INSTITUTO DE NEUROCIENCIAS

ANNUAL REPORT

2013

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INDEX

CSIC Consejo Superior de Investigaciones Científicas

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

Salutation

JUAN LERMA : Director

Despite the long journey of economic crisis that Spain is experiencing, the IN has maintained all the expectations along 2013. We can say with satisfaction that IN's quality figures are well above the national average and exceed comparable centres throughout Europe. Competitive fund rising has been extraordinary in 2013, as it has been the scientific milestones achieved. All this effort has been recognized by the recent accreditation as a Centre of Excellence Severo Ochoa, which not only fills us with pride, but it gives us an important impetus for the future.

In 2013 we maintained a stable ca. 60% women and 40% men proportion, and more than 20% of our staff comes from other countries. Indeed, more than 40% of our contracted researchers are not Spanish in origin, which indicates on the degree of internationalization of our Centre.This year, two support teammates, Sigrid Bars and Josepa Juliá, retired. We wish them to enjoy a well-deserved rest after so many years of intense and dedicated work.

In the scientific arena, the IN has completed its II plan of action, which described the research lines under development since its inception. The IN has achieved delineated objectives, having increased both the fund rising and overall productivity. Noteworthy most of the ¾ parts of the staff correspond to contracts covered with external competitive funds obtained by researchers in this Centre, reflecting the high dedication of its staff. 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.

The comparison of the 4-yr periods 2000-03, the first since its establishment as a joint centre, and 2010-13 shows quite well the evolution of the IN's scientific international impact. This year, we have again increased the number of articles with respect to previous years; we have also increased the averaged impact factor of our papers, reaching a value of 7.03 for the last 4-year period and a value of 8,54 for the last year.

In the past year, the IN has been the subject of a number of relevant actions. For example, the Institute was the protagonist of Chapter 11 of the series "Discover with Tadeo", produced by the FECYT and Tele5 television; we were also distinguished and object of tribute by the Foundation of Family Services of the Valencian Community. Also several members of the IN have achieved significant recognition to their research work. Angel Barco was appointed President of the European Molecular and Cellular Cognition Society; Carlos Belmonte was the Special Honoree for Outstanding Research of the ARVO Foundation and Dowling; Victor Borrell got the Prize SENC-Olympus 2013; Juana Gallar was appointed member of the Committee of Directors of the Association of Ocular Pharmacology and Therapeutics and of the Editorial Board of the Journal of Ocular Pharmacology and Therapeutics; Guillermina López Bendito received the award Izasa Werfen 2013 of the SEBBM; Oscar Marín and Beatriz Rico jointly won the Prize Ciencias de la Salud 2013, awarded by the Fundación Caja Rural from Granada; Angela Nieto was appointed member of the

Salutation

JUAN LERMA : Director

Scientific Advisory Committee of l'Institute of Genomique Fonctionelle, Lyon, and the Centre for Genomic Regulation, Barcelona, as well as a member of the Editorial Committee of the Trends in Genetics. Finally, I was elected member of the Executive Committee of the Confederation of Scientific Societies of Spain (COSCE), President of the newly created PanEuropean Regional Committee of IBRO. I also wish to thank the Generalitat Valenciana for honoring me with the Distinction to the Scientific Merit.

In 2013, the IN has continued with its plan for expenditure containment, just preventing that the crisis and its devastating effect on funding in Spain threatens the most fundamental structures of the Institute. However, the crisis and, in particular, the financial limitations experienced by the CSIC this last year, minimally affected us. We remain committed to incorporating the latest technology to allow our researchers perform experiments and advance in the knowledge of the brain in equal conditions to our European and American colleagues.

Worth mentioning in that from 2013, the Chair of Neurobiology Remedios Caro Almela, so exemplary supported by the Martinez-Caro family, has appointed a new chair. Prof. Richard Morris will collaborate with the IN on a regular basis from now on.

In 2013 we continue our collaboration in the celebration of the World Brain Awareness Week, participating and organizing several actions towards diffusion and advocacy of neuroscience. On this occasion we insisted that neuroscientific knowledge will change the way of thinking and behaving of our society in the future and Neuroscience is called upon to change attitudes and human customs in a radical way. In this task, I would like to thank all those who in one or another position have contributed this year to the Mission of the IN contributing to situate it at the scientific level it has. Also I warmly acknowledge the institutions to which the IN belongs, CSIC and UMH, for the continuous support of our research activity. For the years to come, we are looking forward to developing our program under the auspices of the Severo Ochoa Center of Excellence Award.

A Bit of History

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

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

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

Where We Are

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

The IN houses over fifty 60-70 m^2 laboratories for independent research groups in a building of approximately 9000 m^2 distributed over four floors including a basement. Approximately 30% of the building houses common laboratory facilities with sophisticated research equipment made available for use to all IN researchers. The basement houses a modern animal house for genetically modified mice (See graphic Surface Distribution).

What We Do

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

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

The Institute is organised into three research units: Developmental Neurobiology, Molecular Neurobiology, and Cellular and Systems Neurobiology. Each unit is formed by scientists that share general research interests and technical approaches.

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

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

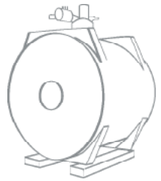
During the Academic Year 2012-2013 we started the Master in Neuroscience: from bench to bedside. This is a one year course totalling 60 ECTS on both basic and advanced aspects of neuroscience offered in several courses by University and CSIC lecturers.

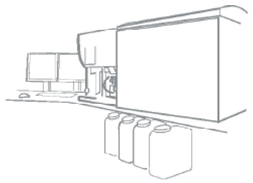
The years following the relocation of the IN to its new building have seen an important period of expansion, resulting in the IN becoming the largest Spanish institute monographically dedicated to the study of the nervous system and its pathologies. The significant increase in personnel has been in both young to senior researchers, several of them of recognized international prestige. The IN currently has 40 tenured researchers (21 from the UMH and 19 from the CSIC), 6 non-tenure scientists, 155 doctoral and postdoctoral researchers and 117 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 for 2012 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 current outlines the guidelines for consolidation, with the clear goal of becoming a center of excellence in the European Research Area. It 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.





erc European Research Council
Funding for top researchers from anywhere in the world

IDEAS

Consolider
Nervous System Development and Plasticity
Programa Consolider-Ingenio

Plan Nacional de I+D+I

Performed the first genome-wide screen for the genomic targets of the inhibitors of histone deacetylases (HDACi), a promising family of compounds that have been shown to be effective in animal and cellular models for different neuropsychiatric conditions, including Huntington, Parkinson and Alzheimer's diseases, brain stroke, cranial traumatism and some congenital intellectual disability syndromes. (Nucl. Acid Res. 41, 8072-84. 2013)

Identified at whole genome level the transcriptional and epigenetic alterations that concur with the progression of Huntington's disease in a mouse model for this disorder. (J. Neurosci. 33, 10471-82. 2013)

Found that the glia of the *Drosophila* larval brain performs an essential non-autonomous role during the development of the optic lobe. (J Cell Sci. 126, 4873-4884. 2013)

Developed a method for evaluating how cortical neurons collectively represent sensory input in a behaving animal and demonstrated that collective activity produces a robust representation of object texture, which can be read by other neurons. (J. Neurosci, 33, 5843-55. 2013)

Demonstration that conserved mir-8/mir-200 microRNA defines a new glial niche that controls neuroepithelial expansion and stem cell generation. (Developmental Cell 27, 174-87. 2013)

Unveiled a new mechanism for protein export from the nucleus, involving the protein synthesis factor eEF1A (Cell Reports, 5, 727-737. 2013).

Unveiled that Sonic receptor Boc acts in a feedback loop-manner to maintain the expression of the transcription factor Zic2 in the retina, critical for the establishement of binocular vision in mammals. (J. Neurosci. 33, 8596-607. 2013)

Demonstrated that the transcription factor Zic2 functions as a general determinant of axon midline avoidance in the CNS and therefore is critical for the proper formation of bilateral circuits in mammals. (Neuron 80, 1392-1406. 2013)

Established that Cajal-Retzius cells, a population of pioneer neurons that play a fundamental role in patterning the cortex, achieve their regular distribution in the surface of the cortex through a mechanism that involves random cell-cell repulsive interactions mediated by Eph/ephrin signaling. This novel mechanism of "cellular tiling" might be common to other neurons in the CNS (Neuron. 77, 457-71. 2013).

Unveiled that sibling GABAergic interneurons have a strong tendency to cluster in the neocortex, independently of their origin and time of birth. In addition, this study also suggests that different interneurons populating deep and superficial layers of the cortex derive from different lineages, which challenges current views on cortical neurogenesis (Nature Neuroscience 16, 1199-1210 2013).

Found that specific loss of ErbB4 in cortical interneurons cause subtle synaptic deficits in these cells, which in turn lead to enhanced excitability, increased gamma synchrony and disrupted social and cognitive behaviour (Neuron 79:1152-1168. 2013)

Described that the ocular discomfort sensations found in patients with allergic keratoconjunctivitis results from both direct activation and sensitization of corneal nociceptors, and the reduction of cold thermoreceptor activity evoked by inflammatory mediators. (Pain 154, 2353-2362. 2013)

Most Relevant Scientific Milestones

The gene Trnp1 is found to be key in cerebral cortex development, by controlling its size and folding both in mice and humans. These functions depend on this gene's relative levels of expression, which determine the abundance and type of progenitor cells generated during embryonic development. (Cell 153:535-549. 2013)

Demonstration that cerebral cortex size and folding depend on the relative abundance of specific types of progenitor cells during embryonic development. For the first time, increased cortical folding is achieved by the genetic manipulation of an already gyrencephalic species. (EMBO J 32:1817-1828. 2013)

Identified a new type of progenitor cell in the mammalian telencephalon, named Bipolar Basal Radial Glia cell. By using 2-photon videomicroscopy it is demonstrated that this new cell type has a great amplification potential, generating a large number of neurons. The abundance of this type of progenitor cell among different species correlates with their respective degree of cortical folding. (Nat. Comm 4:2125. 2013).

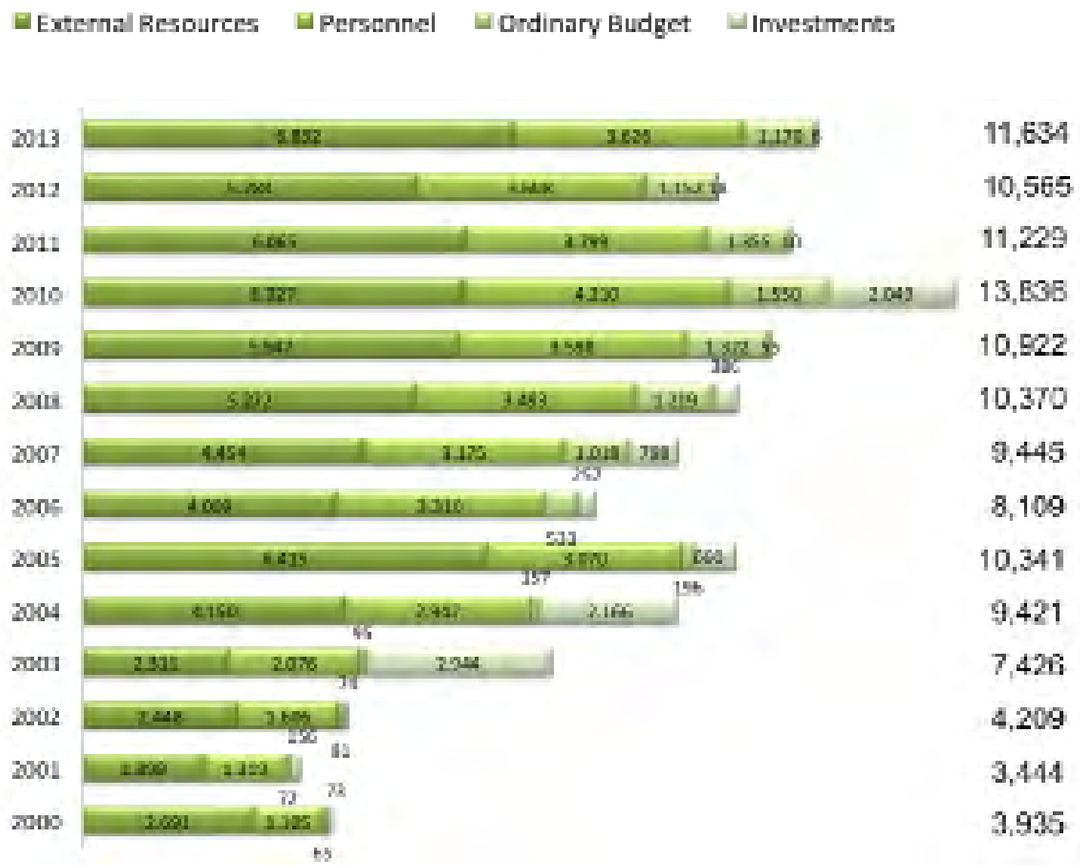
Unveiled that non canonical kainate receptor signaling influences neuronal development by modulating CRMP2 protein activity (J. Neurosci. 13, 18298-18310. 2013).

Patent: Método de diagnóstico y/o pronóstico de la enfermedad de Alzheimer (Sáez-Valero J., y García-Ayllón M.S.) (N.º P201330230; España; 20/02/2013)

Launching of a preclinical stage spin-off company, Avizorex Pharma S.L., This company is focused on developing novel pharmacological treatments addressing major ocular surface diseases. Avizorex's lead program offers a completely novel therapeutic approach for the treatment of dry eye disease.

The Institute in Numbers

Budget Growth in Thousands of Euros



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11,229
13,836
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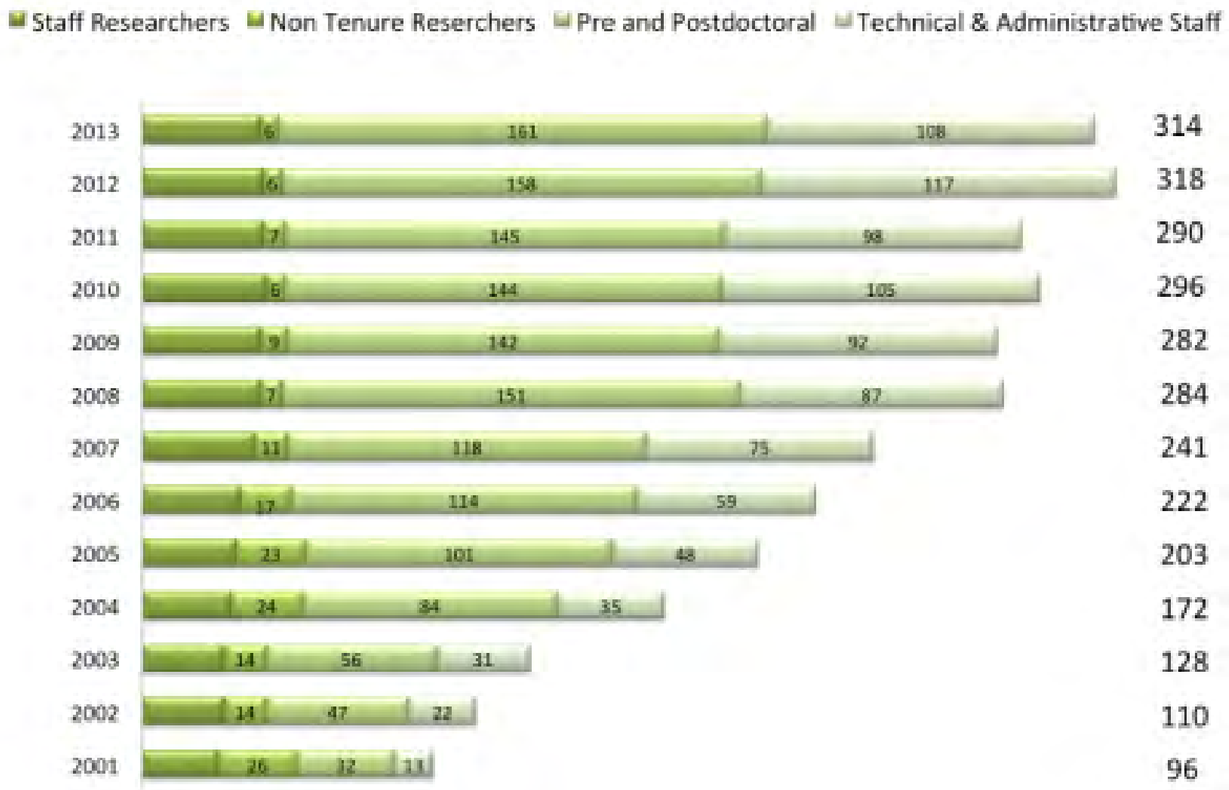
10,370
9,445
8,109
10,341
9,421
7,426
4,209
3,444
3,935

Personnel by Category



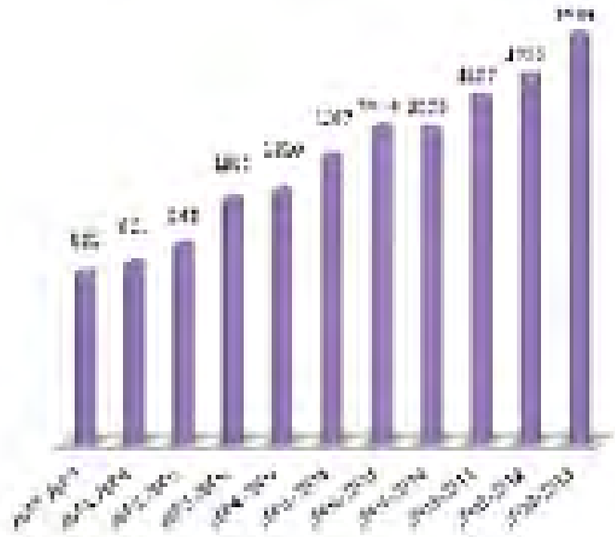
Personnel by Origin & Gender

The Institute in Numbers: Publications & impact

Evolution of Productivity Indexes (4-year intervals)

Number of Papers (ISI & non-ISI)

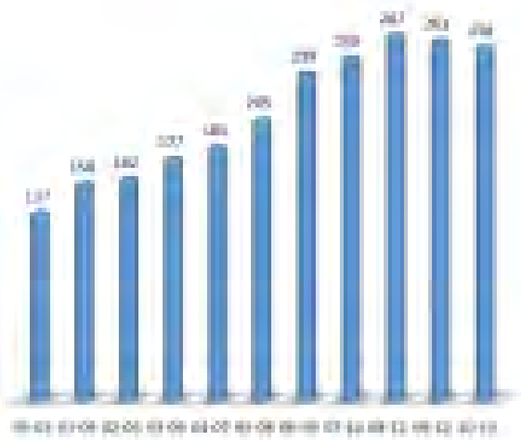
Cumulative Impact Factor



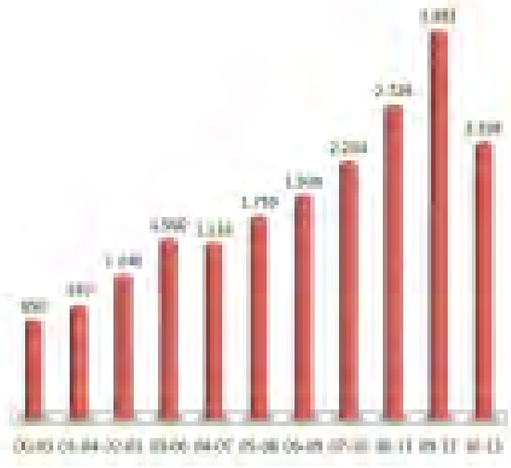
Mean Impact Factor

Productivity Indexes

Number of ISI Papers



Citations to the Period's Papers



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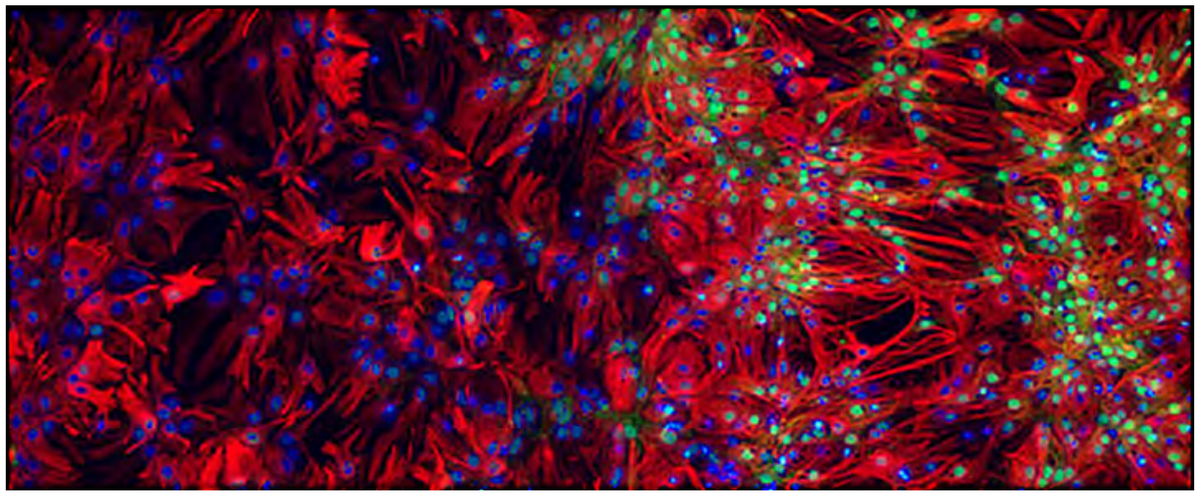
Research Units

CELLULAR AND SYSTEMS NEUROBIOLOGY

Director: M. Maravall

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



DEVELOPMENTAL NEUROBIOLOGY

Director: A. Nieto

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

MOLECULAR NEUROBIOLOGY

Director: L. M. Gutiérrez

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

Research Lines

MORPHOGENESIS

Coord: M.A. Nieto

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

SYNAPTIC TRANSMISSION & PLASTICITY

Coord: J. Lerma

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

SENSORY TRANSDUCTION

Coord: F. Viana

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

NEURONAL MIGRATION AND CIRCUIT ASSEMBLY IN THE CEREBRAL CORTEX

Coord: O. Marín

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

NERVOUS SYSTEM PATHOLOGY

Coord: S. Martínez

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

SYSTEMS NEUROBIOLOGY

Coord: M. Maravall

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

Research Groups

- Involvement of nicotinic acetylcholine receptors in chronic kidney disease
  Juan J. Ballesta
- Transcriptional and epigenetic mechanisms of neuronal plasticity
  Angel Barco
- Sensory transduction and nociception
  Carlos Belmonte, Roberto Gallego & Félix Viana
- Neurogenesis and cortical expansion
  Víctor Borrell
- Molecular control of axonal myelination
  Hugo Cabedo
- Plasticity of brain networks
  Santiago Canals Gamoneda
- PDZ proteins and signaling networks during the specification of neuronal identities
  Ana Carmena
- Molecular neurobiology of neuronal nicotinic receptors
  Manuel Criado
- Cellular and conductual neuroscience
  Carmen de Felipe
- Mechanisms of growth control and cancer in *Drosophila*
  Maria Domínguez
- Cortical development
  Alfonso Fairén
- Neurobiology and neuromodulation of the opioid actions
  Clara C. Faura Giner
- Ocular Neurobiology
  Juana Gallar & Mª Carmen Acosta
- Developmental Neurogenetics
  Luis García-Alonso
- Physiology of the cerebral cortex
  Emilio Geijo
- Mechanotransduction in mammals
  Ana Gomis
- Molecular mechanisms of neurosecretion
  Luis M. Gutiérrez & Salvador Viniegra
- Development and assembly of bilateral neural circuits
  Eloísa Herrera
- Synaptic physiology
  Juan Lerma
- Cellular & molecular mechanisms of brain wiring
  Guillermina López-Bendito
- Translational neuropsychopharmacology of neurological and psychiatric diseases
  Jorge Manzanares
- Dynamics and plasticity of cortical sensory responses
  Miguel Maravall
- Neuronal migration and circuit assembly in the cerebral cortex
  Oscar Marín
- Visual Neuroscience Laboratory
  Luis M. Martínez
- Experimental Embryology
  Salvador Martínez, Constantino Sotelo
- Cell movements in development and disease
  M. Angela Nieto
- Neural circuit formation and remodeling
  Beatriz Rico
- Altered molecular mechanism in Alzheimer's disease and dementia
  Javier Sáez Valero
- Biophysics and pharmacology of ionic channels
  Francisco Sala & Salvador Sala
- Molecular neurogenetics
  Francisco Tejedor
- Cell signalling during neuronal migration
  Miguel Valdeolmillos & Fernando Moya

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.

Involvement of nicotinic acetylcholine receptors in chronic kidney disease

Juan J. Ballesta UMH

Principal Investigator
Juan J. Ballesta

Clinical Collaborator
Carlos del Pozo

Involvement of nicotinic acetylcholine receptors in chronic kidney disease

Juan J. Ballesta UMH

Selected Publications

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

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

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

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

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

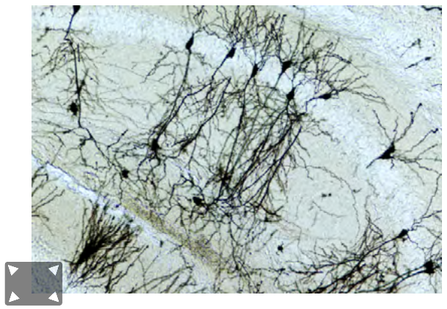
Transcriptional and epigenetic mechanisms of neuronal plasticity & bits

Angel Barco CSIC

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

Role of activity-dependent gene expression in neuronal plasticity. Alterations in patterns of gene expression are thought to underlie the long-lasting changes in the strength of synaptic connections between neurons responsible for the encoding of memories in the nervous system. A number of transcription factors have been involved in this process. We are investigating the details of the participation of the CREB family of transcription factors, as well as other activity-regulated transcription factors, in plasticity and memory using a multidisciplinary approach that combines mouse genetics, molecular and cellular biology, electrophysiology and behaviour. We also apply genome-wide analytical approaches, such as genearrays and ChIPseq, for identifying candidate genes important in these processes.

Chromatin modification and neuronal plasticity. Histone modification is a well-known mechanism for the regulation of gene expression. Specifically, the acetylation and methylation of nucleosomes provides a mechanism for epigenetic regulation of the activity of loci that are relevant in neuronal plasticity and behaviour. We are interested in exploring the contribution of histone modifications to learning, memory and other long-lasting modification of the animal's behaviour. We also investigate on different mouse model for neurological conditions, such as Huntington disease and some intellectual disability syndromes, in which these epigenetic mechanisms seem to be affected.



Transcriptional and epigenetic mechanisms of neuronal plasticity & bits

Angel Barco CSIC

Principal Investigator
Angel Barco

Associated Investigator
Luis M. Valor

PhD Investigator
Satomi Ito
José P. López-Atalaya
Sven Parkel

PhD Student
Manuel Alcaraz
Anna Fiorenza
Deisy Guiretti
Michal Lipinski
Victor Rovira
Marilyn Scandaglia

Technical Staff
Román Olivares

LV SI J L-A SP AF DG ML MS VR RO

Transcriptional and epigenetic mechanisms of neuronal plasticity & bits

Angel Barco CSIC

Selected Publications

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*

Gruart A, Benito E, Delgado-Garcia JM and Barco A. (2012) **Enhanced cAMP Response Element-Binding Protein Activity Increases Neuronal Excitability, Hippocampal Long-Term Potentiation, and Classical Eyeblink Conditioning in Alert Behaving Mice.** J Neurosci *32(48): 17431-41.*

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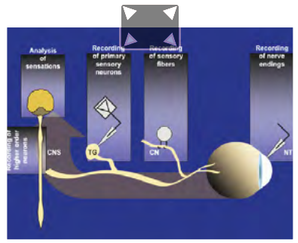
Sensory transduction and nociception

Carlos Belmonte UMH

Roberto Gallego UMH

Félix Viana CSIC



CB

Mammalian somatic sensory receptors are structures specialized in the detection of thermal, mechanical and chemical stimuli, both innocuous and noxious, that impinge upon the organism during changes in the external or internal environment. Activation of these receptors by specific stimuli gives rise to an electrical signal proportional to the intensity and duration of the stimulus.The neural information 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 especially interested in identifying 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 molecular analysis of transduction ion channels and receptor molecules, to recordings of sensory nervous activity in isolated cells, "in vitro" preparations and anesthetized animals.

We are analyzing the problem of sensory transduction at different conceptual levels. From a reductionist point of view, we are trying to establish which transduction molecules and which cellular mechanisms give rise to the preferential response to a particular stimulus and how they are modulated. In a more integrative approach, we are also trying to define the functional relationships between different transduction molecules, the ion channels involved in neuronal excitability and intracellular signal transduction pathways in sensory receptor neurones. 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. The analysis includes the search for selective pharmacological agents capable of interfering with the different steps of the transduction process or their modulatory mechanisms. An additional important research line of our group involves the analysis of the short- and long-term cellular and molecular changes that occur in primary sensory neurons during pathological process such as lesions and inflammation.

RG

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

FV

Sensory transduction and nociception

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Research Group

Sensory transduction and nociception

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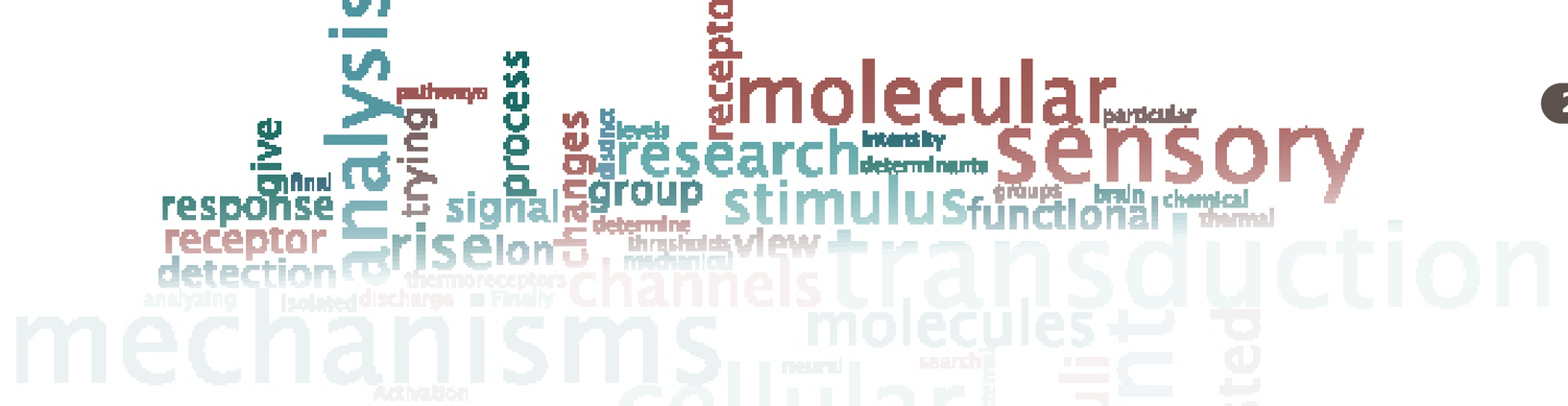

Selected Publications

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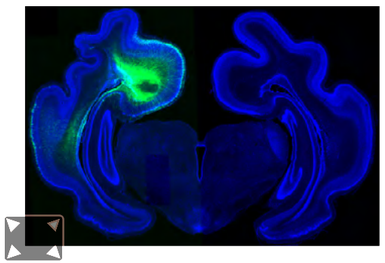
Neurogenesis and cortical expansion

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.

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.



Neurogenesis and cortical expansion

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Neurogenesis and cortical expansion

Víctor Borrell CSIC

Selected Publications

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*

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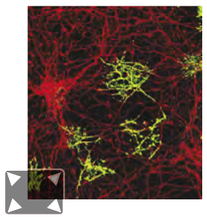
Molecular control of axonal myelination

Hugo Cabedo UMH

Myelination of the peripheral nervous system depends on the appropriate signalling between neurons and Schwann cells. By exposing proteins on the axon surface, neurons control the proliferation, survival and myelination capability of Schwann cell precursors in the peripheral nerves. The most relevant of these factors belong to the neuregulin family of proteins, encoded by NRG1. Axon surface exposed neuregulin activates erbB2 and erbB3 receptors in Schwann cell plasma membrane and elicit intracellular signaling pathways. More than fifteen splicing forms of NRG1 have been described. However, only the neuregulins with a cystein rich region (type III neuregulins) seem to have a promyelinating effect. It is probably because, in contrast to the rest of proteins of this family, type III neuregulins are retained on the axon membrane acting in a juxtacrine way on the neighbouring glial cells. To get further insight in the role of the different splicing forms of NRG1 in vivo we have recently developed transgenic mice expressing the sensory and motor-neuron derived factor (SMDF, a type III neuregulin) under the control of rat neuronal enolase promoter (NSE-SMDF mice). A preliminary examination shows that the transgen has profound effects on the PNS of these mice. The thickness of the peripheral nerves is notably increased, resembling the nerves from patients affected by neurofibromatosis (a human genetic disease with a high prevalence). In addition the microscopic structure of these nerves is also severely altered. Surprisingly (and again recapitulating neurofibromatosis) approximately 15% of these mice develop big peripheral nervous system tumours, which finally produce paralysis and other neurological symptoms.

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



Molecular control of axonal myelination

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Molecular control of axonal myelination

Hugo Cabedo UMH

Selected Publications

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.*

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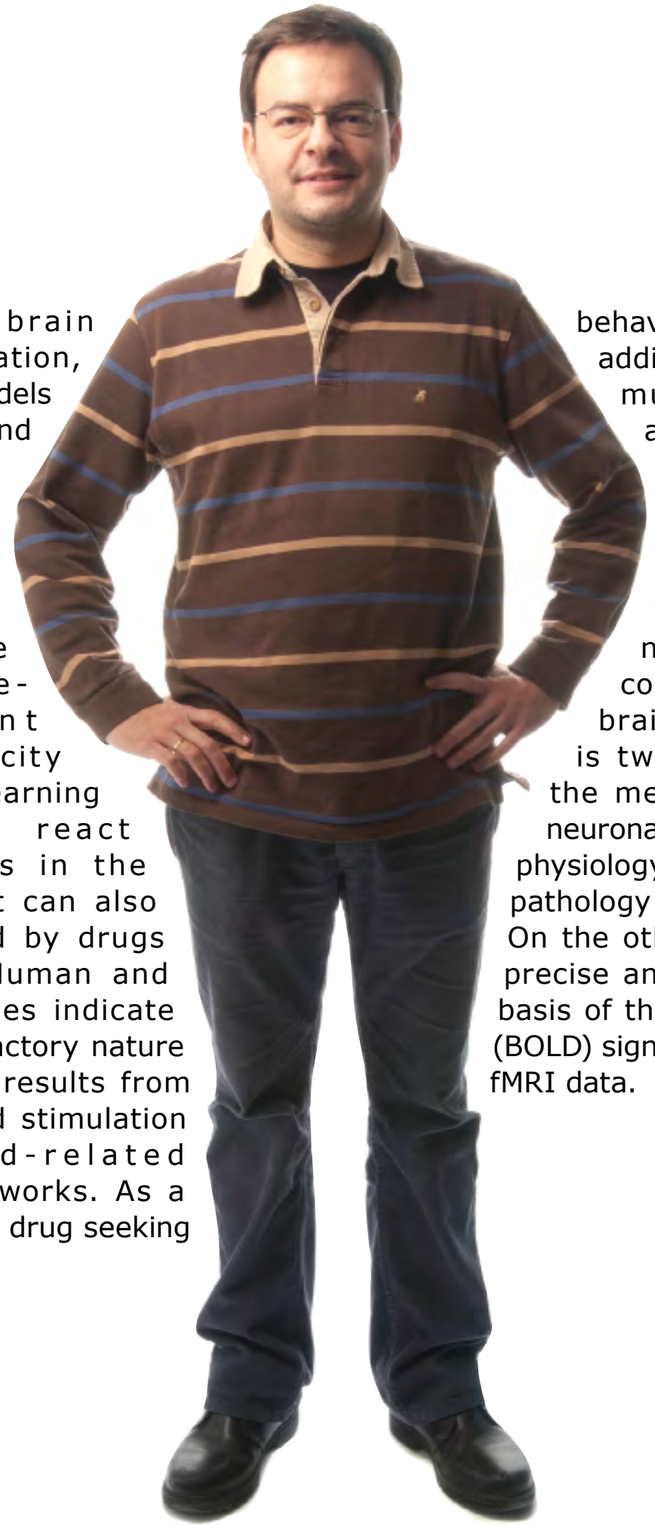
Plasticity of brain networks

Santiago Canals Gamoneda CSIC

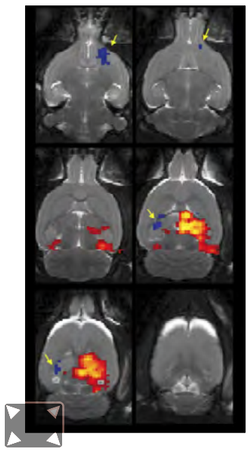


A fast response to changes in environmental conditions increases the fitness and reproductive success of organisims. The work of our group focuses on two research lines: plasticity of brain networks and brain energetics.

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.



Plasticity of brain networks

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Plasticity of brain networks

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Selected Publications

Mishra, A., Schuz, A., Engelmann, J., Beyerlein, M., Logothetis, N.K., Canals, S. (2011) **Biocytin-Derived MRI Contrast Agent for Longitudinal Brain Connectivity Studies.** **ACS Chem. Neurosci.** *2(10):578-87*

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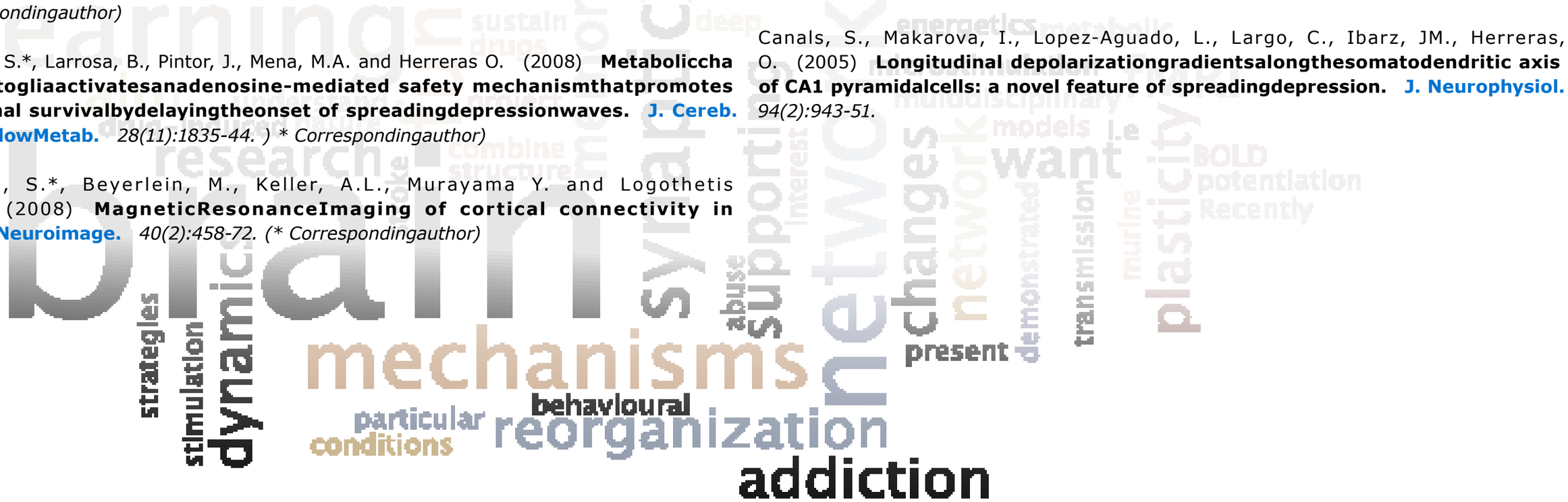
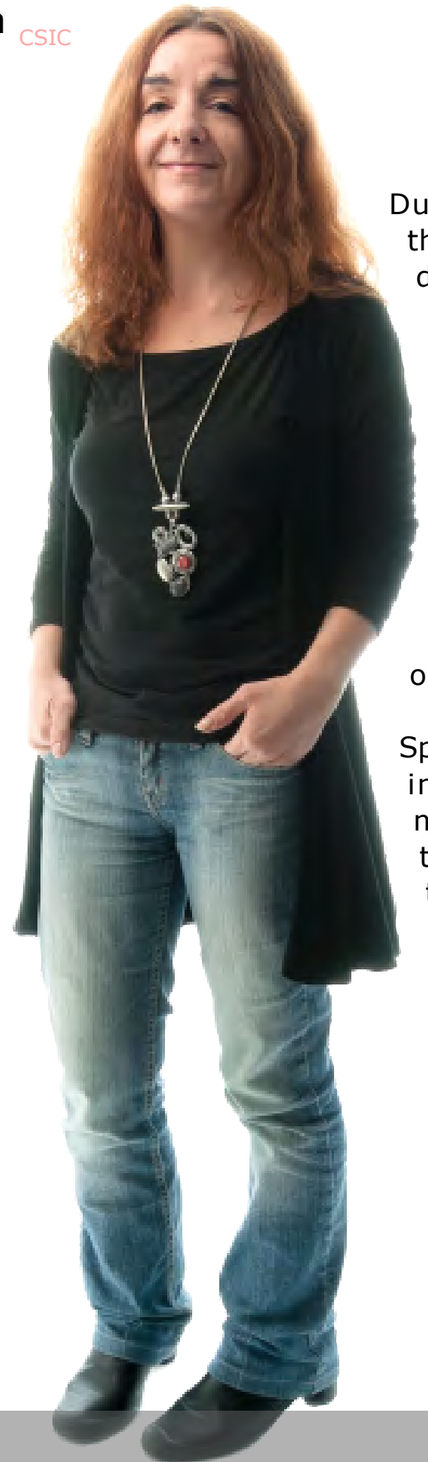


PDZ proteins and signaling networks during the specification of neuronal identities

Ana Carmena CSIC

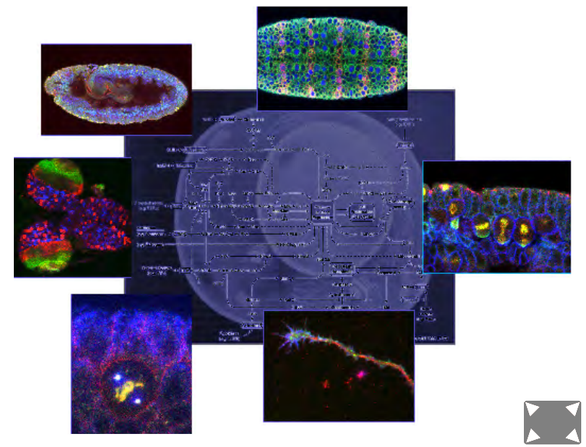


During the development of the nervous system a great diversity of neuronal types is generated. In fact, the human brain has more than 100,000 millions of neurons, most of them specified during the embryonic development. Unravelling the molecular mechanisms that underlie the acquisition of neuronal identities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

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

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

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



PDZ proteins and signaling networks during the specification of neuronal identities

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PDZ proteins and signaling networks during the specification of neuronal identities

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Selected Publications

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

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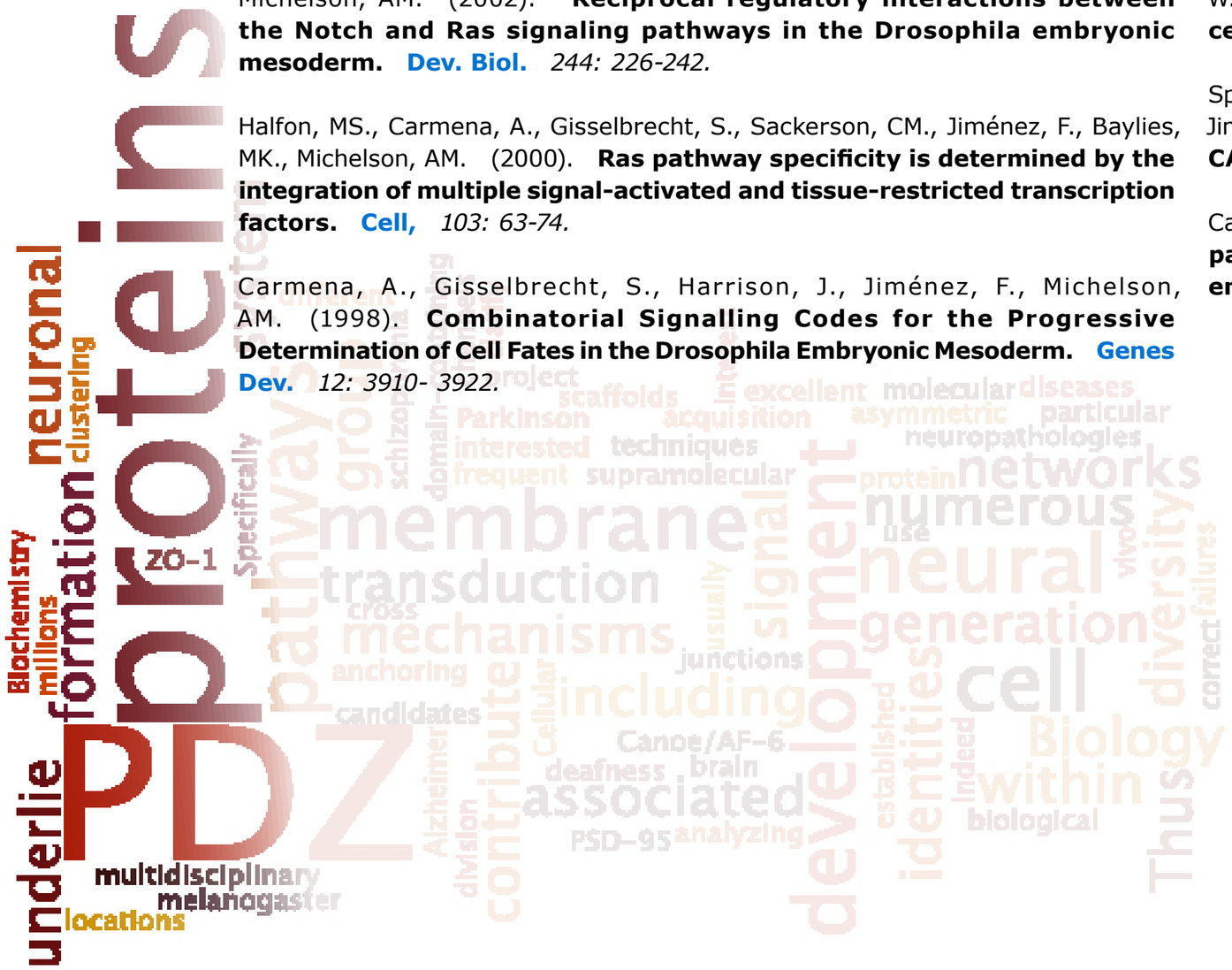
PDZ proteins and signaling networks during the specification of neuronal identities

Ana Carmena CSIC



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Molecular neurobiology of neuronal nicotinic receptors

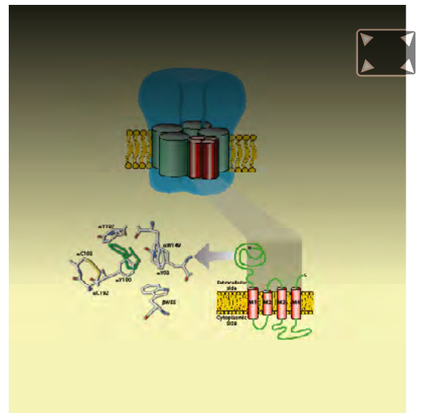
Manuel Criado UMH

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

- 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.



Molecular neurobiology of neuronal nicotinic receptors

Manuel Criado UMH

Principal Investigator
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Technical Staff
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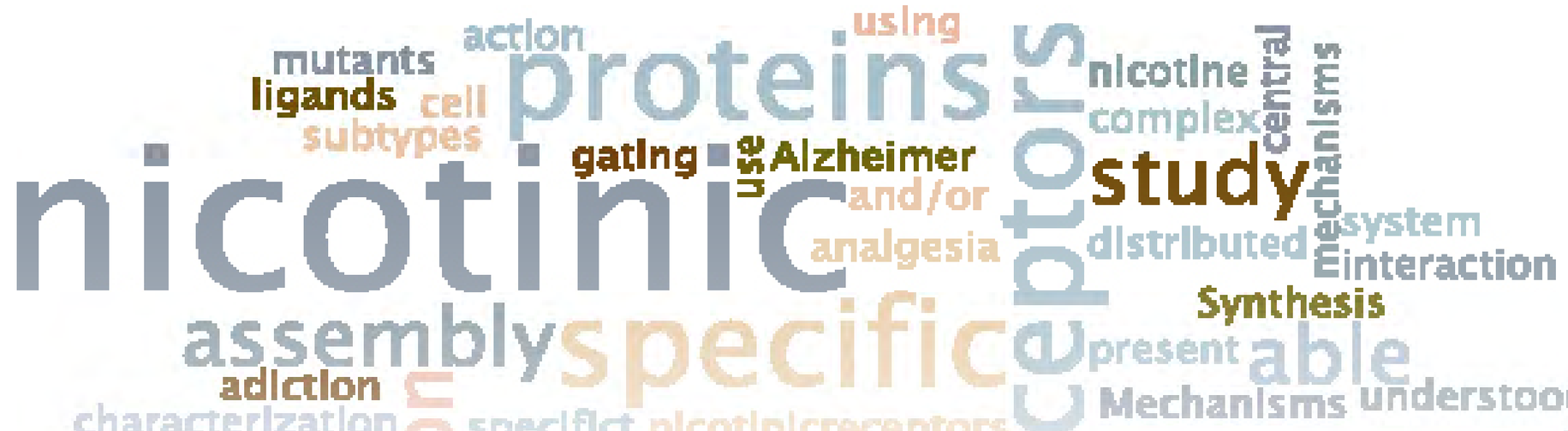
SG

Molecular neurobiology of neuronal nicotinic receptors

Manuel Criado UMH



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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*

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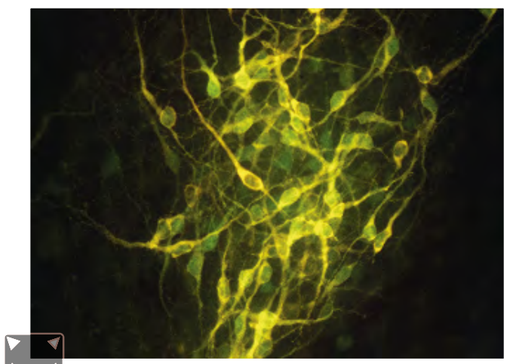
Cellular and conductual neuroscience

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.



Cellular and conductual neuroscience

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Cellular and conductual neuroscience

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Selected Publications

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*

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Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

Our studies are focused on three research projects:

Systemic and local control of organ growth: Animal size is remarkably constant within species and this constancy is even more striking when we consider the coincidence in size of the left and right sides of bilaterian organisms. To attain such precision, growing organs must be capable to sense and communicate their growth to other organs in the organism and to have flexibility to adjust their growth programmes and maturation to repair any disturbances occurring during ontogeny. How they do so have remained a mystery over the past decades. We are addressing this long-standing unresolved question in the imaginal discs of the fruit fly *Drosophila melanogaster*, which are known to have a remarkable flexibility to regulate their size, particularly when they suffer lesions. This year, we reported the identification of a novel insulin-like peptide (*Drosophila* insulin-like peptide 8, DILP8) that appears to mediate the plasticity of growth and maturation time that ensures the proper final size, proportions, and the symmetry in *Drosophila melanogaster*.

At the organ level, the proper control of growth is linked to specialized domains known as "organizers" (i.e. conserved signalling centres). Local activation of Notch and Hedgehog signalling pathways along the dorsal-ventral (DV) and anterior-posterior (AP) axes, respectively, of the growing organs establish these organizers. The DV and AP organizers emit signals that promote global organ growth, patterning and cell fate specification. Intriguingly, similar organizing signals are used repeatedly to promote growth and patterning in widely different organs (e.g. the neural tube, somites, limbs, eyes, etc.). This raises the question of how organ specificity is achieved. Moreover, dorsal-ventral and anterior-posterior organizers promote growth non-redundantly within an organ; yet hoe the distinct organizing signals are integrated to ensure proper final growth remains unknown. Using the powerful genetic tools available in *Drosophila melanogaster*, we have shown that specificity is achieved through the activation of the organ-specific transcription factor, Eyegone [homologue of human PAX6(5a)] and the secreted factor Four-jointed [Fjx in vertebrates]. We have shown that Eyegone is necessary and sufficient to mediate the specific growth response of Notch in the eye. Eyegone encodes a member of the PAX-family of oncogenes, but it differs from the canonical members in that Eyegone protein has a truncated paired

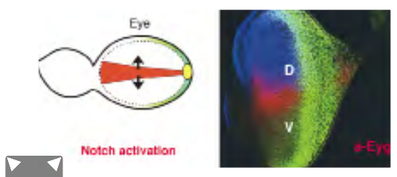
Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

domain —a conserved DNA-binding domain that is presumed to be essential for PAX-associated oncogenic activity. Strikingly, we found that overexpression of human PAX6 (5a), which is structurally related to Eyegone, induces tumours in vivo, whilst the canonical and previously presumed oncogenic PAX6 variant hardly affects growth in vivo. Our findings also redefine the process of organizer formation and function, and they identify Four-jointed as a regulatory node integrating global growth control by Notch organizer and the cell-autonomous control by the tumour suppressor pathway Hippo/MST.

Genetic screens for novel tumour-inducing genes: Over eight years ago, we started complementary high-throughput (gain-of- expression and RNA interference-based) screens for genes that facilitate tumorigenesis by the Notch signal transduction pathway. Through these screens, we identified key genes required for tissue growth control and cancer (see publications). These included two novel epigenetic repressors, Pipsqueak and Lola, that when coupled with Notch overactivation, act as decisive factors in promoting tumour growth and metastases through silencing of the Retinoblastoma-family-protein (Rbf) gene. More recently, we have shown that Notch cooperates with the Pten/PI3K/AKT pathway in promoting tumour invasion. Interestingly, the Notch/Pten/Akt axis is conserved during human leukemogenesis. Our collaborators in the Institute for Cancer Genetics in Columbia (USA), Dr Ferrando and Dr. Palomero, have shown that loss of Pten is responsible for resistance of T-cell acute lymphoblastic leukemic cells to inhibitors of the Notch pathway. In colaboration with Dr. Borggrefe at the Max Planck Institut in Frieburg, we have shown that the histone demethylase Lid/KDM5A is a core component of Notch silencing complex in tissue growth and tumroigenesis and the conserved microRNA miR-200c/miR-8 as a key regulador of Notch pathway activity in development and metastático cancers. More recently, we have shown that downregulation of the histone methyltransferase E(z) facilitates tumorigenesis by the Notch signalling pathway. This mechanism is conserved during human leukemogenesis. Together these data link, for the first time, the Notch signal transduction pathway to the epigenetic silencing pathways, the Pten/PI3K/AKT pathway and the cell-cycle control during the process of tumorigenesis.

Imaging tumour invasion and metastasis: The fruit fly *Drosophila melanogaster* has been a workhorse of genetics and developmental biology for almost a century, but its true potential for the genetic and cell biology analysis of tumour metastasis has only recently been realised. We are using genetic, molecular and cellular methods to study the initiating steps and key genes involved in the transformation of normal healthy cells into cancerous cells capable of metastasing in vivo.



Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

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SJC


EB


IOA


IOA

Research Group

Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

Selected Publications

Morante J.*, Vallejo DM., Desplan C. & Dominguez M.* (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*

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Research Group

Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

Dominguez M and F Berger. (2008). **Chromatin and Cell Cycle meet in Madrid.** **Development.** *135(21):3475-80.*

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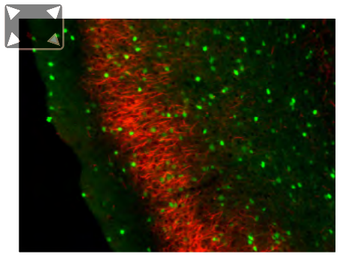
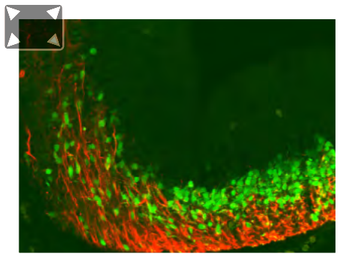
Cortical development

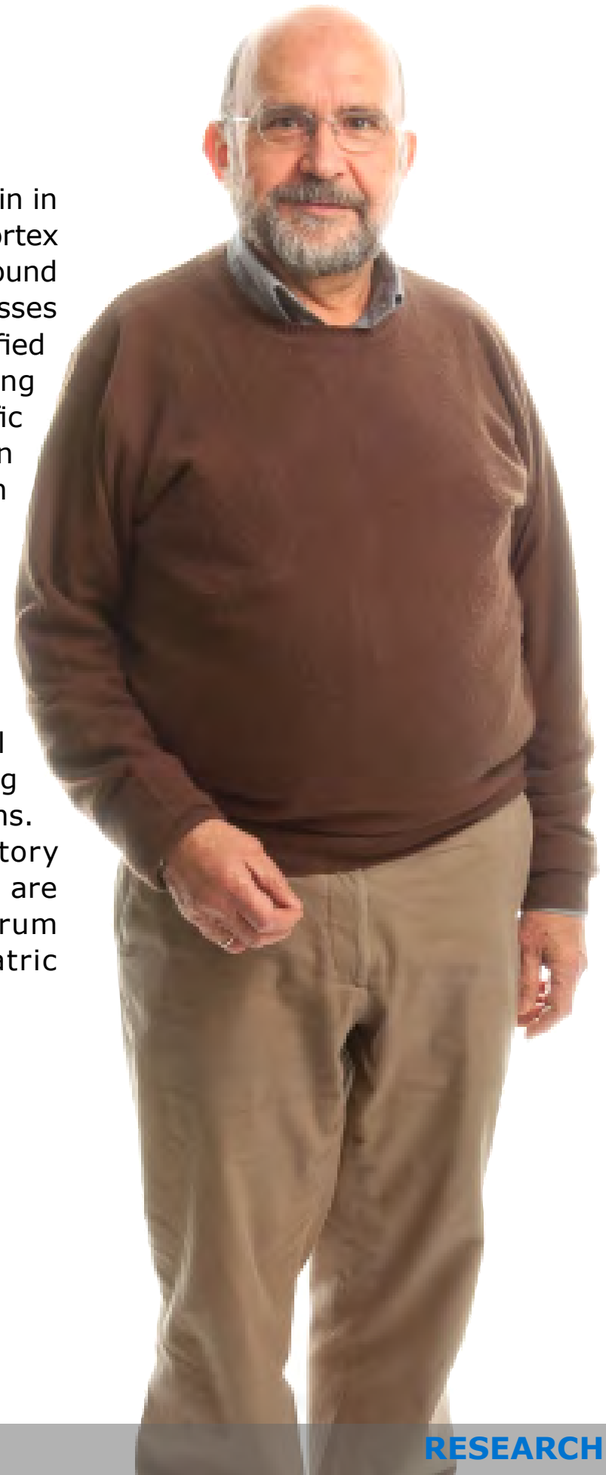
Alfonso Fairén CSIC





Brain function depends on the ordered integration of neurons into microcircuits during development. Our interest has focused on cortical development. First, we are studying the early-differentiating, transient neurons that play functional roles in the development of the cerebral cortex. One of these groups of neurons is formed by Cajal-Retzius cells. These cells synthesize and secrete Reelin, an extracellular matrix molecule that controls the correct laminar organization of the cerebral cortex. We are analyzing the possible roles of second messenger cascades in the control of Reelin processing and secretion by Cajal-Retzius cells. We are also trying to characterize in molecular terms the Cajal-Retzius cells originated in the thalamic eminence versus those of different embryonic origins. Another group of early neurons is formed by neurons whose axons project to the subpallium. These neurons reside first in the preplate, a transient compartment of the pallial anlage and then in the subplate after preplate partition. However, some of these early projecting neurons never associate with the subplate but remain in the marginal zone of the developing cortex along the prenatal period. We have found that the axonal projections of subclasses of early cortical neurons have diversified anatomical distributions in developing rodent brains. However, such specific topographic projections have not been identified yet in other mammalian species. We aim at a comparative approach to these neuronal populations in other mammalian species including humans.

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



Cortical development

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BAB

Cortical development

Alfonso Fairén CSIC

Selected Publications

Espinosa, A., Gil-Sanz, C., Yanagawa, Y., Fairén, A. (2009) **Two separate subtypes of early non-subplate projection neurons in the developing cerebral cortex of rodents.** **Frontiers in Neuroanatomy,** *3:27. doi:10.3389/neuro.05.027.2009.*

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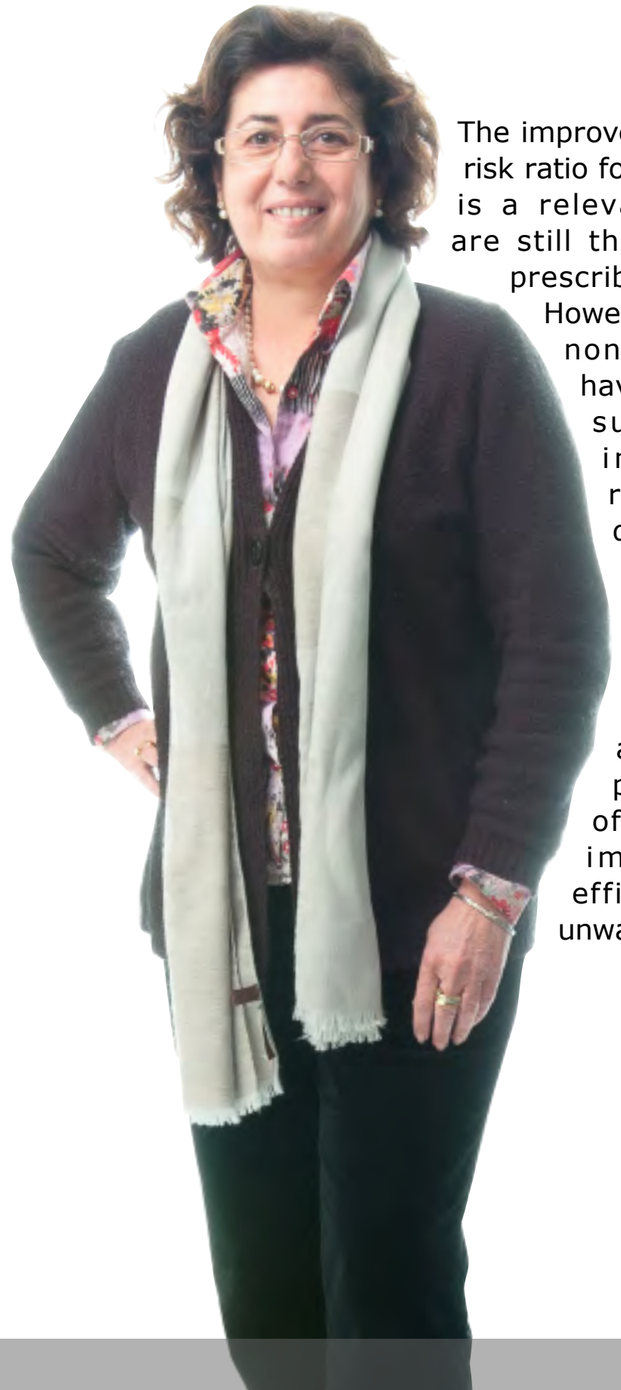
Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH



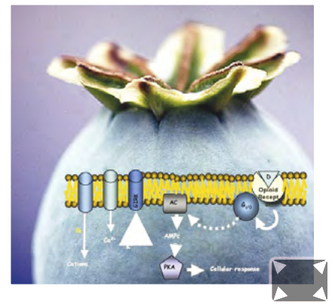
The improvement in the benefit–risk ratio for analgesic therapies is a relevant issue. Opioids are still the most potent and prescribed analgesic drugs. However, their clinical and non-clinical uses still have serious problems such as variability in the analgesic response, tolerance, dependence, addiction 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.

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)



Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH

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Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH

Selected Publications

J J Ballesta, J Cremades, M Rodríguez-Muñoz, J Garzón C CFaura. (2012) **Sensitivityto μ Opioid Receptor MediatedAntinociceptionisDeterminedby Cross−regulationBetween and OpioidReceptors at Supraspinallevel.** **Br J Pharmacol** *DOI: 10.1111/j.1476-5381.2011.01750.x*

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Ocular Neurobiology

Juana Gallar UMH

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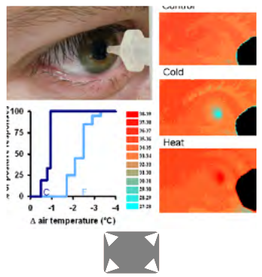
JG

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.

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

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



MCA

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Ocular Neurobiology

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Mª Carmen Acosta UMH

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Ocular Neurobiology

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Selected Publications

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*

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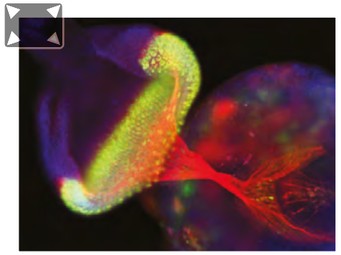
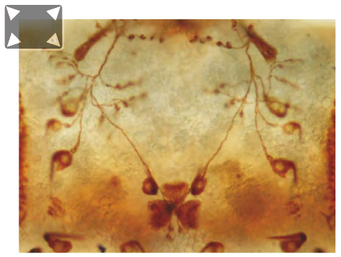
Developmental Neurogenetics

Luis García-Alonso CSIC





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

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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Developmental Neurogenetics

Luis García-Alonso CSIC

Selected Publications

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*

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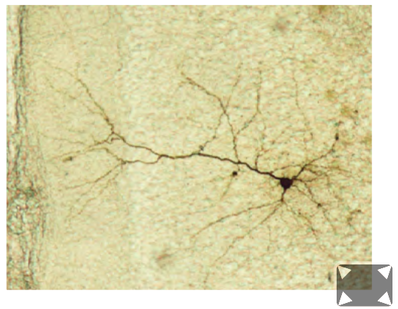
Physiology of the cerebral cortex

Emilio Geijo UMH

Our group is interested in the study of the basic physiological mechanisms of the cortical local microcircuits, in particular of the prefrontal cortex and the anterior cingulated cortex; These cortical areas are implicated in cognitive functions and very specially in short term memory or working memory; also, they are densely innervated by dopaminergic and serotoninergic fibers originated in the diencephalon and brainstem which contribute to the modulation of cortical functions. We use intracellular recording with patch electrodes and microelectrodes in pyramidal and non-pyramidal cortical neurons visually identified with infrared video microscopy and Nomarski optics; in these neurons we record membrane potential and currents and synaptic responses. The specific objectives of our work are the study of: i) the intrinsic electrophysiological properties of pyramidal and non-pyramidal neurons and their modulation by dopamine and serotonin. ii) the mechanisms of excitatory and inhibitory synaptic transmission in the cortex, the modulation of these mechanisms by dopamine and serotonin and the role of intrinsic properties in the mechanisms of synaptic integration. iii) the electrophysiological responses of a mouse genetically modified that is a model of a human cerebral disease: the Lis1 gene mutant mouse (in man, the mutations of the LIS1 gene produce lissencephaly). The experimental work focused on the last objective is carried out in collaboration with Dr Salvador Martínez (Institute of Neurosciences).

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



Physiology of the cerebral cortex

Emilio Geijo UMH

Principal Investigator
Emilio Geijo

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VR

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Physiology of the cerebral cortex

Emilio Geijo UMH

Selected Publications

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

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Mechanotransduction in mammals

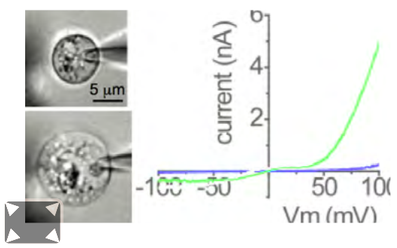
Ana Gomis CSIC

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

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

This project will focus on the characterisation, in cultured neurons of the trigeminal and dorsal root ganglion, of cells that respond to low and to high intensity mechanical stimuli. In parallel, we will work on the identification and characterisation of the responses of the TRP channels evoked by mechanical stimulus. Several stretch activated TRP channels have been cloned recently and the TRPs channels are firm candidates to be sensory mechanotransducction channels. We use single cell electrophysiology and Ca^{2+} imaging at sensory neurones and after transfection of TRP channels in mechanically insensitive HEK293 cells. Moreover, we use molecular biology approaches in collaboration with the sensory transduction and nociception group.

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



Mechanotransduction in mammals

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Mechanotransduction in mammals

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Selected Publications

Imane Jemal, Sergio Soriano, Anna Lucia Conte, Cruz Morenilla and Ana Gomis (2013) **G protein-coupled receptor signalling potentiates the osmo-mechanical activation of TRPC5 channels** **Pflugers Arch - Eur J Physiol** *DOI:10.1007/s00424-013-1392-z*

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.** **PLoS One** *8, e81618-32*

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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.*

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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*

Xiangdong Chen, Edmund M. Talley, Nitin Patel, Ana Gomis, William E. Mcintire, Biwei Dong, Félix Viana, James C. Garrison and Douglas A. Bayliss. I (2006) **Inhibition of a background potassium channel by Gq-protein alpha-subunits** **Proc Natl Acd Sci USA.** *103:3422-3427*

Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH

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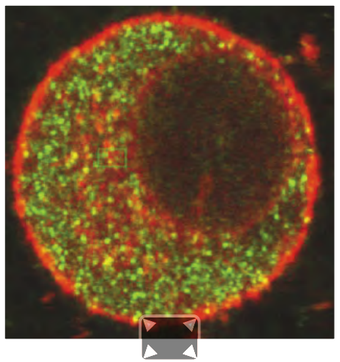
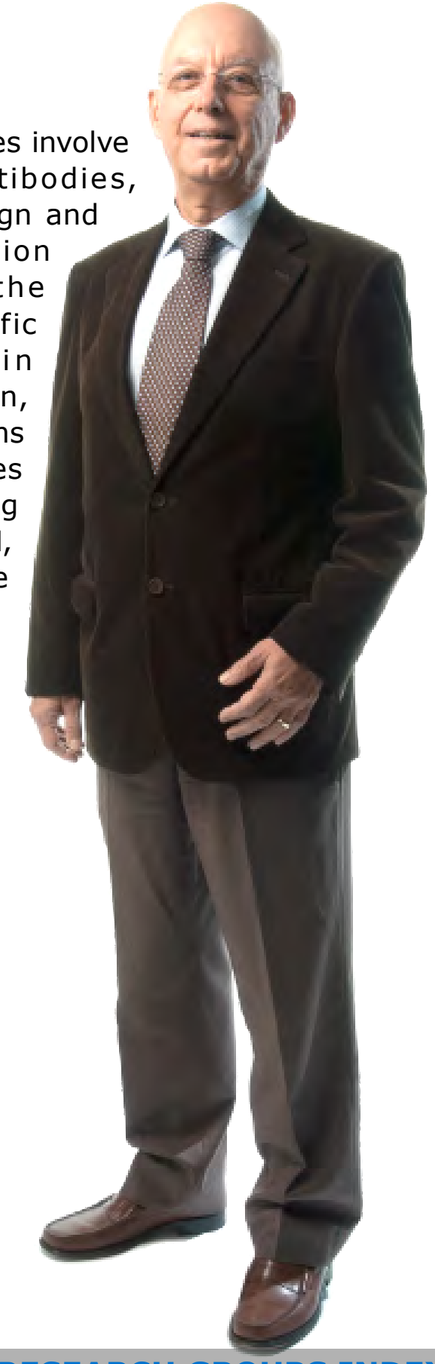
Adrenomedullary chromaffin cells have been used as an excellent experimental model to study the exocytosis and therefore the molecular mechanisms of neuro-transmission. It is now clear that the proteins involved in the processes of vesicle docking, membrane fusion and neurotransmitter release are common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

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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Molecular mechanisms of neurosecretion

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Molecular mechanisms of neurosecretion

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Selected Publications

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*

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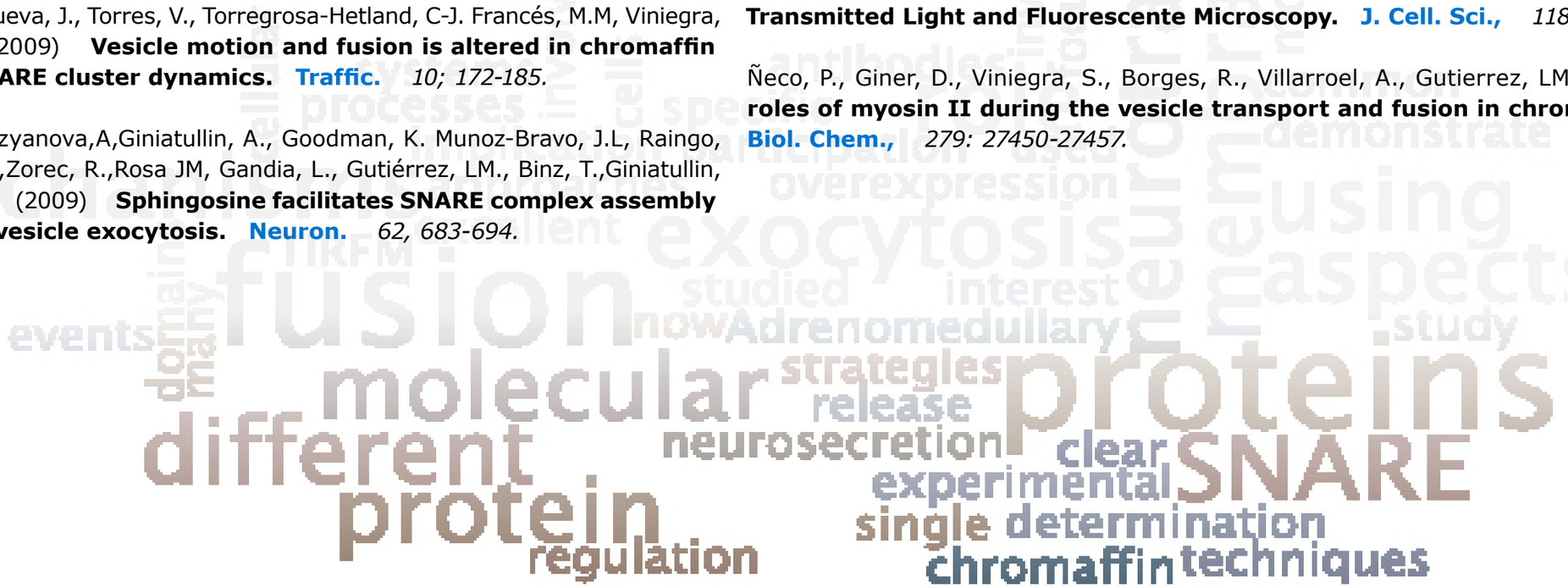
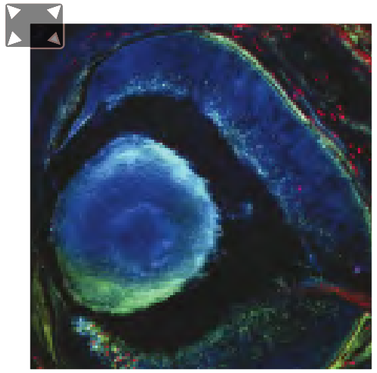


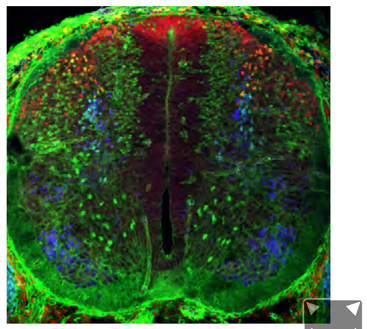
Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC



Most metazoans are bilaterally symmetric and many features of mature neural function including the interpretation of sensory information and the coordination of locomotion depend on the coherent communication between the two brain hemispheres. In order to integrate sensory information from both sides of the body and then elaborate a coordinated response, the nervous system requires both axons crossing at the midline and axons remaining in the ipsilateral side of the brain. Alterations in the axonal decision of crossing the midline or in the assembly of bilateral inputs in the brain may perturb the proper establishment of laterality in the nervous system circuitry leading for instance, to pathological consequences in vision or motor coordination.

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



Development and assembly of bilateral neural circuits

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Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Selected Publications

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*

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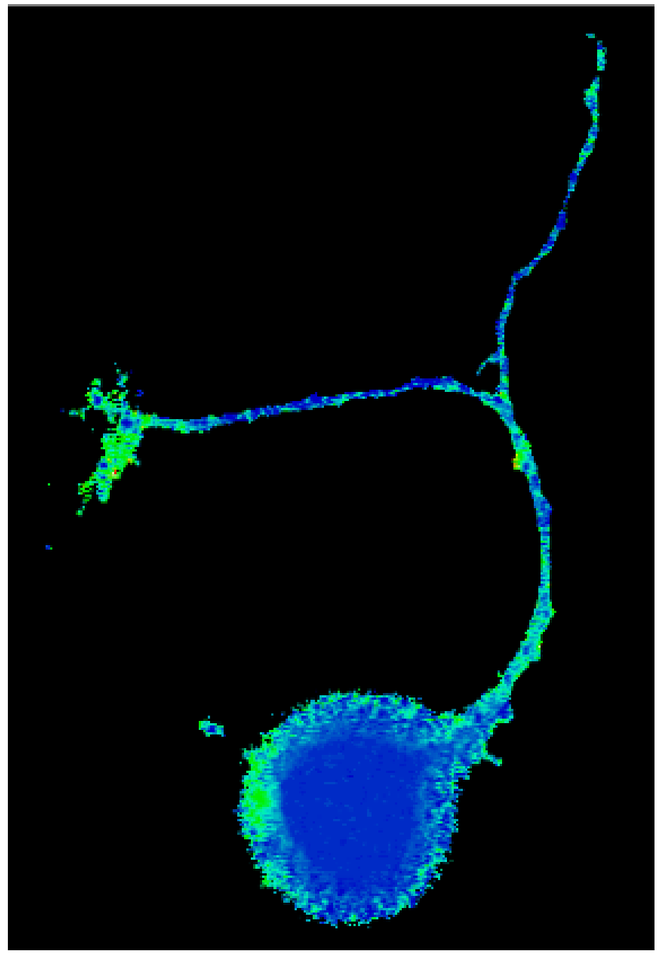
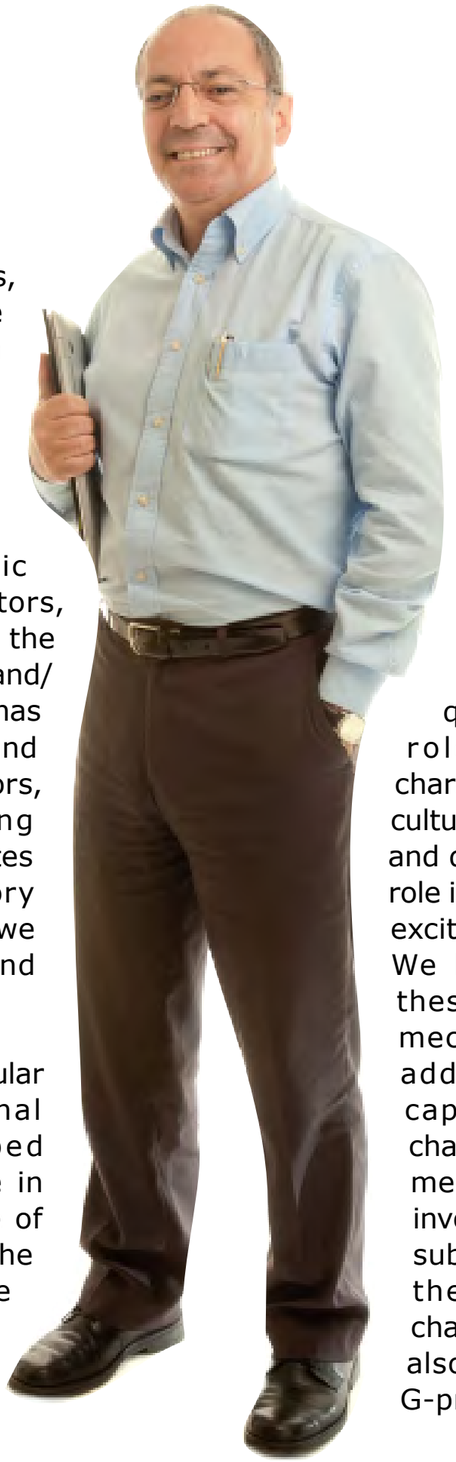
Synaptic physiology

Juan Lerma CSIC

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



In the frame of defining the molecular structures mediating neuronal communication, we described for the first time the existence in central neurons of another type of functional glutamate receptors, the kainate receptor (KAR). We have demonstrated that KAR proteins form functional receptor channels in hippocampal neurons and also provided the tool by which these receptors could be further studied, the drug 2-3-benzodiazepine, GYKI 53655, which allows its pharmacological isolation. Indeed, this finding paved the way for progress in the field. Since then, we and other groups have addressed specific questions on the functional role of KARs. We have characterized these receptors in cultured neurons and brain slices and described their fundamental role in controlling neuronal tissue excitability and epileptogenesis. We have demonstrated that these receptors have a dual mechanism for signalling: in addition to their expected capability of acting as ion channels, they trigger a second messenger-mediated cascade, involving a G-protein. This and subsequent work put forward the new concept that ion channel-forming receptors are also able to signal through a G-protein, opening new vistas

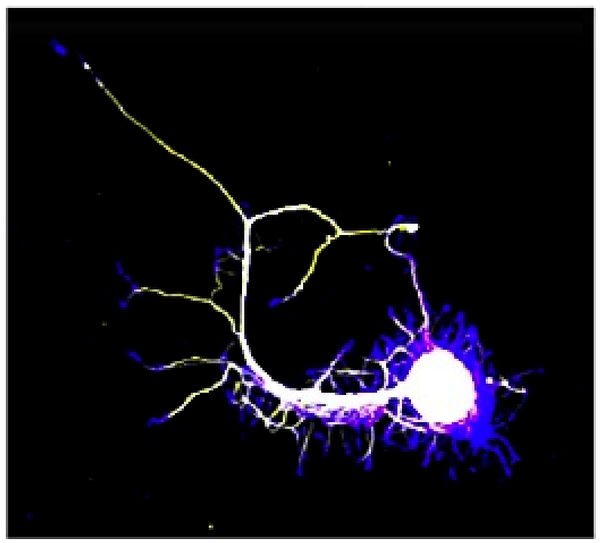


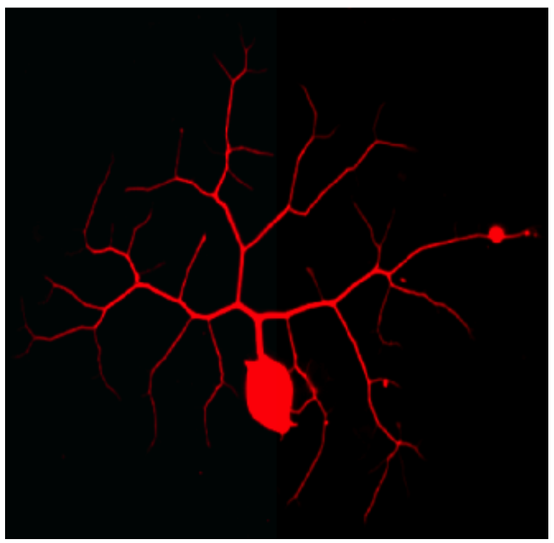
Synaptic physiology

Juan Lerma CSIC

on the mechanisms by which glutamate receptors of the ionotropic type work. Taken together, our data has helped to understand why KAR activation is proconvulsive and pointed them as targets for new treatments of epileptic disease.

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





Synaptic physiology

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Research Group

Synaptic physiology

Juan Lerma CSIC

Selected Publications

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*

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Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

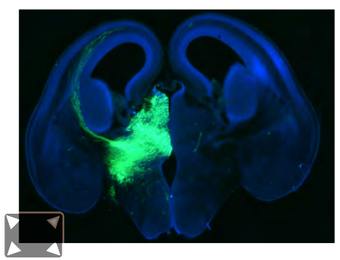
Our research team runs several related projects studying the cellular and molecular mechanisms involved in the development of axonal connections in the brain. In particular, our aim is to uncover the principles underlying thalamocortical axonal wiring, maintenance and ultimately the rewiring of connections,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

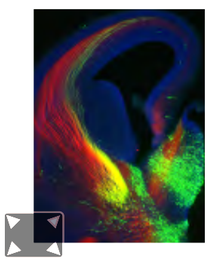
The development of the thalamocortical wiring requires a precise topographical sorting of its connections. Each thalamic nucleus receives specific sensory information from the environment and projects topographically to its corresponding cortical. A second level of organization is achieved within each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

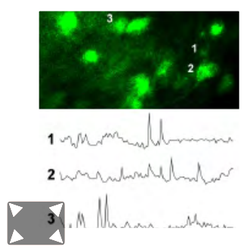
Three major questions are been focused in the laboratory: i) the transcriptional control of thalamocortical topography; ii) integration of distinct signalling pathways in thalamocortical behaviour; and iii) the activity-dependent mechanisms involved in thalamocortical guidance and wiring.

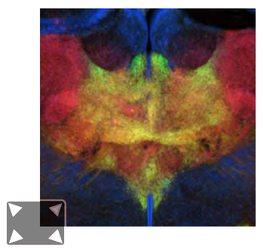
Within these projects we are using several experimental programmes, these include: optical imaging, manipulation of gene expression in vivo, cell and molecular biology, biochemistry, cell culture and electrophysiology. Furthermore, our team has successfully set up the technique of in utero electroporation to specifically target dorsal thalamic neurons in vivo. We have also used gain- and loss-of-function experiments to help unravel new mechanisms involved in the guidance of this major axonal tract (see 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.









Cellular & molecular mechanisms of brain wiring

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CMS

LMRM

RSC

HCM

Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications

Benjumeda I, Escalante A, Law C, Morales D, Chauvin G, Muça G, Coca Y, Márquez J, López-Bendito G, Kania A, Martínez L, Herrera E. (2013) **Uncoupling of EphA/ephrinA signaling and spontaneous activity in neural circuit wiring.** **J Neurosci.** *Nov 13;33(46):18208-18*

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*

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Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

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.*

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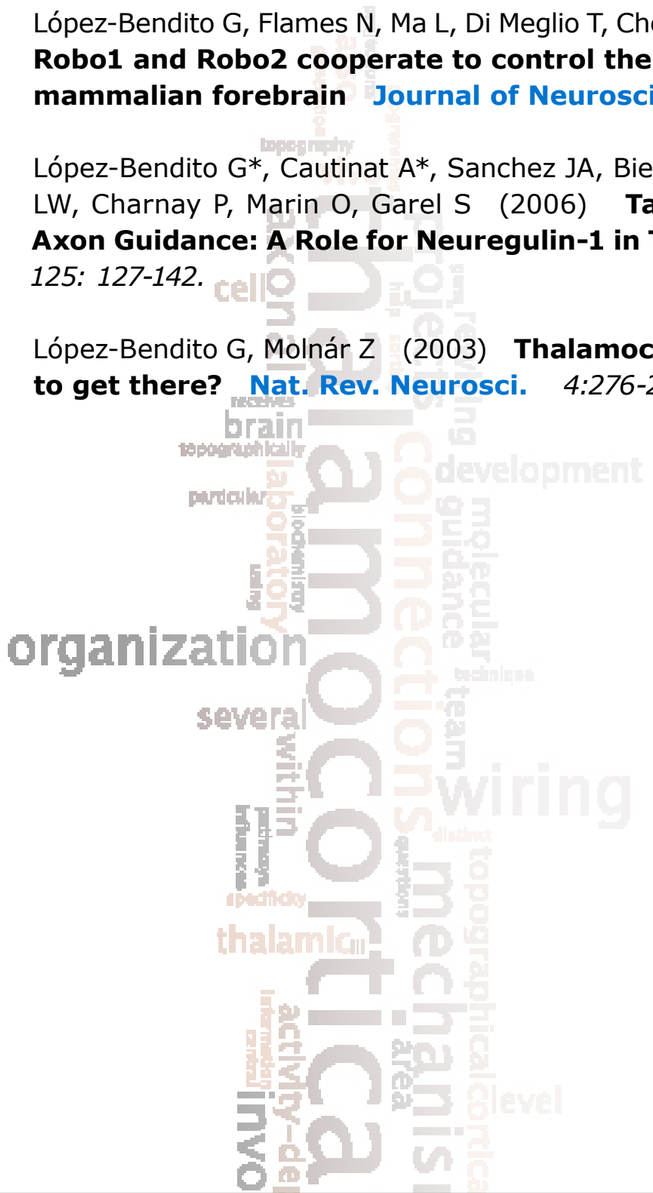

Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

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

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

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

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

Translational neuropsychopharmacology of neurological and psychiatric diseases

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Translational neuropsychopharmacology of neurological and psychiatric diseases

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Selected Publications

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*

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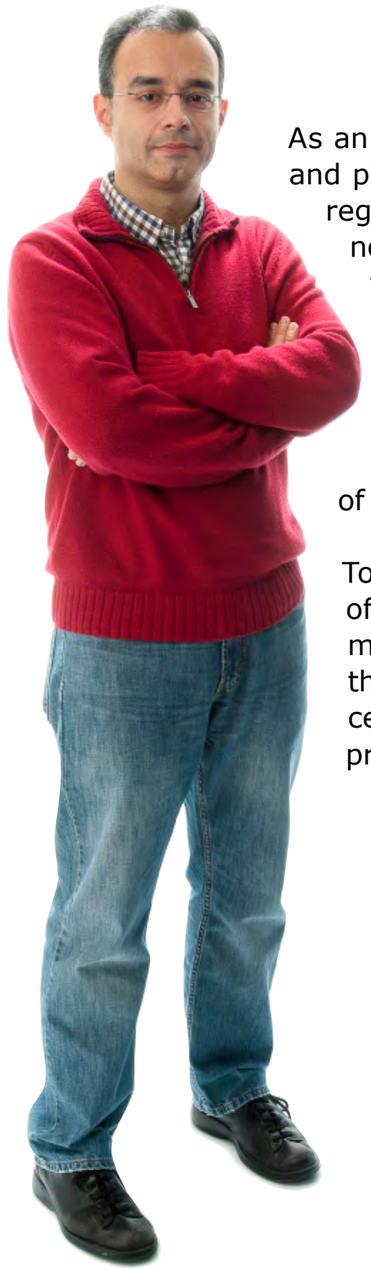
Dynamics and plasticity of cortical sensory responses

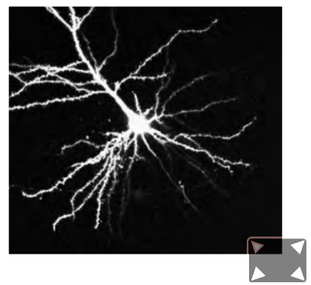
Miguel Maravall CSIC



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.

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.



Dynamics and plasticity of cortical sensory responses

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Michael Bale

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Giovanni Ferrati
Anna Pitas

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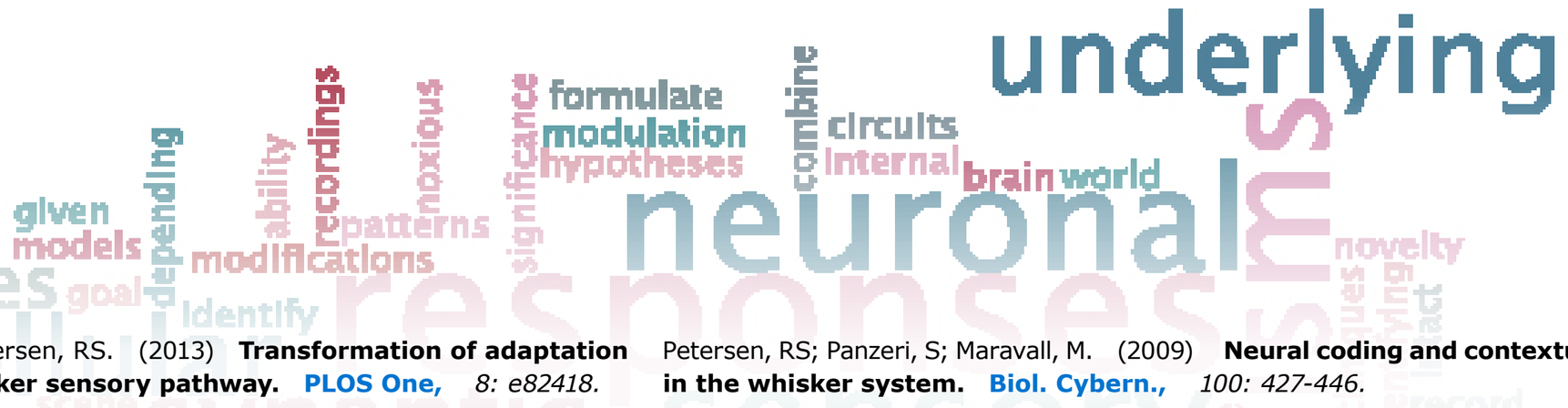
Dynamics and plasticity of cortical sensory responses

Miguel Maravall CSIC



Selected Publications

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

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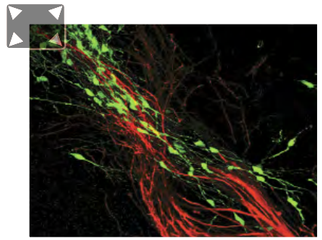
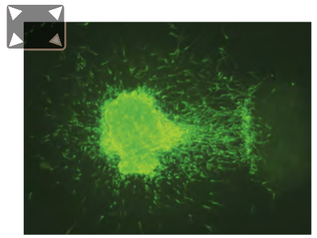
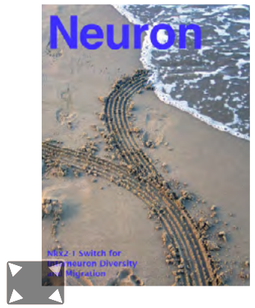
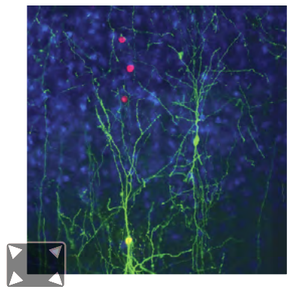
Neuronal migration and circuit assembly in the cerebral cortex

Oscar Marín CSIC









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

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

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

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

Neuronal migration and circuit assembly in the cerebral cortex

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Administration
Virtudes García


JB


CG-F


LL


SRSB


GC


GB


IS


ACB


MAFO


TGG


MPS


CS


VG

Neuronal migration and circuit assembly in the cerebral cortex

Oscar Marín CSIC

Selected Publications

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Visual Neuroscience Laboratory

Luis M. Martínez CSIC

We, like many other mammals, are essentially visual animals. Thus the visual system of our brains must achieve a daunting task: it creates, in real time, an internal representation of the external world that it is used by other parts of the brain to guide our behavior. But, how do we actually see? How does this neural system accomplish the job? A parsimonious explanation proposes that visual information is analyzed in a series of sequential steps starting in the retina and continuing along the multiple visual cortical areas. As a result, the information captured by the approximately 105 millions 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.

Visual Neuroscience Laboratory

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Visual Neuroscience Laboratory

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Selected Publications

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*

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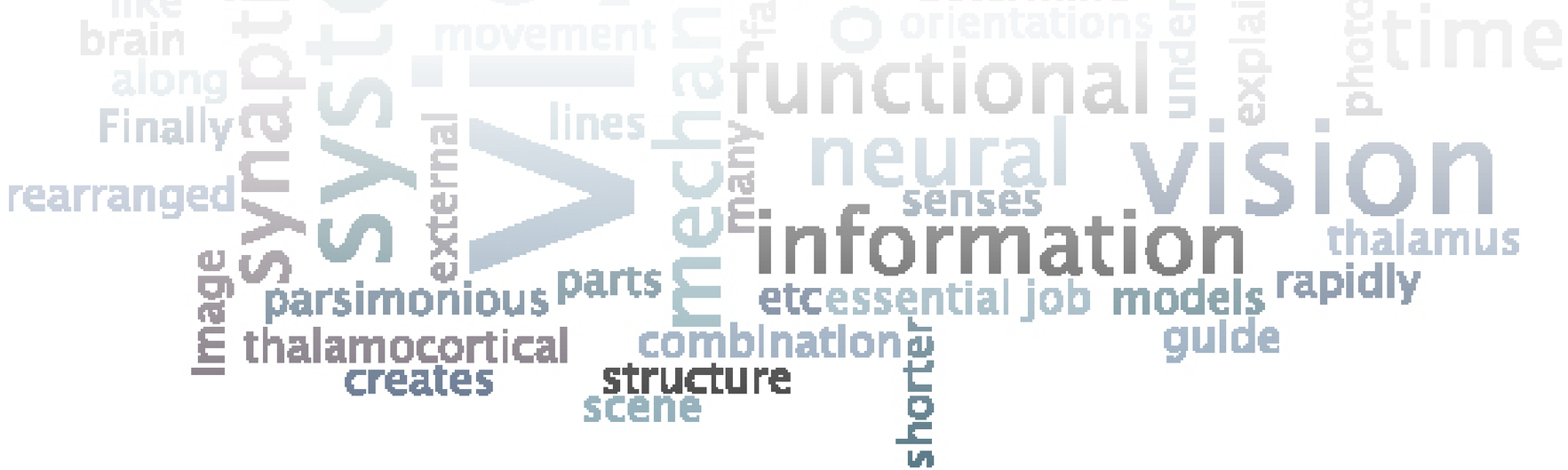
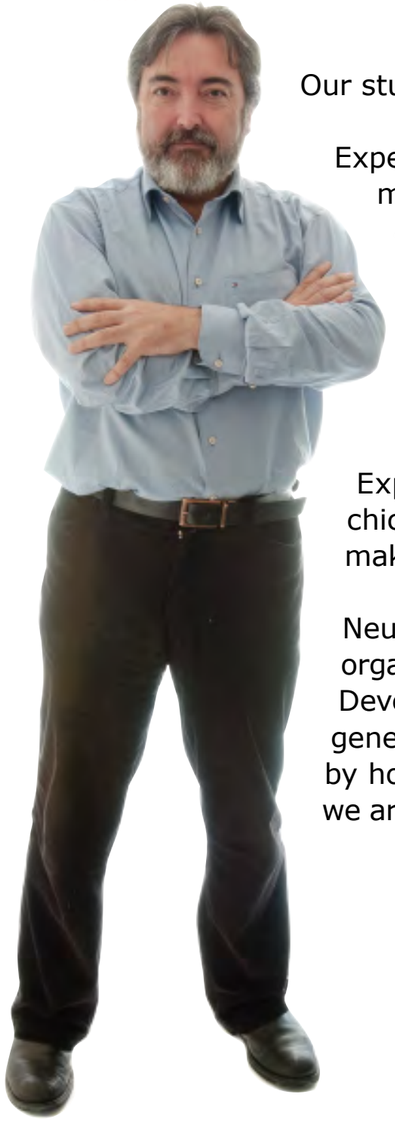


Experimental Embryology

Salvador Martínez UMH

Constantino Sotelo UMH



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Our studies are focused on four research projects:

Experimental Embryology: manipulations in mouse and chick embryos allow us to study cellular and molecular factors that control the regionalization, segmentation, proliferation, differentiation and cellular migration processes of the Central Nervous System. We concentrate our research work in the understanding of the molecular factors that control the development and morphogenetic activity of the secondary organizers of the anterior neural tube of vertebrates. Our work explores particularly the molecular action of signalling molecules like SHH, WNTs and FGFs in the Isthmic organizer, the zona limitans intrathalamic (ZLI) and the anterior neural ridge (ANR).

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

Neurogenetics: We are studying expression patterns of important genes related to the structural organization of the brain through its development. This research line is part of the Allen Institute Brain Development project in which we pretend in a large-scale manner to analyse the expression pattern genes at several embryonic stages of mice (www.brain-map.org). The further genetic manipulation by homologous recombination will help us to elucidate the functional role of these genes. Currently we are also interested in genes important of human neuropathogenesis. Thus, we have created a line

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Experimental Embryology

Salvador Martínez UMH

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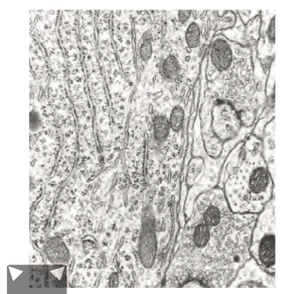
of research investigating the alterations of lisencephaly, several cortical heterotopies, multiple sclerosis and peripheral senso-motoral neuropathologies as well as Down syndrome. Related to this research line we are analysing the genetic alteration associated to functional psychosis (squizophrenia and bipolar disorder), particularly genes related to alteration in cortical architectural development.

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

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

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



Experimental Embryology

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AA


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MJAR


OBP


MRG


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FAG

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Selected Publications

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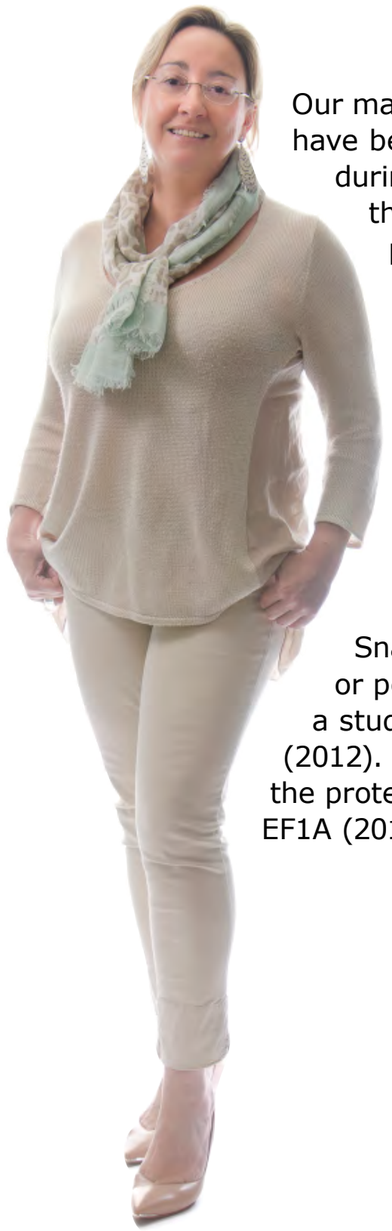
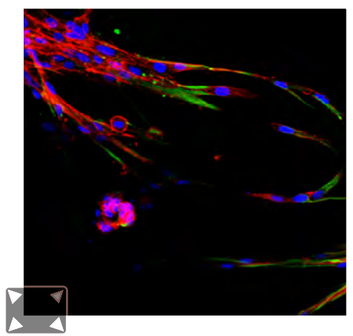
Cell movements in development and disease

M. Angela Nieto CSIC



Our main interest is the study of cell behaviour in development and disease, in particular associated with cell movements. We have been working on the functional analysis of the Snail gene family, and have shown its implication in different processes during embryonic development in vertebrates, including the formation of the mesoderm and the neural crest, both involving the triggering of the epithelial to mesenchymal transition (EMT) and massive cell migrations. We have also found that pathological activation of Snail factors either during development or, in particular, in the adult leads to several prominent pathologies. As such, Snail aberrant activation in tumours leads to the acquisition of invasive and migratory properties (2000-2002), while its activation in the adult kidney leads to renal fibrosis (2006). In addition, we have found that Snail fulfills unexpected roles in cartilage and bone. On one hand, Snail controls bone growth during foetal and postnatal development (2007) and, on the other hand, it controls bone mass in the adult (2009). The pathological aspect of Snail is also conserved in the bone, as we have found that an aberrant Snail function leads to the development of achondroplasia (the most common form of dwarfism in humans) and osteomalacia (bone demineralization in the adult). Going back to fundamental processes at early development, we have shown that the interplay between Snail factors and another transcription factor (Sox3) determines embryonic territories at gastrulation, ensuring the formation of the nervous system (2011).

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

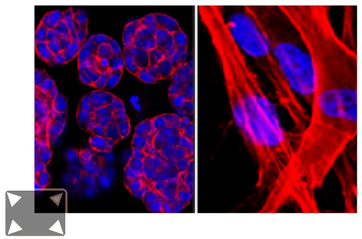


Cell movements in development and disease

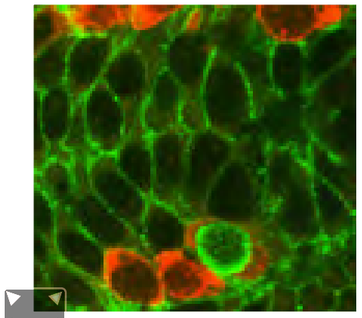
M. Angela Nieto CSIC

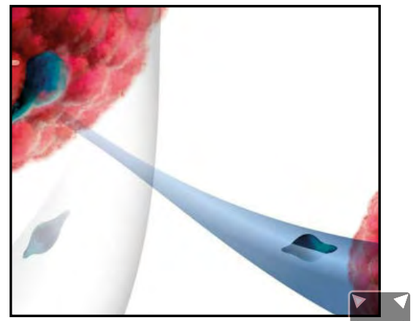
A phylogenetic analysis of this family has allowed us to conclude that the Snail genes constitute, along with the Scratch genes, a subgroup of the C2H2 zinc-finger transcription factors. We have traced back the origin of the superfamily to a protoSnail gene that underwent tandem duplication in the last common ancestor of the Diploblasts and Bilateria (2009). These studies favour the analyses of ancestral and acquired functions. We have found that in addition to the regulation of cell movements, Snail is important for cell survival and for the attenuation of cell cycle in embryos (2004). Its role in survival we had later extended to adult hepatocytes (2010). We have found that Scratch is required for the survival of spinal cord neurons during embryonic development by antagonizing the p53 apoptotic pathway (2011) and also that it prevents postmitotic neurons from re-entering the cell cycle (2013). Therefore, cell survival and the control of cell division are ancestral functions of the Snail/Scratch superfamily with important implications in development and disease .

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



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





Cell movements in development and disease

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DA


JC


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TMR


SM


AC

Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications

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*

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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.*

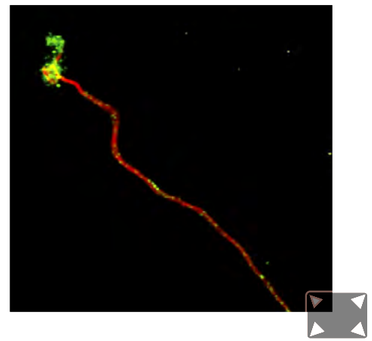
Nieto, M.A. (2011) **The ins and outs of the epithelial to mesenchymal transition in health and disease.** Ann. Rev. Cell Dev. Biol. *27, 347–376.*

Neural circuit formation and remodeling

Beatriz Rico CSIC

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

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



Neural circuit formation and remodeling

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Patricia Maeso

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Neural circuit formation and remodeling

Beatriz Rico CSIC

Selected Publications

Del Pino I#, García-Frigola C#, Dehorter N, Brotons J, Alvarez E, Martínez de Lagrán M, Ciceri G, Gabaldón MV, Moratal D, Dierssen M, Canals S, Marín O*, Rico B* (2013) **ErbB4 deletion from fast-spiking interneurons schizophrenia-like phenotypes.** **Neuron** *79, 1152-1168. #Authors contribute equally. *Corresponding authors.*

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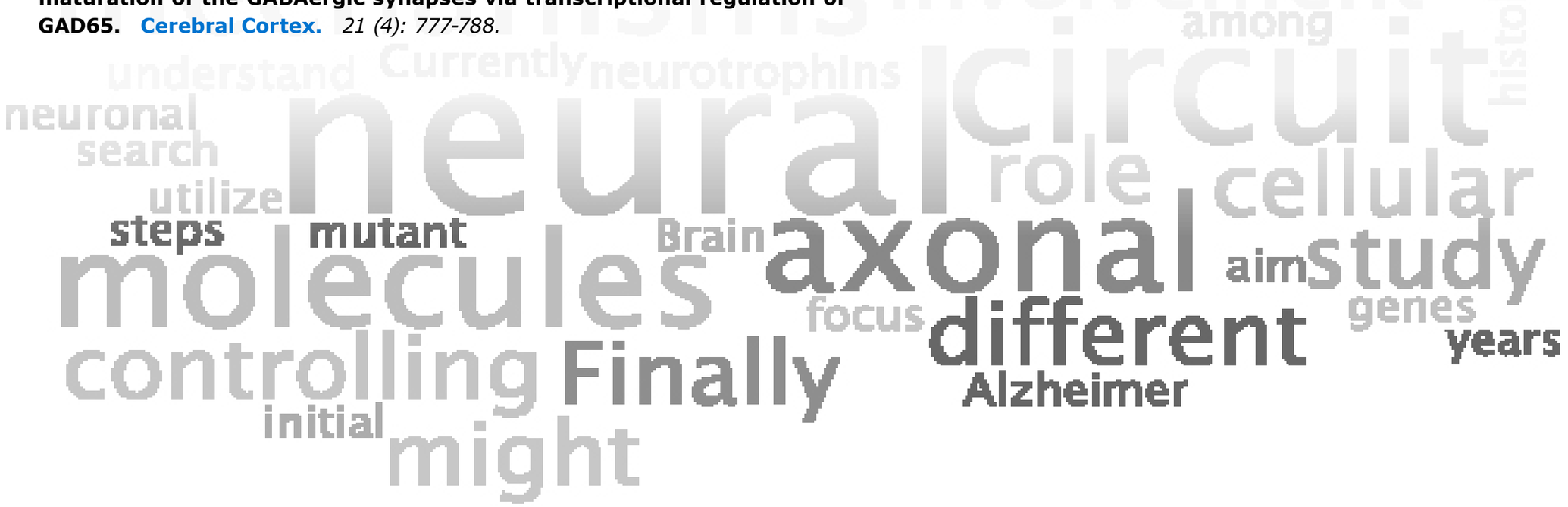


Altered molecular mechanism in Alzheimer's disease and dementia

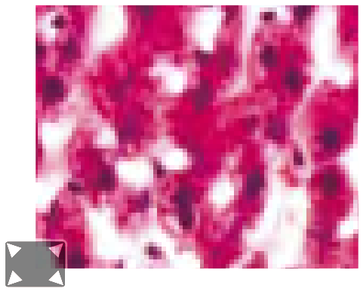
Javier Sáez Valero UMH

Our aim in the IN is to introduce a line of research into Alzheimer's disease (AD) and dementia that originated from a basic point of view but that was relevant to the development of clinical-diagnostic applications. Therefore, the translational benefits of our research lie in the fact that we not only aim to clarify the pathological mechanisms behind these diseases, but also to define potential diagnostic tools and/or processes with therapeutic relevance.

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

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

Furthermore, we evaluate the diagnostic potential and methodological approaches for analysis of particular glycoforms of proteins, which improve sensitivity and specificity of the biomarkers. We also develop assays to indentify secretase-related proteins, related with β-amyloid metabolism, in the cerebrospinal fluid.



Altered molecular mechanism in Alzheimer's disease and dementia

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PhD Student
Valeria Balmaceda
Maria Letizia Campanari


MSG


ICI


VB


MLC

Altered molecular mechanism in Alzheimer's disease and dementia

Javier Sáez Valero UMH

Selected Publications

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*

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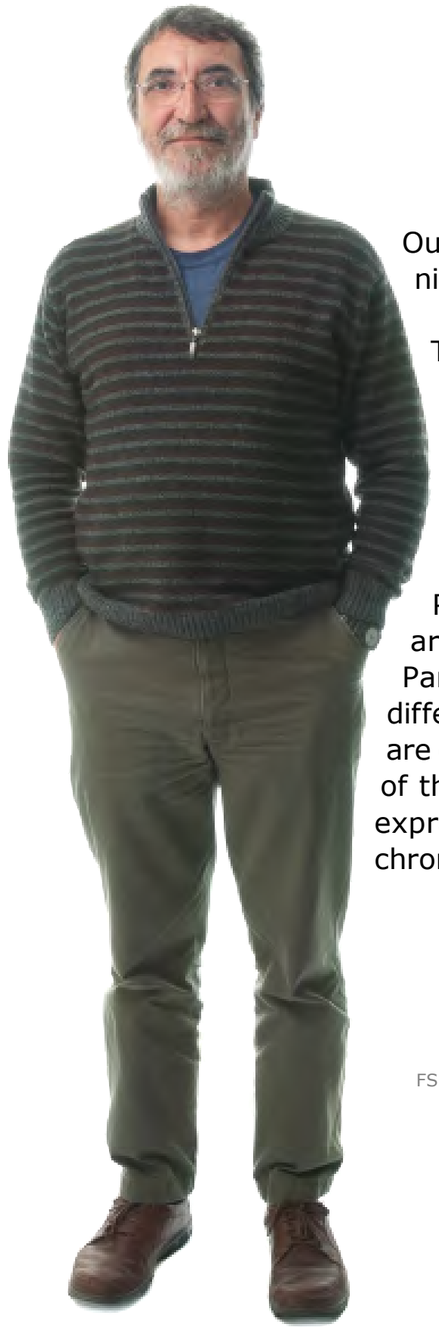
Biophysics and pharmacology of ionic channels

Francisco Sala UMH

Salvador Sala UMH



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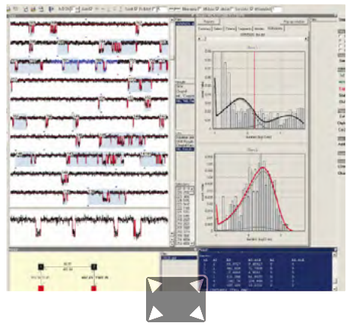
Our research interests are the functional study of ligand-gated ionic channels, mainly the neuronal nicotinic acetylcholine receptors (NNRs). The two major aspects of these studies are:

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.



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Biophysics and pharmacology of ionic channels

Francisco Sala UMH

Salvador Sala UMH

Principal Investigator
Francisco Sala
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Technical Staff
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JM

Biophysics and pharmacology of ionic channels

Francisco Sala UMH

Salvador Sala UMH

Selected Publications

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

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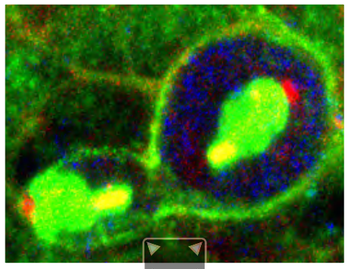
Criado, M., Mulet, J., Bernal, JA., Gerber, S., Sala, S., Sala, F. (2005) **Mutations of a conserved lysine residue in the N-terminal domain of a7 nicotinic receptors affect gating and binding of nicotinic agonists.** **Molecular Pharmacology** *68: 1669-1677.*

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.

Following this approach, we have identified the gene Minibrain (Mnb, also called Dyrk1A in vertebrates) as a major regulator of neural progenitor cell proliferation and neurogenesis in *Drosophila*. Mnb/Dyrk1A encodes a very well evolutionary conserved protein-kinase, which play several functions through brain development. We are focusing on its role in neural proliferation, neurogenesis, and neuronal differentiation. Mnb/Dyrk1A has also raised great interest because it is one of the most interesting candidate genes for the neuropathologies of Down Syndrome (DS) and neurodegeneration processes. Since DS is originated by the triplication of chromosome 21, we are using experimental models to determine how an excess of Mnb function can generate neurobiological alterations reminiscent of DS neuropathologies, particularly, neuronal deficit, dendritic atrophy and neurodegeneration. We are also testing the suitability of MNB/DYRK1A kinase inhibitors to interfere with neuronal functions as a prospect to apply pharmacological therapeutic appraoches to DS neuropathologies.



Molecular neurogenetics

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Molecular neurogenetics

Francisco Tejedor CSIC

Selected Publications

Walter Becker, Ulf Soppa and Francisco J. Tejedor (2013) **DYRK1A: a potential Drug Target for Multiple Down Syndrome Neuropathologies** **CNS Neurol Disord Drug Targets** *Oct 22*

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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*

Colonques J, Ceron J, Tejedor FJ. (2007) **Segregation of postembryonic neuronal and glial lineages inferred from a mosaic analysis of the Drosophila larval brain.** **Mech Dev.** *124(5):327-40*

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.*

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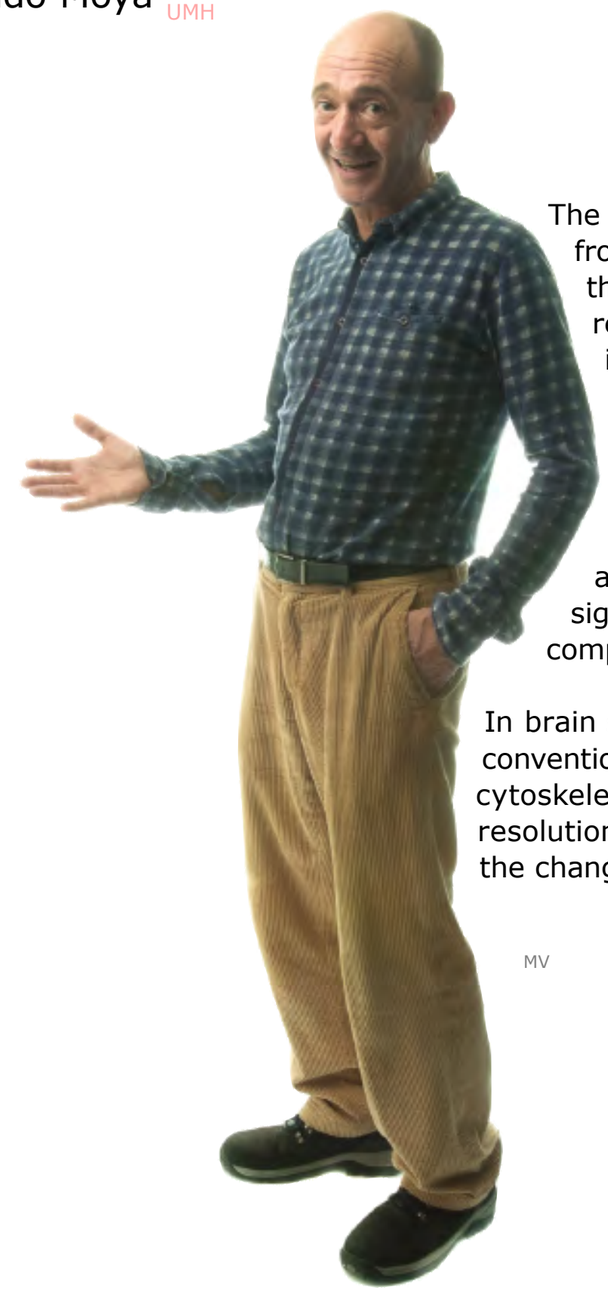
Cell signalling during neuronal migration

Miguel Valdeolmillos UMH

Fernando Moya UMH

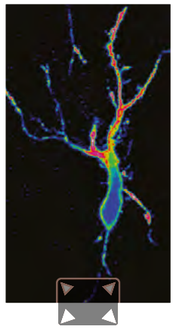


The formation of mature cortical circuits in the mammalian brain requires the migration of neurons from their proliferative niches to their final destination. Several mutations in genes that participate in the process of neuronal migration have been associated in humans to brain malformations, mental retardation or psychiatric diseases. As with other cell types, whose molecular mechanisms involved in cell movement are better known, neuronal movement can be described as the sequential integration of three different phases: elongation of the leading process, nuclear displacement or nucleokinesis into the leading process and retraction of the trailing process.

Our aim is focused on the description of the intracellular signalling pathways that, in response to external clues, guide the migration of neurons. Some of these signals are linked to the temporal and spatial regulation of intracellular calcium levels. It is our objective to determine the role of these signals in the molecular mechanisms that regulate the assembly and disassembly of the cytoskeletal components during the movement of neurons, in particular the dynamics of actomyosin interaction.

In brain slices from mouse embryos and in primary cultures of dissociated cortical cells, we analyze, by conventional and multiphoton fluorescence microscopy, the changes in calcium and the dynamics of several cytoskeletal components during the process of migration. These methods allow the spatial and temporal resolution of the response of these cellular components to factors responsible for neuronal guidance, and the changes occurring at different phases of neuronal migration.

MV



FM

Cell signalling during neuronal migration

Miguel Valdeolmillos UMH

Fernando Moya UMH

Selected Publications

M. Valdeolmillos & F. Moya **(2013) Leading process dynamics during neuronal migration.** In: ***Comprehensive Developmental Neuroscience*** Editor-in-Chiefs: J. Rubenstein and P. Rakic ELSEVIER *Chapter 25.*

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.*

F. Martini & M. Valdeolmillos (2010) **Actomyosin Contraction at the Cell Rear Drives Nuclear Translocation in Migrating Cortical Interneurons.** **The Journal of Neuroscience** *30, 8660–8670.*

F. Martini, M. Valiente, G. López Bendito, G. Szabó, F. Moya, M. Valdeolmillos1 & O. Marín1 (2009) **Biased selection of leading process branches mediates chemotaxis during tangential neuronal migration. (1 corresponding authors)** **Development** *136, 41-50.*

López-Bendito G., Sánchez-Alcañiz J. A., Pla R., Borrell V., Picó E., Valdeolmillos M.& Marín O. (2008) **Chemokine signaling controls intracortical migration and final distribution of GABAergic interneurons.** **The Journal of Neuroscience** *28:1613–1624.*

Marin O., Valdeolmillos M. & Moya F. (2006) **Neurons in motion: signaling mechanisms in neuronal migration.** **Trends in Neuroscience** *29:655-661*

Moya, F., Valdeolmillos, M. (2004) **Polarized increase of calcium and nucleokinesis in tangentially migrating neurons.** **Cerebral Cortex,** *14: 610-8.*

Soria, JM., Valdeolmillos, M. (2002) **Receptor-activated calcium signals in tangentially migrating cortical cells.** **Cerebral Cortex,** *12: 831-9.*

Martínez-Galán, JR., López Bendito, G., Luján, R., Shigemoto, R., Fairén, A., Valdeolmillos, M. (2001) **Cajal-Retzius cells in early early postnatal mouse cortex selectively express functional metabotropic glutamate receptors.** **Eur. J. Neurosci.,** *13: 1147-1154.*

Master & PhD Program

Coord: M. Valdeolmillos

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. For the next academic year, the PhD will run 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).

Collaborations & Agreements

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

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 have formed a network, dedicated to the promotion of the independent work of young investigators. From the interactions between its different nodes, we expect 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.

Collaborations & Agreements

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 has been 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.

Since 2006, the Remedios Caro Almela Chair has sponsored an international prize in Developmental Neurobiology as part of the Chair's activities, and consists of an unrestricted award of 20.000€. This Prize has been so far awarded to Barry Dickson (2006), François Guillemot (2007), Rüdiguer Klein (2008), Steve Wilson (2009), Christine Holt (2011) and Magdalena Götz (2013). The latest Prize Ceremony was held on October 25th, 2013 at the Instituto de Neurociencias. The previous prize winner Dr. Christine Holt, opened the ceremony with the Remedios Caro Almela Lecture

Dr Barry J. Dickson

2006

Dr François Guillermot

2007

Dr Rűdiger Klein

2008

Dr Stephen Wilson

2009

Dr Christine Holt

2011

Dr Magdalena Götz

2013

The Remedios Caro Almela Prize 2013

for Research in Developmental Neurobiology

On June 19th of 2013, The jury of the 6th Edition of the "Remedios Caro Almela" Prize in Developmental Neurobiology integrated by Josep Xavier Barber, Adjunt Vice-Rector of Research and Innovation of the UMH; Juan Lerma, Director of the Instituto de Neurociencias, Christine Holt, winner of the fifth edition of the award, Paola Bovolenta, from the Center of Molecular Biology Severo Ochoa, Patrick Charnay, de l' École Normale Supérieure of Paris and the previous Remedios Caro Almela Chairman, Constantino Sotelo, unanimously decided to award the prize "Remedios Caro Almela in Development Neurobiology to Professor Magdalena Götz, Chair of the Department of Physiological Genomics of the Ludwig-Maximilians-University, and Director of the Stem Cell Institute of the Centre Helmholtz, both in Munich, Germany for her contributions to the understanding of the cellular and molecular mechanisms that govern the formation of the cerebral cortex. Dr. Götz has discovered that radial glial cells are not only guidance structures for migrating neurons, but also generate neurons as well as glial cells in the developing forebrain. Among other important findings, she demonstrated that glial cells can be reprogrammed to functional nerve cells by transfection with some determinants of neuronal specification. Newly formed neurons are able to functionally integrate in adult cortical circuits. This cellular reprogramming opens new avenues for the repair of the brain after traumatic injuries or in neurodegenerative diseases.

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

Professor Götz was born in Germany, in 1962, studied biology at the universities of Tübingen and Zürich. She did his doctorate at the Institute Friedrich-Miescher of the Max-Planck Society, Tübingen. After several postdoctoral stays in Germany and United Kingdom, she continued her work as a group leader at the Max Planck Institute of Neurobiology in Martinsried, until being appointed Chair of Genomic Physiology and Director of the Stem Cell Institute of the Helmholtz Center.

Magdalena Götz is Editor of Development, Associate Editor of Journal of Neuroscience and member of the editorial board of Cell Stem Cell, Development, EMBO Journal, Genes and Development, Journal of Neuroscience, Glia, BMC Developmental Biology, Cell Adhesion and Migration, Frontiers in Neurogenesis, and Current Opinion in Genetics and Development

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

The next Remedios Caro Almela Prize will be awarded in 2015

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.

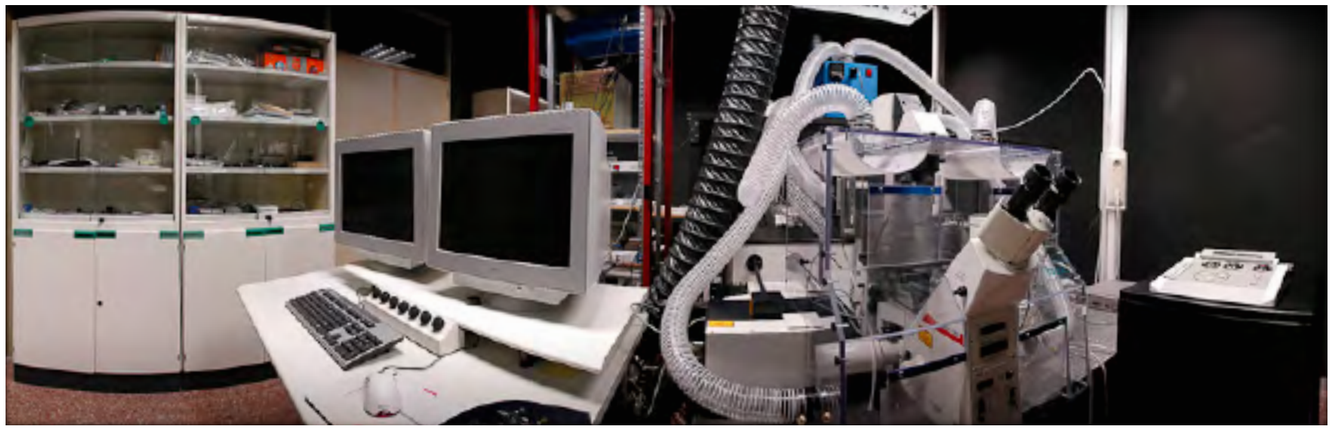
- Multiphoton microscope, equipped with two workstations. One includes an upright microscope for rapid acquisition of images from in vivo preparations or brain slices, with simultaneous electrophysiological facilities. The other consists of an inverted microscope for long-term time-lapse experiments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

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.

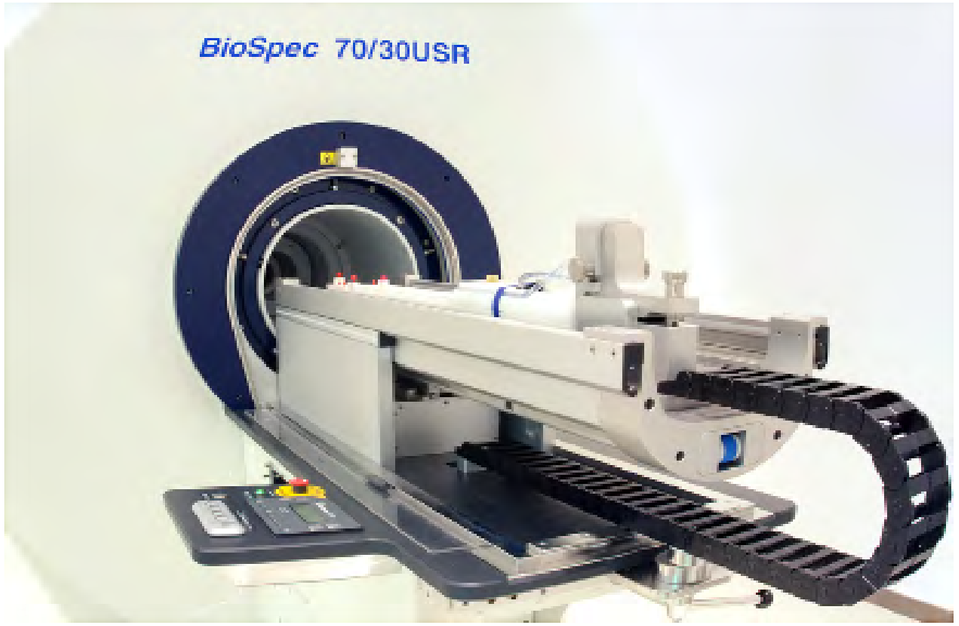
In this common area there are 6 independent spaces and a common area for washing, Equipment such as Skinner box, rotarod, treadmill, 8 arms maze, hot plate and water maze with tracking system allow researchers to study the behaviour of rats and mice (motor function, memory, learning, conditioning, etc). 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 AND PHOTOGRAPHY

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

PURCHASE AND 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 200m^2 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.

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.

ANIMAL HOUSE

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

Breeding and maintenance of lines of genetically modified mice. It houses about 300 lines of genetically modified mice. The lines are handled by specialized personnel under direct advice of researchers through a computer program designed for that purpose.

Breeding of wild type and production of gestational age defined female mice. The area of production of non-transgenic mice serves the needs of this type of mice.

The service defined gestational age females. Designed specifically to support experimental embryology, it provides to researchers of inseminated mice at different stages of gestation.

Quarantine. Where are stocked animals received from other institutions. Before any eternal animal can be admitted, the Aanimals Testing Lab determines their health status and carries out embryo transfer if they are not free of pathogens.

Laboratory of transgenesis. Where the rederivations and other procedures of assisted reproduction such as IVF and freezing of sperm and embryos of mouse are performed.

Experimental zone. It has an area of animal stocking and comprehensive equipment for experiments involving surgery and behavioural studies within the barrier area.

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

Administrative & Service Staff

Manager
Mª Teresa García Hedo

Administration
Mª Luz Arce Fernández
Mª Jesús Arencibia Rojas
Helena Campos Martín
Mª Auxiliadora Casanova Javaloyes
Gisele Díaz Pérez
Virtudes García Hernández
Ana María López Martínez
Virtudes Monasor Gómez
Isabel Romero García
Ruth Rubio Sánchez
Rosa Mª Sánchez Cayuela
Mª Luisa Sánchez Vázquez
Beatriz Yunta Arce


MTGH


HCM


AMLM


IRG


MLSV

Administrative & Service Staff

Purchase & Storage
Isabel Ortega Castillo

Maintenance
Jesús Campos Roldán

Imaging
Joana Expósito Romero

Computing
Mª Isabel Sánchez Febrero

Radioactivity Control
Emilio Gutiérrez Flores

Scientific Illustration
Stuart Bailey Ingham

Cell Culture
Sara Carratalá Gosálbez
Rosa García Velasco

Glassware & Autoclaving
Trinidad Guillén Carrillo

Brain Imaging Service
Jesús Pacheco Torres


IOC


JCR


JER


SBI


SCG


RGV


TGC


JPT

Administrative & Service Staff

Veterinary Staff
Mª Jesús Molina Cimadevilla
Gonzalo Moreno del Val

Animal House
Antonio Caler Escribano
Mª Carmen Checa Lara
Sandra González Mosteiro
Verónica Jiménez Villar
Ana Lorena Marín Sánchez
Patricia Muñoz Robledano
Rebeca Ortiz Méndez
Raúl Pardo Mérida
Eva María Sabater Sánchez
Sonia Segura Llobregat
Mª Ángeles Soler Ripoll
Lucía Yuste Jiménez

Drosophila Service
Alicia Sánchez Rincón

Zebrafish Facility
Diana Abad Bataller
Teresa Martín Rey


MJMC


GMdV


MCCL


SGM


VJV


ALMS


PMR


ROM


RPM


SSL


MASR


LYJ


ASR


DAB

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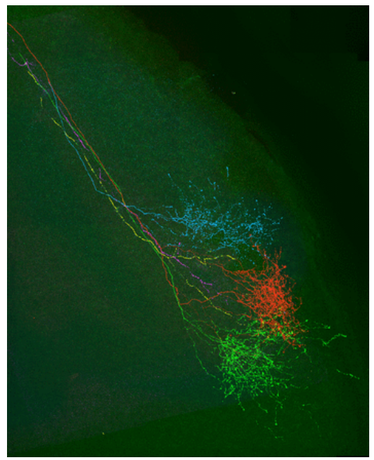

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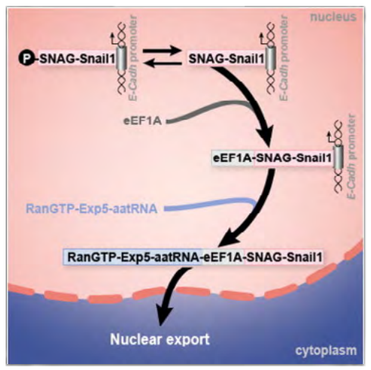

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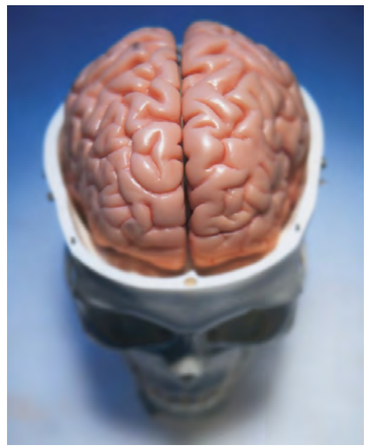

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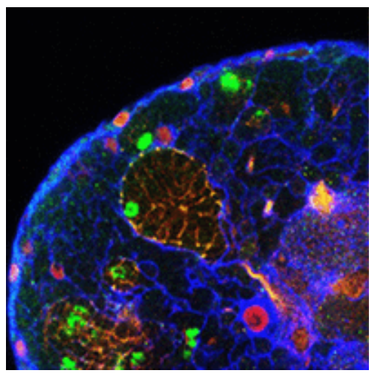

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Valdeolmillos M., Moya F. **Leading Process Dynamics During Neuronal Migration.** **Cellular Migration and Formation of Neuronal Connections** *Elsevier Inc, Ed. p245-260*

Seminars

11/01 **Dissecting associative memory circuits with novel genetic approaches** **Dr. Mazahir Hasan** Max Planck Institute for Medical Research.

18/01 **Connectomics: the dense reconstruction of neuronal circuits"** **Dr. Moritz Helmstaedter** Max Planck Institute of Neurobiology.

01/02 **From fly glia to mouse immune system** **Dra. Angela Giangrande** IGBMC, Strasbourg.

08/02 **Transcriptional Control of the Genesis of Photoreceptors in Mammalian Retina.** **Dr. Anand Swaroop** National Eye Institute (NEI), National Institues of Health, Bethesda.

15/02 **Nitric oxide and zinc-mediated protein assemblies involved in opioid receptor regulation of glutamate NMDA receptors.** **Dr. Javier Garzón** Instituto Cajal.

22/02 **Prefrontal cortex-based circuits in depression and schizophrenia.** **Dr. Francesc Artigas** Department of Neurochemistry and Neuropharmacology, Institut d'Investigacions Biomediques de Barcelona, CSIC-IDIBAPS.

01/03 **Oligodendrocyte regneration: from biology to medicine** **Dr. Robin Franklin** Trust-Medical Research Council Stem Cell Institute.

13/03 **Of Mice and Monkeys: A Journey into the Visual System** **Dr. Ed Callaway** Salk Institute for Biological Studies, La Jolla, California.

22/03 **Heterogeneity among hair cell synapses enables wide dynamic range sound encoding** **Dr. Tobias Moser** Bernstein Center for Computational Neuroscience. University Medical Center, Goettingen.

19/04 **Stem cells to synapses: regulation of self-renewal and differentiation in the nervous system** **Dra. Andrea Brand** Gurdon Institute, University of Cambridge.

26/04 **The role of short- and long-range GABAergic neurones for spatial coding and rhythmic activity in the hippocampal-entorhinal formation** **Dra. Hanna Monyer** University of Heidelberg.

03/05 **Combining Proteomic, genomic and genetic approaches to study synapse organisation and behaviour.** **Dr. Seth Grant** Centre for Clinical Brain Sciences and Centre for Neuroregeneration, University of Edinburgh.

Seminars

17/05 **Long-term plasticity: regulating synaptic strength or synaptic lifetime?** **Dr. Thomas Oertner** Institute of Synaptic Physiology, Center for Molecular Neurobiology, Hamburg.

24/05 **Molecular mechanisms of GABAergic synapse plasticity** **Dr. Jean-Marc Fritschy** Neuroscience Center, Zurich.

31/05 **Regulation of M-channel density at the plasma membrane** **Dr. Alvaro Villarroel** Unidad de Biofísica CSIC-UPV/EHU, Bilbao.

07/06 **Signal integration by p38 MAP kinases** **Dr. Angel Nebreda** IRB, Barcelona.

14/06 **Intrinsic diversity and connectivity of neuronal circuits.** **Dr. Troy Margrie** MRC National Institute for Medical Research.

25/07 **Neuronal Dicer1 gene loss in adult mice causes rapid obesity development due to over-activation of mTOR** **Dr. Witold Konopla** Nencki Institute, Warsow.

04/10 **Parallels between wound healing and cancer** **Dr. Sabine Werner** Institute of Molecular Health Sciences, ETH, Zürich.

10/10 **Neural mechanisms of reward and aversion** **Dr. Robert Malenka** Stanford School of Medicines.

24/10 **Discover novel strategies to target cancer stem cells by using Drosophila as an incubator** **Dr. Cheng-yu Lee** Dept. Internal Medicine, University of Michigan.

22/11 **Multisensory integration under the yoke of attention** **Dr. Salvador Soto Faraco** Universitat Pompeu Fabra.

29/11 **The structure and function of cortico-cortical connections** **Dr. Leopoldo Petreanu** Champalimaud Neuroscience Programme

20/12 **Reconstructing the evolution of cognition.** **Dr. Josep Call** School of Psychology & Neuroscience, University of St Andrews & Max Planck Institute for Evolutionary Anthropology.

OUTREACH

29/01 **¿Por qué 20 años con un caracol?.** **Dra. Angela Nieto** Instituto de Neurociencias.

26/02 **Del desarrollo del Sistema Nervioso al ensayo clínico en enfermedades neurodegenerativas.** **Dr. Salvador Martinez** Instituto de Neurociencias.

26/03 **Señalización axón-glía durante la regeneración nerviosa post-traumática y desarrollo de tumores en el sistema nervioso periférico.** **Dr. Hugo Cabedo** Instituto de Neurociencias.

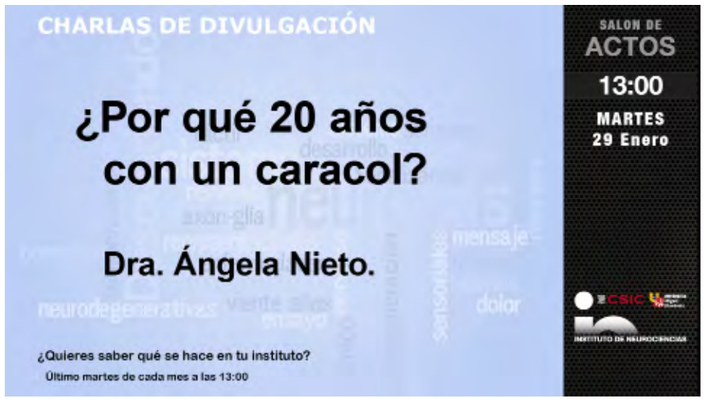
02/05 **¿Cómo se conectan nuestras neuronas y que sucede cuando no lo hacen correctamente?** **Dra. Beatriz Rico** Instituto de Neurociencias.

28/05 **Descubriendo los sensores moleculares del dolor y la temperatura.** **Dr. Félix Viana** Instituto de Neurociencias.

18/06 **Cada neurona, un mensaje diferente: representaciones sensoriales en el sistema táctil de los roedores.** **Dr. Miguel Maravall** Instituto de Neurociencias.

29/10 **Aprendiendo sobre el mecanismo de la neurotransmisión: de lo básico al diseño de agentes cosméticos.** **Dr. Luis Miguel Gutierrez** Instituto de Neurociencias.

27/11 **Optimizando herramientas en la lucha contra el Alzheimer** **Dr. Javier Saez Valero** Instituto de Neurociencias.



Aracil Fernández , Maria Auxiliadora **Papel del receptor cannabinoide cb2 en la vulnerabilidad por el consumo de alcohol y cocaína.**
Jorge Manzanares Robles

Benjumeda Wijnhoven , Isabel **Disentangling the roles of molecular guidance cues and spontaneous activity in the emergence of brain topography.**
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Escalante Rodríguez , Augusto **The role of the transcription factor ZIC2 as a determinant of axonal laterality in the spinal cord.**
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Félix Viana de la Iglesia

Mezzera , Cecilia **Thalamic Intrinsic Mechanisms Control Thalamocortical Wiring and Cortical Plasticity.**
Guillermina López-Bendito

Molano Mazón , Manuel **(Cómo el tálamo cambia) Lo que el ojo del gato le dice al cerebro del gato.**
Luis Miguel Martínez Otero & Miguel Maravall Rodríguez

Other Activities

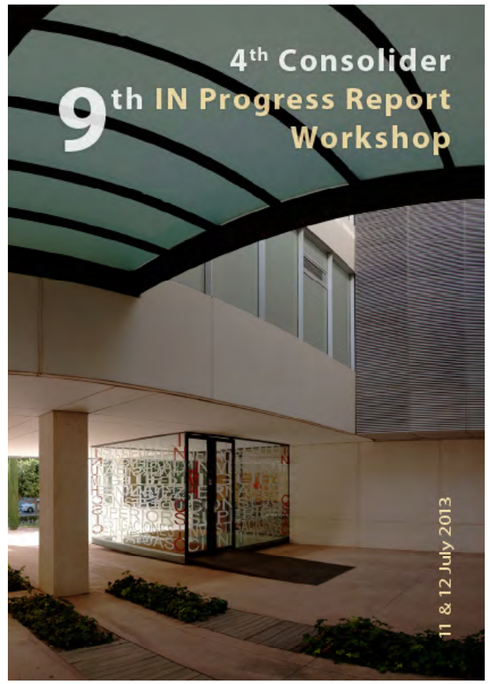
10th Christmas Meeting of the Instituto de Neurociencias (joint with the 2nd Prometeo KARTACO meeting)

4nd Congress of 5P Sindrome and rare diseases

V Simposium PROMETEO NEC2. Anomalias genéticas del desarrollo cortical y disfunción cerebral

4nd Consolider & 9th IN Progress Report Workshop.

"Brain Awarenes Week 2013" activities.



Promega Prize to the best talk

Other Activities

Abandonando el nido, Vanessa Villar Carrillo. Concurso ¿Cómo ves la Ciencia? 2012 (categoría B).

Expertos del Instituto de Neurociencias de Alicante nos proponen un viaje por nuestro órgano más complejo: cómo funciona, los descubrimientos más recientes y sus aplicaciones a la vida cotidiana, así como los retos del futuro.

Días 14, 21 y 28 de octubre 2013 · 17:30h

Teatre del Mercat d'Aldaia (c/ Les Eres s/n, Aldaia).

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Choques al azar entre neuronas crean las diferencias cerebrales

▶ El Instituto de Neurociencias de Alicante halla por primera vez colisiones aleatorias de células en el cerebro embrionario

LEVANTE-EMV VALENCIA

■ Investigadores del Instituto de Neurociencias de Alicante, centro mixto del Consejo Superior de Investigaciones Científicas (CSIC) y la Universidad Miguel Hernández de Elx, han demostrado por primera vez que colisiones al azar entre neuronas del cerebro en desarrollo dan lugar a una organización ordenada de las mismas en ausencia de señales que guíen su destino. Este hallazgo podría ser clave para explicar las diferencias individuales en la organización del cerebro.

La corteza cerebral es una de las regiones más complejas del cerebro de los mamíferos, alcanzando su máximo desarrollo en humanos. Para que ésta se forme correctamente, son necesarias multitud de señales químicas que dirigirán a las células que lo componen hacia la posición que finalmente van a ocupar y que determinarán la función que van a desempeñar. El grupo que dirige el profesor Óscar Marín ha demostrado que el movimiento de las células de Cajal-Retzius, unas neuronas del cerebro embrionario y que juegan un papel clave en el desarrollo de la corteza cerebral, responde al contacto al azar y la posterior repulsión entre neuronas.

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