e98.*

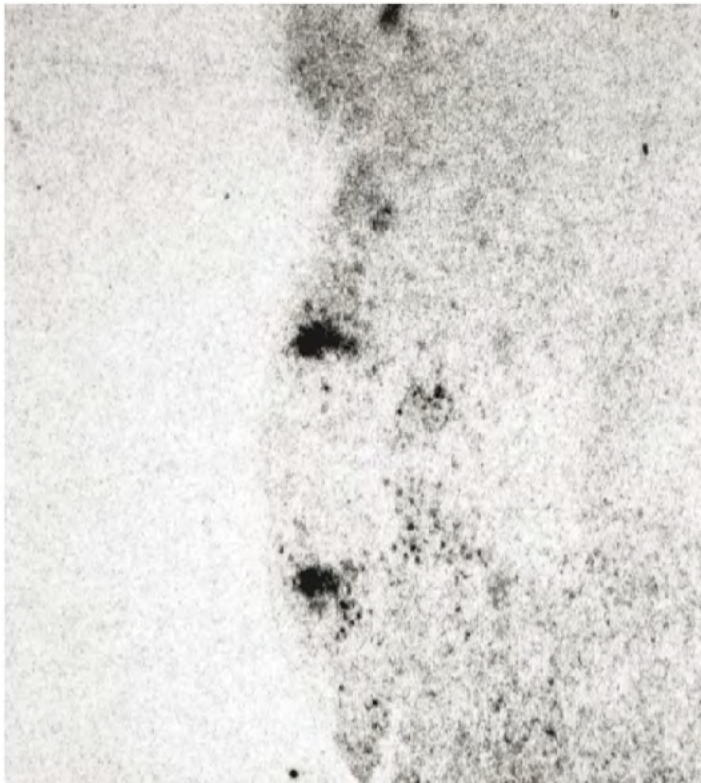
López-Bendito G, Flames N, Ma L, Di Meglio T, Chedotal A, Tessier-Lavigne M, Marin O (2007) **Robo1 and Robo2 cooperate to control the guidance of major axonal tracts in the mammalian forebrain** **Journal of Neuroscience** *27: 3395- 3407.*

López-Bendito G*, Cautinat A*, Sanchez JA, Bielle F, Flames N, Garrat AN, Tagmale D, Role LW, Charnay P, Marin O, Garel S (2006) **Tangential Neuronal Migration Controls Axon Guidance: A Role for Neuregulin-1 in Thalamocortical Axon Navigation.** **Cell** *125: 127-142.*

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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Rodriguez-Arias M, Navarrete F, Daza-Losada M, Navarro D, Aguilar MA, Berbel P, Miñarro J, Manzanares J. (2013) **CB1 cannabinoid receptor-mediated aggressive behavior** **Neuropharmacology** *75:172-80*

Perez-Ortiz, J.M., García-Gutiérrez, Navarrete, F., Giner, S., Manzanares, J. (2013) **FKBP5 alterations in the dorsal prefrontal cortex and amygdala of suicide victims** **Psychoneuroendocrinology** *38(8):1251-1258*

García-Gutiérrez MS, Ortega-Álvaro A, Busquets-García A, Pérez-Ortiz JM, Caltana L, Ricatti MJ, Brusco A, Maldonado R, Manzanares J. (2013) **Synaptic plasticity alterations associated with memory impairment induced by deletion of CB2 cannabinoid receptors.** **Neuropharmacology** *73:388-96*

Navarrete, F., Rodriguez-Arias, M., Martín, E., Navarro, D., García-Gutiérrez, M.S., Aracil Fernández, A., Aguilar, M.A., Miñarro, J., Berbel, P., Maldonado, R., and Manzanares, J. (2013) **Role of CB2 cannabinoid receptors in the rewarding, reinforcing, and physical effects of nicotine** **Neuropsychopharmacology** *38(12):2515-24.*

Aracil-Fernández, A., Trigo, J.M., García-Gutiérrez, M.S., Ortega-Álvaro, A., Ternianov, A., Maldonado, R., Manzanares, J. (2012) **.Decreased cocaine motor sensitization and self-administration in mice overexpressing cannabinoid CB_2 receptors.** **Neuropsychopharmacology** *37(7):1749-1763*

Zarruk, J.G., Fernández-López, D., García-Yébenes, I., García-Gutiérrez, M.S., Vivancos, J., Sánchez-Prieto, J., Burguete, M.C., Manzanares, J., Lizasoain, I., Moro, M.A. (2012) **CB2R activation down-regulates stroke-induced classic and alternative brain macrophage/microglial activation concomitant to neuroprotection** **Stroke** *43(1):211-219*

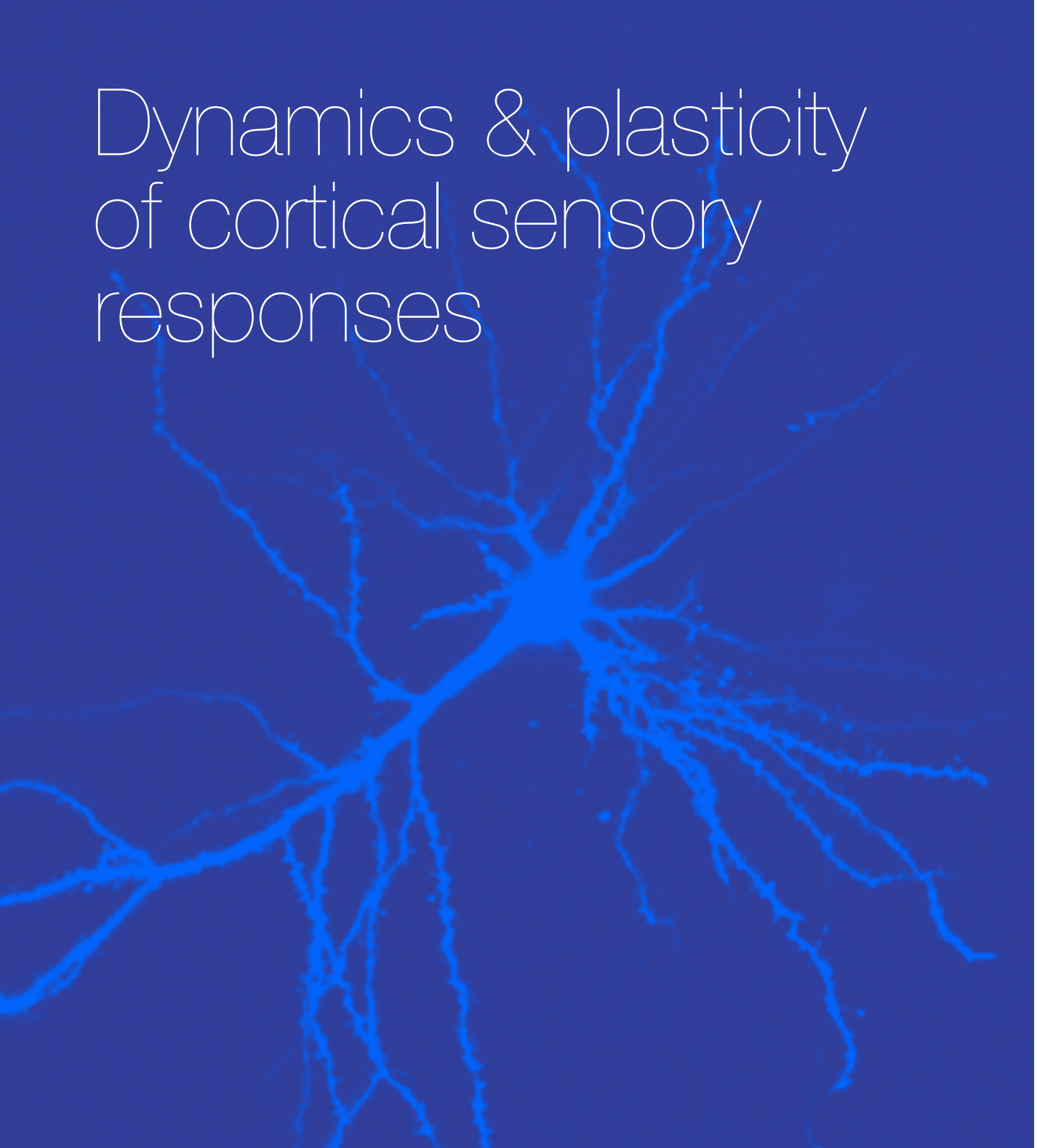
Ternianov, A., Pérez-Ortiz, J.M., Solesio, M., García-Gutiérrez, M.S., Ortega, A., Navarrete, F., Leiva, C., Galindo, M., Manzanares, J. Cannabinoid (2012) **CB2 receptors overexpression reduced vulnerability to 6-OHDA lesion.** **Neurobiology of Aging** *33:421. e1– 421.e16*

Pérez-Rial, S., Molina, J.A., García-Gutiérrez, MS, Gómez Pérez-Nievas, Ledent, C., B., Leiva, C., Leza, J.C., Manzanares, J., (2011) **Increased vulnerability to 6-hydroxydopamine lesion and reduced development of dyskinesias in mice lacking CB1 cannabinoid receptors.** **Neurobiology of Aging,** *32: 631-645*

Zoppi, S., García-Bueno, B., Pérez-Nievas, B.G., Madrigal, J.L.M., Manzanares, J. and Leza, J.C. (2011) **The regulatory role of cannabinoid CB1 receptor in stress-induced excitotoxicity and neuroinflammation.** **Neuropsychopharmacology** *36(4):805-818*

Ortega, A., Aracil, A., García-Gutiérrez, M.S., Navarrete, F., Manzanares, J. (2011) **Deletion of CB2 cannabinoid receptor induces schizophrenia-related behaviors.** **Neuropsychopharmacology** *36(7):1489-504*

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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Maravall, M; Diamond, ME. (2014) **Algorithms of whisker-mediated touch perception.** **Curr. Opin. Neurobiol.,** *25: 176-186.*

Díaz-Quesada, M; Martini, FJ; Ferrati, G; Bureau, I; Maravall, M. (2014) **Diverse thalamocortical short-term plasticity elicited by ongoing stimulation.** **J. Neurosci.,** *34: 515-526.*

Maravall, M; Alenda, A; Bale, MR; Petersen, RS. (2013) **Transformation of adaptation and gain rescaling along the whisker sensory pathway.** **PLOS One,** *8: e82418.*

Ciceri, G; Dehorter, N; Sols, I; Huang, ZJ; Maravall, M; Marín, O. (2013) **Lineage-specific laminar organization of cortical GABAergic interneurons.** **Nat. Neurosci.,** *16: 1199-1210.*

Safaai, H; von Heimendahl, M; Sorando, JM; Diamond, ME; Maravall, M. (2013) **Coordinated population activity underlying texture discrimination in rat barrel cortex.** **J. Neurosci.,** *33: 5843-5855.*

Lundstrom, BN; Fairhall, AL; Maravall, M. (2010) **Multiple timescale encoding of slowly varying whisker stimulus envelope in cortical and thalamic neurons in vivo.** **J. Neurosci.,** *30: 5071-5077.*

Alenda, A; Molano-Mazón, M; Panzeri, S; Maravall, M. (2010) **Sensory input drives multiple intracellular information streams in somatosensory cortex.** **J. Neurosci.,** *30: 10872-10884.*

Petersen, RS; Panzeri, S; Maravall, M. (2009) **Neural coding and contextual influences in the whisker system.** **Biol. Cybern.,** *100: 427-446.*

Petersen, RS; Brambilla, M; Bale, MR; Alenda, A; Panzeri, S; Montemurro, MA; Maravall, M. (2008) **Diverse and temporally precise kinetic feature selectivity in the VPm thalamic nucleus.** **Neuron,** *60: 890-903.*

Díaz-Quesada, M; Maravall, M. (2008) **Intrinsic mechanisms for adaptive gain rescaling in barrel cortex.** **J. Neurosci.,** *28: 696-710.*

Maravall, M; Petersen, RS; Fairhall, AL; Arabzadeh, E; Diamond, ME. (2007) **Shifts in coding properties and maintenance of information transmission during adaptation in barrel cortex.** **PLoS Biol.** *5: e19. doi: 10.1371/journal.pbio.0050019.*

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

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

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

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

L.M. Martinez (2011) **A new angle on the role of feedforward inputs in the generation of orientation selectivity in primary visual cortex** **Journal of Physiology** *589.12:2921-2922*

Stepanyants A, Martinez LM, Ferecskó AS & Kisvárday ZF (2009) **The fractions of short- and long-range connections in the visual cortex.** **PNAS.** *106:3555-3560*

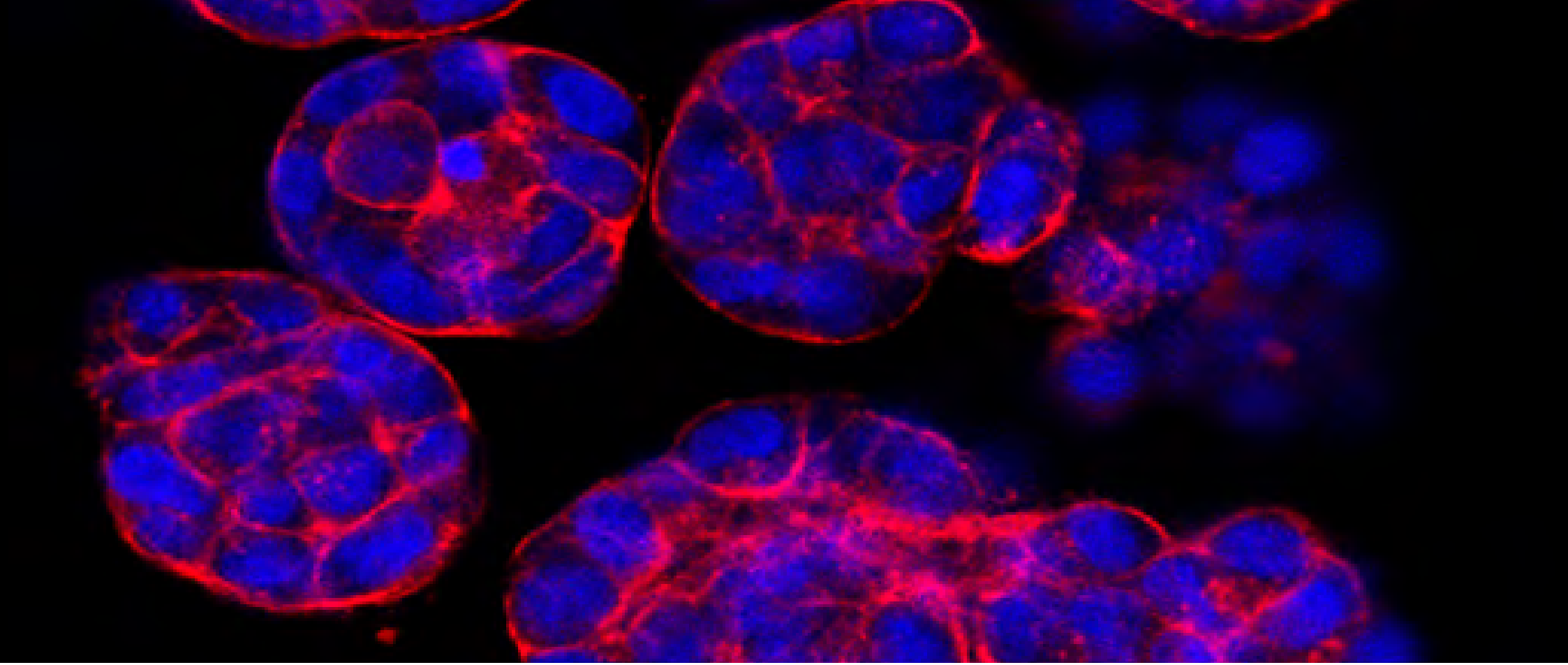
Stepanyants A, Hirsch JA, Martinez LM, Kisvárday ZF, Ferecskó AS & Chklovskii DB (2008) **Potential connectivity in local circuits of cat primary visual cortex.** **Cerebral Cortex.** *18:13-28.*

Hirsch JA & Martinez LM (2006) **"Circuits that build visual cortical receptive fields."** **Trends in Neurosciences.** *29:30-39.*

Hirsch JA & Martinez LM (2006) **"Laminar processing in the cortical column"** **Current Opinion in Neurobiology** *16:377-384.*

Martinez LM, Wang Q, Reid RC, Pillai C, Alonso JM, Sommer FT & Hirsch JA (2005) **"Receptive field structure varies with layer in the primary visual cortex."** **Nature Neuroscience.** *8:372-379.*

HirschJA,MartinezLM,PillaiC,AlonsoJM,WangQ&SommerFT (2003) **"Functionally distinct inhibitory neurons at the first stage of visual cortical processing."** **Nature Neuroscience.** *6:1300-1308.*



Cell movements in development & disease

M. Angela Nieto CSIC

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

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

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

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

Cell movements in development & disease

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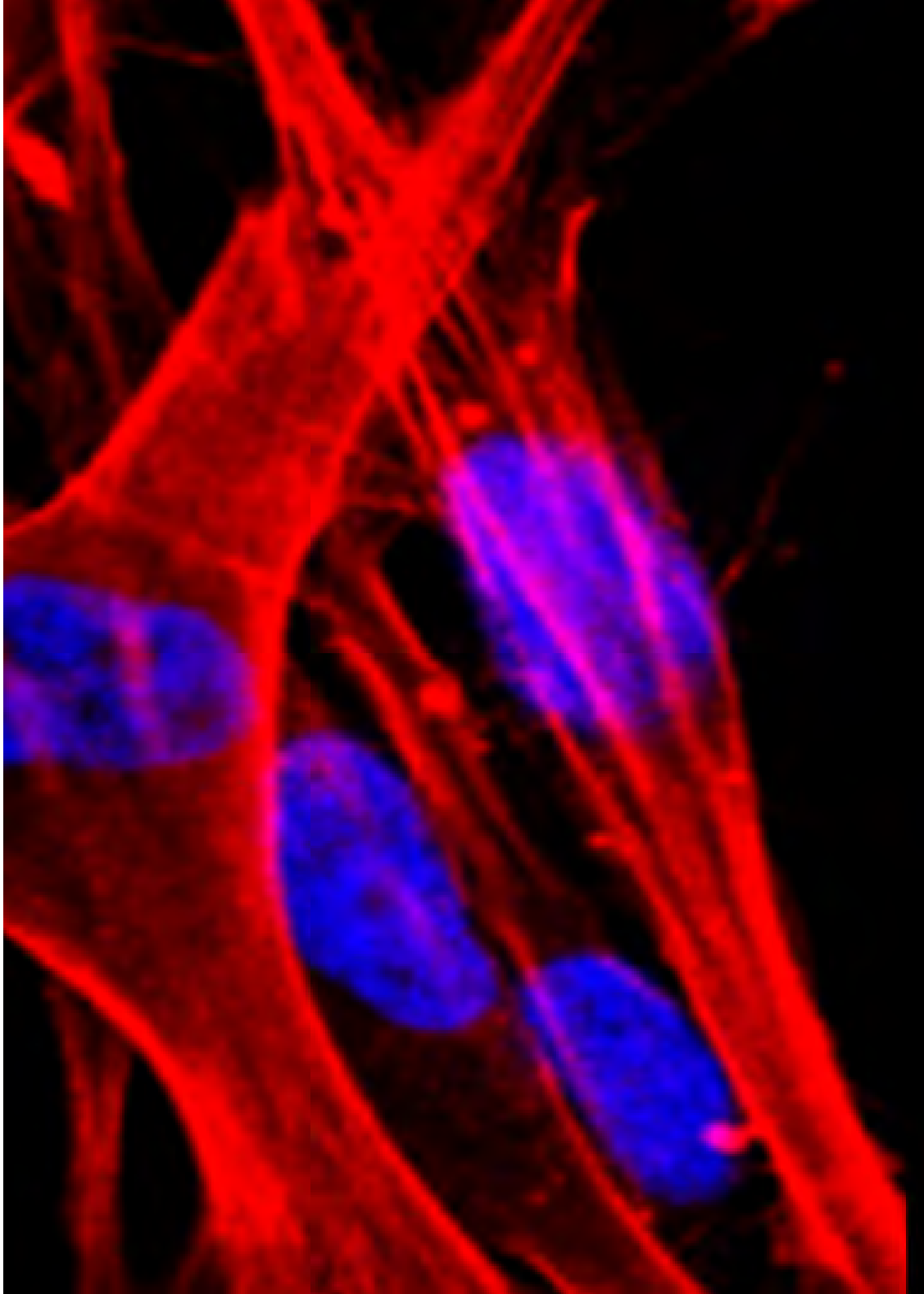


Cell movements in development & disease

Grande, M.T., Lopez-Blau, C., Sanchez-Laorden B.L., De Frutos, C.A., Boutet, A., Rowe, G., Weiss, S. J., Arévalo, M., Lopez-Novoa, J.M. and Nieto, M.A. (2015) **Snail1-induced partial epithelial-to-mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease.** **Nat. Med.** *21, 989-997*

Nieto, M.A. (2013) **Epithelial plasticity: a common theme in embryonic and cancer cells.** **Science** *342, 1234850.*

Mingot, J.M., Vega, S., Cano, A., Portillo, F. and Nieto, M.A. (2013) **eEF1A mediates the nuclear export of SNAG-containing proteins via the Exportin5-aatRNA complex.** **Cell Rep.** *5, 727-737*

Rodriguez-Aznar, E., Barrallo-Gimeno, A. and Nieto, M.A. (2013) **Scratch2 prevents cell cycle re-entry by repressing miR-25 in postmitotic neurons** **J. Neurosci.** *33, 5095-5105.*

Zhang, K., Rodriguez-Aznar, E., Yabuta, N., Owen, R.J., Mingot, J.M., Nojima, H., Nieto, M.A. and Longmore, G.D. (2012) **Lats2 kinase potentiates Snail1 activity by promoting nuclear retention upon phosphorylation.** **EMBO J.** *31, 29-43.*

Ocaña, O.H., Córcoles, R., Fabra, A., Moreno-Bueno, G., Acloque, H., Vega, S., Barrallo-Gimeno, A., Cano, A. and Nieto, M.A. (2012) **Metastatic colonization requires the repression of the epithelial-mesenchymal transition inducer Prrx1.** **Cancer Cell** *22, 709-724.*

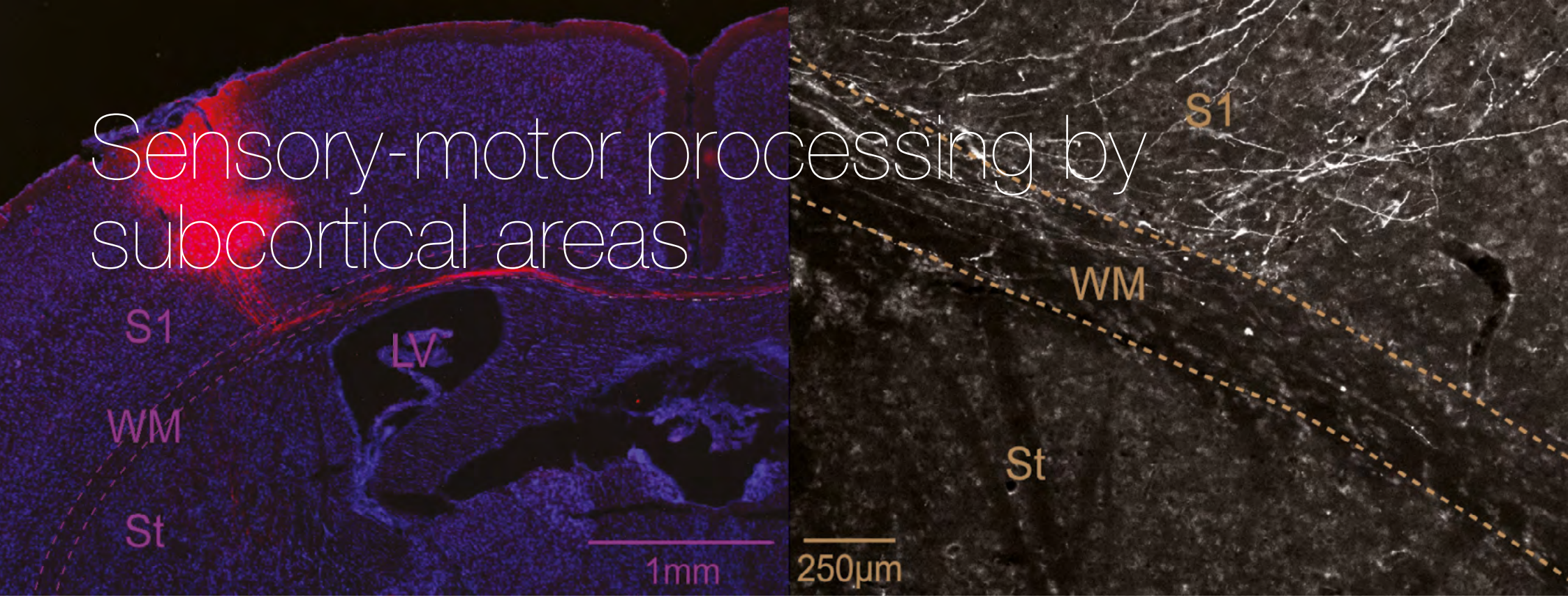
Rodriguez-Aznar, E. and Nieto, M.A (2011) **Repression of Puma by Scrtach2 is required for neuronal survival during embryonic development.** **Cell Death Diff.** *18, 1196-1207.*

Heredia, F. and Nieto, M.A. (2011) **An epigenetic mark to protect the epithelial phenotype in health and disease.** **Cell Stem Cell** *8, 462-463.*

Acloque, H., Ocaña, O.H., Matheu, A., Rizzoti, K., Wise,C., Lovell-Badge, R. and Nieto, M.A. (2011) **Reciprocal repression between Sox3 and Snail transcription factors defines embryonic territories at gastrulation.** **Dev. Cell.** *21, 546-558.*

Nieto, M.A. (2011) **The ins and outs of the epithelial to mesenchymal transition in health and disease.** **Ann. Rev. Cell Dev. Biol.** *27, 347–376.*

Sensory-motor processing by subcortical areas



Ramón Reig García CSIC

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

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

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

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

Principal Investigator
Ramón Reig García

Graduate Student
María Sáez García

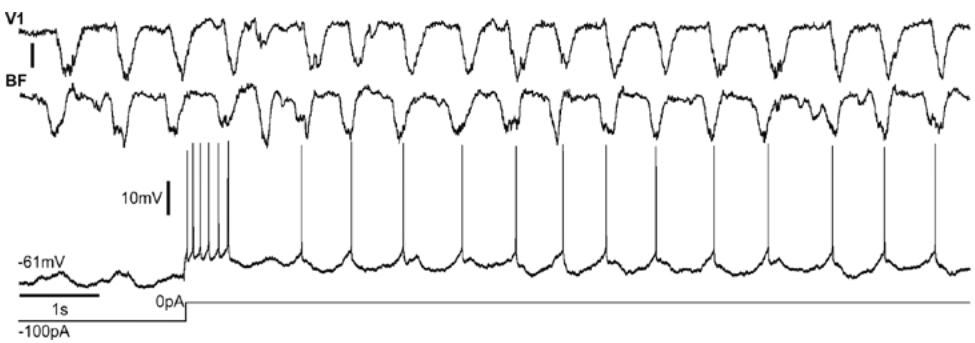
Reig R , Zerlaut Y, Vergara R, Destexhe A, Sanchez-Vives MV. (2015) **Gain modulation of synaptic inputs by network state in auditory cortex in vivo** **J. Neurosci.** *35(6) , 2689 – 2702*

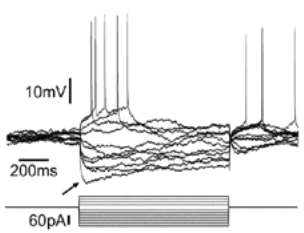
Reig R , Silberberg G. Multisensory integration in the mouse striatum. (2014) **Multisensory integration in the mouse striatum.** **Neuron.** *83(5) , 1200 – 1212.*

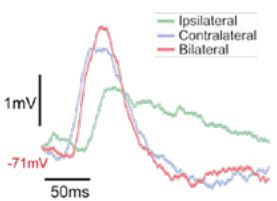
Sanchez-Vives MV , Mattia M, Compte A, Perez-Zabalza M, Winograd M, Descalzo VF, Reig R. (2010) **Inhibitory modulation of cortical up states** **J. Neurophysiol.** *104(3) , 1314 - 1324*

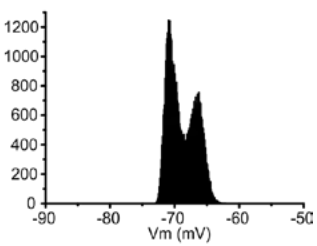
Reig R , Mattia M, Compte, Belmonte C & Sanchez-Vives MV. (2009) **Temperature modulation of slow and fast cortical rhythms** **J Neurophysiol.** *103(3) , 1253 - 1261*

Reig R , Sanchez-Vives MV. (2007) **Synaptic transmission and plasticity in an active cortical network.** **PloS ONE.** *2(7) , e – 670*





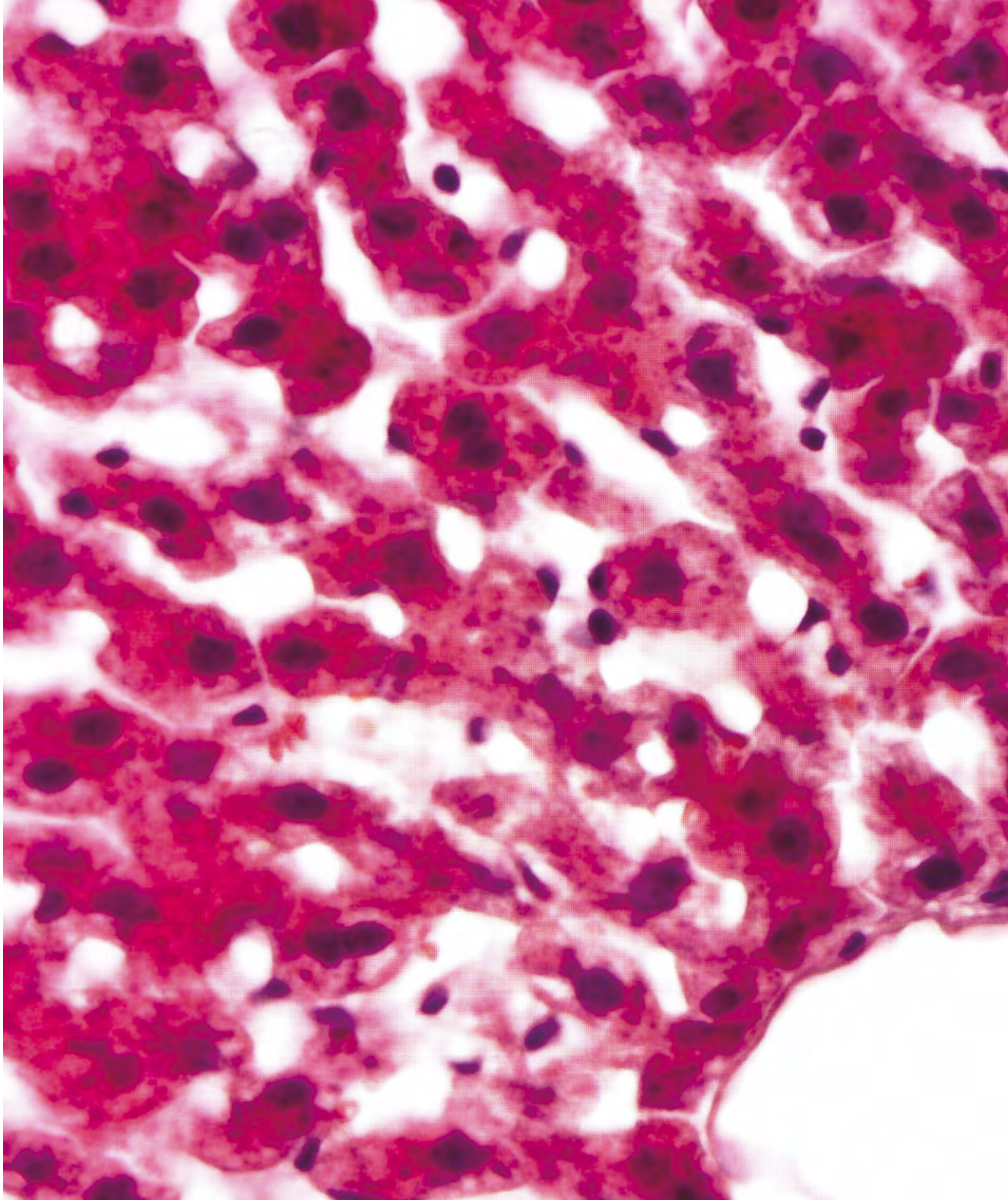




Altered molecular mechanism in Alzheimer's disease & dementia

Javier Sáez Valero UMH

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



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

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

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

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

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Altered molecular mechanism in Alzheimer's disease & dementia

Cuchillo-Ibañez I, López-Font I, Boix-Amorós A, Brinkmalm G, Blennow K, Molinuevo JL, Sáez-Valero J (2015) **Heteromers of amyloid precursor protein in cerebrospinal fluid** **Mol Neurodegener** *10, 2*

Balmaceda V, Cuchillo-Ibáñez I, Pujadas L, García-Ayllón MS, Saura CA, Nimpf J, Soriano E, Sáez-Valero J. (2014) **ApoER2 processing by presenilin-1 modulates reelin expression.** **FASEB J** *28, 1543-1554*

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*

García-Ayllón MS, Campanari ML, Brinkmalm G, Rábano A, Alom J, Saura CA, Andreasen N, Blennow K, Sáez-Valero J (2013) **CSF Presenilin-1 complexes are increased in Alzheimer's disease.** **Acta Neuropathol Commun** *1, 46*

Cuchillo-Ibañez I, Balmaceda V, Botella-López A, Rábano A, Ávila J, Sáez-Valero J (2013) **Beta-amyloid impairs Reelin signaling.** **PLoS One** *8, e72297*

García-Ayllón MS, Cauli O, Silveyra MX, Rodrigo R, Candela A, Compañ A, Jover R, Pérez-Mateo M, Martínez S, Felipo V, Sáez-Valero J. (2008) **Brain cholinergic impairment in liver failure.** **Brain** *131, 2946-2956*

Silveyra MX, Evin G, Montenegro MF, Vidal CJ, Martínez S, Culvenor J, Sáez-Valero J (2008) **Presenilin-1 interacts with acetylcholinesterase and alters its enzymatic activity and glycosylation.** **Mol Cell Biol** *28, 2908-2919*

Botella-Lopez A., Burgaya, F; Gavin, R; Garcia-Ayllon, MS; Gomez-Tortosa, E; Peña-Casanova, J; Ureña, JM; Del Rio, JA; Blesa, R; Soriano, E; Saez-Valero, J. (2006) **Reelin expression and glycosylation patterns are altered in Alzheimer's disease.** **Proc. Natl Acad. Sci. USA.** *103, 5573-5578*

García-Ayllón MS, Silveyra MX, Candela A, Compañ A, Clària J, Jover R, Pérez-Mateo M, Felipo V, Martínez S, Galcerán J, Sáez-Valero J (2006) **Changes in liver and plasma acetylcholinesterase of rats with bile duct ligation.** **Hepatology** *96, 97-104*

Sáez-Valero J, Sberna G, McLean CA, Masters CL, Small DH (1997) **Glycosylation of acetylcholinesterase as diagnostic marker for Alzheimer's disease.** **Lancet** *350, 929*

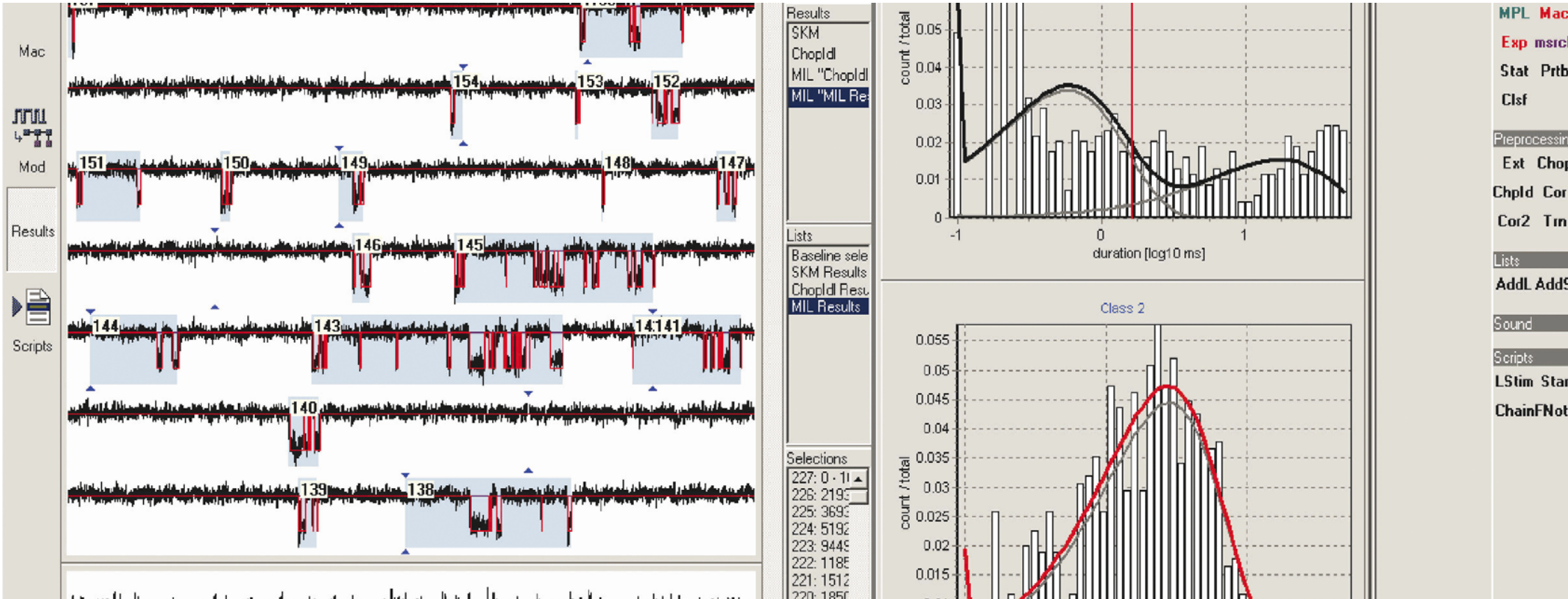
Biophysics & pharmacology of ionic channels

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.

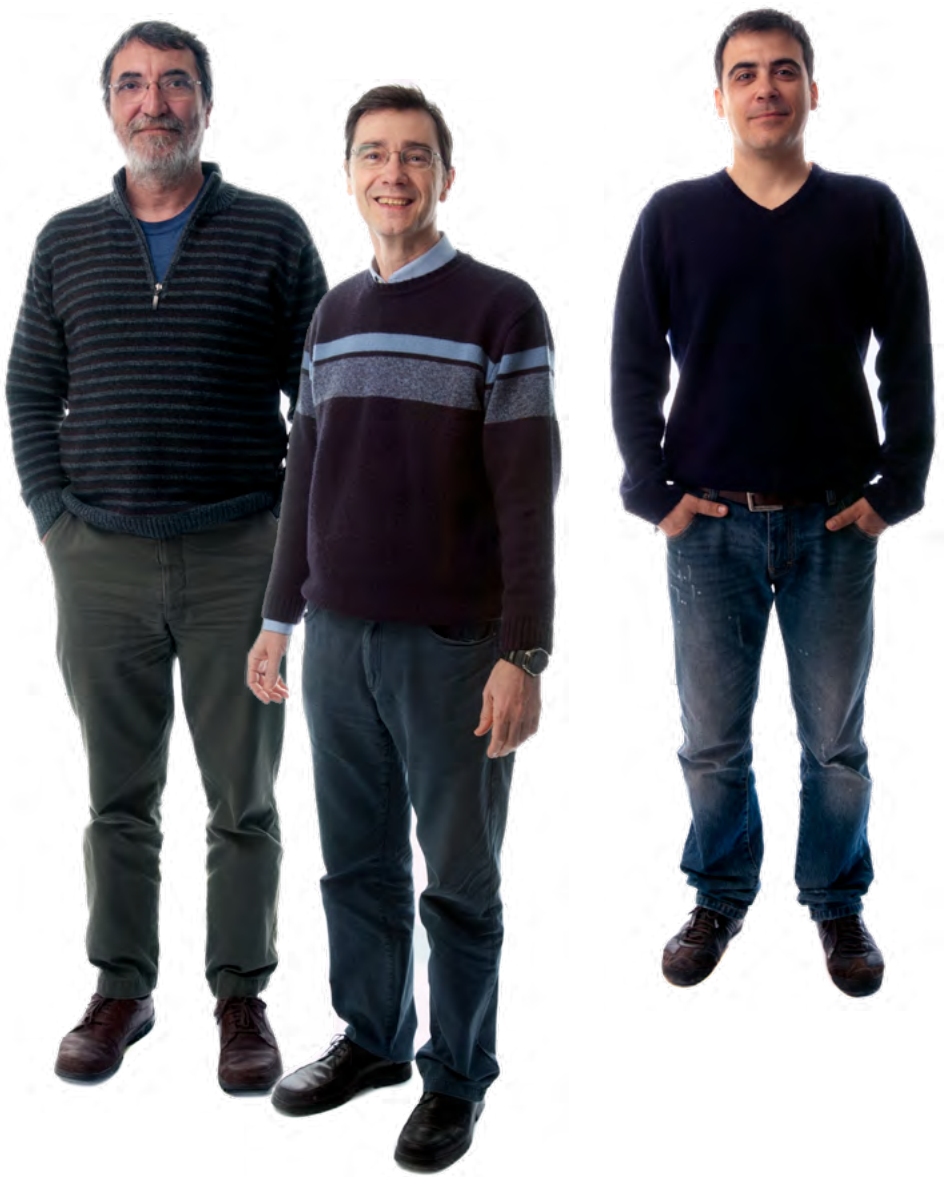
Principal Investigators

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*

Criado M, Mulet J, Gerber S, Sala S, Sala F. (2011) A small cytoplasmic region adjacent to the fourth transmembrane segment of the a 7 nicotinic receptor is essential for its biogenesis. **FEBS Lett.** *585, 2477-2480*

Criado M, Mulet J, Gerber S, Sala S, Sala F. (2011) Mutants ofb-strand 3 and the loop B in the interface between a 7 subunits of a homomeric acetylcholine receptor show functional and pharmacological alterations. **J Neurochem.** *118, 968-978*

Criado M, Svobodová L, Mulet J, Sala F, Sala S. (2011) Substitutions of amino acids in the pore domain of homomeric a 7 nicotinic receptors for analogous residues present in heteromeric receptors modify gating, rectification and binding properties. **J Neurochem.** *119, 40-49.*

Aldea, M., Castillo, M.; Mulet, J., Sala, S., Criado, M., Sala, F. (2010) Role of the extracellular transmembrane domain interface in gating and pharmacology of a heteromeric neuronal nicotinic receptor . **Journal of Neurochemistry** *113, 1036-1045*

Bernal, J.A. Mulet, J., Castillo, M., Criado, M., Sala, F., Sala, S. (2009) Single Channel Study of the Binding-Gating Coupling in the Slowly Desensitizing Chimeric alpha7- 5HT3A Receptor. **FEBS Letters** *583, 1045-1051*

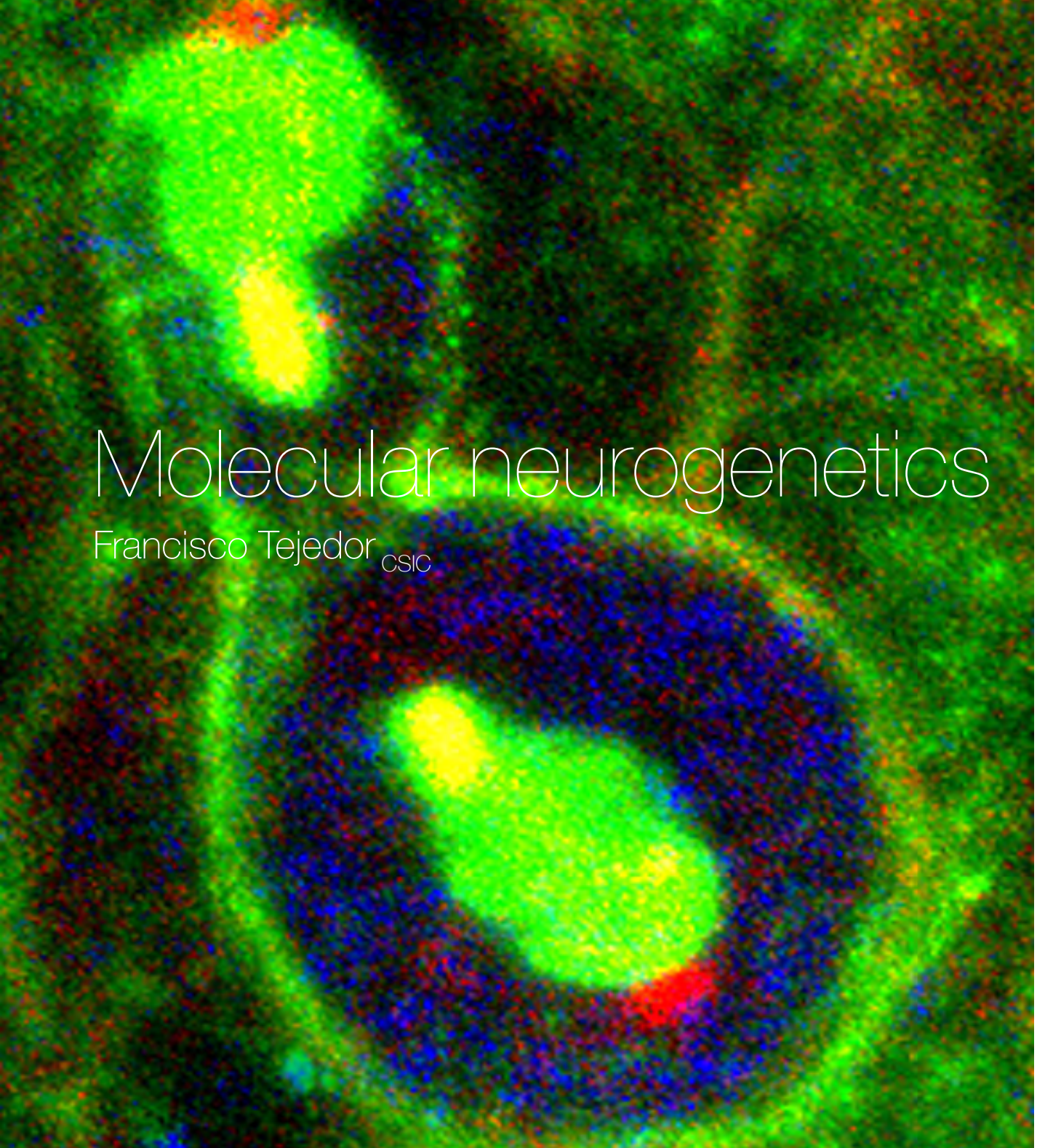
Criado, M., Mulet, J., Castillo, M., Aldea, M., Sala, S. & Sala, F. (2008) Interactions between loop 5 and beta-strand beta6' are involved in alpha7 Nicotinic Acetylcholine Receptors Channel Gating. **Journal of Neurochemistry** *104, 719-730*

Aldea, M.., Mulet, J.., Sala, S.., Sala, F.., Criado, M. (2007) Non charged amino acids from three different domains contribute to link agonist binding to channel gating in alpha7 nicotinic acetylcholine receptors. **Journal of Neurochemistry** *103, 725-735*

Castillo, M.., Mulet, J.., Bernal, J.A.., Criado, M.., Sala, F.., Sala, S. (2006) Improved gating of a chimeric alpha7-5HT(3A) receptor upon mutations at the M2-M3 extracellular loop. **FEBS Letters** *580, 256-260*

Sala, F., Mulet, J., Sala, S., Gerber, S., Criado, M. (2005) Charged Amino Acids of the N-terminal Domain Are Involved in Coupling Binding and Gating in alpha7 Nicotinic Receptors. **Journal of Biological Chemistry** *280: 6642-6647.*

Criado, M., Mulet, J., Bernal, JA., Gerber, S., Sala, S., Sala, F. (2005) Mutations of a conserved lysine residue in the N-terminal domain of a7 nicotinic receptors affect gating and binding of nicotinic agonists. **Molecular Pharmacology** *68: 1669-1677.*



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.

Molecular neurogenetics

Following this approach, we have identified the gene *minibrain* (*mnb*, also called *Dyrk1A* in vertebrates) as a major regulator of neural progenitor cell proliferation and neurogenesis in Drosophila. *Mnb/Dyrk1A* encodes a very well evolutionary conserved protein-kinase, which play several functions through brain development. We are focusing on its roles in the regulation of neural proliferation, cell cycle, neurogenesis, and neuronal differentiation, unravelling the underlying molecular mechanisms. *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 what cellular functions and molecular mechanisms are altered by an excess of *Mnb/Dyrk1* function to generate neurobiological alterations reminiscent of DS neuropathologies, particularly, neuronal deficit, dendritic atrophy and neurodegeneration. We are also testing the suitability of MNB/DYRK1A kinase inhibitors to interfere with neuronal functions as a prospect to apply pharmacological therapeutic appraoches to DS neuropathologies.

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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*

Walter Becker, Ulf Soppa and Francisco J. Tejedor (2014) DYRK1A: a potential Drug Target for Multiple Down Syndrome Neuropathologies **CNS Neurol Disord-Drug Targets** *13, 26-33*

F.J. Tejedor and B. Hämmerle (2011) MNB/DYRK1A as a multiple regulator of neuronal development **FEBS J 278(2):223-35**

J. Colonques, J. Ceron, H. Reichert and F.J. Tejedor (2011) A Transient Expression of Prospero Promotes Cell Cycle Exit of Drosophila Postembryonic Neurons Through the Regulation of Dacapo **PLoS ONE,** *6(4):e19342. doi:10.1371/journal.pone.0019342*

Hämmerle B, Ulin E., Guimera J, Becker W, Guillemot F, and Tejedor F.J. (2011) Transient expression of Mnb/Dyrk1A couples cell cycle exit and differentiation of neuronal precursors by inducing p27KIP1 expression and suppressing NOTCH signalling. **Development** *138, 2543-2554 doi:10.1242/dev.066167*

Hammerle B, Elizalde C., Tejedor F.J. (2008) The Spatio-Temporal and Subcellular Expression of the Candidate Down Syndrome Gene Mnb/Dyrk1A in the Developing Mouse Brain Suggests Distinct Sequential Roles in Neuronal Development. **Eur. J. Neurosci.** *27, 1061–1074*

Hammerle B and Tejedor FJ (2007) A novel function of DELTA-NOTCH signalling mediates the transition from proliferation to neurogenesis in neural progenitor cells. **PLoS ONE** *2(11): e1169. doi:10.1371/journal.pone.0001169*

B. Hämmerle., Carnicero, A., Elizalde, C., Cerón, J., Martínez, S., Tejedor, FJ. (2003) Expression patterns and subcellular localization of the Down Syndrome candidate protein MNB/DYRK1A suggest a role in late neuronal differentiation. **Eur. J. Neurosci.,** *17: 2277-86.*

Hämmerle, B., Vera, E., Spreicher, S., Arencibia, R., Martínez, S., Tejedor, FJ. (2002) Mnb / Dyrk1A is transiently expressed and asymmetrically segregated in neural progenitor cells at the transition to neurogenic divisions. **Dev. Biol.,** *246: 259-73.*

Tejedor F, Zhu XR, Kaltenbach E, Ackermann A, Baumann A, Canal I, Heisenberg M, Fischbach KF, Pongs O**.** (1995) " *minibrain*: A new protein-kinase family involved in postembryonic Neurogenesis in *Drosophila* **Neuron** *14, 287-301*

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.

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Sensory transduction and nociception

Meseguer V, Alpiza YA, Luis E, Tajada S, Denlinger B, Fajardo O, Manenschijn JA, Fernández-Peña C, Talavera A, Kichko T, Navia B, Sánchez A, Señarís R, Reeh P, Pérez-García MT, López-López JR, Voets T, Belmonte C, Talavera K, Viana F 2014 **TRPA1 channels mediate acute neurogenic inflammation and pain produced by bacterial endotoxins** **Nature Communications** *DOI: 10.1038/ncomms4125*

Morenilla-Palao C, Luis E, Fernández-Peña C, Quintero E, Weaver JL, Bayliss DA, Viana F 2014 **Ion channel profile of TRPM8 cold receptors reveals a role of TASK-3 potassium channels in thermosensation** **Cell Reports** *DOI:10.1016/j.celrep.2014.08.003.*

Pertusa M, González A, Hardy P, Madrid R, Félix Viana F 2014 **Bidirectional Modulation of Thermal and Chemical Sensitivity of TRPM8Channels by the Initial Region of the N-Terminal Domain.** **J Biol Chem** *DOIi: 10.1074/jbc.M114.565994*

de la Peña E, Mälkiä A, Vara H, Caires R, Ballesta JJ, Belmonte C, Viana F 2012 **The influence of cold temperature on cellular excitability of hippocampal networks** **PlosOne** *7(12):e52475*

Pertusa M, Madrid R, Morenilla-Palao C, Belmonte C, Viana F. 2012 **The N-glycosylation of TRPM8 channels modulates the temperature sensitivity of cold-thermoreceptor neurons.** **J Biol Chem** *287:18218-18229.*

Orio P, Parra A, Madrid R, González O, Belmonte C, Viana F. 2012 **Role of Ih in the firing pattern of mammalian cold thermoreceptor endings.** **J Neurophysioly** *108:3009-3023.*

Parra A, Madrid R, Echevarria D, Del Olmo S, Morenilla, Palao C, Acosta MC, Gallar J, Dhaka A, Viana F, Belmonte C. 2010 **Ocular surface wetness is regulated by TRPM8 dependent cold thermoreceptors of the cornea.** **Nature Medicine** *16:1396-1399.*

Rocher A, Caceres AI, Almaraz L, Gonzalez C. 2009 **EPAC signalling pathways are involved in low PO2 chemoreception in carotid body chemoreceptor cells.** **Journal of Physiology.** *587:4015-4027.*

Madrid R*, de la Peña E*, Donovan Rodriguez T, Belmonte C, Viana F. 2009 **Variable threshold of cold-sensitive neurons is determined by a balance between TRPM8 and Kv1 potassium channels.** **Journal of Neuroscience** *29:3120-3131 (* co authors).*

Talavera K, Gees M, Karashima Y, Vanoirbeek JAJ, Damann N, Meseguer V, Everaerts W, Benoit M, Janssens A, Vennekens R, Viana F, Nemery B, Nilius B, Voets T. 2009 **Nicotine activates the chemosensory cation channel TRPA1.** **Nature Neuroscience** *12:1293-1299*

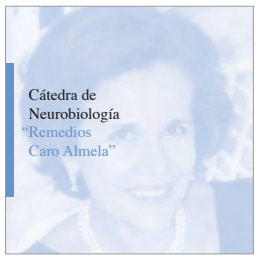
Malkia A*, Pertusa M*, Fernández Ballester G, Ferrer Montiel A, Viana F. 2009 **Differential role of the me binding residue Y745 in the antagonism of TRPM8 channels nthol** **Molecular Pain** *5:62 (* co authors).*

Fajardo O, Meseguer V, Belmonte C, Viana F. 2008 **TRPA1 channels: novel targets of 1,4dihydropyridines.** **Channels** *2: 429-438.*

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

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European Network of Neuroscience Institutes

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

Research Professorship in Neurobiology

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

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

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

Richard Morris & Constantino Sotelo

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

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

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

Dr Silvia Arber
2015

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 2015

The jury of the 7th Edition of the "Remedios Caro Almela" Prize in Developmental Neurobiology met on June 19th of 2015 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, Magdalena Götz, winner of the sixth edition of the award, David Wilkinson, from the MRC in London, Patricia Gaspar, from the Institut du Fer à Moulin in 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 Silvia Arber, Researcher of the Friedrich Miescher Institute for Biomedical Research in Basilea for her contributions to the knowledge of cellular and molecular mechanisms orchestrating the formation of motor connexions and motor control.

Silvia Arber studies aims to identify the general principles that allow the neural circuits orchestrating accurate control and appropriate motor output in response to a variety of stimuli, whether voluntary initiation of movement or sensory signals. To decipher how the motor circuits exercise this control, his group has

determined the organization and functioning of the neuronal circuits through the study of synaptic connectivity, its molecular and genetic identity, as well as its functional properties.
The combination of these approaches allowed unveiling the connectivity and manipulating its function to determine the role of the different elements that form the spinal circuits during animal behavior. In addition, it allowed discovering the mechanisms involved in their assembly during the development, as well as how they re-organize during learning, disease or after injury. For example, after an incomplete spinal cord injury, the body can partially recover basic motor function. Both the muscle spindles and the associated sensory circuits that feedback to the spinal cord, promote the establishment of new neuronal connections after injury. Silvia has clarified the mechanism at the circuit level underlying the process of motor recovery. These results can contribute to design innovative strategies for timely treatment after spinal cord injury, a problem that greatly affects society and for which remedies are urgent.
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.

The Professor Arber was born in Geneva, in 1968. He studied Biology at the University of Basel. He received his doctorate at the Friedrich Miescher Institute of the University of Basel. After several years of postdoctoral stay at Columbia University, he joined the Friedrich Miescher Institute/ Biozentrum in Basel as a group leader, where he is currently Professor and Deputy Director of the Biozentrum.
Silvia Arber is a member of several editorial boards of scientific journals (Cell, Current Op. Neurobiol, etc) and has received numerous awards and distinctions, including the E. Fisher Prize, the EMBO Young Investigator Award, Eppendorf Young Investigator Award, the Schellenberg Prize, among others, and is a member of EMBO and the Switzerland Academy of Medical Sciences.

The next Remedios Caro Almela Prize will be awarded in 2017

Services & Facilities

Zebrafish Facility

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

Molecular Biology & Microbiology

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

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

Centrifugation Facility

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

Experimental Embryology

(two units; one of them allocated a the genetically modified mice animal house)
This service is specifically designed to carry out experimental embryology procedures in mammals. It is equipped with a micro dissection

laser, biolistic system and fluorescence stereoscopic microscope with digital image capture and processing system. The Unit also has a CUY21 electroporator system, which is designed for in utero electroporation of DNA plasmids in embryonic brains, and an ultrasonic system that allows the electroporation of DNA or the injection of cells in precise regions of the brain.

Live Cell Imaging Platform

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

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

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

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

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

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

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

Surgery Room

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

Cell Culture Facility

The facilities are distributed in several areas of common use:

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

Electronics Workshop

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

Fluorescence Assisted Cell Sorting

The Institute runs the latest generation "Fluorescence Activated Cell Sorting" (FACS) currently available. Our FACSAria is a digital analyzer/sorter of high precision and sensitivity for sorting and analysis of cell populations with differently tagged structures, used in studies such as: the search for

molecules involved in neuronal development and plasticity, the search for molecules implicated in tumour development, neuropsychiatric and neurodegenerative disorders, and cell therapy: stem cell isolation for transplant in animal models for neuropsychiatric and neurodegenerative diseases.

Behavioural Studies Area

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

Illustration & Photography

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

Purchase & Storage

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

fMR Brain Imaging

The Institute's Brain Imaging Service is equipped with a Bruker Biospec 70/30 Magnetic Resonance Imaging system with high performance (up to 675 mT/m) gradients and capacity for the application of modern techniques of multimodal and parallel Imaging in animal experimentation (rat, mouse, rabbit and cat)

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

Animal House

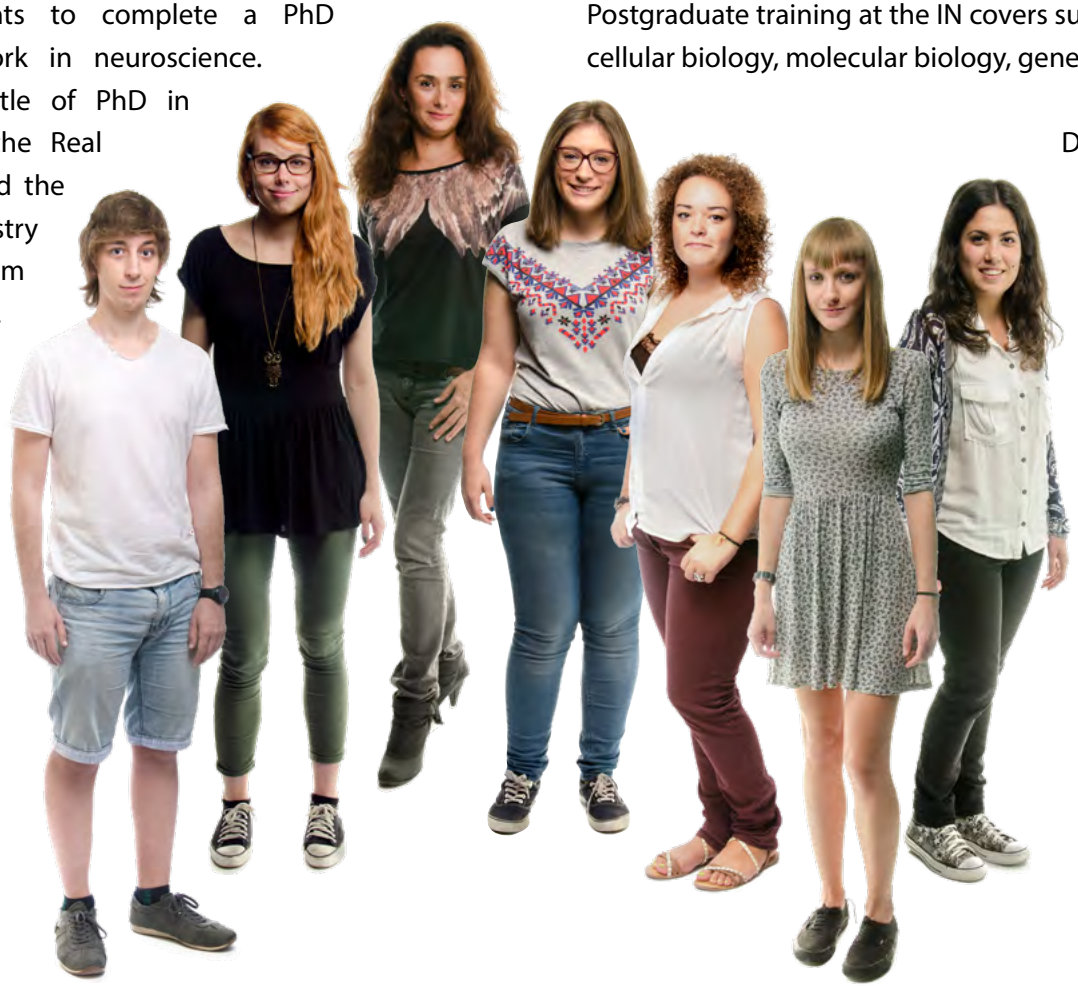
The IN Service of Genetically Modified Mice belongs to the UMH Animal Experimentation Service and houses about 8000 mice under specific pathogen-free conditions. It has an approximate area of 2000 square meters and it includes the following areas:

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

Master & PhD Program

The PhD Program has been an ongoing activity at the Institute since its foundation, and it has played an important role in the professional formation of scientists in the field. A high percentage of students completing the program have subsequently been incorporated into national research teams or have taken up overseas postdoctoral positions. The program is intended for graduate students to complete a PhD thesis based on experimental work in neuroscience.

The Program offers the official title of PhD in Neurosciences as established by the Real Decreto 1393/2007 and has received the "Quality Mention" of the Spanish Ministry of Education. This year the PhD program was under the RD 99/2011 normative.



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

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

Master in Neuroscience: from Bench to Bedside.

Introduction to the Study of the CNS.

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

Neuroscience Today.

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

Functional Concepts in Neurosciences.

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

Neuropathology and Therapy.

- Neuropathology.
- New therapies.

Advanced Studies in Neuroscience.

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

Techniques in Neurosciences.

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

Master Research Work

PhD Program

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

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

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

Administrative & Service Staff

Manager

Mª Teresa García Hedo

Administration

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Radioactivity Control
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Raúl Pardo Mérida
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Mª Ángeles Soler Ripoll
Lucía Yuste Jiménez

Drosophila Service

Alicia Sánchez Rincón
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Zebrafish Facility

Diana Abad Bataller
Teresa Martín Rey

Publications

Article

Aller MI., Pecoraro V., Paternain AV., Canals S., Lerma J. **Increased Dosage of High-Affinity Kainate Receptor Gene grik4 Alters Synaptic Transmission and Reproduces Autism Spectrum Disorders Features.** J. Neurosci. 35(40):13619-13628

Antonello ZA., Reiff T., Ballesta-Illan E., Dominguez M. **Robust intestinal homeostasis relies on cellular plasticity in enteroblasts mediated by miR-8-Escargot switch.** Embo J. 34(15):2025-2041

Ateca-Cabarga JC., Cosa A., Pallares V., Lopez-Atalaya JP., Barco A., Canals S., Moratal D. **Brain size regulations by cbp haploinsufficiency evaluated by in-vivo MRI based volumetry.** Sci Rep 5:16256-

Bale Mr., Campagner D., Erskine A., Petersen RS. **Microsecond-Scale Timing Precision in Rodent Trigeminal Primary Afferents.** J. Neurosci. 35(15):5935-5940

Bale MR., Ince RAA., Santagata G., Petersen RS. **Efficient population coding of naturalistic whisker motion in the ventro-posterior medial thalamus based on precise spike timing.** Front. Neural Circuits 9:A50-14

Barao S., Gartner A., Leyva-Diaz E., Demyanenko G.,Munck S., Vanhoutvin T., Zhou L., Schachner M., Lopez-Bendito G., Maness PF., De Strooper B. **Antagonistic Effects of BACE1 and APH1B-?-Secretase Control Axonal Guidance by Regulating Growth Cone Collapse.** Cell Reports 12(9):1367-1376

Belmonte C. **Andrés Laguna Master Lecture: Exploration of the brain and Spanish neuroscience: Standing on the shoulders of giants (Lección Magistral Andrés Laguna: La exploración del cerebro y la neurobiología española. Aupados a hombros de gigantes)** Educacion Medica 16(2):141-148

Belmonte C., Acosta MC., Merayo-Lloves J., Gallar J. **What Causes Eye Pain?** Curr Ophthalmol Rep. 3(2):111-121

Blessing EM., Steenkamp MM., Manzanares J., Marmar CR. **Cannabidiol as a Potential Treatment for Anxiety Disorders.** Neurotherapeutics 12(4):825-836

Caires R., Luis E., Taberner FJ., Fernandez-Ballester G., Ferrer-Montiel A., Balazs EA., Gomis A., Belmonte C., De la Peña E. **Hyaluronan modulates TRPV1 channel opening, reducing peripheral nociceptor activity and pain.** Nat. Commun. 6:art.-8095

Callejo G., Castellanos A., Castany M., Gual A., Luna C., Acosta MC., Gallar J., Giblin JP., Gasull X. **Acid-sensing ion channels detect moderate acidifications to induce ocular pain.** Pain 156(3):483-495

Carvajal F., Alcaraz-Iborra M., Lerma-Cabrera JM., Valor LM., de la Fuente L., Sanchez-Amate MC., Cubero I. **Orexin receptor 1 signaling contributes to ethanol binge-like drinking: Pharmacological and molecular evidence.** Behav. Brain Res. 287:230-237

Castillo-Paterna M., Moreno-Juan V., Filipchuk A., Rodriguez-Malmierca L., Susin R., Lopez-Bendito G. **DCC functions as an accelerator of thalamocortical axonal growth downstream of spontaneous thalamic activity.** EMBO Rep. 16(7):851-862

Cuccioli V., Bueno C., Belvindrah R., Lledo PM., Martinez S. **Attractive Action of FGF-Signaling Contributes to the Postnatal Developing Hippocampus.** Hippocampus 25(4):486-499

Cuchillo-Ibañez I., Lopez-Font I., Boix-Amoros A., Brinkmalm G., Blennow K., Molinuevo JL., Saez-Valero J. **Heteromers of amyloid precursor protein in cerebrospinal fluid.** Mol. Neurodegener. 10(1):art-2

De Juan Romero C., Borrell V. **Coevolution of radial glial cells and the cerebral cortex.** Glia 63(8):1303-1319

De Juan Romero C., Bruder C., Tomasello U., Sanz-Anquela JM., Borrell V. **Discrete domains of gene expression in germinal layers distinguish the development of gyrencephaly.** Embo J. 34(14):1859-1874

Dehorter N., Ciceri G., Bartolini G., Lim L., Del Pino I., Marin O. **Tuning of fast-spiking interneuron properties by an activity-dependent transcriptional switch.** Science 349(6253):1216-1220

Del Blanco B., Medrano A., Barco A. **Neuroepigenética, en la interfase entre genoma y cerebro.** SEBBM 183:21-26

Dienes L., Kiss HJ., Perenyi K., Szepessy Z., Nagy ZZ., Barsi A., Acosta MC., Gallar J., Kovacs I. **The effect of tear supplementation on ocular surface sensations during the interblink interval in patients with dry eye.** PLoS ONE 10(8):e-0135629

Fiorenza A., Lopez-Atalaya JP., Rovira V., Scandaglia M., Geijo-Barrientos E., Barco A. **Blocking miRNA Biogenesis in Adult Forebrain Neurons Enhances Seizure Susceptibility, Fear Memory, and Food Intake by Increasing Neuronal Responsiveness.** Cereb. Cortex *in press*

Garcia-Gutierrez MS., Navarrete F., Aracil A., Bartoll A., Martinez-Gras I., Lanciego JL., Rubio G., Manzanares J. **Increased vulnerability to ethanol consumption in adolescent maternal separated mice.** Addict. Biol.W

Garcia-Lopez R., Pombero A., Dominguez E., Geijo-Barrientos E., Martinez S. **Developmental alterations of the septohippocampal cholinergic projection in a lissencephalic mouse model.** Exp. Neurol. 271:215-227

Garcia-Martinez V., Montes MA., Villanueva J., Gimenez-Molina Y., De Toledo GA., Gutierrez LM. **Sphingomyelin derivatives increase the frequency of microvesicle and granule fusion in chromaffin cells.** Neuroscience 295:117-125

Grande MT., Sanchez-Laorden B., Lopez-Blau C., de Frutos CA., Boutet A., Arevalo M., Grant Rowe R., Weiss SJ., Lopez-Novoa JM., Nieto

MA. **Snail1-induces partial epitelial-to-mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease.** Nat. Med. 21(9):989-997

Grasso S., Martinez-Lacaci I., Barbera VM., Castillejo A., Soto JL., Gallego-Plazas J., Lopez-Riquelme N., Garcia-Morales P., Mata-Balaguer T., Ferragut JA., Saceda M. **HGUE-C-1 is an atypical and novel colon carcinoma cell line.** BMC Cancer 15(1):number-240

Hallaq R., Volpicelli F., Cuchillo-Ibañez I., Hooper C., Mizuno K., Uwanogho D., Causevic M., Asuni A., To A., Soriano S., Giese KP., Lovestone S., Killick R. **The Notch intracellular domain represses CRE-dependent transcription .** Cell. Signal. 27(3):621-629

Hirsch JA., Wang X., Sommer FT., Martinez LM. **How Inhibitory Circuits in the Thalamus Serve Vision.** Annu. Rev. Neurosci 38:309-329

Jones J., Estirado A., Redondo C., Pacheco-Torres J., Sirerol-Piquer MS., Garcia-Verdugo JM., Martinez S. **Mesenchymal Stem Cells Improve Motor Functions and Decrease Neurodegeneration in Ataxic Mice.** Mol. Ther. 23(1):130-138

Keder A., Rives-Quinto N., Aerne BL., Franco M., Tapon N., Carmena A. **The Hippo Pathway Core Cassette Regulates Asymmetric Cell Division.** Curr. Biol. 25(21):2739-2750

Kruse N., Persson S., Alcolea D., Bahl JMC., Baldeiras I.,Capello E., Chiasserini D...., Garcia-Ayllon MS., ... Genc S.,Gkatzima O., Heegaard NHH. Janeiro AM..., Saez-Valero J., Struyfs H.,Tanassi JT..., Zetterberg H., Mollenhauer B. **Validation of a quantitative cerebrospinal fluid alpha-synuclein assay in a European-wide interlaboratory study.** Neurobiol. Aging 36(9):2587-2596

La Porta C., Bura SA., Llorente-Onaindia J., Pastor A., Navarrete F., Garcia-Gutierrez MS., De la Torre R., Manzanares J., Monfort J., Maldonado R. **Role of the endocannabinoid system in the emotional manifestations of osteoarthritis pain.** Pain 156(10):2001-2012

Laurent F., Brotons-Mas JR., Cid E., Lopez-Pigozzi D., Valero M., Gal B., De la Prida LM. **Proximodistal structure of theta coordination in the dorsal hippocampus of epileptic rats.** J. Neurosci. 35(11):4760-4775

Lopez-Moya F., Colom-Valiente MF., Martinez-Peinado P., Martinez-Lopez JE., Puelles E., Sempere-Ortells JM., Lopez-Llorca LV. **Carbon and nitrogen limitation increase chitosan antifungal activity in Neurospora crassa and fungal human pathogens.** Fungal Biol. 119(2-3):154-169

Madrigal MP., Moreno-Bravo JA., Martinez-Lopez JE., Martinez S., Puelles E. **Mesencephalic origin of the rostral Substantia nigra pars reticulata.** Brain Struct Funct *in press*

Martinez-Ferre A., Lloret-Quesada C., Prakash N., Wurst W., Rubenstein JLR., Martinez S. **Fgf15 regulates thalamic development by controlling the expression of proneural genes.** Brain Struct Funct *in press*

Martinez-Lopez JE., Moreno-Bravo JA., Madrigal MP., Martinez S., Puelles E. **Mesencephalic basolateral domain specification is dependent on Sonic Hedgehog.** Front Neuroanat 9:art-12

Martinez-Lopez JE., Moreno-Bravo JA., Madrigal MP., Martinez S., Puelles E. **Red nucleus and rubrospinal tract disorganization in the absence of Pou4f1.** Front Neuroanat 9:art-8

Martin-Moldes Z., Zamarro MT., Del Cerro C., Valencia A., Gomez MJ., Arcas A., Udaondo Z, Garcia JL., Nogales J., Carmona M., Diaz E. **Whole-genome analysis of Azoarcus sp. strain CIB provides genetic insights to its different lifestyles and predicts novel metabolic features** Syst. Appl. Microbiol. 38(7):462-471

Minocha S., Valloton D., Ypsilanti AR., Fiumelli H., Allen EA., Yanagawa Y., Marin O., Chedotal A., Hornung JP., Lebrand C. **Nkx2.1-derived astrocytes and neurons together with Slit2 are indispensable for anterior commissure formation.** Nat. Commun. 6:-6887

Morello F., Prasad AA., Rehberg K., de Sa RV., Anton-Bolaños N., Leyva Diaz E., Adolfs Y., Tissir F., Lopez-Bendito G., Pasterkamp RJ. **Frizzled3 controls axonal polarity and intermediate target entry during striatal pathway development.** J. Neurosci. 35(42):14205-14219

Moreno A., Morris R., Canals S. **Frequency-Dependent Gating of Hippocampal–Neocortical Interactions.** Cereb. Cortex *in press*

Moreno M., Fernandez V., Monllau JM., Borrell V., Lerin C., de la Iglesia N. **Transcriptional Profiling of Hypoxic Neural Stem Cells Identifies Calcineurin-NFATc4 Signaling as a Major Regulator of Neural Stem Cell Biology.** Stem Cell Rep. 5(2):157-165

Murcia-Belmonte V., Esteban PF., Martinez-Hernandez J., Gruart A., Lujan R., Delgado-Garcia JM., de Castro F. **Anosmin-1 over-expression regulates oligodendrocyte precursor cell proliferation, migration and myelin sheath thickness.** Brain Struct Funct *in press*

Murillo B., Ruiz-Reig N., Herrera M., Fairen A., Herrera E. **Zic2 Controls the Migration of Specific Neuronal Populations in the Developing Forebrain.** J. Neurosci. 35(32):11266-11280

Navarro D., Alvarado M., Navarrete F., Giner M., Obregon MJ., Manzanares J., Berbel P. **Gestational and early postnatal hypothyroidism alters VGluT1 and VGAT bouton distribution in the neocortex and hippocampus, and behavior in rats.** Front Neuroanat 9:1-24

Ortega-Alvaro A., Navarrete F., Aracil-Fernandez A., Navarro D., Berbel P., Manzanares J. **Differential Pharmacological Regulation of Sensorimotor Gating Deficit in CB1 Knockout Mice and Associated Neurochemical and Histological Alterations.** Neuropsychopharmacology 40(11):2639-2647

Ortega-Alvaro A., Ternianov A., Aracil-Fernandez A., Navarrete F., Garcia-Gutierrez MS., Manzanares J. **Role of cannabinoid CB2 receptor in the reinforcing actions of ethanol.** Addict. Biol. 20(1):43-55

Palacios-Filardo J., Aller MI., Lerma J. **Synaptic Targeting of Kainate Receptors.** Cereb. Cortex *in press*

Pallares V., Moya J., Samper-Belda FJ., Canals S., Moratal D. **Neurosurgery planning in rodents using a magnetic resonance imaging assisted framework to target experimentally defined networks.** Comput. Meth. Programs Biomed. 121(2):66-76

Pombero A., Martinez S. **The alpha2-subunit of the nicotinic cholinergic receptor is specifically expressed in medial subpallium-derived cells of mammalian amygdala.** J. Comp. Neurol. 523(11):1608-1621

Quallo T., Vastani N., Horridge E., Gentry C., Parra A., Moss S., Viana F., Belmonte C., Andersson DA., Bevan S. **TRPM8 is a neuronal osmosensor that regulates eye blinking in mice.** Nat. Commun. 6:-7150

Quesada MP., Jones J., Rodriguez-Lozano FJ., Moraleda JM., Martinez S. **Novel aberrant genetic and epigenetic events in Friedreich's ataxia.** Exp. Cell Res. 335(1):51-61

Rabasa C., Pastor-Ciurana J, Delgado-Morales R., Gomez-Roman A., Carrasco J., Gagliano H., Garcia-Gutierrez MS., Manzanares J., Armario A. **Evidence against a critical role of CB1 receptors in adaptation of the hypothalamic-pituitary-adrenal axis and other consequences of daily repeated stress.** Eur. Neuropsychopharmacol. 25(8):1248-1259

Rancz EA., Moya J., Drawitsch F., Brichta AM., Canals S., Margrie TW. **Widespread Vestibular Activation of the Rodent Cortex** J. Neurosci. 35(15):5926-5934

Reiff T., Jacobson J., Cognigni P., Antonello Z., Ballesta E., Tan KJ., Yew JY., Dominguez M., Miguel-Aliaga I. **Endocrine remodelling of the adult intestine sustains reproduction in Drosophila.** eLife 4::-e06930

Reis S., Hu Y., Babino A., Andrade JA., Canals S., Sigman M., Makse H. **Avoiding catastrophic failure in correlated networks of networks.** Nat. Phys. *in press*

Rios-Barrera LD., Gutierrez-Perez I., Dominguez M., Riesgo-Escovar JR. **acal is a long non-coding RNA in JNK signaling in epithelial shape changes during drosophila dorsal closure.** PLoS Genet. 11(2):-e1004927

Rodriguez-Arias M., Navarrete F., Blanco-Gandia MC., Arenas MC., Aguilar MA., Bartoll-Andres A., Valverde O., Miñarro J., Manzanares J. **Role of CB2 receptors in social and aggressive behavior in male mice.** Psychopharmacology 232(16):3019-3031

Rutkowska-Wlodarczyk I., Aller MI., Valbuena S., Bologna JC., Prezeau L., Lerma J. **A Proteomic Analysis Reveals the Interaction of GluK1 Ionotropic Kainate Receptor Subunits with Go Proteins.** J. Neurosci. 35(13):5171-5179

Scandaglia M., Benito E., Morenilla-Palao C., Fiorenza F., del Blanco B., Coca Y., Herrera E., Barco A. **Finetuned SRF activity controls**

asymmetrical neuronal outgrowth: Implications for cortical migration, neural tissue lamination and circuit assembly. Sci Rep *in press*

Suarez-Pereira I., Canals S., Carrion AM. Adult newborn neurons are involved in learning acquisition and long-term memory formation: The distinct demands on temporal neurogenesis of different cognitive tasks. Hippocampus 25(1):51-61

Vallejo DM., Juarez-Carreño S., Bolivar J., Morante J., Dominguez M. A brain circuit that synchronizes growth and maturation revealed through Dilp8 binding to Lgr3. Science 350(6262):aa67-67

Valor LM. Transcription, Epigenetics and Ameliorative Strategies in Huntington's Disease: a Genome-Wide Perspective. Mol. Neurobiol. 51(1):406-423

Valor LM. Epigenetic-based therapies in the preclinical and clinical treatment of Huntington's disease. Int. J. Biochem. Cell Biol. 67:45-48

Villar-Cerviño V., Kappeler C., Nobrega-Pereira S., Henkemeyer M., Rago L., Nieto MA., Marin O. Molecular mechanisms controlling the migration of striatal interneurons. J. Neurosci. 35(23):8718-8729

Wende CZ., Zoubaa S., Blak A., Echevarria D., Martinez S., Guillemot F., Wurst W., Guimera J. Hairy/Enhancer-of-Split MEGANE and Proneural MASH1 Factors Cooperate Synergistically in Midbrain GABAergic Neurogenesis. PLoS ONE 10(5):-e0127681

Zhao D., Pacheco-Torres J., Hallac RR., White D., Peschke P., Cerdan S., Mason RP. Dynamic oxygen challenge evaluated by NMR T1 and T2* - insights into tumor oxygenation. NMR Biomed. 28(8):937-947

Editorial Material

Barco A., Brambilla R., Rosenblum K. Editorial. Neurobiol. Learn. Mem. 124:1-2

Belmonte C., Hollyfield JG. In memoriam Exp. Eye Res. 140:iii-iv

News Item

Lopez-Font I., Cuchillo-Ibañez I., Sogorb-Esteve A., Garcia-Ayllon MS., Saez-Valero J. Transmembrane amyloid-related proteins in CSF as potential biomarkers for Alzheimer's disease. Frontiers in Neurology 6:number-125

Review

Benito E., Barco A. **The Neuronal Activity-Driven Transcriptome.** Mol. Neurobiol. 51(3):1071-1088

Peters M., Muñoz-Lopez M., Morris RGM. **Spatial memory and hippocampal enhancement.** Curr. Opin. Behavioral Sci. 4:81-91

Sotelo C. **Molecular Layer Interneurons of the Cerebellum: Developmental and Morphological Aspects.** Cerebellum 14(5):534-556

Seminars

16.01 **Homeoprotein signaling : why, when & where?**
Dr. Alain Prochiantz Collège de France, Paris, France

20.01 **Measuring Behavior in Similarity Timescapes**
Dr. Alex Gómez-Marín Champalimaud Neuroscience Programme, Lisbon, Portugal

23.01 **Sensory-evoked LTP in the mouse barrel cortex**
Dr. Anthony Holtmaat Universite de Geneve, Switzerland

30.01 **Long noncoding RNA expression & molecular function in the CNS**
Dr. Chris Ponting Department of Physiology, Anatomy & Genetics, University of Oxford, UK

06.02 **Transcriptional & epigenetic control of glial development & myelination**
Dr. Michael Wegner Friedrich-Alexander University Erlangen-Nurenberg, Erlangen, Germany

13.02 **Molecular identification of the volume-regulated anion channel VRAC - a key player in volume regulation & amino acid release**
Dr. Thomas Jentsch Max-Delbrück-Center for Molecular Medicine (MDC), Berlin, Germany

20.02 **Diverse coupling of neurons to populations in sensory cortex**
Dr. Kenneth Harris University College London, London, UK

27.02 **Genetic & Epigenetic Networks in Intellectual Disability**
Dr. Hans van Bokhoven Radboud University Medical Center, Nijmegen, The Netherlands

06.03 **The life of a synaptic vesicle: youth, old age & retirement**
Dr. Silvio Rizzoli University Medical Center Göttingen

11.03 **Técnicas de reproducción asistida y criopreservación disponibles en el Laboratorio de Criopreservación del IN. Aplicaciones y utilidad en investigación**
Gonzalo Moreno del Val
Laboratorio de Transgénicos y Criopreservacion , Instituto de Neurociencias de Alicante

27.03 **Decoding the Notch Response**
Dr. Sarah Bray
Department of Physiology, Development & Neuroscience, University of Cambridge, UK

01.04 **Conditional expansion of neural stem cells**
Dr. Federico Calegari CRTD-DFG Research Center for Regenerative Therapies,Dresden , Germany

10.04 **Motor neuron functional diversification & movement control in mouse**
Dr. Till Marquardt European Neuroscience Institute Göttingen, Germany

13.04 **Neuronal Migration & Brain Map Formation**
Dr. Pasko Rakic Yale University, USA

15.04 **Navigating spinal cord circuits in motor control & sensory perception**
Dr. Sonia Paixao Max Planck Institute of Neurobiology, Munich, Germany

24.04 **Neural Stem & Progenitor Cells & Neocortex Expansion in Development & Evolution**
Dr. Wieland Huttner
Max Planck Institute of Molecular Cell Biology an d Genetics, Dresden, Germany

30.04 **Genetic dissection of visual circuitry in Drosophila**
Dr. Mathias Wernet New York University Abu Dhabi

15.05 **Dopamine, valuation & risk**
Dr. Ray Dolan Wellcome Trust Centre for Neuroimaging, London, UK

22.05 **Development, evolution & function of brain commissures**
Dr. Alain Chedotal INSERM, París, France

29.05 **Synaptic transfer of visual information in the retina**
Dr. Leon Lagnado School of Life Sciences, University of Sussex, UK

03.06 **La importancia del fondo genético en los modelos de ratón en biomedicina**
Dr. Fernando Benavides MD Anderson Cancer Center, USA

05.06 **The origins of Mutational Robustness**
Dr. Mario Fares Instituto de Biología Molecular y Celular de Plantas (CSIC-UPV)

11.06 **Taller informativo: Bioinformática aplicada a la investigación. Conceptos y consideraciones**
Juan Carlos Triviño Pardo Sistemas Genomicos

12.06 **Cortical circuit dynamics during learning**
Dr. Daniel Huber Département des Neurosciences Fondamentales, CMU, Switzerland

19.06 **Temporal patterning generates neuronal diversity in the Drosophila brain**
Dr. Chris Doe HHMI - Institute of Molecular Biology, University of Oregon, USA

26.06 **Deciphering the function of the non-coding genome using CRISPR-Cas9 in mice**
Dr. Lluis Montoliu CNB-CSIC, Madrid

04.09 **Functional Architecture of Spatial Circuits in the Brain**
Dr. Menno Witter Kavli Institute for Systems Neuroscience, Trondheim, Norway

11.09 **Neural circuits for zebrafish behavior**
Dr. Herwig Baier Max Planck Institute of Neurobiology, Munich, Germany

18.09 **Tuning Myelinated Axons to Increase Action Potential Conductance Velocity & Precision - Deviations from a Canonical Concept**
Dr. Benedikt Grothe Ludwig-Maximilians-Universitaet Muenchen, Germany

02.10 **Insights into the molecular basis of Huntington's disease & the validation of therapeutic targets**
Dr. Gillian Bates King's College London. London, UK

06.11 **In search of functional principles: microcircuits underlying visually guided behaviors**
Dr. Johann Bollmann Max Planck Institute, Heidelberg

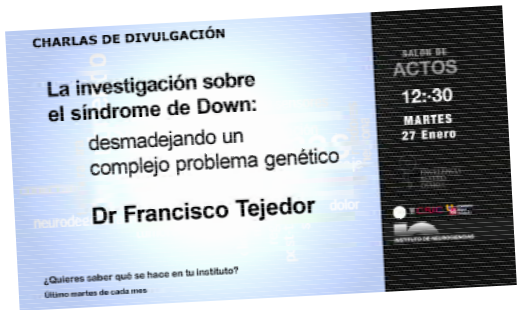
11.11 **Novel optogenetic tools for applications in neuroscience**
Dr. Peter Hegemann Humboldt-Universität zu Berlin, Berlin, Germany

13.11 **Neural Circuits for Elementary Motion Detection**
Dr. Axel Borst Max Planck Institute of Neurobiology, Munich, Germany

20.11 **Functional explorations of reptilian cerebral cortex**
Dr. Gilles Laurent Max Planck Institute for Brain Research, Frankfurt, Germany

27.11 **Wnt transport & morphogenetic field formation in vertebrates**
Dr. Steffen Scholpp Karlsruhe Institute of Technology (KIT), Germany

Seminars



30.11 **Stem Cell-based Treatment Strategies for Retinal Neurodegeneration**
Dr. Anand Swaroop National Eye Institute, NIH, Bethesda

03.12 **Taking a closer look at the nature & nurture of learning**
Dr. Stefan Bonn German Center for Neurodegenerative Diseases, Goettingen, Germany

04.12 **From image processing to computational neuroscience: applications to cinematography**
Dr. Marcelo Bertalmio UPF, Barcelona

11.12 **Growth control by the Hippo signalling pathway**
Dr. Nic Tapon The Francis Crick Institute, London UK

27.01 Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto?
La investigación sobre el síndrome de Down: desmadejando un complejo problema genético
Dr. Francisco Tejedor Instituto de Neurociencias

24.02 Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto?
¿Cómo vemos?
Dr. Luis Miguel Martínez Otero Instituto de Neurociencias

26.05 Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto?
Fotografiando el Pensamiento
Dr. Santiago Canals Instituto de Neurociencias

30.06 Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto?

El arte de criar ratones

Mª Jesús Molina Cimadevila Instituto de Neurociencias

01.10 Charlas de divulgación: ¿Quieres saber qué se hace en tu instituto?

El organizador ístmico y Janus:
haciendo y deshaciendo el cerebro

Dr. Diego Echevarría Instituto de Neurociencias

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La Drosophila como modelo biológico:
moscas humanizadas para entender las enfermedades humanas

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Cómo se forma un cerebro inteligente?

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22.01 Jornada Informativa:

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13.02 Jornada Informativa:

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PhD Thesis

09.01 **Papel de Sonic Hedgehog en Determinación Morfológica del Rombómero 1 y en la Guía Axonal del Fascículo Retroflejo**
Moreno Bravo, Juan Antonio **Director: Dr. Eduardo de Puelles Martínez de la Torre**

13.01 **The Effect of Age & Induced Tear-deficiency on Corneal Nerve Structure & Function**
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13.02 **Synapse-to-network Plasticity in the Hippocampus**
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09.07 **Mechanisms Underlying Diverse Short-Term Plasticity of Thalmocorical Synaptic Response in the Whisker System**
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16.07 **Developmental Regulation of Cortical Expansion: Radial Glia Cell Lineage & Neuronal Migration**
Martínez Martínez, Maria Angeles **Director: Dr. Víctor Borrell Franco**

20.07 **Epithelial-Mesenchymal Transitions & Cell Behaviour**
Córcoles Córcoles, Rebeca **Director: Dr. Angela Nieto Toledano**

14.09 **Lysine Deacetylation & Transcriptional Dysregulation in Neurological Disorders: Huntington's Disease & the Rubinstein-taybi Syndrome**
Guiretti, Deisy Mariela **Dr. Angel Barco Guerrero & Dr. Luis M.Valor Becerra**

30.09 **Regulation of Neuronal Plasticity & Responsiveness by the MIRNA System**
Fiorenza, Anna **Director: Dr. Angel Barco Guerero**

30.10 **Modulación de la Actividad del Canal Iónico TRPV1 por el Hialuronato Sódico**
Caires Mugarra, Rebeca **Director: Dr. Carlos Belmonte Martínez & Dr. Elvira de la Peña García**

17.11 **Los Canales Iónicos Termosensibles TRMP8 y TRPA:**
Papel en la Termosensación y la Termorregulación en Condiciones Fisiológicas y en un Modelo Experimental de Neuropatía Inducida por el Oxaliplatino
Fernández-Peña Acuña, Carlos **Director: Dr. Félix Viana de la Iglesia**

26.11 **Addressing the Complexity of Notch-induced Cancer**
Gutierrez Pérez, Irene **Director: Dr. María Domínguez Castellano**

Events

11th Christmas Meeting of the Instituto de Neurociencias

7th Congress of 5P Syndrome and rare diseases

10th IN Progress Report Workshop.

"Brain Awareness Week 2015" Neuroscience Institute Open Days

“Brain Awareness Week 2015”Brain and society series:“Neuroscience and Education”

“15th Anniversary of the Remedios Caro Almela Chair”Commemorative Symposium

Writing in Science Course

What Make Us Human Series II: Mirror Neuron Network on Social Cognition

Events


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Mañanas: 10:00 - 13:30 Tardes: 16:00 - 18:00
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Disentangling
Neuronal Circuits for
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Caro Almela Lecture
Alicante


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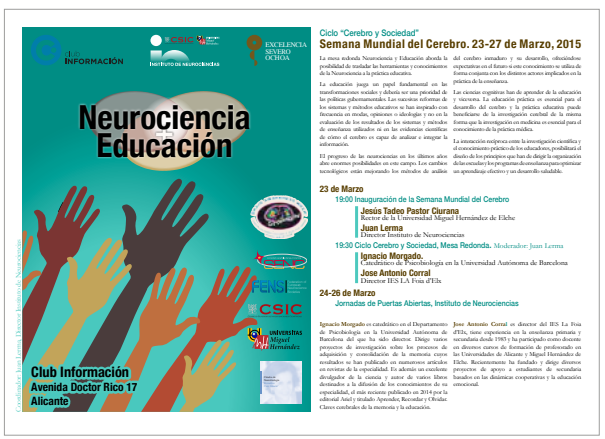
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23 de Marzo
19:00 Inauguración de la Semana Mundial del Cerebro
Jesús Tadeo Pastor Ciurana
Rector de la Universidad Miguel Hernández de Elche
Juan Lerma
Director Instituto de Neurociencias
19:30 Ciclo Cerebro y Sociedad, Mesa Redonda. Moderador: Juan Lerma
Ignacio Morgado.
Catedrático de Psicobiología en la Universidad Autónoma de Barcelona
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24-26 de Marzo
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Investigadores avanzan en la validación de nuevos marcadores para el diagnóstico del Alzheimer

Un grupo de investigadores del Instituto de Neurociencias, centro mixto de la Universidad Miguel Hernández (UMH) de Elche y del Consejo Superior de Investigaciones Científicas (CSIC), ha publicado en la edición digital de la revista Molecular Neurodegeneration el trabajo de investigación "Heterómeros de la proteína precursora amiloide en el líquido cefalorraquídeo" ("Heteromers of amyloid precursor protein in cerebrospinal fluid").

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