INSTITUTO DE NEUROCIENCIAS

ANNUAL REPORT

2012

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INDEX

CSIC Consejo Superior de Investigaciones Científicas

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

Salutation

JUAN LERMA : Director

One more year, the Instituto de Neurociencias (IN) continues its progress towards to become a Centre of excellence in Neuroscience. Despite the long journey of economic crisis we are experiencing, we have even increased the number of people working at the IN as well as the level of competitive fund raising. We can say with satisfaction that IN's quality figures are well above the national average and exceed comparable centres throughout Europe. However, we are deeply disappointed for not having been awarded with the Centre of Excellence Severo Ochoa label, despite of getting the highest score possible (100/100), paralleling the score of all five centres being appointed this year. We still wonder why.

Concerning the staff, we maintain a stable ca 60% women and 40% men proportion, and more than 20% of our staff comes from other countries. Indeed, more than 30% of our contracted researchers are not Spanish in origin, which indicates on the degree of internationalization of our Centre. During this last year we suffered the painful premature loss of two of our dearest collaborators, Angelines Barrios and Alfonso Perez-Vegara. We will never forget them since with their exemplifying work were amongst us since the beginning of this centre.

In the scientific arena, the IN continues with the development of its plan of action 2010-2013, which describes the research lines under development since its inception. In this sense, the IN progress in both attracting resources and productivity, following the path delineated in the previous strategic plan. Noteworthy most of the ¾ parts of the staff correspond to contracts covered with external competitive funding obtained by researchers in this Center. This determines that the scientific production and the international impact of the IN continue increasing, reflecting the high dedication of its staff to the tasks that have been entrusted. And this past year has been full of relevant findings. It fulfils the Mission of the IN to generate knowledge about the brain and its mechanisms. 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 2009-12 shows quite well the evolution of the IN's scientific international impact. This year, we have not only 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 6.49 for the last 4-year period. But perhaps more important is that the number of citations received in the period, continues to grow comparatively. This figure measures the real impact of our work in the international scientific community.

In the past year, several members of the IN achieved significant recognition to his research activity. On one hand, Carlos Belmonte received the Honory Medal of the Royal academy of Medicine of Valladolid, the First "Antonio Gallego Award" in medical education and the Award for Stimulating Research in the field of Pain Treatment (Fundolor Foundation). Guillermina López Bendito was appointed EMBO YIP; Oscar Marin won the FENS EJN Young Investigator Award; Angela Nieto was elected Vicechair of the EMBL Council. Thereby, the IN and its staff reinforce their national and international presence. We also received from the hands of the Chancellor of the University of Alicante, the "San Alberto Magno 2012" Award as an acknowledgement of our contribution to the "Training Programme in Enterprises", a very much appreciated honour.

Salutation

JUAN LERMA : Director

If last year I was proud to inform that two of our researchers were awarded with prestigious European Research Council (ERC) grants, I am very excited announcing now that in 2012 we got 3 more ERC grants: Angela Nieto (ERC Advanced Grant), Beatriz Rico (ERC Starting Grant) and Victor Borrell (ERC Starting Grant). These achievements set our institute with the highest level of accomplishment amongst all CSIC and Spanish University centres. Thus, Alicante is situated at the scientific excellence epicentre.

In 2012, 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, 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.

In 2012 we celebrated the Year of Neuroscience in Spain. The Instituto de Neurociencias has participated of this celebration organizing several actions towards diffusion and advocacy of neuroscience. With this occasion and from the Instituto de Neurociencias we insist that neuroscientific knowledge will change the way of thinking and behaviour of our society in the future and 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 is has. Also I warmly acknowledge the institutions to which the IN belongs, CSIC and UMH, for the continuous support of our research activity.

A Bit of History

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

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

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

Where We Are

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

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

What We Do

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

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

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

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

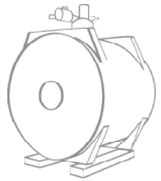
The IN undertakes an important training activity through its International PhD Programme in Neuroscience, which has been awarded with a mention as "Programme of Excellence" by the Ministry of Education. It also strives to be a centre of reference in terms of both national and international collaborations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

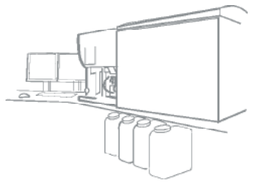
The years following the relocation of the IN to its new building have seen an important period of expansion, resulting in the IN becoming the largest Spanish institute monographically dedicated to the study of the nervous system and its pathologies. The significant increase in personnel has been in both 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 SystemDevelopment and Plasticity
Programa Consolider-Ingenio 2007-2011

Plan Nacional de I+D+I

Most Relevant Scientific Milestones

Evidenced for the first time a mechanism by which neurons in the developing brain control the rate of growth of their connections (Nature Neurosci 2012)

Revealed that Lhx2 is capable of controlling the program of thalamo-cortical guide in different populations of thalamic neurons by regulating Robo1 and Robo2 receptors (J Neurosci., 2012).

Identified the factor Prxx1 as an agent preventing cancer cells from colonizing distant organs, thereby avoiding the formation of secondary tumors or metastasis (Cancer Cell, 2012).

Identified the presence of mutations and deletions in the genes EZH2 and SUZ12 25 in leukemias (Nature Medicine, 2012)

Dilp8 (Drosophila insulin-like peptide 8) as a secreted hormone peptide has been identified to coordinate tissue growth with developmental timing in the fruit fly (Science 2012)

Demonstrated that cooperation between NOTCH1 aberrant activation and the inactivation of PCR2 function is sufficient to induce tumors in vivo and in vitro (Nature Medicine, 2012)

Discovered an unsuspected role as suppressor of tumours of the PCR2 complex in the context of the oncogene NOTCH1 (Nature Medicine, 2012)

Found that cell lines derived from Rubinstein-Taybi patients show defects on histone acetylation that primarily affect histones H2A and H2B and can be reversed with HDAC inhibitors (J Med Genet 2012).

Demonstration that enhanced CREB activity increases hippocampal long-term potentiation (LTP) and transiently improves learning in alert behaving mice (J Neurosci. 2012).

Found that Canoe/AF-6 is a novel positive regulator of the Slit-Robo signaling pathway during CNS midline axon pathfinding (J Neurosci. 2012)

The feasibility and safety of autologous bone marrow stem cells transplantation demonstrated in ALS patients. This study is the first being registered internationally (Stem Cells 2012)

Completed the annotation of the expression of 2000 transcription factors in stages E11.5-13.5 and 15.5 (published as on the page: http://www.brain-map.org and http://developingmouse.brain-map.org/) as well as the expression pattern of the same genes in stage E18.5.

Demonstrated that basal Radial Glia cells, a newly discovered type of cortical progenitor, are necessary but not sufficient to drive folding of the mammalian cerebral cortex (Cerebral Cortex 2012)

Found that Robo1 and Robo2 play additional and unexpected roles in the developing brain. In particular, these receptors seem to directly regulate neurogenesis by modulating the division of progenitor cells (Neuron 2012).

Discovered a novel mechanism through which FAK controls filopodia formation and actin nucleation during axonal development (Development 2012).

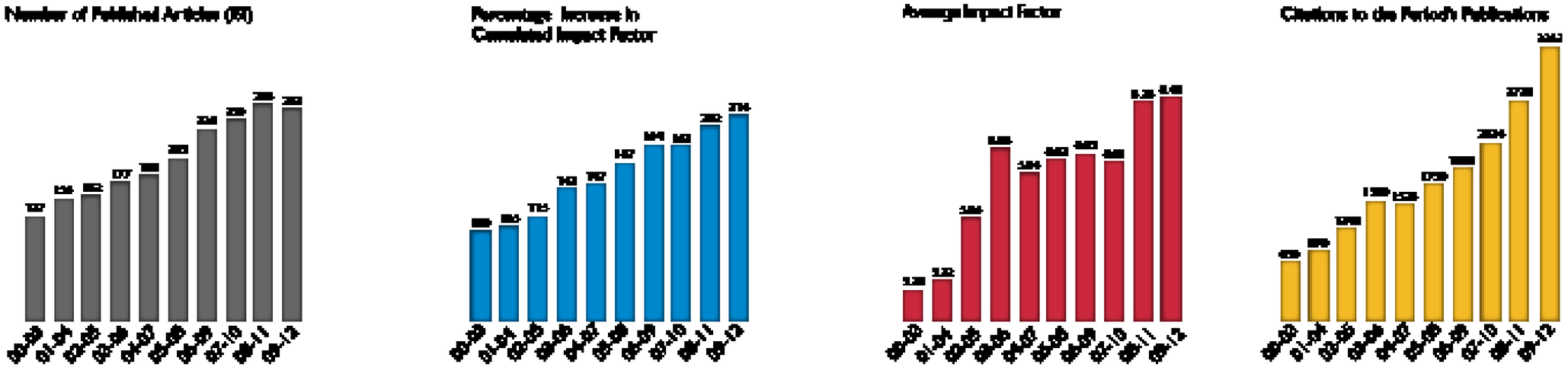
Demonstrated that lissencephaly in modern primates was a secondary evolution from gyrencephalic ancestors (Cerebral Cortex 2012)

Demonstrated that cross-talk between μ and δ-opioid receptors determines the sensitivity to anti-nociception induced by μ-opioid receptor agonists, such as morphine and determines the interindividual variability to perception of pain (British J Pharmacol, 2012)

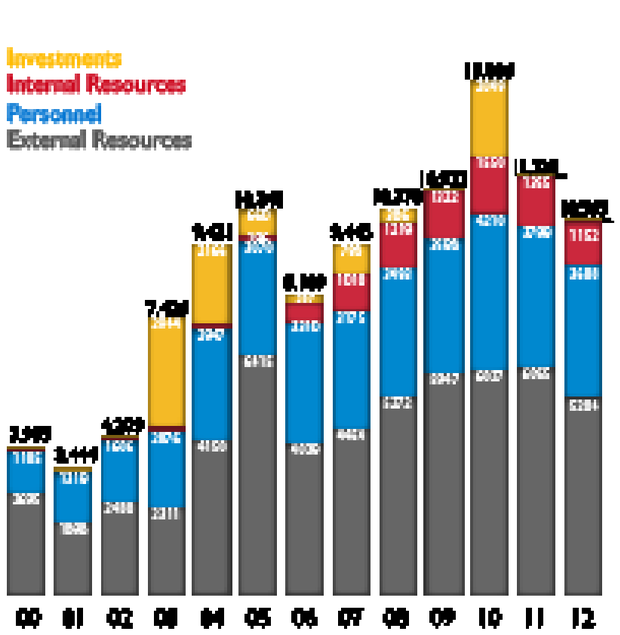
Demonstrated that the down-regulation of major brain nicotinic acetylcholine receptors subtype (α4β2) underlies the cognitive impairment observed in an experimental model of chronic renal failure (Exp Neurol, 2012).

The Institute in Numbers

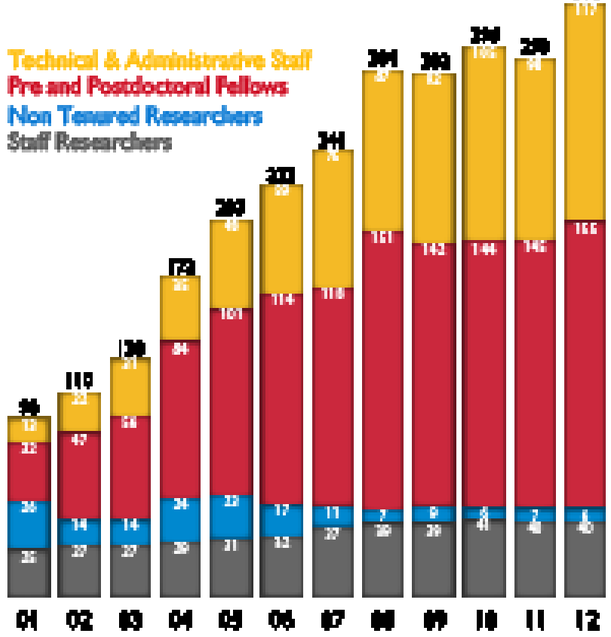
PUBLICATIONS AND IMPACT



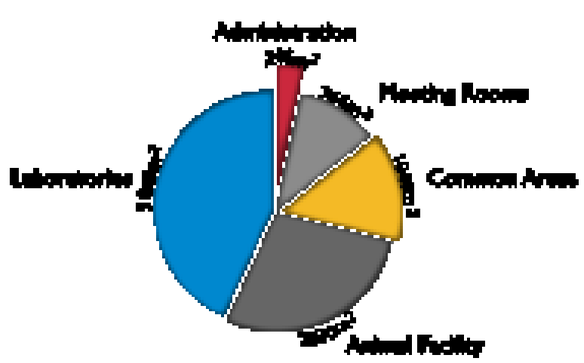
BUDGET GROWTH IN THOUSANDS OF EUROS



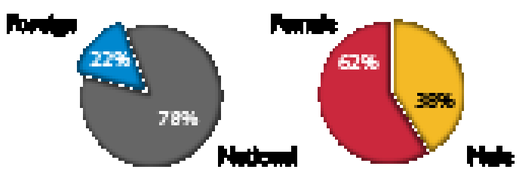
PERSONNEL BY CATEGORY



SURFACE DISTRIBUTION



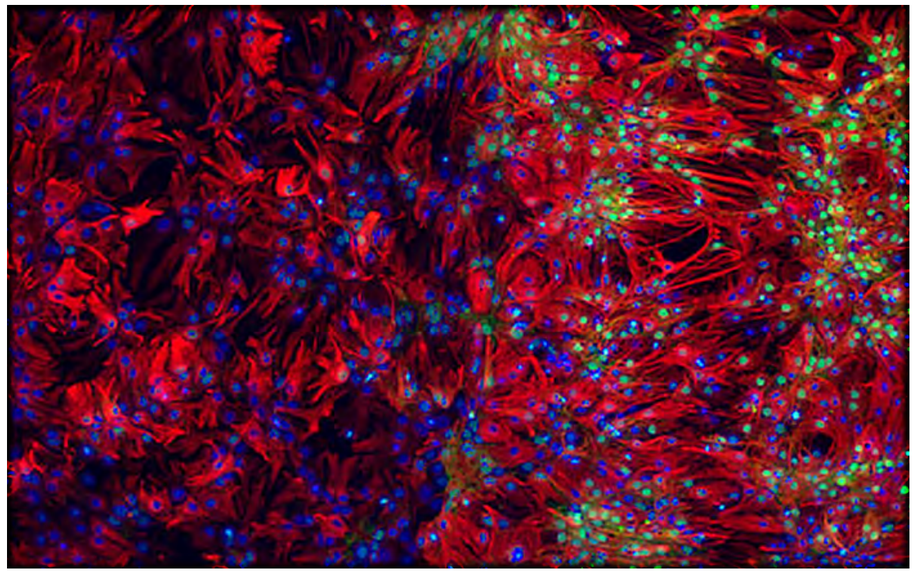
PERSONNEL BY ORIGIN & GENDER



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 and C. elegans) 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 four sublines that this research line encompasses.

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.

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.

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.

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.

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 Colaborator
Carlos del Pozo

CdP

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, Fl. Juíz, JM. Viniegra, S. Ballesta, JJ. (1997). **Differentialexpression of a-bungarotoxin neuronal nicotinicreceptors in adrenergicchromaffincells: a role fortranscription factor Egr-1.** **TheJournal of Neuroscience** *17: 6554-6564.*

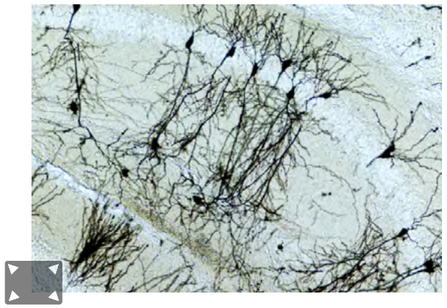
Transcriptional and epigenetic mechanisms of neuronal plasticity

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

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
Marilyn Scandaglia

Technical Staff
Román Olivares

Transcriptional and epigenetic mechanisms of neuronal plasticity

Angel Barco CSIC

Selected Publications

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

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.*

Valor LM, Pulopulos MM, Jimenez-Minchan M, Olivares R, Lutz B and Barco A. (2011) **Ablation of CBP in forebrain principal neurons causes modest memory and transcriptional defects and a dramatic reduction of histone acetylation, but does not affect cell viability.** **J Neurosci** *31(5):1652-63.*

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

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

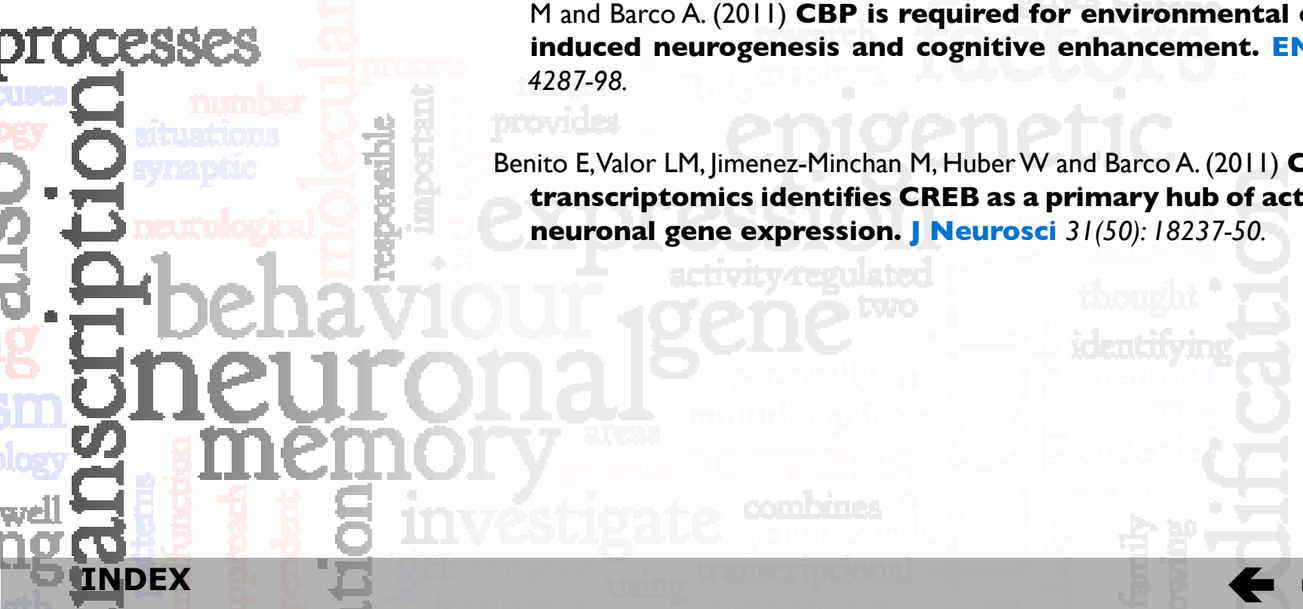
Valor LM, Jancic D, Lujan R and Barco A. (2010) **Ultrastructural and transcriptional profiling of neuropathological misregulation of cAMP-response element binding protein function.** **Cell Death Differ** *17(10):1636-44.*

Lopez de Armentia M, Jancic D, Olivares R, Alarcon ER, Kandel ER and Barco A. (2007) **CREB-mediated gene expression increases the intrinsic excitability of CA1 pyramidal neurons.** **J Neurosci** *27(50): 13909-18.*

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

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

Barco A, Alarcon JM and Kandel ER. (2002) **Expression of constitutively active CREB protein facilitates the late phase of long-term potentiation by enhancing synaptic capture.** **Cell** *108(5): 689-703.*

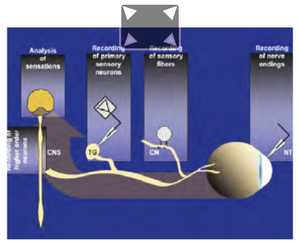


Sensory transduction and nociception

Carlos Belmonte UMH

Roberto Gallego UMH

Félix Viana CSIC

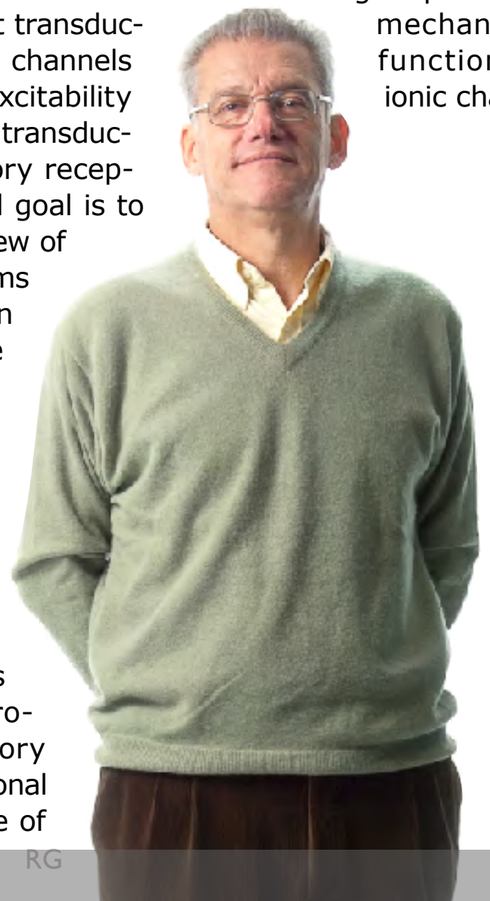


Mammalian somatic sensory receptors are structures specialized in the detection of thermal, mechanical and chemical stimuli, both innocuous and noxious, that impinge upon the organism during changes in the external or internal environment. Activation of these receptors by specific stimuli gives rise 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.

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



Sensory transduction and nociception

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Sensory transduction and nociception

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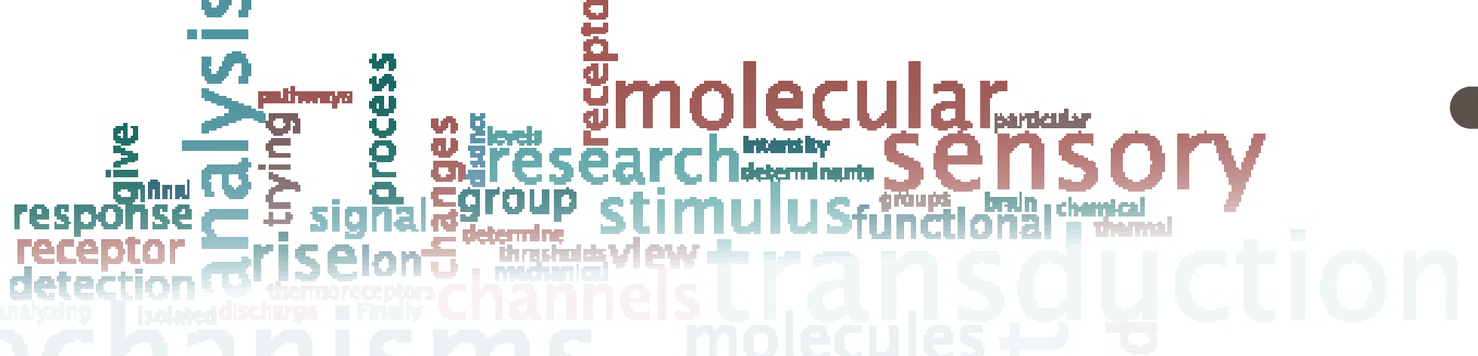

Selected Publications

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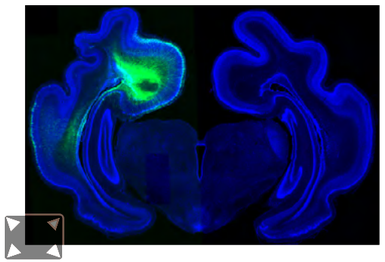
Neurogenesis and cortical expansion

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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Technical Staff
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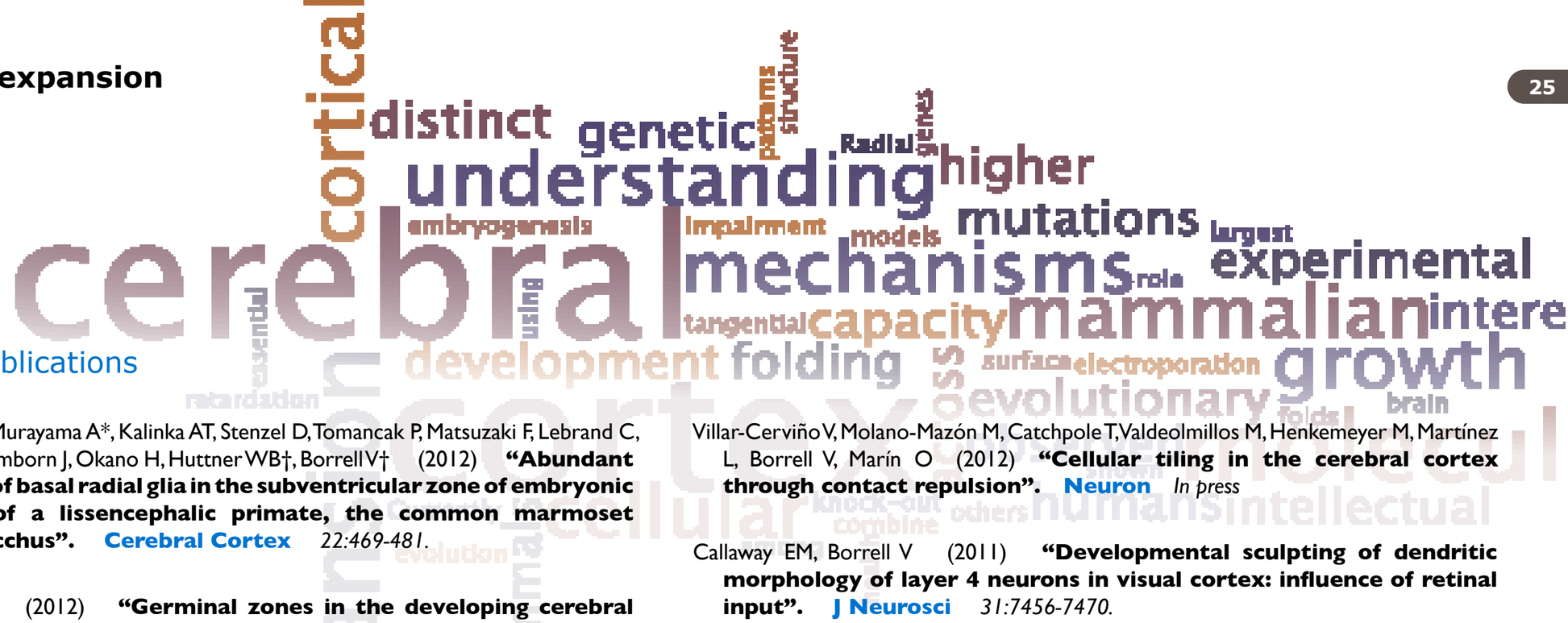
Neurogenesis and cortical expansion

Víctor Borrell CSIC



Selected Publications

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

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Callaway EM, Borrell V (2011) **"Developmental sculpting of dendritic morphology of layer 4 neurons in visual cortex: influence of retinal input".** **J Neurosci** *31:7456-7470.*

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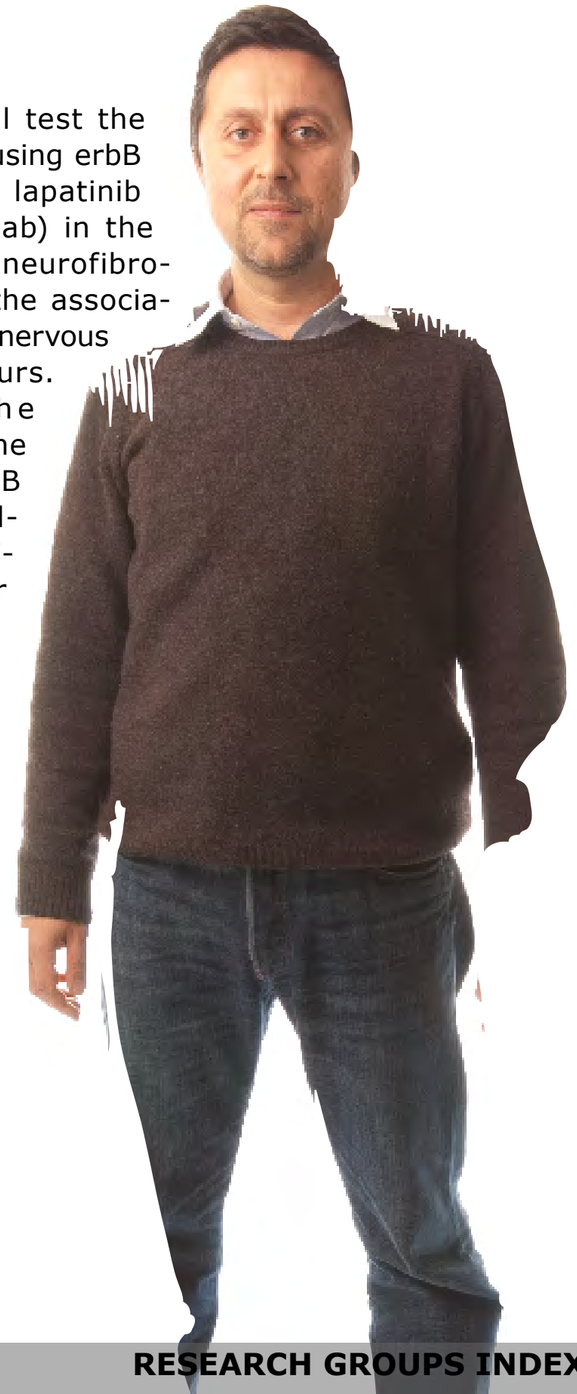
Molecular control of axonal myelination

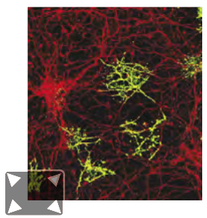
Hugo Cabedo UMH

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

Hugo Cabedo UMH

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Molecular control of axonal myelination

Hugo Cabedo UMH

Selected Publications

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

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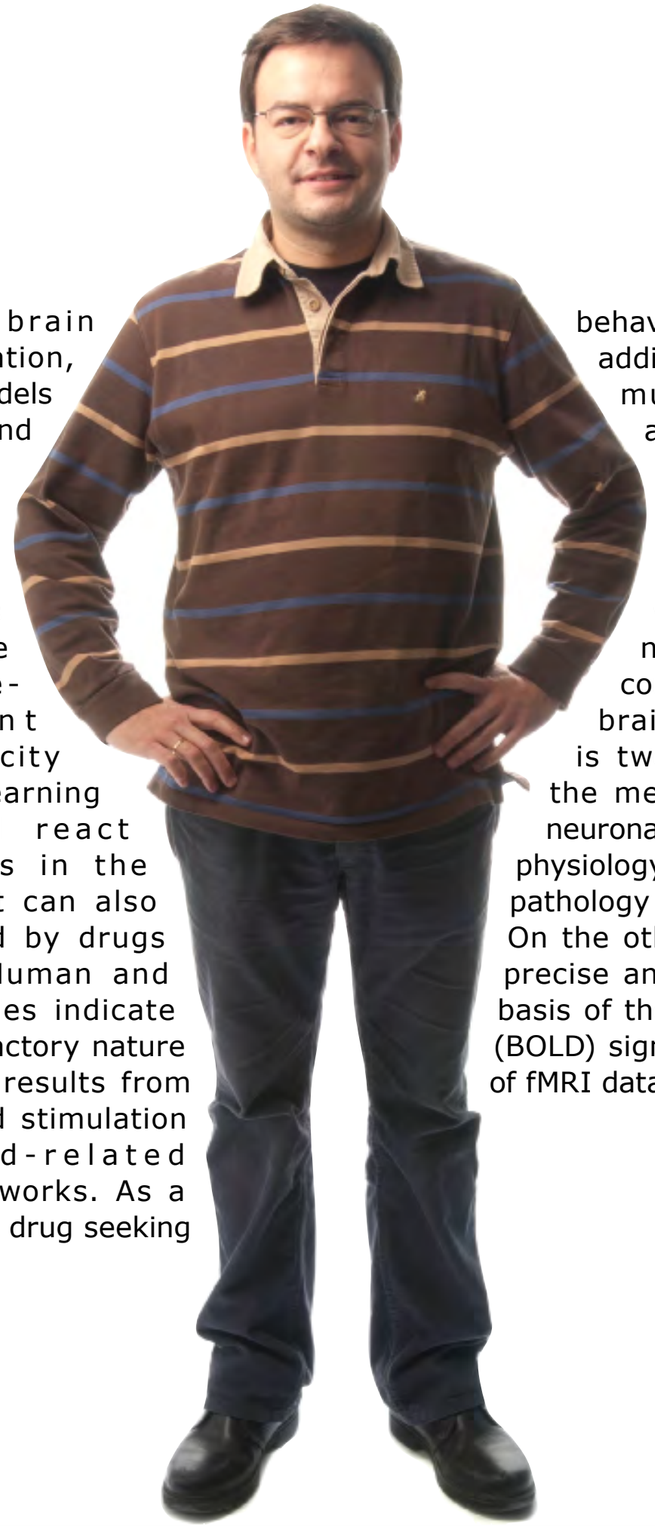
Plasticity of brain networks

Santiago Canals Gamoneda CSIC

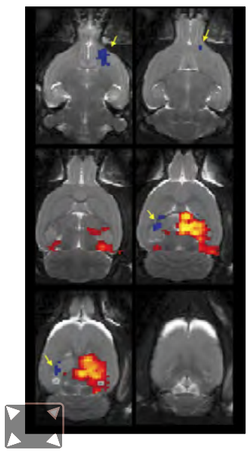


A fast response to changes in environmental conditions increases the fitness and reproductive success of organisims. The work of our group focuses on two research lines: plasticity of brain networks and brain energetics.

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

Canals, S.*, Larrosa, B., Pintor, J., Mena, M.A. and Herreras O. (2008) **Met abolicchallengetogliaactivatesanadenosine-mediated safety mechanismthatpromotes neuronal survivalbydelayingtheonset of spreadingdepressionwaves.** **J. Cereb. BloodFlowMetab.** *28(11):1835-44.) * Correspondingauthor)*

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Angelovski,G.,Fouskova,P.,Mamedov,I.,Canals,S.,Toth,E.,Logothetis,N.K. (2008) **Smart MRI agentssensingextracellularcalciumfluctuations.** **Chem. Bio. Chem.** *9(11):1729-1734.*

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Canals, S., López-Aguado, L., Herreras, O. (2005) **Synaptically recruited apical currents are requiredtoinitiateaxonal and apical spikes in hippocampalpyramidalcells: modulationbyinhibition.** **J. Neurophysiol.** *93(2):909-18.*

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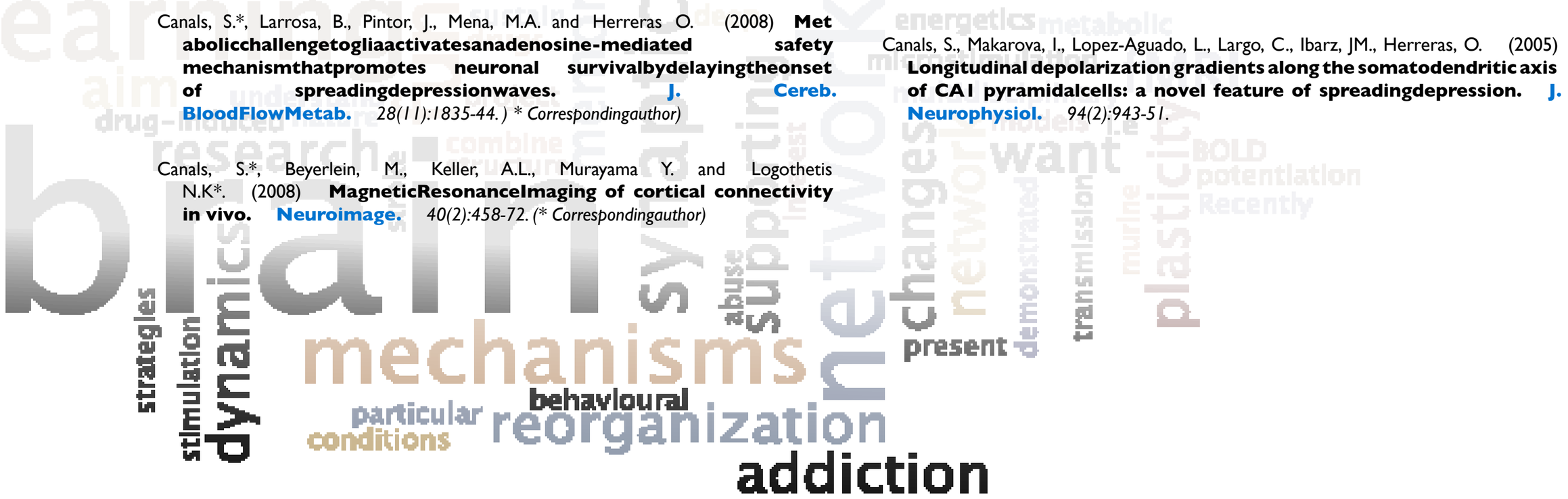
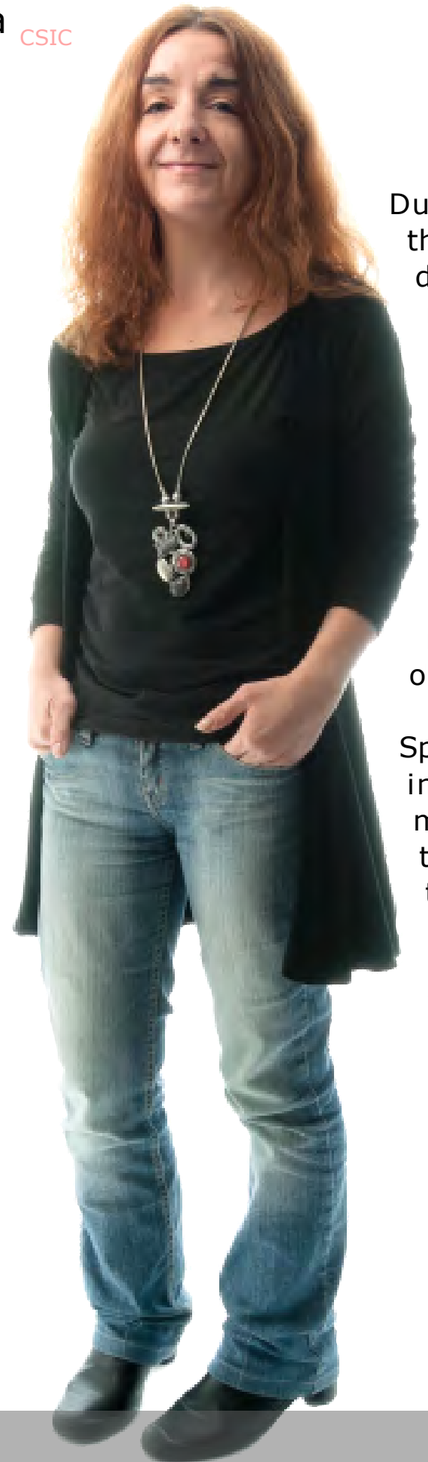


PDZ proteins and signaling networks during the specification of neuronal identities

Ana Carmena CSIC

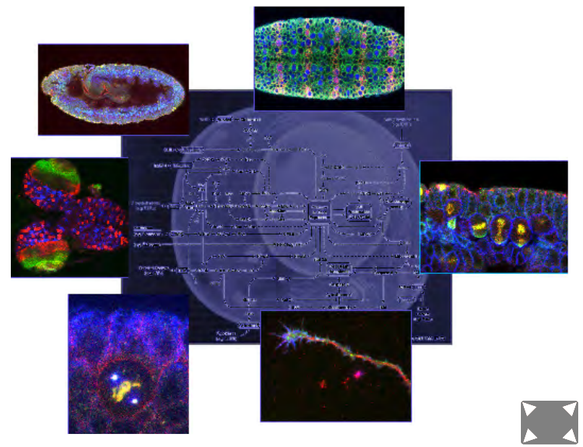


During the development of the nervous system a great diversity of neuronal types is generated. In fact, the human brain has more than 100,000 millions of neurons, most of them specified during the embryonic development. Unravelling the molecular mechanisms that underlie the acquisition of neuronal identities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

PDZ proteins and signaling networks during the specification of neuronal identities

Ana Carmena CSIC

Selected Publications

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

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

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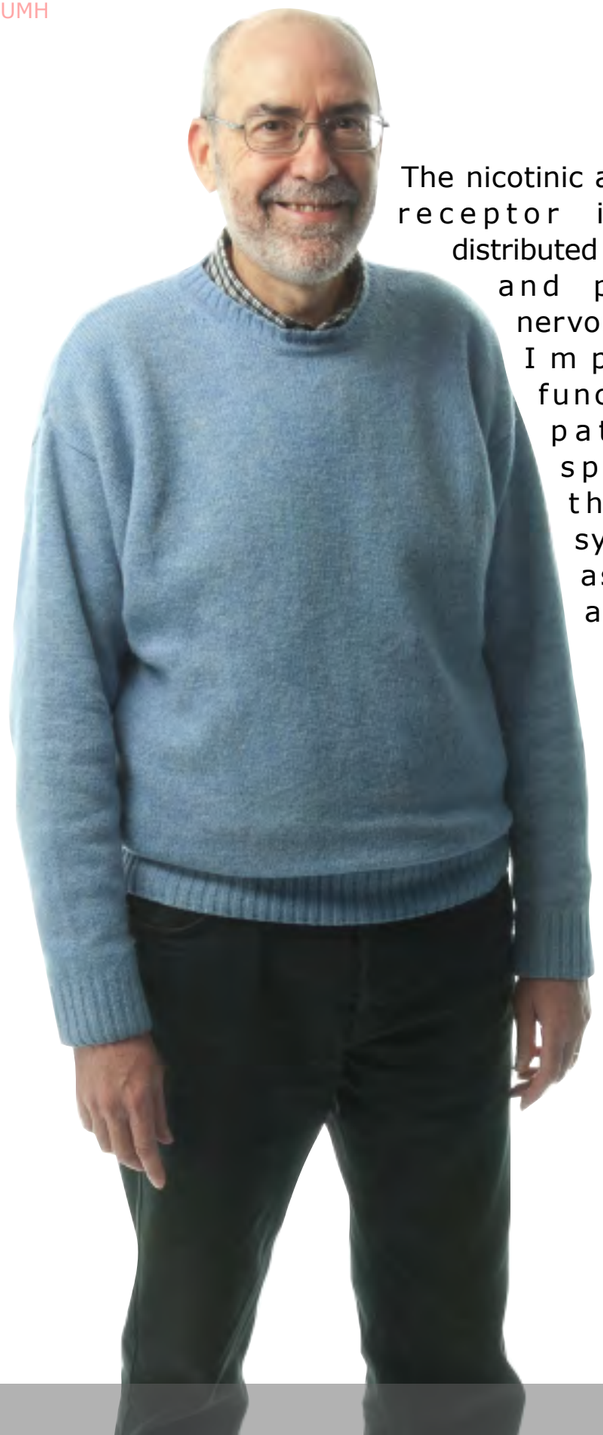
Molecular neurobiology of neuronal nicotinic receptors

Manuel Criado UMH

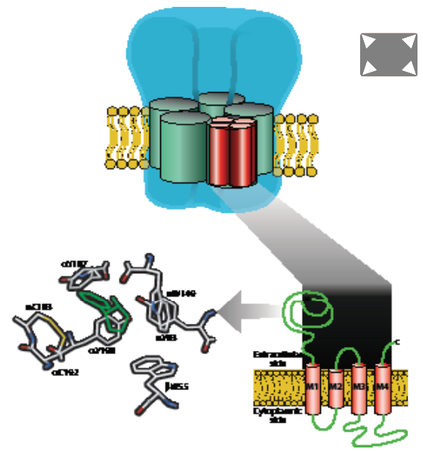


The nicotinic acetylcholine receptor is widely distributed in the central and peripheral nervous systems. Important functions and pathologies specifict o thenervous system, such as memory, anxiety, analgesia, cerebral circulation, nicotine adiction and Alzheimer disease, could be better understood and/or 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 tor egulate receptor biogenesis and function. Synthesis, assembly and localization of nicotinic receptors are complex processes that needt he 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 nicotinicreceptors.Antagonists as well as positive allostericmodulators are being studied.



Molecular neurobiology of neuronal nicotinic receptors

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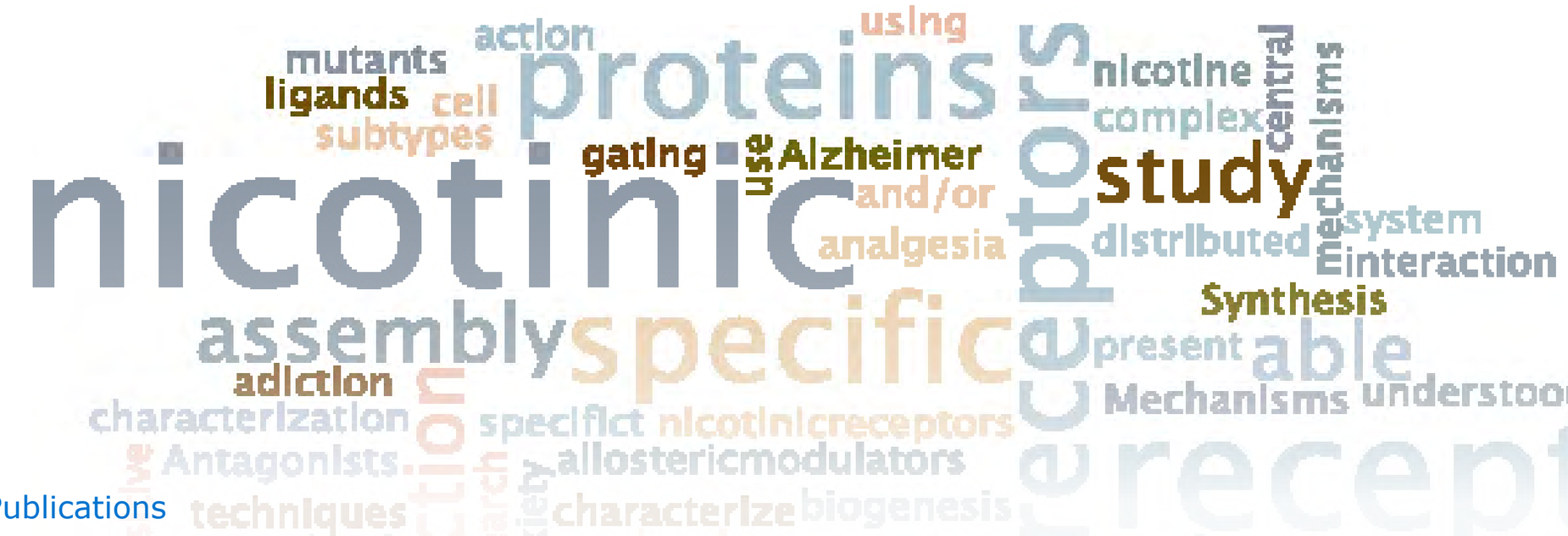
Molecular neurobiology of neuronal nicotinic receptors

Manuel Criado UMH



Selected Publications

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

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

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

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

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

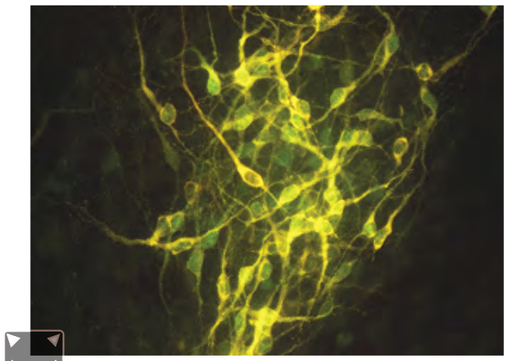
Alexander, J., Sagher, D., Krivoshein, A., Criado, M., Jefford, G., Green, W. (2010) **Ric-3 promotes alpha7 nicotinic receptor assembly and trafficking through the ER sub-compartment of dendrites.** **J. Neurosci.** *30, 10112-10126*

Cellular 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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PhD Student
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Macarena Herrera
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Cellular and conductual neuroscience

Carmen de Felipe UMH

Selected Publications

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

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

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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

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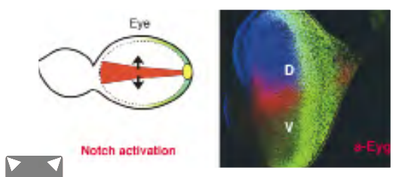
Maria Domínguez CSIC

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

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

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Rosa Garcia Cayuela

Mechanisms of growth control and cancer in Drosophila

Maria Domínguez CSIC

Selected Publications

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

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Palomero T., Sulis, ML*., Cortina M*., Real PJ., Barnes K., Ciofani M., Caparros E., Buteau J., Brown K., Perkins SL., Bhagat G., Mishra A., Basso G., Parsons R., Zúñiga-Pflücker JC., Dominguez M# and Ferrando AA#. (2007). **Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia.** **Nature Medicine** *13(10):1203-10. (*,Equally contributing authors;# Authors for correspondence).*

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Villa-Cuesta, E., Navascués, J., Diez del Corral, R., Ruiz-Gómez, M., Dominguez, M., de Celis, JF., Modolell, J. (2003). **Tufted is a gain-of-function allele that promotes ectopic expression of the proneural gene amos in Drosophila.** **Genetics,** *163:1403-1412.*

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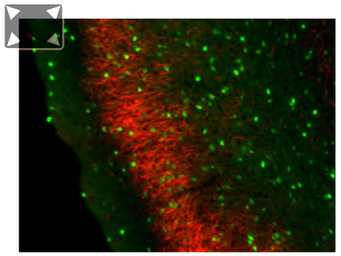
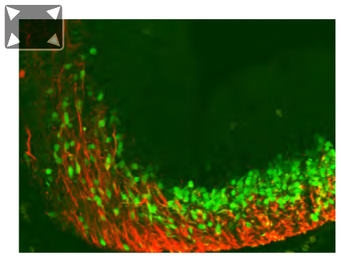
Cortical development

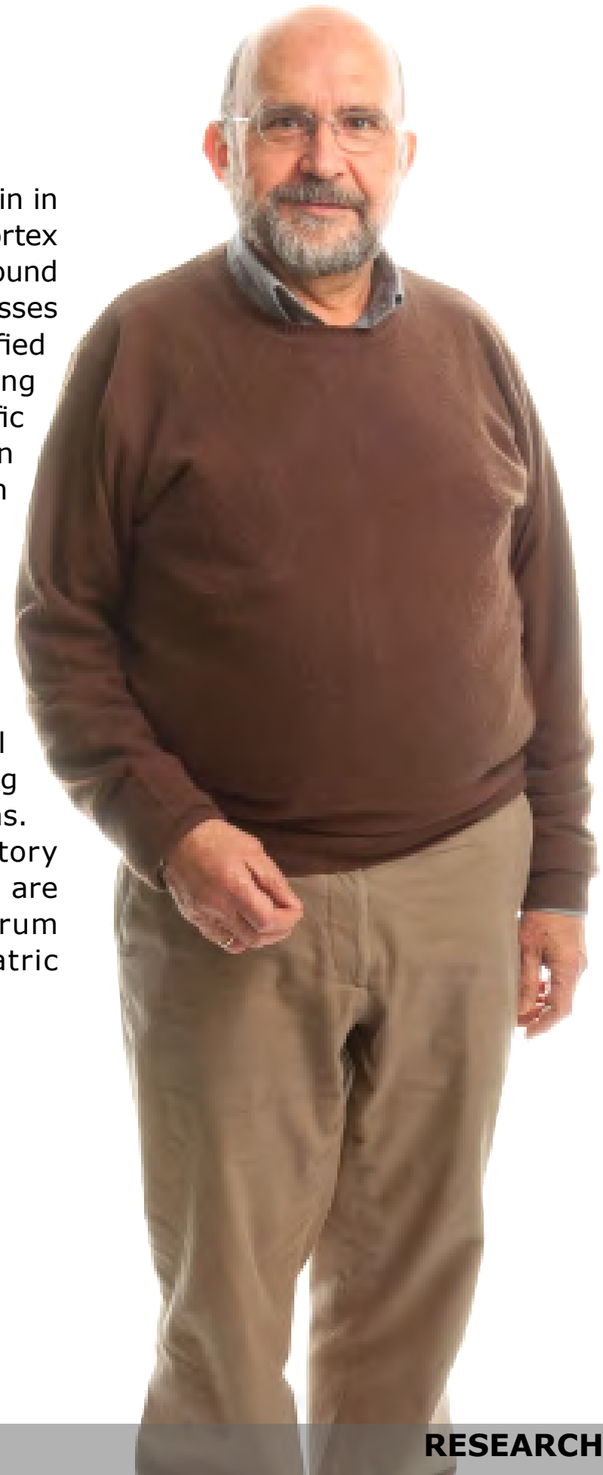
Alfonso Fairén CSIC





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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Cortical development

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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.*

Petilla Interneuron Nomenclature Group:Ascoli, G.A.,Alonso-Nanclares, L.,Anderson, S.A., Barrionuevo, G., Benavides-Piccione, R., Burkhalter, A., Buzsaki, G., Cauli, B., DeFelipe, J., Fairén, A., Feldmeyer, D., Fishell, G., Fregnac, Y., Freund, T.F., Karube, F., Gardner, D., Gardner, E.P., Goldberg, J.H., Helmstaedter, M., Hestrin, S., Kisvarday, Z., Lambolez, B., Lewis, D., Marin, O., Markram H., Muñoz, A., Packer, A., Petersen, C., Rockland, K., Rossier, J., Rudy, B., Somogyi, P., Staiger, J.F., Tamas, G., Thomson, A.M., Toledo-Rodriguez, M., Wang, Y., West, D.C., and Yuste, R. (2008) **Petilla Terminology: Nomenclature of features of GABAergic interneurons of the cerebral cortex.** **Nature Reviews Neuroscience,** *9:557-568.*

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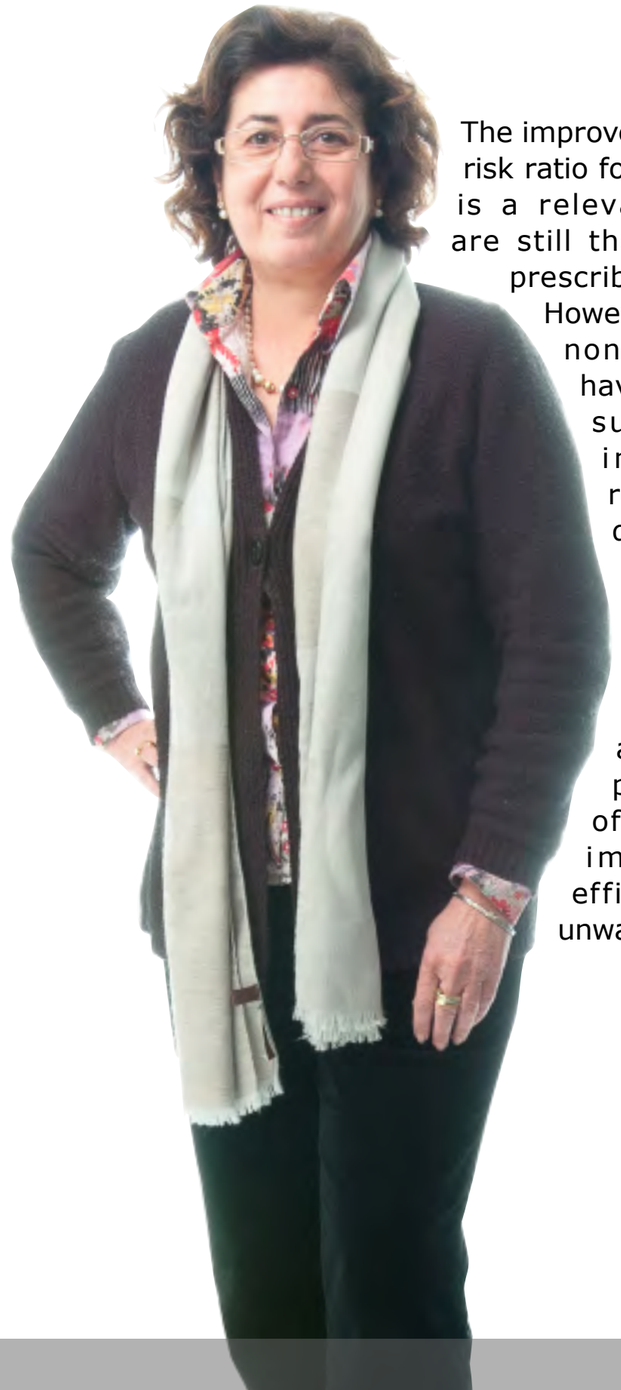
Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH



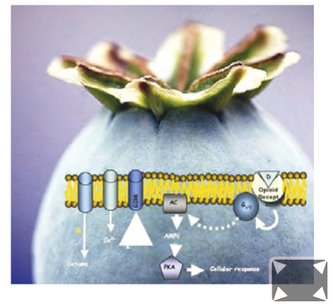
The improvement in the benefit–risk ratio for analgesic therapies is a relevant issue. Opioids are still the most potent and prescribed analgesic drugs. However, their clinical and non-clinical uses still have serious problems such as variability in the analgesic response, tolerance, dependence, addiction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

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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–regulationBetweenm and d OpioidReceptors at Supraspinallevel.** **Br J Pharmacol** *DOI: 10.1111/j.1476-5381.2011.01750.x*

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Ocular Neurobiology

Juana Gallar UMH

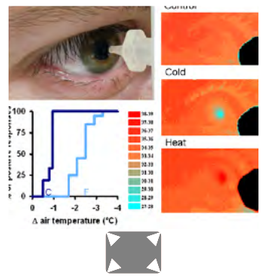
Mª Carmen Acosta UMH

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

Ocular Neurobiology

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(Ophthalmology, University of Helsinki, Helsinki, Finlandia)
Javier Belmonte
(Hospital General Universitario de Alicante)

KM

Ocular Neurobiology

Juana Gallar UMH

Mª Carmen Acosta UMH

Selected Publications

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

Neira-Zalentein W, Holopainen JM, Tervo TMT, Borrás F, Acosta MC, Belmonte C, Gallar J. (2011) **Corneal sensitivity to selective stimulation of diabetic patients subjected to retinal laser photocoagulation.** **Invest Ophthalmol Vis Sci.** *52: 6043–6049.*

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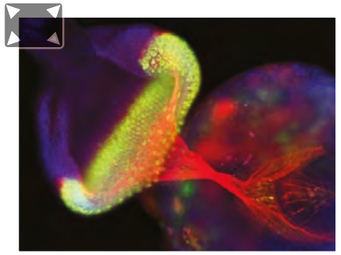
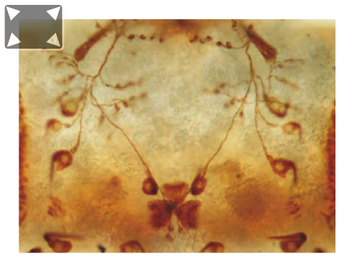
Developmental Neurogenetics

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.

Developmental Neurogenetics

Luis García-Alonso CSIC

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PhD Student
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Technical Staff
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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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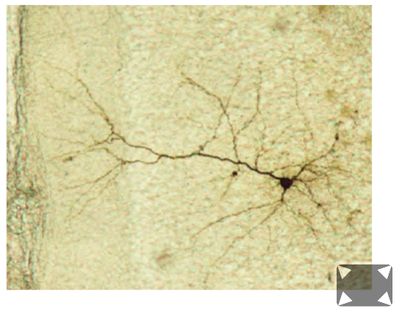
Physiology of the cerebral cortex

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
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Eduardo Domínguez (with Dr. S. Martínez)
Alejandro Sempere
Scientist Collaborator
Carlos Pastore (Hospital Universitario de San Juan)
Ofelia González (Hospital Universitario de San Juan)

VR

ED

AS

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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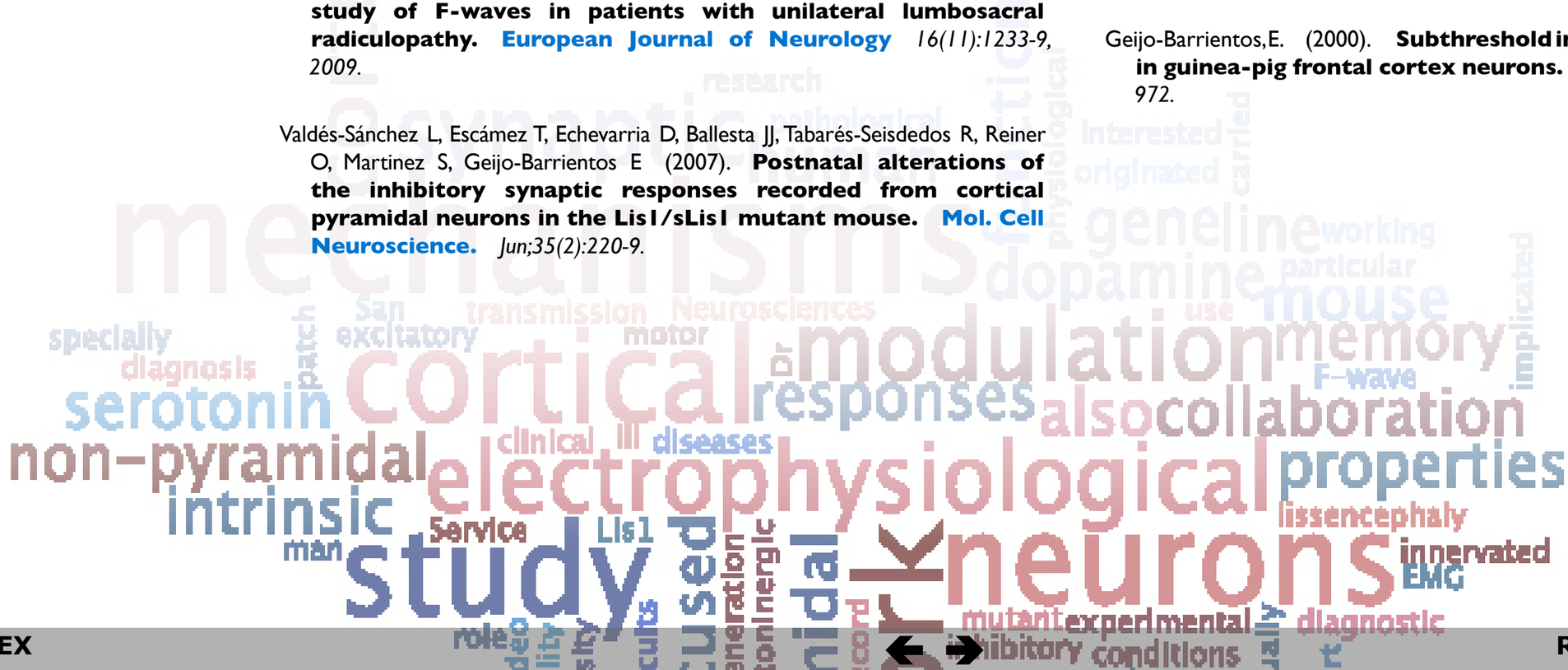


Mechanotransduction in mammals

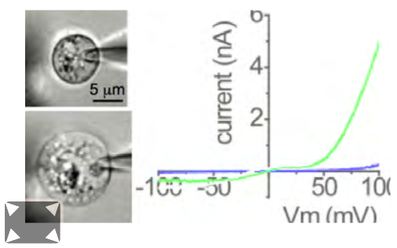
Ana Gomis CSIC

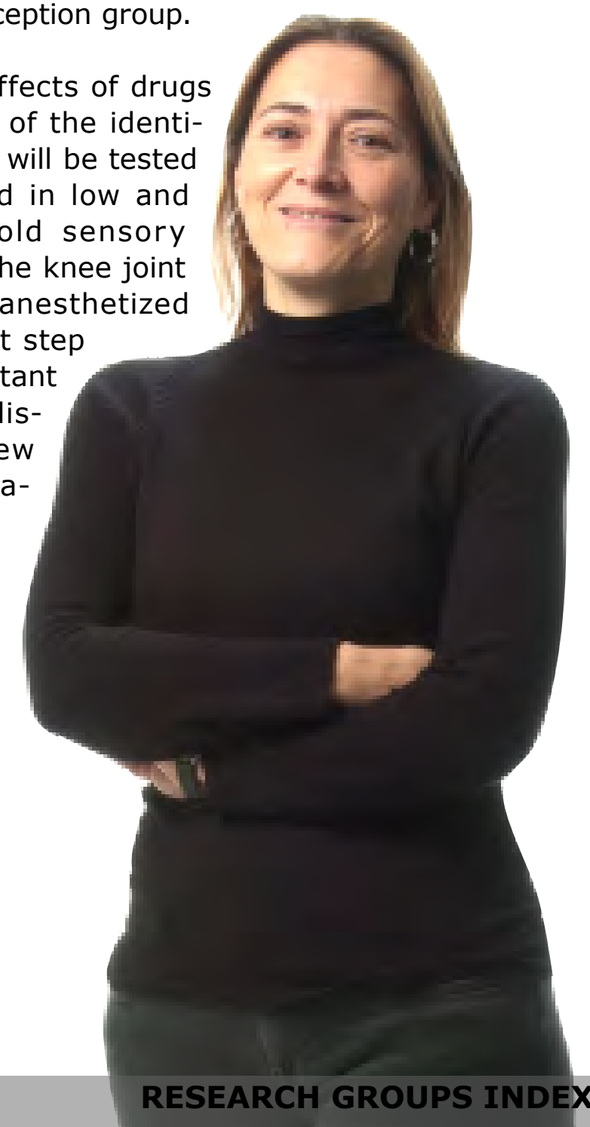
The first step in pain sensation is the activation by noxious stimuli of a subpopulation of primary sensory neurons named "nociceptive neurons". Based upon the form of energy to which they respond preferentially, nociceptive neurons have been classified as sensitive to mechanical, irritant chemicals 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

Ana Gomis CSIC

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Research Group

Mechanotransduction in mammals

Ana Gomis CSIC

Selected Publications

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

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

PierluigiValente,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.*

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Nuria García-Sanz, PierluigiValente,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*

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Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH

Salvador Viniegra UMH

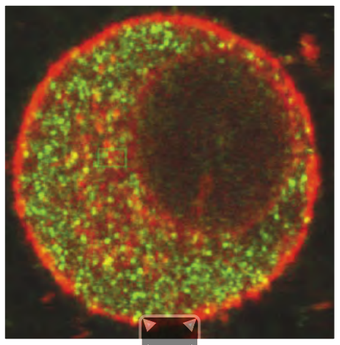
LMG

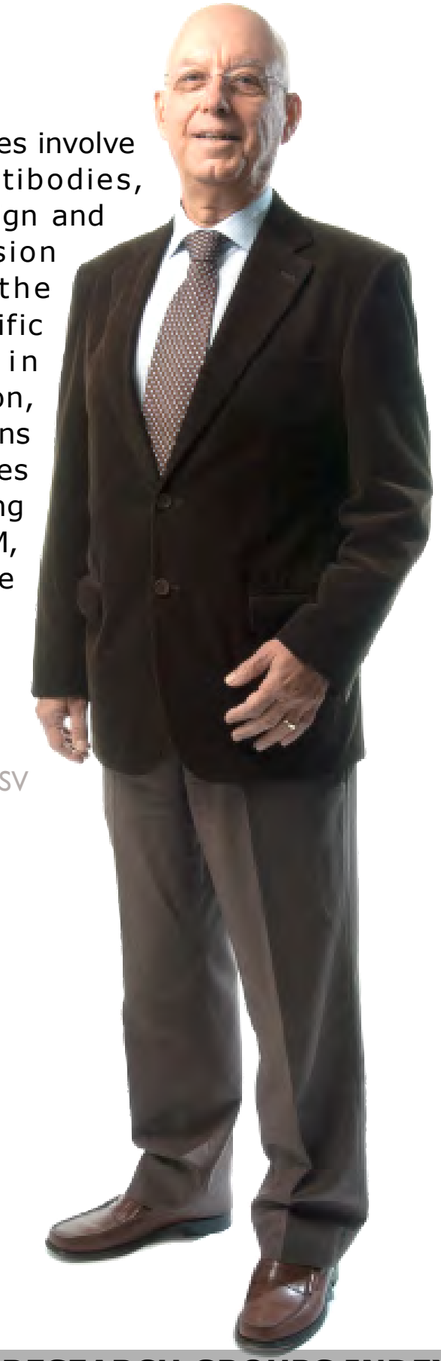
Adrenomedullary chromaffin cells have been used as an excellent experimental model to study the exocytosis and therefore the molecular mechanisms of neuro-transmission. It is now clear that the proteins involved in the processes of vesicle docking, membrane fusion and neurotransmitter release are common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

Luis M. Gutiérrez UMH

Salvador Viniegra UMH

Principal Investigator
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PhD Investigator
José Heliodoro Villanueva
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Cristina Juana Torregrosa-Hetland
Virginia Garcia-Martinez

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María del Mar Francés


JHV


IL


CJTH


VG-M


MdMF

Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH

Salvador Viniegra UMH

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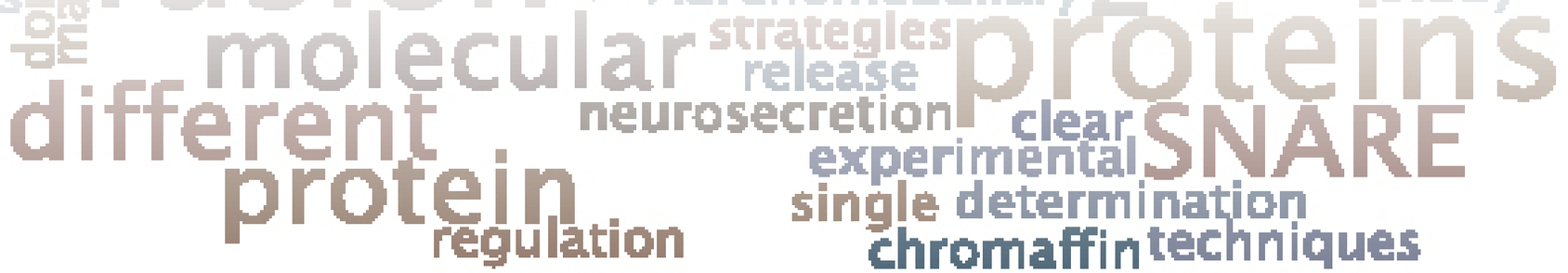
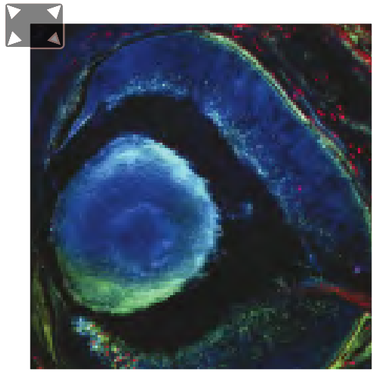
Ñeco, P., Giner, D.,Viniegra, S., Borges, R.,Villarroel,A., Gutierrez, LM. (2004) **New roles of myosin II during the vesicle transport and fusion in chromaffin cells. J. Biol. Chem.,** *279: 27450-27457.*



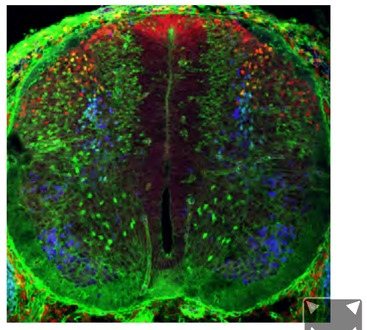
Development and assembly of bilateral neural circuits

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

Eloísa Herrera CSIC

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Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Selected Publications

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

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

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

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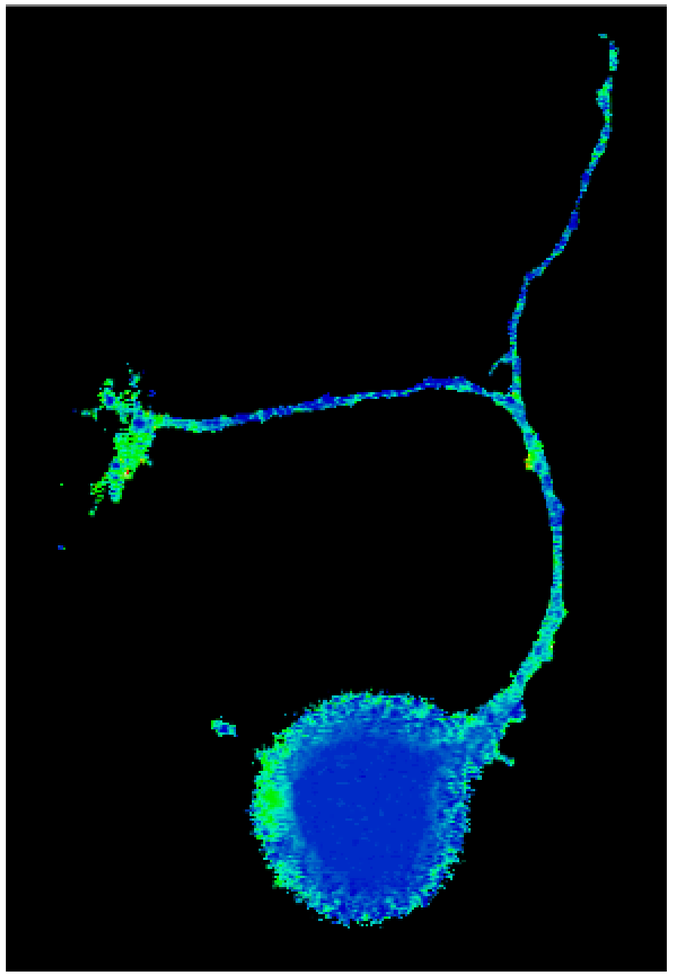
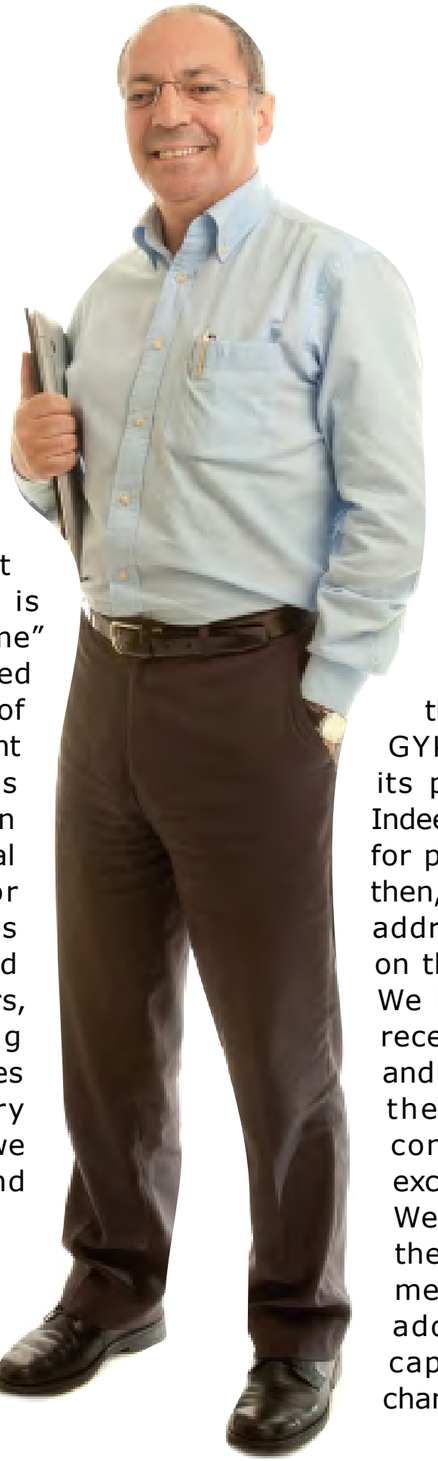
Herrera, E., Brown, L., Aruga, J., Rachel, R., Dolen, G., Mikoshiba, K., Brown, S., Mason, CA. (2003) **Zic2 patterns binocular vision by specifying the uncrossed retinal projection.** **Cell,** *114: 545-557. (Cover Caption).*

Synaptic physiology

Juan Lerma CSIC





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

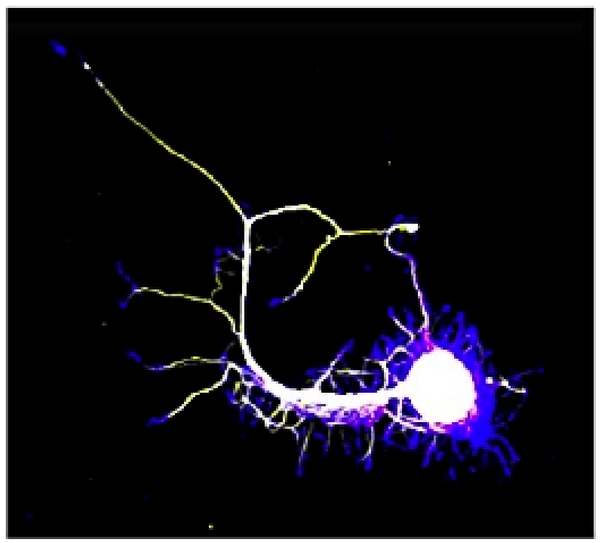
In the frame of defining the molecular structures mediating neuronal communication, we described for the first time the existence in central neurons of another type of functional glutamate receptors, the kainate receptor (KAR). We have demonstrated that KAR proteins form functional receptor channels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

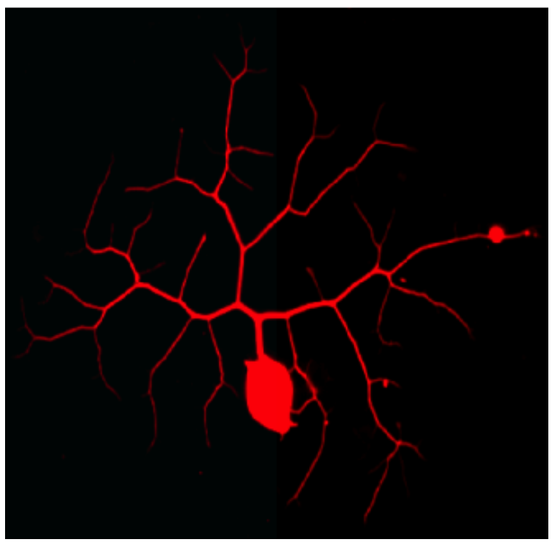
Synaptic physiology

Juan Lerma CSIC

messenger-mediated cascade, involving a G-protein. This and subsequent work put forward the new concept that ion channel-forming receptors are also able to signal through a G-protein, opening new vistas on the mechanisms by which glutamate receptors of the ionotropic type work. Taken together, our data has helped to understand why KAR activation is proconvulsive and pointed them as targets for new treatments of epileptic disease.

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





Synaptic physiology

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Synaptic physiology

Juan Lerma CSIC

Selected Publications

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

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

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

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Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

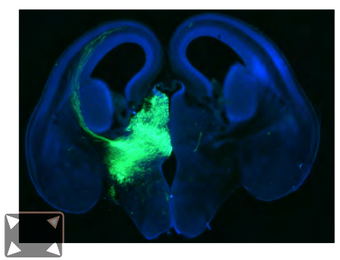
Our research team runs several related projects studying the cellular and molecular mechanisms involved in the development of axonal connections in the brain. In particular, our aim is to uncover the principles underlying thalamocortical axonal wiring, maintenance and ultimately the rewiring of connections,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

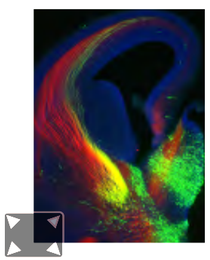
The development of the thalamocortical wiring requires a precise topographical sorting of its connections. Each thalamic nucleus receives specific sensory information from the environment and projects topographically to its corresponding cortical. A second level of organization is achieved within each 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.

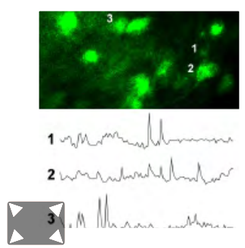
Three major questions are been focused in the laboratory: i) the transcriptional control of thalamocortical topography; ii) integration of distinct signalling pathways in thalamocortical behaviour; and iii) the activity-dependent mechanisms involved in thalamocortical guidance and wiring.

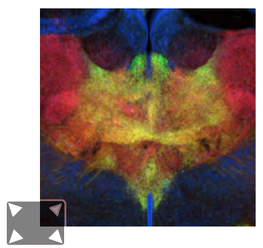
Within these projects we are using several experimental programmes, these include: optical imaging, manipulation of gene expression in vivo, cell and molecular biology, biochemistry, cell culture and electrophysiology. Furthermore, our team has successfully set up the technique of in utero electroporation 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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Helena Campos Martín


MdMCP


HG


GNM

ELD


CM


NAB


VMJ


CMS


LMRM


RSC


HCM

Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications

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*

Yamamoto N, López-Bendito G. (2012) **Shaping brain connections through spontaneous neural activity.** **Eur J Neurosci** *May;35(10):1595-604*

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

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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.*

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López-Bendito G, Molnár Z (2003) **Thalamocortical development: how are we going to get there?** **Nat. Rev. Neurosci.** *4:276-289.*

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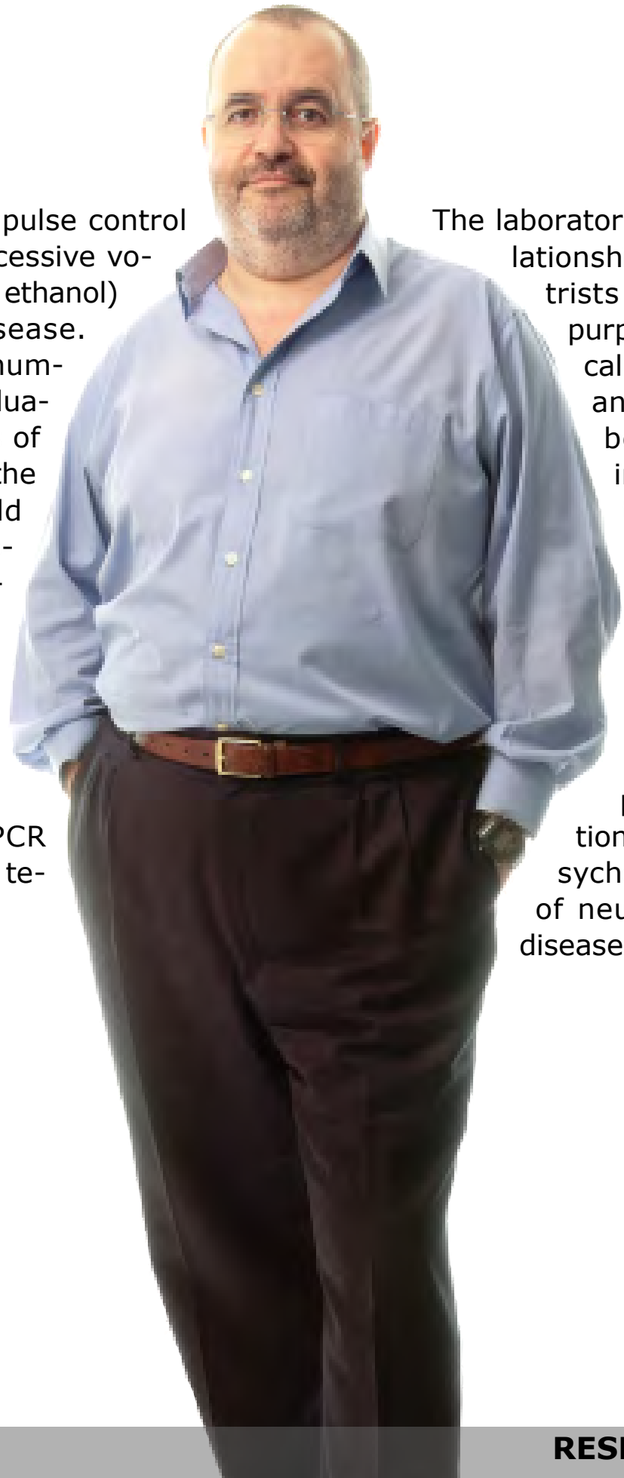
Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

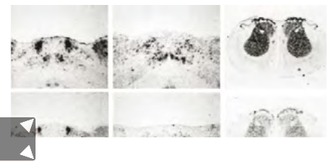
The laboratory is focused in the identification of key receptors and genes underlying behavioral and molecular alterations involved in the occurrence of neuropsychiatric disorders (anxiety, depression, drug dependence, Parkinson, etc..) and that may represent potential new targets to treat these diseases.

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

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



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



Translational neuropsychopharmacology of neurological and psychiatric diseases

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Translational neuropsychopharmacology of neurological and psychiatric diseases

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Selected Publications

Vinod, K.Y, Maccioni P., Garcia-Gutierrez, M.S., Femenia, T. Xie S., Carai A.M., Manzanares, J., Cooper, T.B, Hungund, B.L. and Colombo G.. (2012) **Innate difference in the endocannabinoid signaling and its modulation by alcohol consumption in alcohol-preferring sP rats,** **Addiction Biology** *17(1):62-75*

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García-Gutiérrez MS, García-Bueno B, Zoppi S, Leza JC, Manzanares J. (2012) **Chronic blockade of cannabinoid CB(2) receptors induces anxiolytic-like actions associated to alterations in GABA(A) receptors.** **British Journal of Pharmacology** *165(4):951-964*

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

Silvia Zoppi, José L.M. Madrigal, Beatriz G. Pérez-Nievas, Ignacio Marín-Jiménez, Javier R. Caso, Luis Alou, Borja García-Bueno, Arturo Colón, Jorge Manzanares, M. Luisa Gómez-Lus, Luis Menchen, Juan C. Leza. (2012) **Endogenous cannabinoid system regulates intestinal barrier function in vivo through cannabinoid type I receptor activation.** **Am J Physiol Gastrointest Liver Physiol** *302: G565–G571*

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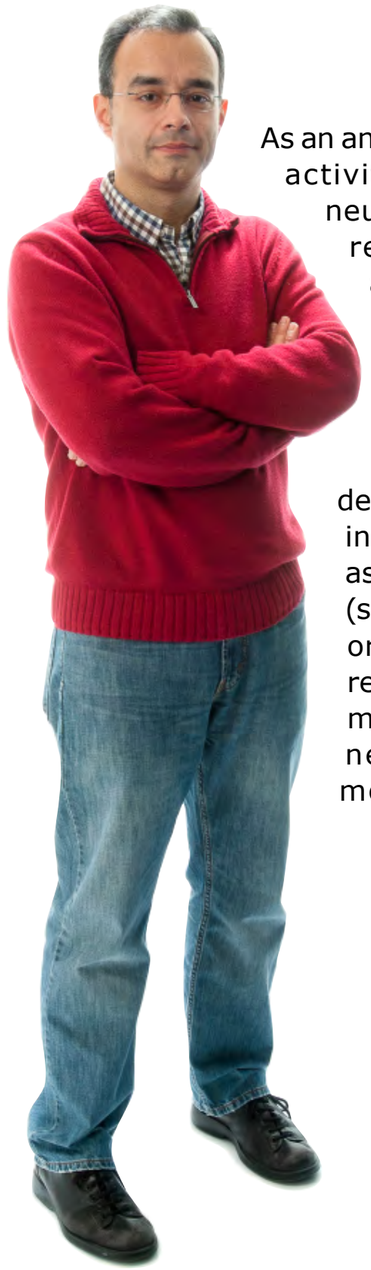
Pérez-Rial, S., Molina, J.A., García-Gutiérrez, MS, Gómez Pérez-Nievas, Ledent, C., B., Leiva, C., Leza, J.C., Manzanares, J., (2011) **Increased vulnerability to 6-hydroxydopamine lesion and reduced development of dyskinesias in mice lacking CB1 cannabinoid receptors.** **Neurobiology of Aging,** *32: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

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

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

Dynamics and plasticity of cortical sensory responses

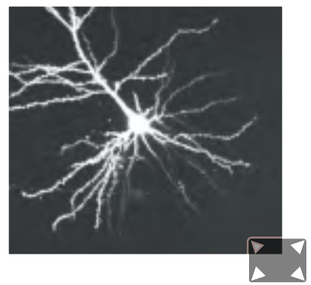
Miguel Maravall CSIC



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

Miguel Maravall CSIC

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PhD Student
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Giovanni Ferrati

Technical Staff
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GF

AP

Dynamics and plasticity of cortical sensory responses

Miguel Maravall CSIC

Selected Publications

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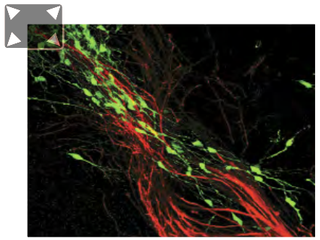
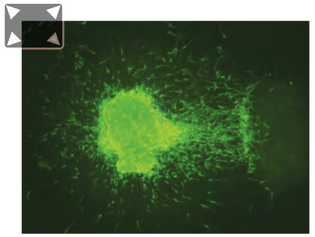
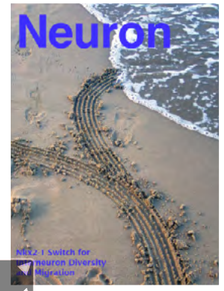
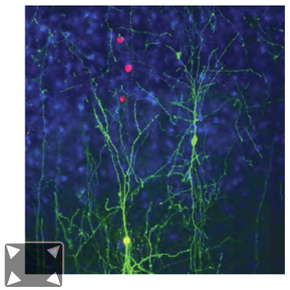
Neuronal migration and circuit assembly in the cerebral cortex

Oscar Marín CSIC







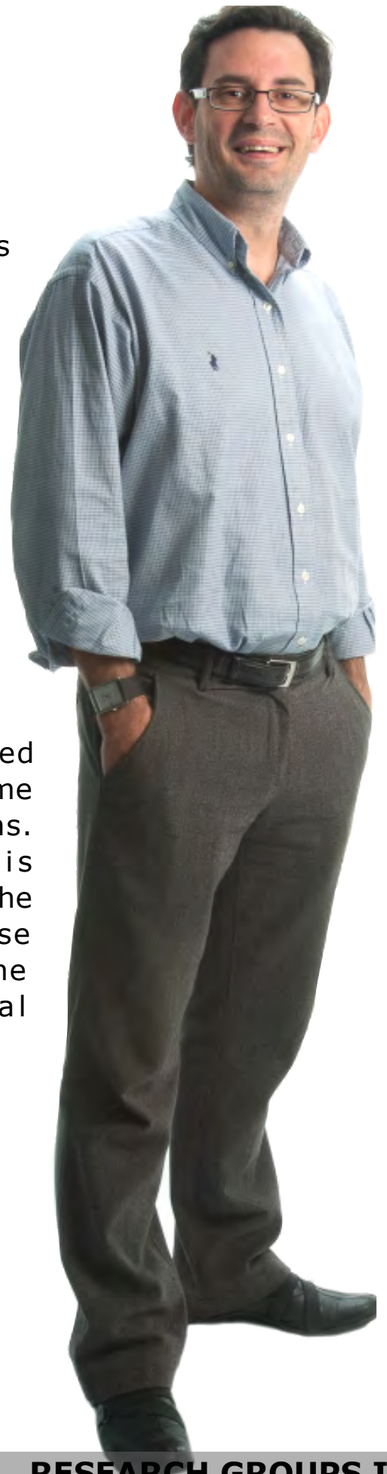


The main aim of our laboratory is to understand the molecular and cellular mechanisms controlling the development of the most anterior region of the brain, the telencephalon. The telencephalon contains key structures for the function of the mammalian brain, such as the basal ganglia and the cerebral 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 JAS-A 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

Borrell V, Cardenas A, Ciceri G, Galceran J, Flames N, Pla R, Nobrega-Pereira S, Garcia-Frigola C, Peregrin S, Zhao Z, Ma L, Tessier-Lavigne M, Marín O. (2012) **Slit/Robo signaling modulates the proliferation of central nervous system progenitors** **Neuron,** *78: 338-52*

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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* Alonso JM* & Martinez LM* (1998) **"Functional connectivity between simple cells and complex cells in cat striate cortex."** **Nature Neuroscience.** *1:395-403. * Co-author*

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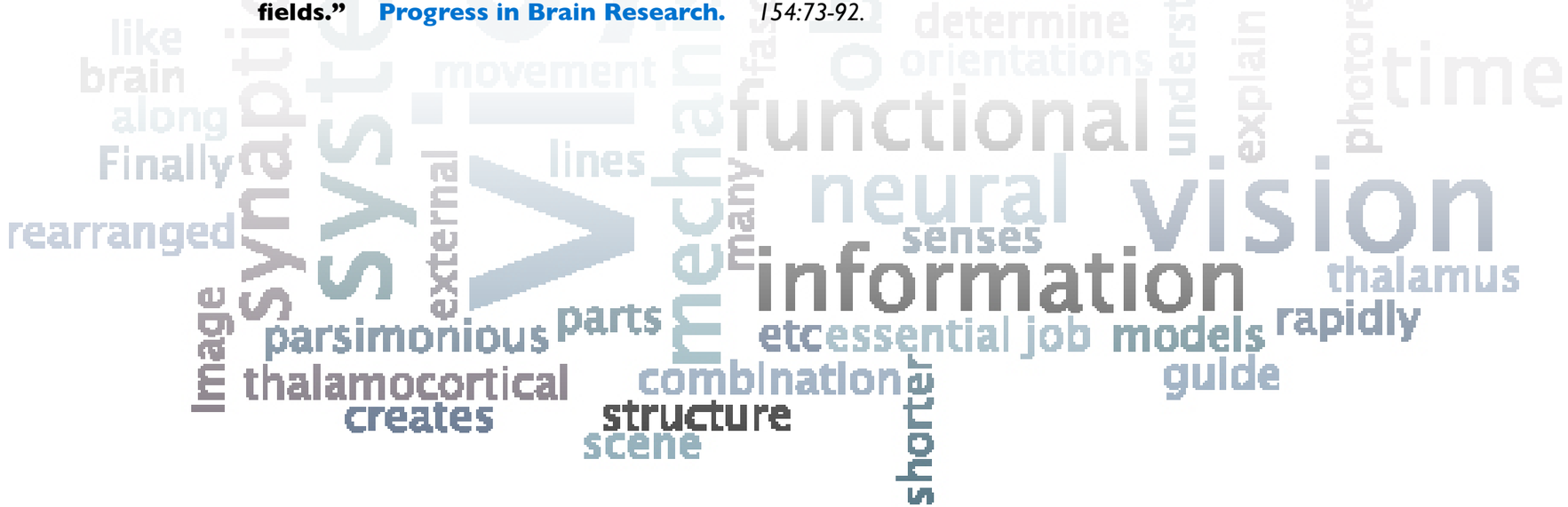
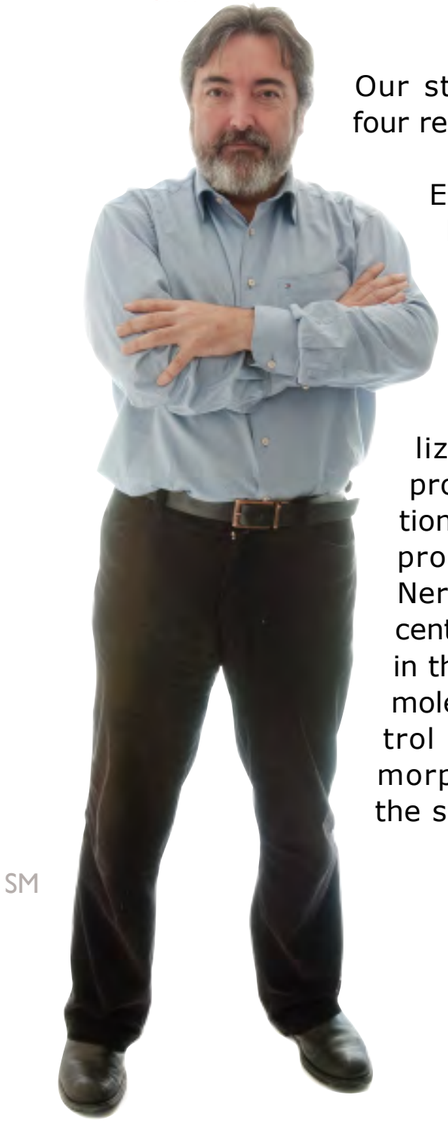


Experimental Embryology

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 an EU Grant in which we pretend in a large scale manner to analyse the expression pattern of 16.000 genes at several embryonic stages of mice (www.eurexpress.org/ee/). The further genetic manipulation by homologous recombination will help us to elucidate the functional role of these genes. Currently we are also interested in genes important of human neuropathogenesis. Thus, we have created a line of research investigating the alterations of lisencephaly, several cortical heterotopies, multiple sclerosis

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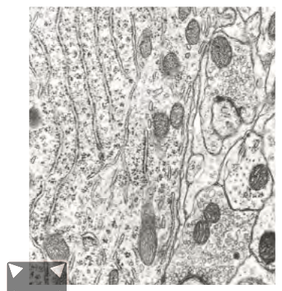

Experimental Embryology

Salvador Martínez UMH

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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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Eva Sabater Sánchez


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DEA


MABL


CBL


RGL


JJB


AMF


AIPG


CRG

Experimental Embryology

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VC


JM-L


JAMB


MNG


EDS


ASF


AA


MPMV


MJAR


OBP


MRG


AEB


FAG

Experimental Embryology

Salvador Martínez UMH

Constantino Sotelo UMH

Selected Publications

Lebrun C, Avci HX, Wehrlé R, Doulazmi M, Jaudon F, Morel MP, Rivals I, Ema M, Schmidt S, Sotelo C, Vodjdani G, Dusart I 2012 **Klf9 is necessary and sufficient for Purkinje cell survival in organotypic culture.** **Molecular and Cellular Neuroscience Nov 29.** *doi:pii: S1044-7431(12) 00209-6.*

Bouslama-Oueghlani L, Wehrlé R, Doulazmi M, Chen XR, Jaudon F, Lemaigre-Dubreuil Y, Rivals I, Sotelo C, Dusart I. 2012 **Purkinje cell maturation participates in the control of oligodendrocyte differentiation: role of sonic hedgehog and vitronetrin.** **PLoS One** *7(11):e49015. doi: 10.1371/journal.pone.0049015*

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Jonathan Jones, Alicia Estirado, Carolina Redondo, Carlos Bueno, Salvador Martinez* 2012 **Human adipose stem cell-conditioned mediaum increases survival of Friedreich's ataxia cell submitted to oxidative stress** **Stem Cells Dev** *10;21(15):2817-26*

María I. Arribas, Jonathan Jones, Salvador Martínez and Enrique Rochea*,. 2012 **Adipose Cell-Derived Stem Cells:Neurogenic and Immunomodulatory Potentials** **Advances in Neuroimmune Biology** *3 (2012) 19–30 DOI 10.3233/NIB-2012-012037*

Miguel Blanquer Blanquer, A Jose M. Moraleda*, Jimenez A, Francisca Iniesta Martínez, A Joaquín Gomez Espuch, A,B Jose Meca Lallana, C Ramon Villaverde Gonzalez, B Miguel Angel Pérez Espejo, D Francisco José Ruiz López, E José María Garcia Santos, F Patricia Bleda Diaz, A Virginia Izura Azanza ,G Maria Saez Gallego, G Pedro De Mingo Casado, G Laura Vivancos Moreau, H Rafael Carles Dies, Judith Jimenez Veiga, Joaquin Hernandez Palazón, I Julia Guardiola Jiménez, E Silvia Torres Del Rio, F Carmen Antunez Almagro, B Pedro De La Rosa Jimenez, D Maria Juliana Majado Martinez, Andres_Sánchez Salinas, Javier López, Juan Francisco Martinez-Lage, Sánchez, Salvador Martínes Pérez 2012 **Neurotrophic Bone Marrow Cellular Nests Prevent Spinal Motoneuron Degeneration In Amyotrophic Lateral Sclerosis Patients:A Pilot Safety Stud** **Stem Cells.** *Jun;30(6):1277-85. doi: 10.1002/stem.1080*

Experimental Embryology

Salvador Martínez UMH

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Martinez-Ferre A, Martinez S. 2012 **Molecular regionalization of the diencephalon** **Front Neurosci** *2012;6:73. Epub 2012 May 25*

Crespo-Enriquez I, Partanen J, Martinez S, Echevarria D. 2012 **Fgf8-related secondary organizers exert different polarizing planar instructions along the mouse anterior neural tube.** **PLoS One..** *2012;7(7):e39977. Epub 2012 Jul 6*

Silveyra MX, Garca-Aylln MS, de Barreda EG, Small DH, Martnez S, Avila J, Sez-Valero J. 2012 **Altered expression of brain acetylcholinesterase in FTDP-17 human tau transgenic mice.** **Neurobiol Aging. 2012** *Mar;33(3):624.e23-34. Epub*

Teresa Escamez, Olga Bahamonde, Rafael Tabares-Seisdedos, Eduard Vieta, Salvador Martinez, and Diego Echevarria 2012 **Developmental Dynamics of PAFAH1B Subunits During Mouse Brain Development** **J Comp Neurol.** *Dec 1;520(17):3877-94.*

Emilio Geijo-Barrientos, Ofelia González, and Carlos Pastore-Olmedo. 2012 **Presence of repeater F-waves in the early stage of Guillain-Barré syndrome** **Journal of the Peripheral Nervous System** *17:128–131*

Juan A. Moreno, Jesus E. Martínez and Eduardo Puelles 2012 **Mesencephalic neuronal populations. New insights on the ventral differentiation programs.** **Histology and Histopathology** *(2012) 27: 1529-1538*

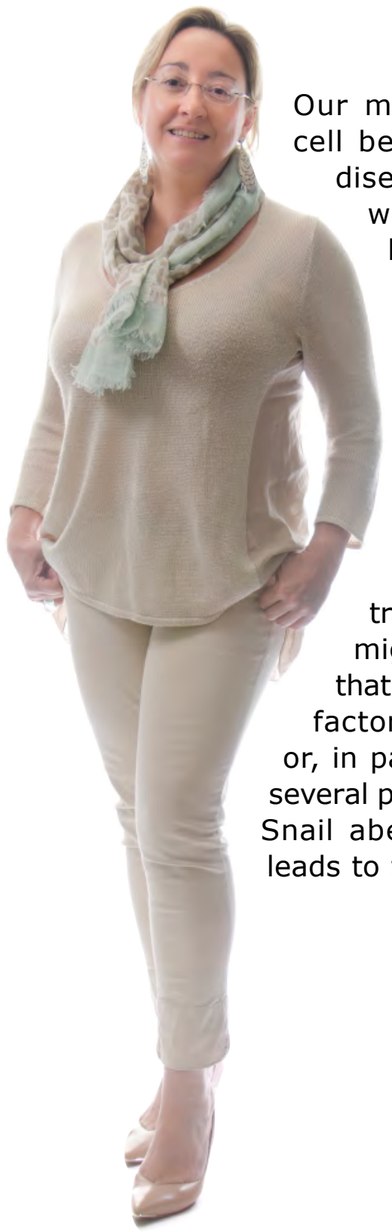
Pastor Diego, Viso-Leon Mari Carmen, Botella Lopez Arancha, Moraleda Jose, Jones Jonathan, Mártinez Salvador **Bone marrow transplantation in hindlimb muscles of motor-neuron degenerative mice reduces neuronal death and improves motor function.** **Cell Transplantation** *In press*

Bueno Carlos, Ramirez Carmina, Ramirez-Lozano, Francisco, Tabares-Seisdedos, Rafael, Rodenas Monica, Moraleda Jose, Jones Jonathan, Martinez Salvador. **Human adult periodontal ligament-derived stem cells engraft and differentiate into the adult mammalian brain** **Cell Transplantation** *In press*

Almudena Martinez-Ferre, Maria Navarro-Garberi, Carlos Bueno and Salvador Martinez. **Wnt signal specifies the intrathalamic limit and its organizer properties by regulating Shh induction in the alar plate** **Journal of Neuroscience** *In press*

Cell movements in development and disease

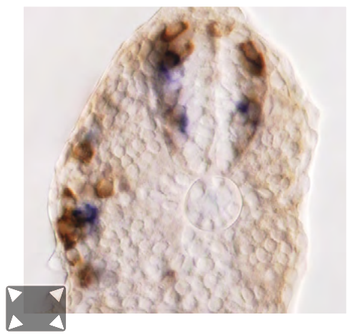
M. Angela Nieto CSIC

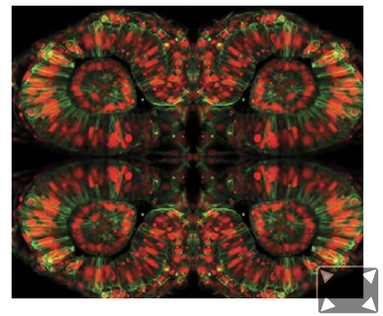


Our main interest is the study of cell behaviour in development and disease, in particular associated with cell movements. We have been working on the functional analysis of the Snail gene family, and have shown its implication in different processes during embryonic development in vertebrates, including 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 now we have participated in a study that defines a novel phosphorylation of the Snail protein, promoting its nuclear retention and therefore, its activity (2012).

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





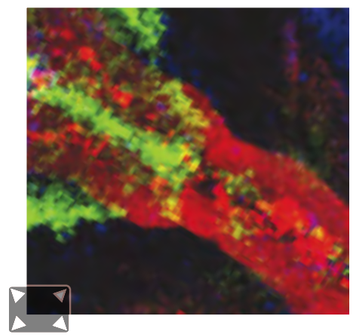
Cell movements in development and disease

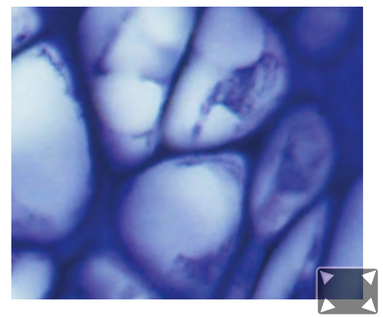
M. Angela Nieto CSIC

found that Scratch is not involved in the regulation of cell movements, but rather it is important for cell survival (2011), a role that we found associated with Snail in epithelial cells (2004) and that we have extended to adult hepatocytes (2010). Scratch is required for the survival of spinal cord neurons during embryonic development by antagonizing the p53 apoptotic pathway (2011). Therefore, cell survival is an ancestral function 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).

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

M. Angela Nieto CSIC

Principal Investigator
M. Angela Nieto

Associated Investigator
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PhD Investigator
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Fabiana Heredia de Oliveira
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Oscar Ocaña
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Sonia Vega

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Rebeca Córcoles

Technical Staff
Diana Abad
Josepa Chuliá
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Administration
Sonia Martin


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JMM


FHdO


MTG


EG


OO


ERA


SV


JMF


RC


DA


JC


CL


SM

Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications

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

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

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

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

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

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

Barrallo-Gimeno, A. and Nieto, M.A. (2009) **The evolutionary history of the Snail/Scratch superfamily.** **Trends Genet.** *25, 248-252.*

De Frutos, C.A., Dacquin, R., Vega, S., Jurdic, P., Machuca-Gayet, I. and Nieto, M.A. (2009) **Snail1 controls bone mass by regulating Runx2 and VDR expression during osteoblast differentiation.** **EMBO J.** *28, 686-696.*

Thiery, J.P, Acloque, H., Huang, R.Y. and Nieto, M.A. (2009) **Epithelial-mesenchymal transitions in development and disease: the remarkable plasticity of the mesenchymal state.** **Cell** *139, 871-890.*

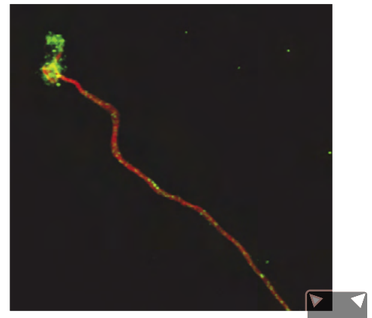
De Frutos, C.A., Vega, S., Manzanares, M., Flores, J.M., Huertas, H., Martinez-Frías, M.L. and Nieto M.A. (2007) **Snail 1 is a transcriptional effector of FGFR3 signaling during chondrogenesis and achondroplasias.** **Dev. Cell** *13, 872-883.*

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

Beatriz Rico CSIC

Principal Investigator
Beatriz Rico

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Cristina García Frigola (with Oscar Marín)
Jorge Brotons (with Oscar Marín)

PhD Student
Emilia Favuzzi
Antonio Jesús Hinojosa
Ana Navarro

Technical Staff
Diana Baeza

CGF JB EF AJH AN BS

Neural circuit formation and remodeling

Beatriz Rico CSIC

Selected Publications

Rico B (2012) **Finding a druggable target for schizophrenia** **PNAS** *Jul 9.*

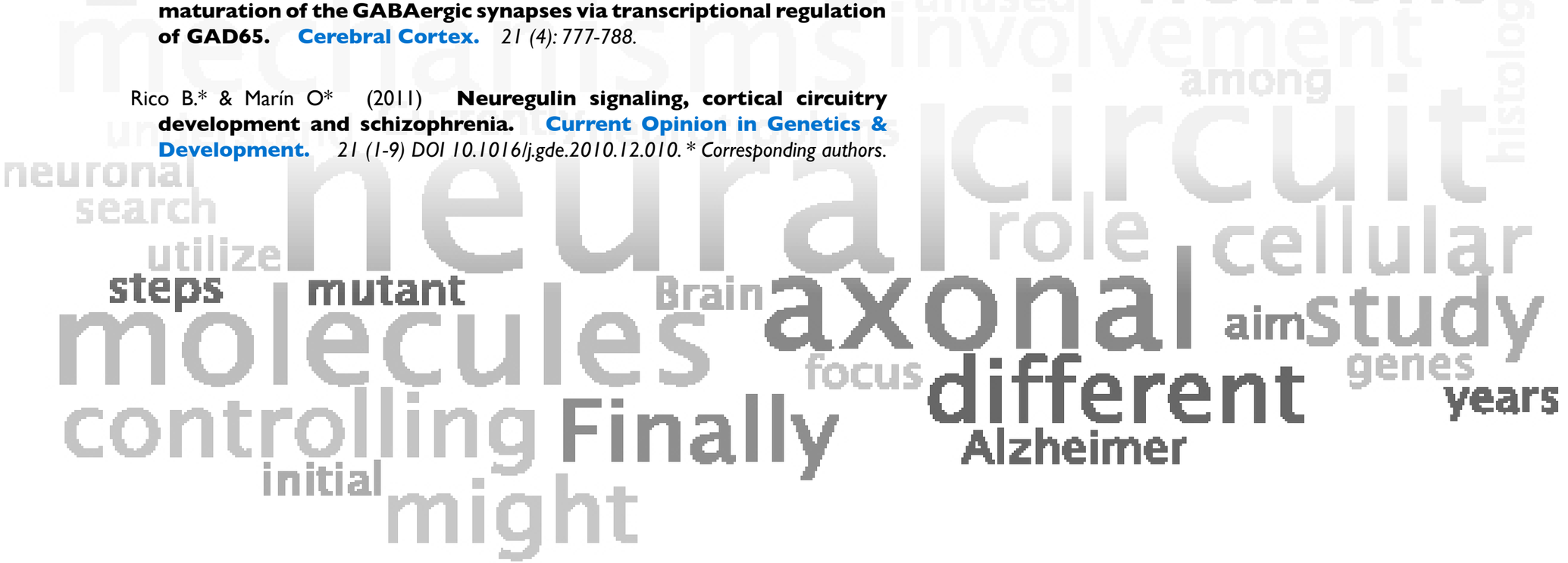
Chacón MR, Navarro A, Cuesto G, Pino I, Scott R, Morales M, Rico B (2012) **Focal Adhesion Kinase regulates actin nucleation during neuronal filopodia formation** **Development** *139: 3200-3210.*

Sánchez-Huertas and Rico B. (2011) **BDNF/TrkB signaling controls the maturation of the GABAergic synapses via transcriptional regulation of GAD65.** **Cerebral Cortex.** *21 (4): 777-788.*

Rico B.* & Marín O* (2011) **Neuregulin signaling, cortical circuitry development and schizophrenia.** **Current Opinion in Genetics & Development.** *21 (1-9) DOI 10.1016/j.gde.2010.12.010. * Corresponding authors.*

Fazzari F., Paternain A.V., Valiente M., Pla R., Luján R., Lloyd K., Lerma L., Marín M.* Rico B*. (2010) **Control of cortical GABAergic circuitry development by Nrg1/ErbB4 signalling.** **Nature,** *464, 1376-1380 * corresponding authors.*

Chacón M.R., Fernández G., Rico B*. (2010) **Focal adhesion kinase mediates axonal remodeling by linking Semaphorin 3A signaling with the cytoskeleton.** **Molecular Cellular Neuroscience,** *44: 30-41.*



Altered molecular mechanism in Alzheimer's disease and dementia

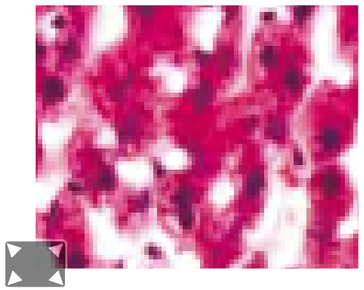
Javier Sáez Valero UMH

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

Javier Sáez Valero UMH

Principal Investigator
Javier Sáez Valero

PhD Investigator
Mª Salud García
Inmaculada Cuchillo Ibañez

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

Silveyra MX, García-Ayllón MS, Serra-Basante C, Mazzoni V, García-Gutierrez MS, Manzanares J, Culvenor JG, Sáez-Valero J. (2012) **Changes in acetylcholinesterase expression are associated with altered presenilin-1 levels.** **Neurobiol Aging** *33:627.e27-37*

Silveyra MX, García-Ayllón MS, Gómez de Barreda E, Small DH, Martínez S, Avila J, Sáez-Valero J. (2012) **Altered expression of brain acetylcholinesterase in FTDP-17 human tau transgenic mice.** **Neurobiol Aging** *33:624.e23-34*

Botella-López A, Cuchillo-Ibañez I, Cotrufo T, Mok SS, Li Q-X, Barquero M-S, Dierssen M, Soriano E, Sáez-Valero J. (2010). **Altered glycosylation of Reelin in Alzheimer's disease is induced by b-amyloid.** **Neurobiol Dis** *37, 682-691*

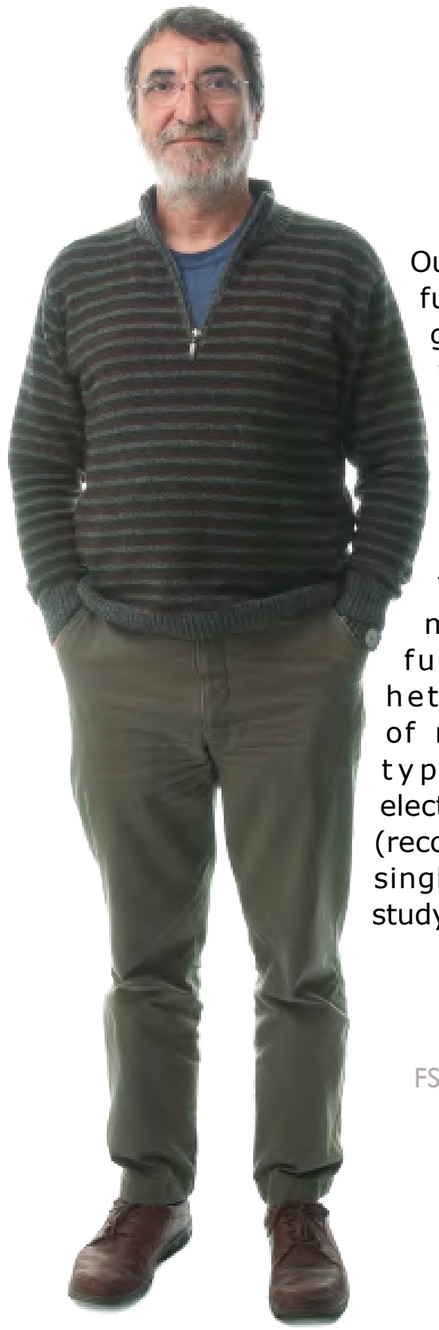
Silveyra MX, Evin, G; Montenegro, MF; Vidal, CJ; Martínez, S; Culvenor, J; Sáez-Valero, J. (2008) **Presenilin-1 interacts with acetylcholinesterase and alters its enzymatic activity and glycosylation.** **Mol Cell Biol.** *28, 2908-2919*

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

Biophysics and pharmacology of ionic channels

Francisco Sala UMH

Salvador Sala UMH



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

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

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

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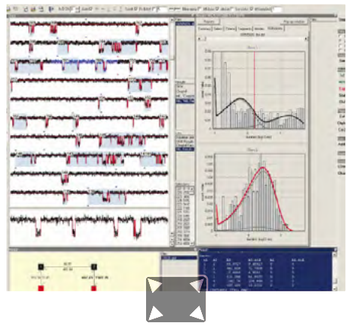


SS

Research Group

Biophysics and pharmacology of ionic channels

Francisco Sala UMH

Salvador Sala UMH

Principal Investigator
Francisco Sala
Salvador Sala

Technical Staff
José Mulet

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*

Criado M, Mulet J, Gerber S, Sala S, Sala F. (2011) **A small cytoplasmic region adjacent to the fourth transmembrane segment of the α7 nicotinic receptor is essential for its biogenesis.** **FEBS Lett.** *585, 2477-2480*

Criado M, Mulet J, Gerber S, Sala S, Sala F. (2011) **Mutants of b-strand b3 and the loop B in the interface between α7 subunits of a homomeric acetylcholine receptor show functional and pharmacological alterations.** **J Neurochem.** *118, 968-978*

Criado M, Svobodová L, Mulet J, Sala F, Sala S. (2011) **Substitutions of amino acids in the pore domain of homomeric α7 nicotinic receptors for analogous residues present in heteromeric receptors modify gating, rectification and binding properties.** **J Neurochem.** *119, 40-49.*

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

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

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

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

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

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

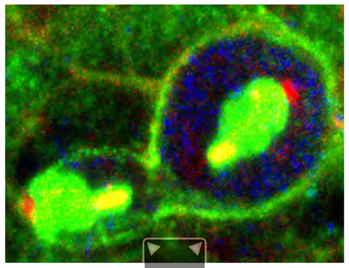
Criado, M., Mulet, J., Bernal, JA., Gerber, S., Sala, S., Sala, F. (2005) **Mutations of a conserved lysine residue in the N-terminal domain of α7 nicotinic receptors affect gating and binding of nicotinic agonists.** **Molecular Pharmacology** *68: 1669-1677.*

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 and 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 which has been related to 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 and dendritic atrophy. 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

Francisco Tejedor CSIC

Principal Investigator
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EUA

SMN

EL

SJG

Research Group

Molecular neurogenetics

Francisco Tejedor CSIC

Selected Publications

F.J. Tejedor and B. Hämmerle (2011) **MNB/DYRK1A as a multiple regulator of neuronal development** **FEBS J.** *277*

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

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

N. Göckler, G. Jofre, C. Papadopoulos, U. Soppa, F J. Tejedor, and W. Becker (2009) **Harmine specifically inhibits protein kinase DYRK1A and interferes with neurite formation.** **FEBS J.** *276(21):6324-37.*

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.*

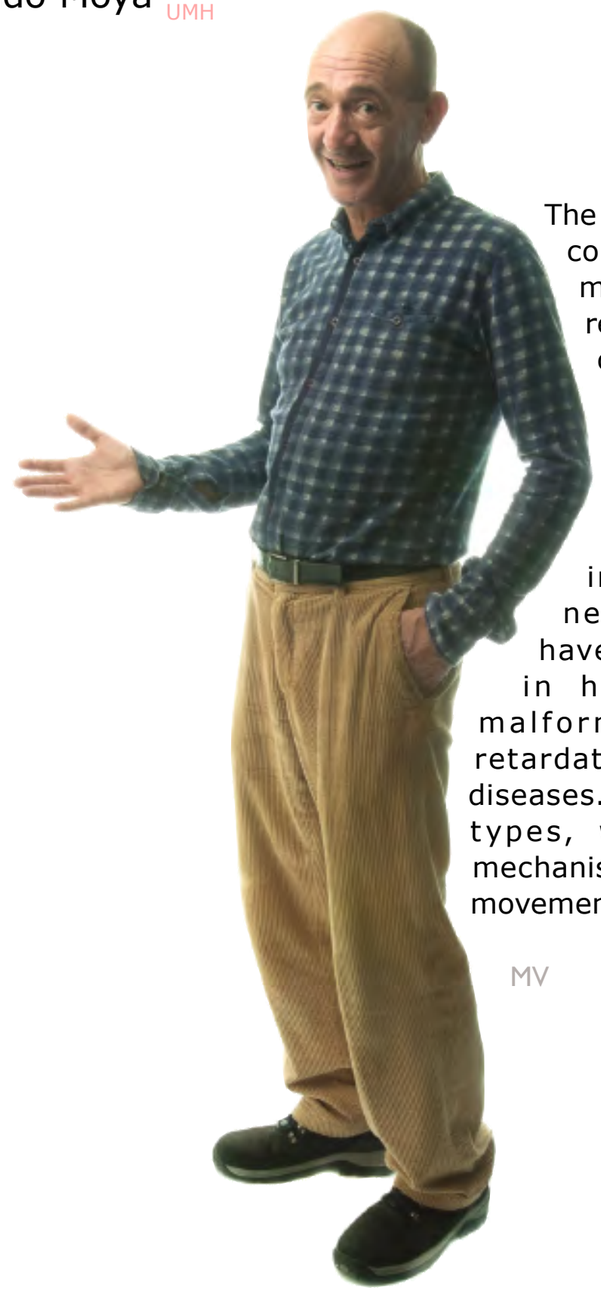
Hämmerle, B., Vera, E., Spreicher, S., Arencibia, R., Martínez, S., Tejedor, FJ. (2002) **Mnb / Dyrk1A is transiently expressed and asymmetrically segregated in neural progenitor cells at the transition to neurogenic divisions.** **Dev. Biol.,** *246: 259-73.*

Ceron, J., Gonzalez, C., Tejedor, FJ. (2001) **Patterns of cell division and expression of asymmetric cell fate determinants in the postembryonic neuroblast lineage of Drosophila.** **Dev. Biol.,** *230: 125-138.*

Cell signalling during neuronal migration

Miguel Valdeolmillos UMH

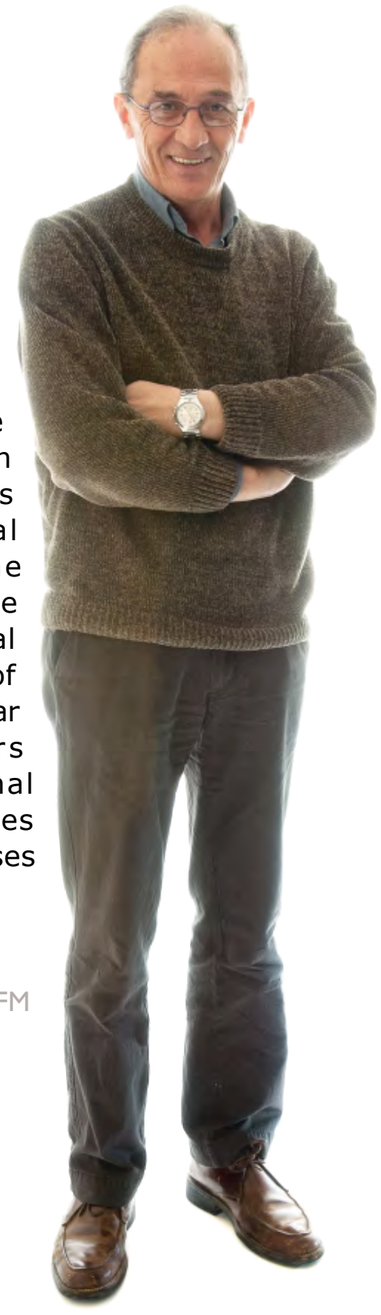
Fernando Moya UMH



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.



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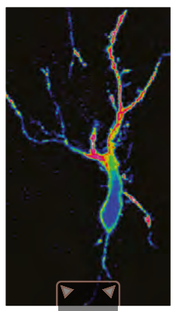
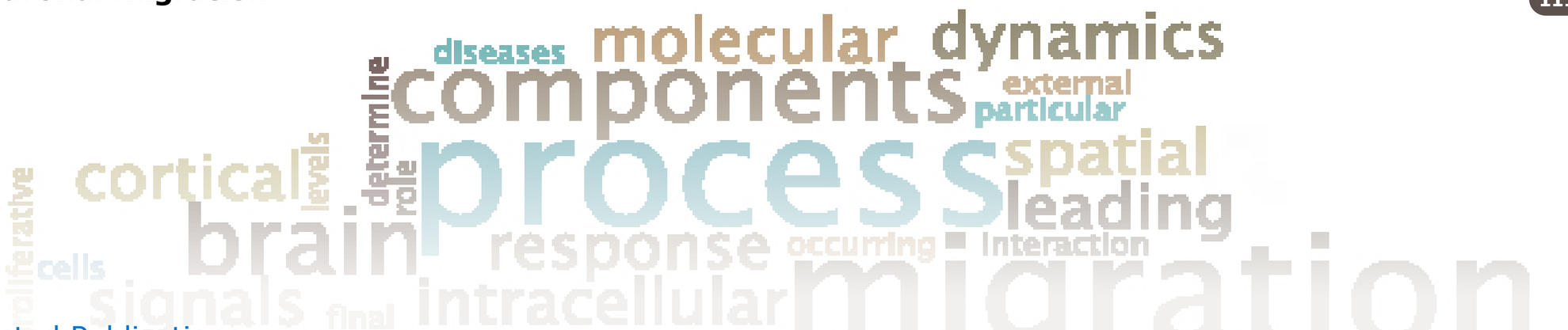


FM

Cell signalling during neuronal migration

Miguel Valdeolmillos UMH

Fernando Moya UMH



Selected Publications

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*

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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.*

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.

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.

The first year consists of studies totalling 60 ECTS credits on both basic and advanced aspects of neuroscience offered in several courses (see the 2009-2010 program) These courses, offered by University and CSIC lecturers and researchers from a wide range of disciplines, cover fundamental concepts and themes related to neuroscience, and include a full series of seminars of invited speakers throughout the entire year and lab rotations at the Institute. After completion of these credits each student will 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).

Course A.

Basic Concepts in Neurosciences

(24 ECTS, 8 Modules) (Nov 2011–Jan 2012)

Module 1: Embryology
Module 2: Genetic Analysis
Module 3: Neuroanatomy
Module 4: Cellular components of the nervous system
Module 5: Intracellular signalling
Module 6: Electrical signalling in the nervous system
Module 7: Synaptic transmission
Module 8: Neural Systems

Course B.

Lab Rotations and Institute Seminars

(12 weeks and 12 ECTS)

Course C.

Cellular and Molecular Mechanisms of Neural Function

(16 ECTS, 4 Modules) (Feb 2012)

Module 1C: Neurogenesis
Module 2C: Synaptic function
Module 3C: Information processing
Module 4C: Neuropathology

Collaborations & Agreements

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

- 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
- Cátedra de Neurobiología Remedios Caro Almela
- 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.

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 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) and Christine Holt (2011). The latest Prize Ceremony was held on October 28th, 2011, at the Instituto de Neurociencias. The previous prize winner Dr. Stephen Wilson, 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

20011

The Remedios Caro Almela Prize 2011 for Research in Developmental Neurobiology

On June 29th of 2011, the international Scientific Committee commissioned to award the fifth Remedios Caro Almela Prize for Research in Developmental Neurobiology. The committee, composed of Dr Stephen Wilson , winner of the 2009 prize, from the University College of London, Research Vice-Dean of the Faculty of Life Sciences; Dr. Paola Bovolenta, head of the Dept. Regulation of Nervous System Morphogenesis at the Cajal Institute; Dr. Patrick Charnay, Head of the Nervous System Development team at the Ecole Normale Supérieure in Paris, France; Constantino Sotelo, the holder of the Remedios Caro Almela Chair until 2012; Juan Lerma, Director of the Instituto de Neurociencias and Josep Xavier Barber, Joint Vicechancelor for Research and Innovation for the Rector of the UMH, decided to present the prestigious award to Dr. Christine E. Holt, Professor of Developmental Neuroscience in Cambridge University (U.K.).

Christine Holt has made big contributions to our comprehension of a fundamental aspect of developmental neurobiology: the mechanisms by which axons navigate towards their objectives inside the brain. By using innovative technical approaches, Christine Holt has helped reveal the complex nature of the decisions that are taken to correctly orientate an axon during its growth. She pioneered the idea of that proteins synthesize and degenerate at a local level in the cone of growth, and in a convincing manner, she demonstrated that this process is necessary for a response to the orientation signals liberated by other cells. These important findings open new perspectives on the problem of central axon regeneration in relation to traumatic injuries of the nervous system

Her work has received wide international recognition, in recent years she has been invited to lecturer in major international congresses dedicated to the study of the development of the nervous system. The jury has emphasized the innovation, and solid quality of her contributions, and the high productivity of her present research team.

Professor Holt was born in Wylam (U.K.) in 1954, She graduated in Biological Sciences from Sussex's University and read her thesis in Zoology at the MRC, Kings College, London. After postdoctoral stays in the United States and Germany, she continued her research in the Cambridge University, where in 2003 she was made Professor in Developmental Neuroscience. She is a member of numerous scientific societies including: EMBO (European Molecular Biology Organization), the Royal Society (FRS), the Medical Sciences Academy (FMedSci); reviewer for many prestigious publications in the field and author of 96 articles in leading publications.

The next Remedios Caro Almela Prize will be awarded in 2013

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.

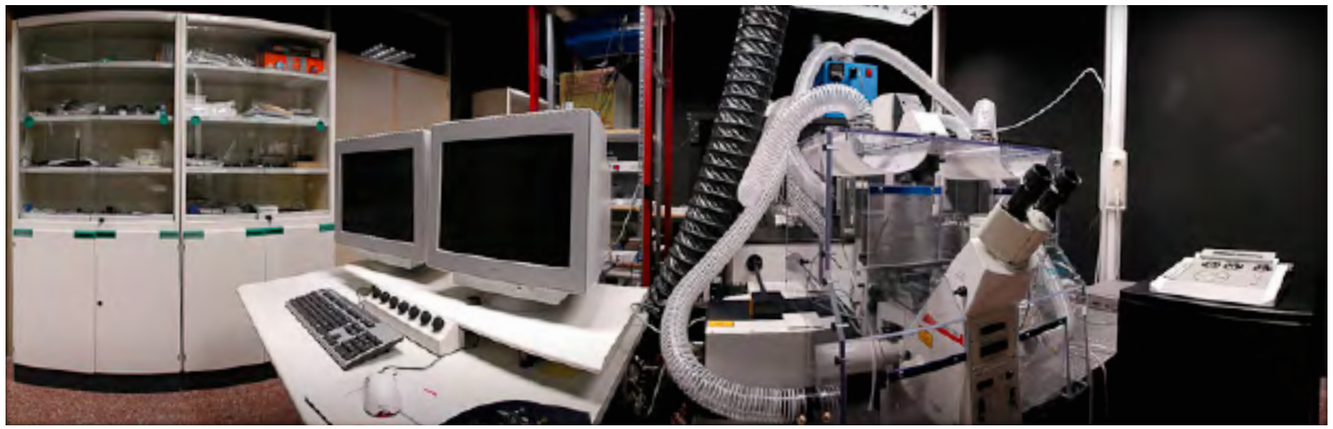
- Multiphoton microscope, equipped with two workstations. One includes an upright microscope for rapid acquisition of images from in vivo preparations or brain slices, with simultaneous electrophysiological facilities. The other consists of an inverted microscope for long-term time-lapse experiments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

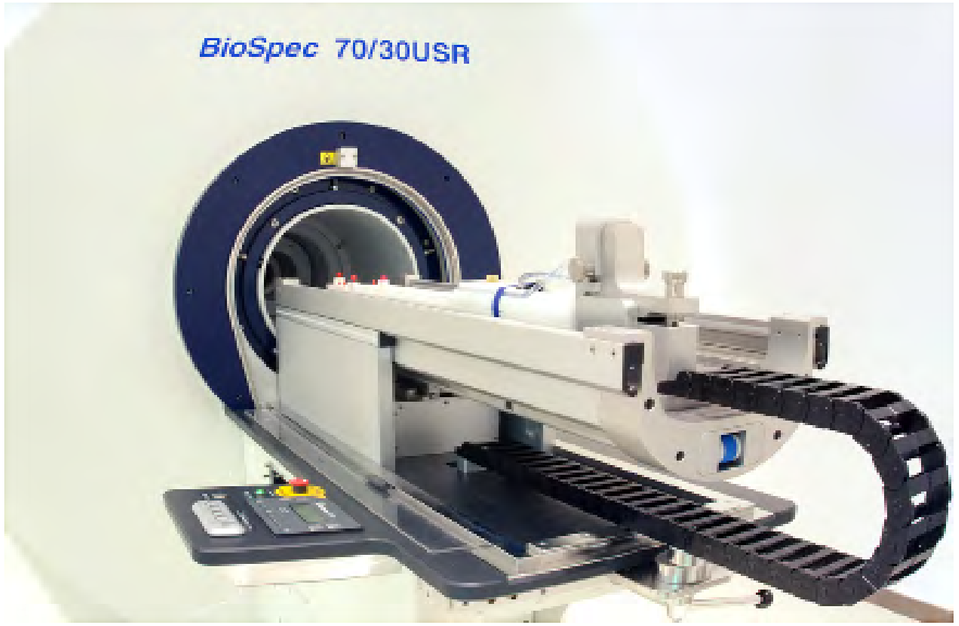
In this common area there are 6 independent spaces and a common area for washing, Equipment such as Skinner box, rotarod, treadmill, 8 arms maze, hot plate and water maze with tracking system allow researchers to study the behaviour of rats and mice (motor function, memory, learning, conditioning, etc).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

PURCHASING AND STORES

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.



fMRI 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
Gisele Díaz Pérez
Virtudes García Hernández
Ana María López Martínez
Isabel Márquez Pérez
Eva Molina Bonet
Mª Teresa Pérez Vegara
Isabel Romero García
Ruth Rubio Sánchez
Mª Luisa Sánchez Vázquez


MTGH


HCM


AMLM


IMP


EMB


MTPV


IRG


MLSV

Administrative & Service Staff

Purchasing & Stores
Laura Giner Grao
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


LGG


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
Antón Núñez Valera
Rebeca Ortiz Méndez
Raúl Pardo Mérida
Abigail Segura García
Sonia Segura Llobregat
Mª Ángeles Soler Ripoll
Lucía Yuste Jiménez

Drosophila Service

Alicia Sánchez Rincón

Zebrafish Facility

Diana Abad Bataller


MJMC


GMdV


MCCL


SGM


VJV


ALMS


PMR


ROM


RPM


SSL


MASR


LYJ


ASR


DAB

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Letters

Scott RS. **NextGen speaks** **Science** *335(6077):34-34*

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Belmonte C. **Cap.: The Neurobiological Basis of Ocular Surface Sensation in Normal and Pathological Conditions.** **Book: A Vision for Horizon 2020–A European Strategic Roadmap for Vision Research and Ophthalmology.**

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PhD Programme

01/13/2012 The malleable engram: Erasing and enhancing long-term memory associations in cortex **Yadin Dudai**
Weizmann Institute of Science, Rehovot, Israel

01/20/2012 Maf transcription factors in the development of touch sensing neurons **Patrick Carroll**
Institut des Neurosciences de Montpellier (INM). Hospital St. Eloi. France

01/26/2012 Dissecting the early steps of neuronal specification in mammals **Tristan Rodriguez**
MRC, Imperial College London

01/27/2012 How Epithelia Respond to a Crisis **António Jacinto**
Instituto de Medicina Molecular, Lisboa, Portugal

02/03/2012 Role of P2X7 receptor in the nervous system: from development to neuro(de/re)generation **María Teresa Miras-Portugal**
Dpto. Bioquímica y Biología Molecular IV. Universidad Complutense de Madrid.

02/10/2012 Optimización de la gestión de colonias de ratones modificados genéticamente **Mª Jesús Molina Cimadevila**
Animalario del Instituto de Neurociencias de Alicante

02/17/2012 GDNF is required for adult central catecholaminergic neurons maintenance **Alberto Pascual Bravo**
Instituto de Biomedicina de Sevilla (IBiS).

02/24/2012 Development of the Drosophila brain: building a massively parallel connectivity matrix **Heinrich Reichert**
Biozentrum, University of Basel. Switzerland

03/02/2012 Optogenetic Control of Arousal and Brain Reward **Luis de Lecea**
Standford University. Standford, CA, USA

03/09/2012 Oligodendrocyte Dynamics in the Adult CNS; What Does It Mean? **William Richardson**
Wolfson Institute for Biomedical Research, University College London, London UK

Seminars

03/16/2012 Neurological Basis for Cognition **Rodolfo Llinás**
NYU Langone Medical Center, New York, USA

03/23/2012 What are all these wires for? The puzzle of neocortical circuits **Kevan Martin**
Institute for Neuroinformatics. Zurich. Switzerland.

03/30/2012 mRNA metabolism and intellectual disabilities: insights from the Fragile X Syndrome **Claudia Bagni**
Faculty of Medicine. Dept. of Experimental Medicine & Biochemical Sciences. University of Rome "Tor Vergata"

04/13/2012 Emerging Roles for Lgi Proteins in Nervous System Development and Function **Dies Meijer**
Dept. of Cell Biology & Genetics. Erasmus MC. Rotterdam. Netherlands

04/27/2012 Cellular and Molecular Mechanisms of Neurogenesis from Glial Cells **Magdalena Götz**
Faculty of Medicine Department of Physiological Genomics, LMU, Helmholtz Zentrum Munich Institute of Stem Cell Research

05/04/2012 Babelians in the craddle. Learning two languages from 0 to 24 months **Nuria Sebastián**
Brain and Cognition Unit. Dept. of Technology. Universitat Pompeu Fabra. Barcelona

05/11/2012 Neurovascular link: vessel and neuronal guidance **Amparo Acker-Palmer**
Molecular and Cellular Neurobiology. Institute of Cell Biology and Neuroscience. Frankfurt Institute for Molecular Life Science.

05/18/2012 Molecular mechanisms of synaptic plasticity in health and disease **Jose Antonio Esteban**
Centro de Biología Molecular "Severo Ochoa", CSIC, UAM, Madrid

05/25/2012 Molecular and Cellular Mechanisms of Memory Allocation in Neuronal Networks **Alcino J. Silva**
Brain Research Institute. University of California, Los Angeles (UCLA). USA

06/01/2012 Symmetry is attractive and increases fitness but how does body symmetry emerge even though organs grow independently? **María Domínguez Castellano**
Instituto de Neurociencias de Alicante

Seminars

06/07/2012 Autonomic regulation of the bone marrow stem-cell niche **Simon Mendez-Ferrer**
Fundación CNIC Carlos III, Madrid

06/08/2012 Building cortical circuits with experience Insights from visual cortex **David Fitzpatrick**
Max Planck Florida Institute, USA

06/14/2012 Local Protein Translation in Neurons **Erin Schuman**
Department of Synaptic Plasticity, Max Planck Institute for Brain Research, Frankfurt am Main, Germany

06/20/2012 The proline-rich membrane anchor (PRiMA)-linked form acetylcholinesterase in muscle and brain: oligomer assembly and transcriptional regulation **Karl WK Tsim**
Hong Kong University of Science and Technology, China

Scientific Programme

06/28 &29/2012 Jornadas IN **Investigadores IN**
Instituto de Neurociencias UMH-CSIC

09/28/2012 Neural coding underlying active object localization **Karel Svoboda**
Janelia Farm Resesearch Campus. Howard Hughes Medical Institute

10/05/2012 Molecular mechanisms of synaptic plasticity in the context of intellectual disabilities **Claudia Bagni**
University of Rome "tor Vergata", Italy & Faculty of Medicine/VIB Center for Biology of Disease Catholic University of Leuven, Belgium.

10/26/2012 Homeostatic plasticity: from synapses to the axon initial segment **Juan Burrone**
King's College London

Seminars

11/09/2012 Growth factor signaling in development and disease of the nervous system **Yves Alain Barde**
Biozentrum, University of Basel.

11/16/2012 Stimulus detection in the cortico-thalamic loop of the primate. **Javier Cudeiro**
Universidade da Coruña

11/21/2012 Mimetización funcional de enzimas para diseño de catalizadores sólidos **Avelino Corma**
Instituto de Tecnología Química -Universidad Politécnica de Valencia y CSIC

11/23/2012 Metastatic colonization requires the repression of the epithelial-mesenchymal transition inducer Prrx1 **Dra. Angela Nieto**
Instituto de Neurociencias

11/30/2012 The Literate Brain: Cognitive processes and neural pathways involved in reading. **Manuel Carreiras**
Basque Center on Cognition, Brain and Language, Donostia- San Sebastián

12/14/2012 Architectural remodeling of neuronal cell nucleus in plasticity **Dr. Grzegorz Wilczynski**
Nencki Institute, Warsow

13-01-2012 Parra Martín Andrés

Cold thermoreceptors of the cornea: functional characteristics and physiological role

Advisor: Carlos Belmonte Martínez / Rodolfo Madrid

27-01-2012 Navarro Daniela Vanesa

Hormonas tiroideas maternas y desarrollo cortical fetal. Un modelo de hipotiroxinemia temprana en prematuros

Advisor: Pere Berbel Navarro

08-03-2012 Colonques Bellmunt Jordi

Análisis de las funciones de los genes GCM, PROS y MNB en la gliogénesis y la neurogénesis postembrionaria de Drosophila

Advisor: Francisco Tejedor Rescalvo

18-04-2012 Marcos Mondejar Paula

Topographic specification of thalamocortical projection: role of LHX2 transcription factor & targets cells at the ventral telencephalon

Advisor: Guillermina López Benditoz Bendito

07-05-2012 Crespo Enriquez Ivan

Experimental study of FGF8 morphogenetic activity in the establishment of neuroepithelial positional information in mouse brain development

Advisor: Salvador Martinez Perez / Diego Echevarria Aza

17-05-2012 Viosca Ros José

Common molecules in memory formation and congenital intellectual disability: a role for the RAS-ERK-CREB pathway in cognition

Advisor: Angel Barco Guerrero

31-05-2012 Lakoma Jarmila

Role of reelin in cortical neurogenesis.

Advisor: Luis García Alonso

20-07-2012 Torregrosa Hetland Cristina Juana

Papel del citoesqueleto subcortical de F-actina como elemento organizador de la maquinaria secretora en células cromafines bovinas

Advisor: Luis Miguel Gutiérrez Pérez

27-07-2012 Perales Cano Mercedes

El receptor auditivo y la vía auditiva central en un modelo transgénico de hipotiroidismo congénito (TSHRHYT) y sus alteraciones neuroquímicas.

Advisor: Carmen de Felipe Fernández / Jorge Prieto Cueto

13-11-2012 Slováková Jana

Functional analysis of the PDZ protein Canoe/AF-6 during Drosophila neural differentiation

Advisor: Ana Carmena

18-12-2012 Fons Romero Juan Manuel

El antagonismo entre Snail y Pax2 controla la plasticidad epitelial en el desarrollo embrionario.

Advisor: Angela Nieto Toledano







Other Activities

Promega Prize to the best talk

9th Christmas Meeting of the Instituto de Neurociencias

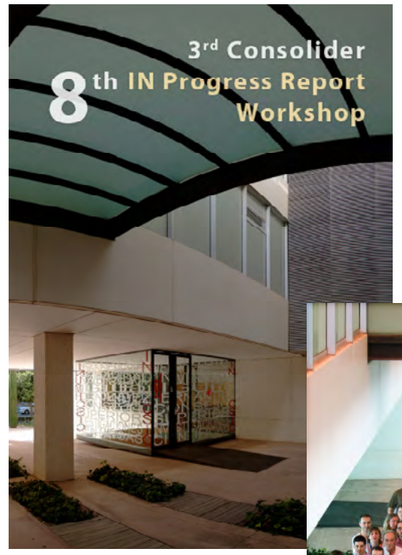
3nd Congress of 5P Sindrome and rare diseases

IV Simposium PROMETEO NEC_2. Anomalias genéticas del desarrollo cortical y disfunci ón cerebral

3nd Consolider & 8th IN Progress Report Workshop.

VII Jornadas Informativas de Adema. Asociación de Esclerosis Múltiple de Alicante

"Brain Week 2012" activities.



INVESTIGACIÓN ESPAÑOLA

Prrx1: el culpable de las metástasis

Al activarse hace que la célula enferma empiece a moverse y al apagarse que anide en otro tejido, extendiendo el cáncer a otros órganos.

LD/AGENCIAS

Un grupo de investigadores españoles ha hallado un nuevo componente celular que impide que las células aniden en otros órganos y generen nuevos focos de cáncer y ha constatado, además, que frenar el flujo de células cancerosas favorece la propagación de tumores.

Estas son algunas conclusiones de un estudio que se publica en la revista *Cancer Cell*, en el que participan científicos del Instituto de Neurociencias (centro mixto del CSIC y la Universidad Miguel Hernández) y del Instituto de Investigaciones Biomédicas Alberto Sols (centro mixto de la Universidad Autónoma de Madrid y CSIC). Además, ha contado con la colaboración del Instituto de Investigación Biomédica de Bellvitge y la Fundación MD Anderson.

En concreto, los investigadores han descrito el **componente celular Prrx1**, cuya presencia en los tumores primarios puede impedir la generación de metástasis, la causa de más del 90 por ciento de las muertes por cáncer, según sendas notas del CSIC y la Autónoma de Madrid. Las células cancerosas se desprenden del tumor original y se diseminan por el cuerpo anclándose a otros órganos y formando nuevos tumores denominados metástasis.

Esta investigación señala que el componente celular Prrx1 **impide que células cancerosas aniden** en otros órganos y, por lo tanto, generen nuevos focos de cáncer.

Para que un foco de cáncer se propague a otros órganos sus células sufren un proceso conocido como transición epitelio-mesénquima (EMT, de sus siglas en inglés) debido al cual **se vuelven móviles e invasivas**, y comienzan a viajar por el torrente sanguíneo. No obstante, para volver a anclarse a un nuevo órgano o tejido deben recuperar sus características iniciales, es decir, perder la movilidad.

Este trabajo ha detectado que la **transición de célula cancerosa móvil a inmóvil** implica la pérdida del componente Prrx1.

La investigadora del Instituto de Neurociencias Ángela Nieto, que ha dirigido el estudio, ha detallado: "Aunque este componente es uno de los factores que favorecen la diseminación inicial de las células cancerosas y su llegada a otros órganos, es necesario que se apague para que esas células se agrupen para formar otros tumores". Los tumores con elevadas cantidades de Prrx1 son, por tanto, los de **mejor pronóstico** ya que no pueden formar metástasis.

Los resultados de esta investigación básica han sido obtenidos gracias al estudio de diversos modelos animales: pollo, pez cebra y ratón, y el análisis de muestras de pacientes.