INSTITUTO DE NEUROCIENCIAS

ANNUAL REPORT

2011

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INDEX

CSIC
Consejo Superior de Investigaciones Científicas

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

01 SALUTATION

JUAN LERMA : Director

The Instituto de Neurociencias (IN) has consolidated definitively as a competitive Centre of Excellence, being the most important centre of research in neuroscience on the national scene. Despite the long journey of economic crisis we are experiencing, the number of people working at the IN has remained constant and the level of competitive funds has not declined. This has allowed us to increase our productivity and the full global impact of our studies. We can say with satisfaction that IN's quality figures are well above the national average and exceed comparable centres throughout Europe. Indeed, the IN was one of the 22 centres selected in all fields of knowledge all around Spain to compete for the Severo Ochoa Excellence Awards in 2011.

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. Also in the past year, our colleague Jorge Manzanares has reached the status of University Professor and has been appointed Dean of the Faculty of Pharmacy of the UMH.

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 progresses in both attracting resources and productivity, following the path delineated in the previous strategic plan. Noteworthy most of the ¾ parts of the staff corresponds to contracts covered with external competitive funding obtained by researchers in this centre. 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 fulfills the Mission of the IN generating knowledge about the brain and its mechanisms. We are confident that the selection of these 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 2008-11 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 6.9. 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 for their research activity. On one hand, Oscar Marin received the prize Rey Jaime I of Basic Research; Carlos Belmonte received the High Distinction of the Generalitat Valenciana to the Scientific Merit, as well as the European Vision Award. He was named Doctor honoris causa by the University of Castilla-la-Mancha and one of the works he directed received the Pfizer Award. The undersigned was appointed President of the Spanish Society for Neurosciences and re-elected Chair of the IBRO's Western Europe Regional Committee. Guillermina López Bendito received the Olympus-SENC Prize for Young Neuroscientist; Angel Barco was elected member of the Council of the Molecular and Cellular Cognition Society. Angela Nieto was elected President of the TMS International Association (TEMTIA) and member of the Scientific Committee of the National Center for Oncology Research (CNIO). On the other hand, Miguel Maravall received the prestigious Alberto Sols Prize to the best research work. Thereby, the IN and its staff reinforce their national and international presence.

I am also proud to inform that two of our researchers were awarded with prestigious European Research Council (ERC) grants: Oscar Marin (ERC Advanced Grant) and Eloisa Herrera (ERC Starting Grant), which will allow them to develop research work during the next five years. Thus, Alicante is situated at the scientific excellence epicenter.

In this year, the IN also awarded the Vth Remedios Caro Almela Prize in Developmental Neurobiology. On this occasion, the award-winner was Dr. Christine E. Holt from the University of Cambridge. Preceding the award ceremony, the previous winner, Dr. Stephen Wilson, from the University College of London, delivered the "Caro Almela Lecture". Afterwards, D. Fernando Martinez Ramos, promoter and sponsor of the Remedios Caro Almela Chair, recently deceased, was given with the Gold Medal of the Institute of Neurosciences. The spirit that D. Fernando imposed on these activities of patronage has been endorsed by his daughters and son, as they took the commitment to keep the Remedios Caro Almela Prize for at least another ten years.

In 2010, just initiated our second plan of action, we incorporated to our centre last generation technologies, as the image by high field Nuclear Magnetic Resonance (NMR) and fluorescence assisted cell shorting (FACS). However, in 2011 we have been careful in our investments, perhaps thinking that the funding of science in Spain could threaten the most fundamental structures of our 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 celebrate the Year of Neuroscience in Spain. On this occasion and from the Instituto de Neurociencias we insist that Neuroscience will change the way of thinking and behavior 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.

03 WHERE WE ARE

The IN is located on the Mediterranean coast, iin 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).

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 knowledge 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.

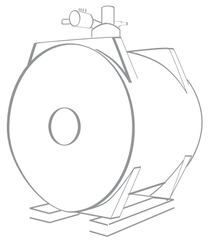
There is a second level of organization based on research lines. These lines constitute a horizontal organisation, grouping members of different research units around more specific research subjects. This horizontal-vertical structure facilitates greater interactions between institute members, through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

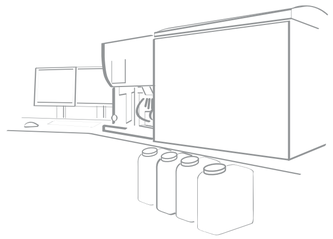
The IN undertakes an important training activity through its International PhD Programme in Neuroscience, which has been awarded with a mention as "Programme of Excellence" by the Ministry of Education. It also strives to be a centre of reference in terms of both national and international collaborations 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), 7 non-tenure scientists, 145 doctoral and postdoctoral researchers and 98 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 2011 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).

05 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.

06 MOST RELEVANT SCIENTIFIC MILESTONES

Demonstrated that the CBP gene, a histone acetyltransferase which regulates gene expression and whose mutation causes the intellectual disability known as Rubinstein Taybi syndrome, is necessary for cognitive improvement and the genesis of neurons associated with the environmental enrichment, proving evidences that experience modulates brain gene expression through the regulation of proteins, such as CBP, that modifies the neural epigenome.

Demonstration that the loss of CBP protein in neurons of the forebrain, whose deficiency in humans causes intellectual disability of Rubinstein-Taybi syndrome, produces a severe reduction of the neural histone acetylation resulting in defects in memory and activity-dependent gene expression, without affecting cell viability.

Identified hundreds of activity-regulated genes and identified the central role of the transcription factor CREB for transducing signals from the membrane to the neuronal nucleus.

Discovered a mechanism that ensures the formation of the nervous system during embryonic development, which depends on two antagonistic genes, Snail and Sox3.

Found that CanoeAF-6 and cadherin proteins perform important functions in the glia within the complex of WrapperNeurexin-IV during neuron-glia interactions.

A new function described for the signaling network Rap1-Norberto-Ral-canoe in cortical polarity regulation and spindle guidance during asymmetric neuroblast division.

Identified a series of palmitoilated peptides that behave as non-competitive specific antagonists of the TRPV1 cationic channels. These peptides, named 'TRPducines' may have therapeutical possibilities for pain treatment

Demonstration of the role of the protein reelin in the control of neurogenesis in the cerebral cortex.

Discovered a new molecular mechanism whereby BDNF controls the maturation of the inhibitory circuits, directing the expression of one of the enzymes responsible for the synthesis of GABA.

Discovered that the chemokine receptor Cxcr7 is necessary to regulate Cxcr4 protein levels, thereby adapting chemokine responsiveness in migrating cells. This is the first demonstration that a chemokine receptor modulates the function of another chemokine receptor by controlling the amount of protein that is made available for signaling at the cell surface

Discovered that the transcription factor Foxd1 specifies retinal temporal identity by controlling the expression of multiple targets, included the EphA/ephrinAs guidance molecules which are involved in the establishment of retinotopic maps in the visual targets.

Completed the collaborative project of the EU (EU contract "Eurexpress" FP6) in which the pattern of expression of more than 16,000 genes in the 14.5 days of development mouse embryo has been annotated, making public the nearly complete transcriptome of mouse embryonic life.

Described the palial origin of the cholinergic neurons from the basal prosencephalon (nuclei of Meinert and horizontal of diagonal band) projecting to the brain's prefrontal cortex and play an important role in brain cognitive system.

Proof provided that, contrary to neodarwinism postulates, the generation of a new protein named occurred in a single evolutionary step following a deletion that induced alternative intron retention at an essential gene. A systematic analysis of ~250 million years of evolutionary history of this locus also demonstrated that natural selection significantly contributed to the generation of protein novelty.

In a genetic search in the fruit fly *Drosophila melanogaster*, it has been discovered that the microRNA miR-200 (miR-8 in flies) regulates Notch-induced overgrowth involving ZEB1 factor, which is key in certain human

07 THE INSTITUTE IN NUMBERS

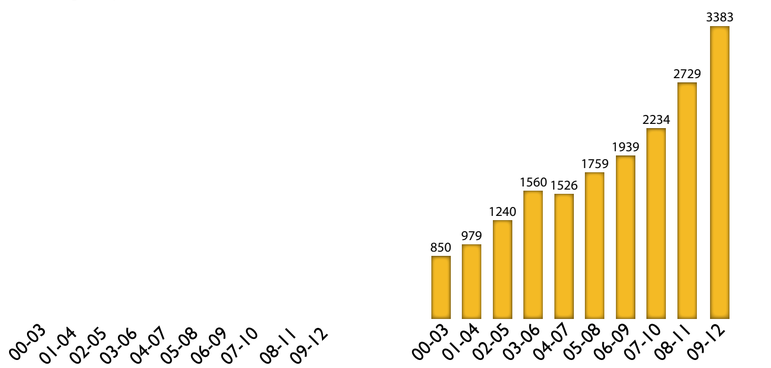
PUBLICATIONS AND IMPACT

Number of Published Articles (ISI)

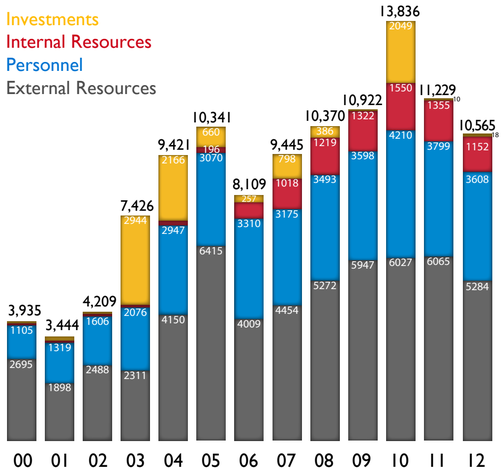
Percentage Increase in Cumulated Impact Factor

Average Impact Factor

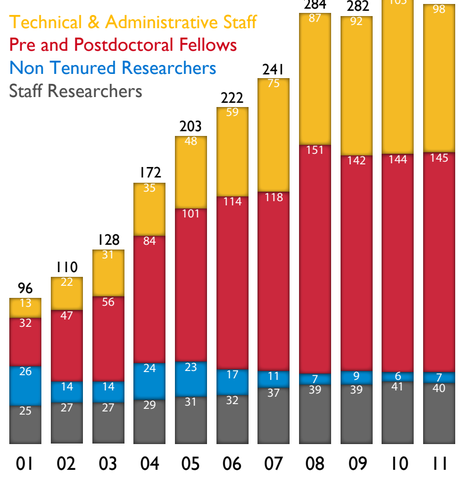
Citations to the Period's Publications



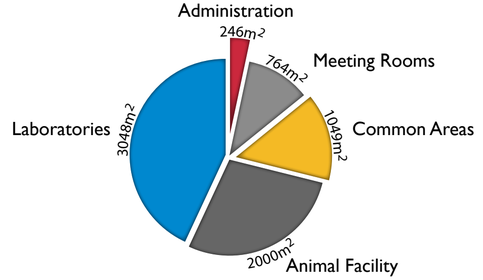
BUDGET GROWTH IN THOUSANDS OF EUROS



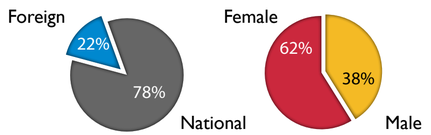
PERSONNEL BY CATEGORY



SURFACE DISTRIBUTION



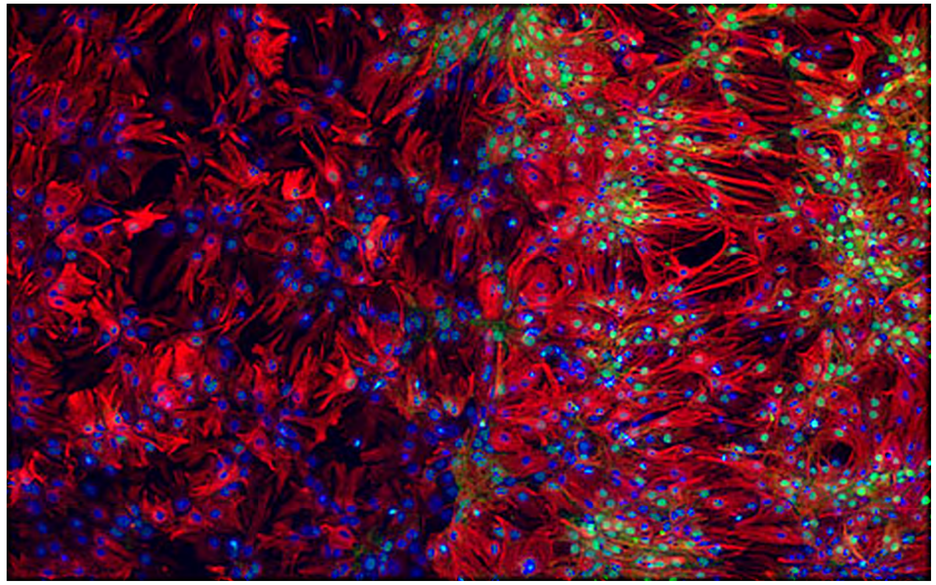
PERSONNEL BY ORIGIN & GENDER



CELLULAR AND SYSTEMS NEUROBIOLOGY

DIRECTOR: FELIX VIANA

The Cellular and Systems Neurobiology Unit consists of nine groups whose research focuses on how the cerebral cortex and various sensory systems function, primarily through the use of electrophysiological, computational and imaging techniques.



DEVELOPMENTAL NEUROBIOLOGY

DIRECTOR: ANGELA NIETO

The Developmental Neurobiology Unit consists of fifteen 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: ANGEL BARCO

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.

SYNAPTIC TRANSMISSION AND 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.

SYSTEMS NEUROBIOLOGY.

COORD: M. MARAVALL

Systems neurobiology is an emergent research area within the Institute and benefits from tremendous recent progress in computational, imaging and molecular techniques. Research in this line addresses the relationships between structure and function in neural circuits.

NEURAL DIFFERENTIATION AND SPECIFICATION

COORD: O. MARÍN

The study of the mechanisms that govern the genesis of neurons and their precursors is of great value to get insights on how the nervous system is generated and organized. Also, axon guidance and the study of migratory cell movements during development are considered to be amongst the most important topics in modern neuroscience.

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.

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.

10 RESEARCH GROUPS

01 **MECHANISMS AND RECEPTORS INVOLVED IN ANALGESIA AND ADDICTION**
Juan J. Ballesta

02 **TRANSCRIPTIONAL REGULATION OF NEURAL PLASTICITY**
Angel Barco

03 **SENSORY TRANSDUCTION AND NOCICEPTION**
Carlos Belmonte, Roberto Gallego, Félix Viana

04 **NEUROGENESIS AND CORTICAL EXPANSION**
Víctor Borrell

05 **MOLECULAR CONTROL OF AXONAL MYELINATION**
Hugo Cabedo

06 **PLASTICITY OF BRAIN NETWORKS**
Santiago Canals Gamoneda

07 **PDZ PROTEINS AND SIGNALING NETWORKS**
Ana Carmena

08 **MOLECULAR NEUROBIOLOGY OF NEURONAL NICOTINIC RECEPTORS**
Manuel Criado

09 **CELLULAR AND CONDUCTUAL NEUROSCIENCE**
Carmen de Felipe

10 **MECHANISMS OF GROWTH CONTROL AND CANCER IN DROSOPHILA**
Maria Domínguez

11 **CORTICAL DEVELOPMENT**
Alfonso Fairén

12 **NEUROBIOLOGY AND NEUROMODULATION OF THE OPIOID ACTIONS**
Clara C. Faura Giner

13 **OCULAR NEUROBIOLOGY**
Juana Gallar, Mª Carmen Acosta

14 **DEVELOPMENTAL NEUROGENETICS**
Luis García-Alonso

15 **PHYSIOLOGY OF THE PREFRONTAL CORTEX & CAROTID BODY**
Emilio Geijo

16 **MECHANOTRANSDUCTION IN MAMMALS**
Ana Gomis

17 **MOLECULAR MECHANISMS OF NEUROSECRETION**
Luis M. Gutiérrez, Salvador Viniegra

18 **DEVELOPMENT AND ASSEMBLY OF BILATERAL NEURAL CIRCUITS IN MAMMALS**
Eloísa Herrera

19 **SYNAPTIC PHYSIOLOGY**
Juan Lerma

20 **CELLULAR & MOLECULAR MECHANISMS OF BRAIN WIRING**
Guillermina López-Bendito

21 **TRANSLATIONAL NEUROPSYCHOPHARMACOLOGY OF NEUROLOGICAL AND PSYCHIATRIC DISEASES**
Jorge Manzanares

22 **DYNAMICS AND PLASTICITY OF CORTICAL SENSORY RESPONSES**
Miguel Maravall

23 **NEURONAL SPECIFICATION AND MIGRATION**
Oscar Marín

24 **VISUAL NEUROSCIENCE LABORATORY**
Luis M. Martínez.

25 **EXPERIMENTAL EMBRYOLOGY**
Salvador Martínez, Constantino Sotelo

26 **CELL MOVEMENTS IN DEVELOPMENT AND DISEASE**
M. Angela Nieto

27 **NEURAL PLASTICITY AND SYNAPTOGENESIS**
Beatriz Rico

28 **ALTERED MOLECULAR MECHANISM IN ALZHEIMER'S DISEASE AND DEMENTIA**
Javier Sáez Valero

29 **BIOPHYSICS AND PHARMACOLOGY OF IONIC CHANNELS**
Francisco Sala, Salvador Sala

30 **MOLECULAR NEUROGENETICS**
Francisco Tejedor

31 **CELL SIGNALLING DURING NEURONAL MIGRATION**
Miguel Valdeolmillos, Fernando Moya

01 Mechanisms and receptors involved in analgesia and addiction

Juan J. Ballesta UMH

Selected Publications
Personnel

Nowadays, the most potent clinically used analgesics are the opioids. However, their clinical use is limited by their problems, such as tolerance, dependence and addiction. Neuronal nicotinic receptors are also involved in antinociceptive mechanisms, being some nicotinic agonists more potent analgesics than morphine. The clinical use of nicotinic agonists as analgesics is limited, as is the case of opioids, for the development of tolerance, dependence and addiction. On the other hand, in Spain tobacco smoking is the most common addiction, being its prevalence about a 30% in people older than 15. The dramatism of this addiction is emphasized by the fact that half of the smokers will die from smoking-related diseases. Nicotine is the main addictive substance of tobacco, and in the tolerance, dependence and addiction to tobacco several subtypes of neuronal nicotinic receptors, as well as other receptors, such as dopaminergic, glutamatergic, opioid and cannabinoid receptors are implicated.

In this context we are involved in the study of the role of different receptors and post-transductional mechanisms in: (1) the tolerance to the analgesic effects of nicotinic agonists, and (2) the dependence and addiction to nicotine. To assess these issues we use a variety of biochemical approaches and behavioural tests.

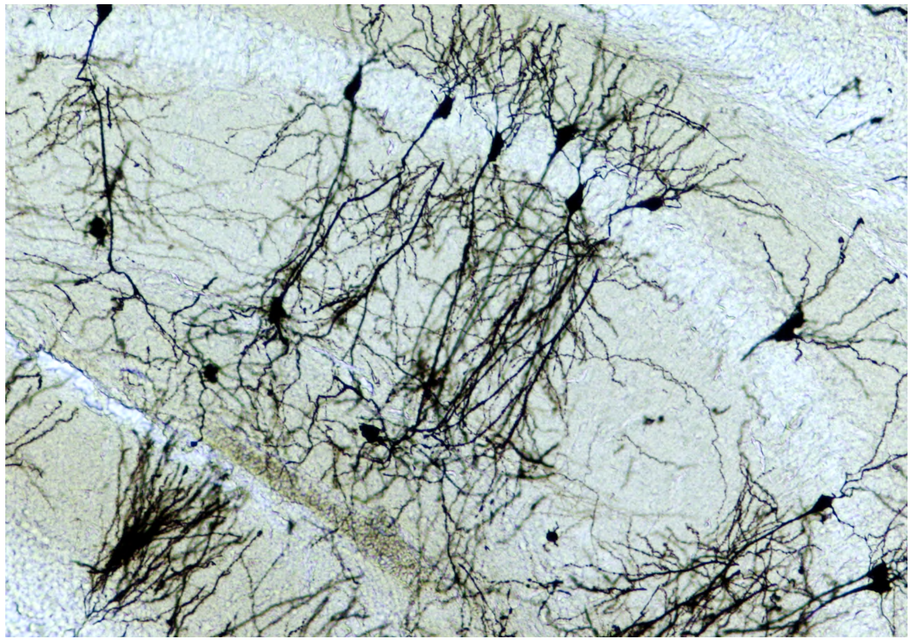
02 Transcriptional and epigenetic mechanisms of neuronal plasticity

Angel Barco CSIC

Selected Publications
Personnel

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.

03 Sensory transduction and nociception

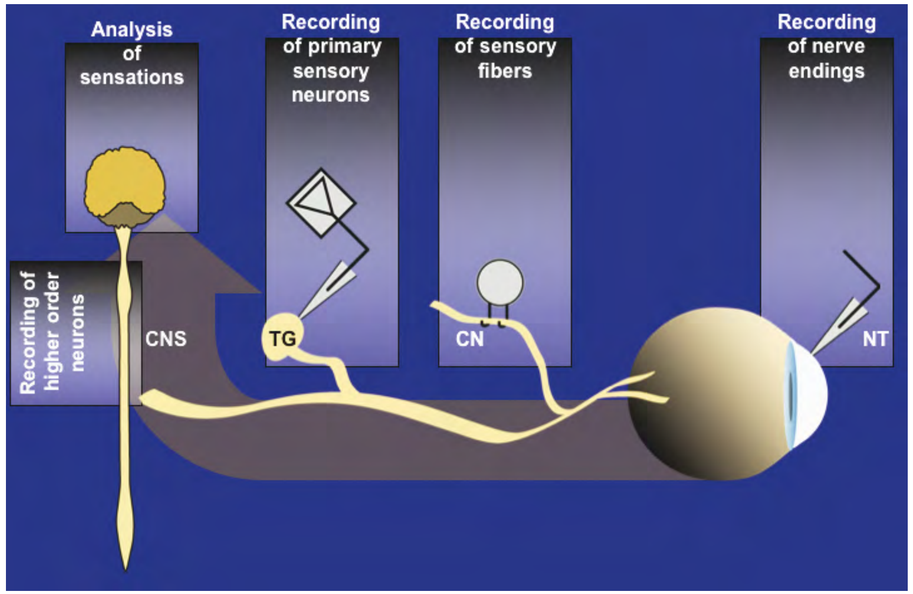
Carlos Belmonte UMH
Roberto Gallego UMH
Félix Viana CSIC

Selected Publications
Personnel

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 the functional study of ionic channels.

04 Neurogenesis and cortical expansion

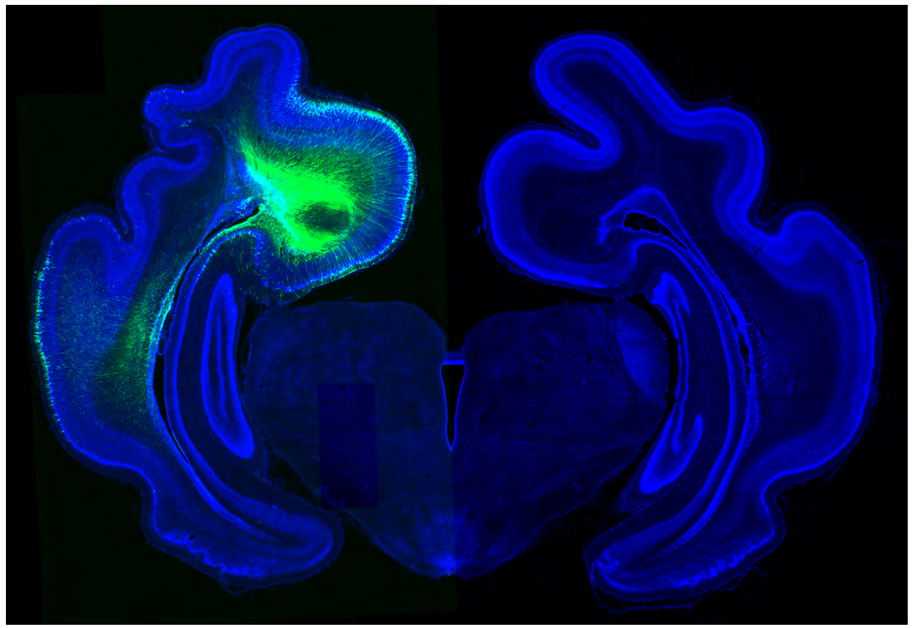
Víctor Borrell CSIC

Selected Publications
Personnel

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 the 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 analysis of the cellular and molecular mechanisms involved in the normal expansion and folding of the mammalian cerebral cortex. 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 these processes.



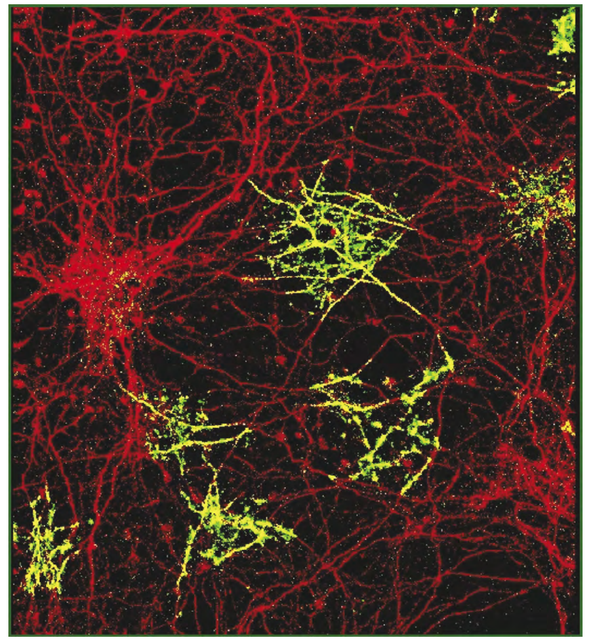
05 Molecular control of axonal myelination

Hugo Cabedo UMH

Selected Publications
Personnel

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.



06 Plasticity of brain networks

Santiago Canals Gamoneda CSIC

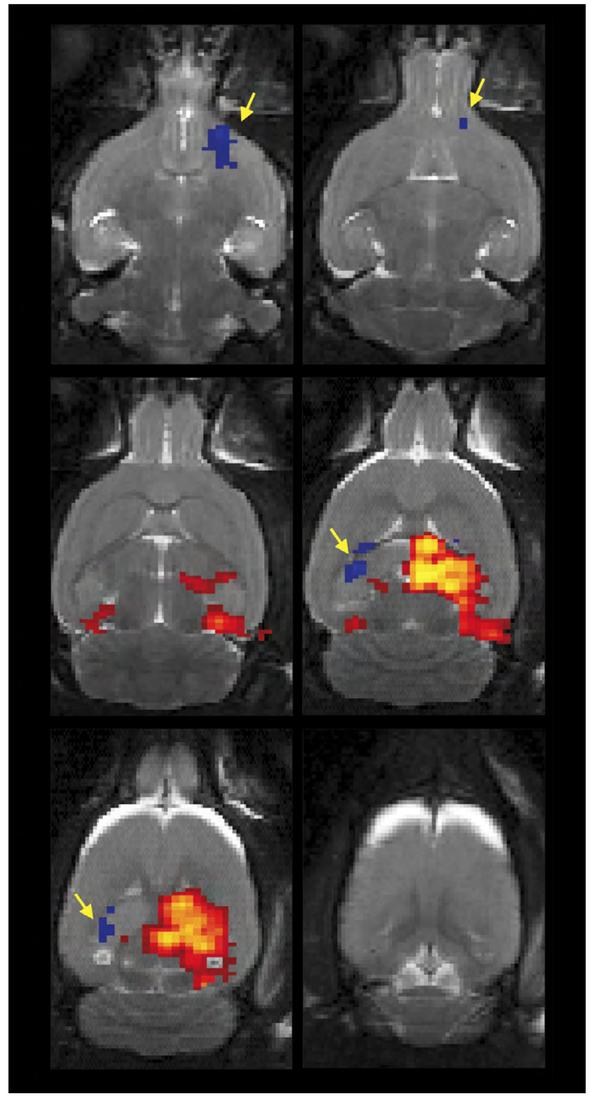
Selected Publications
Personnel

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.



07 PDZ proteins and signaling networks during the specification of neuronal identities

Ana Carmena CSIC

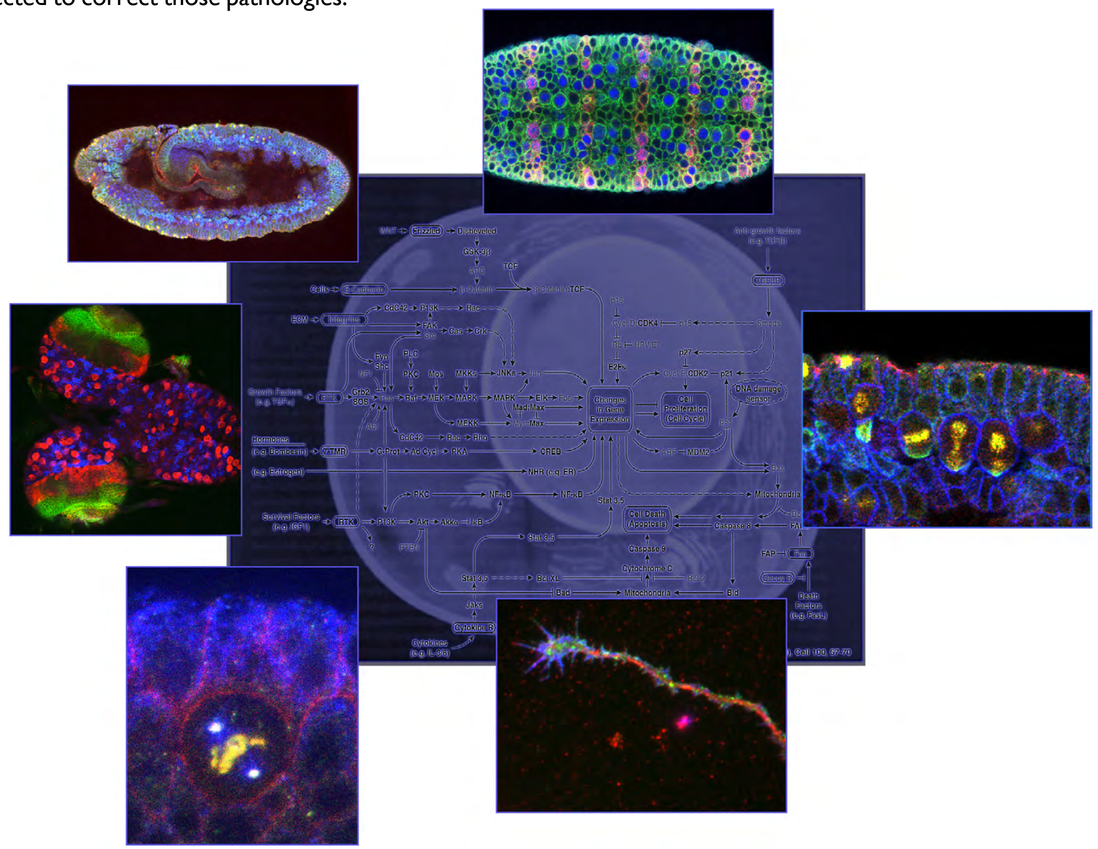
Selected Publications
Personnel

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 signalling 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.



08 Molecular neurobiology of neuronal nicotinic receptors

Manuel Criado UMH

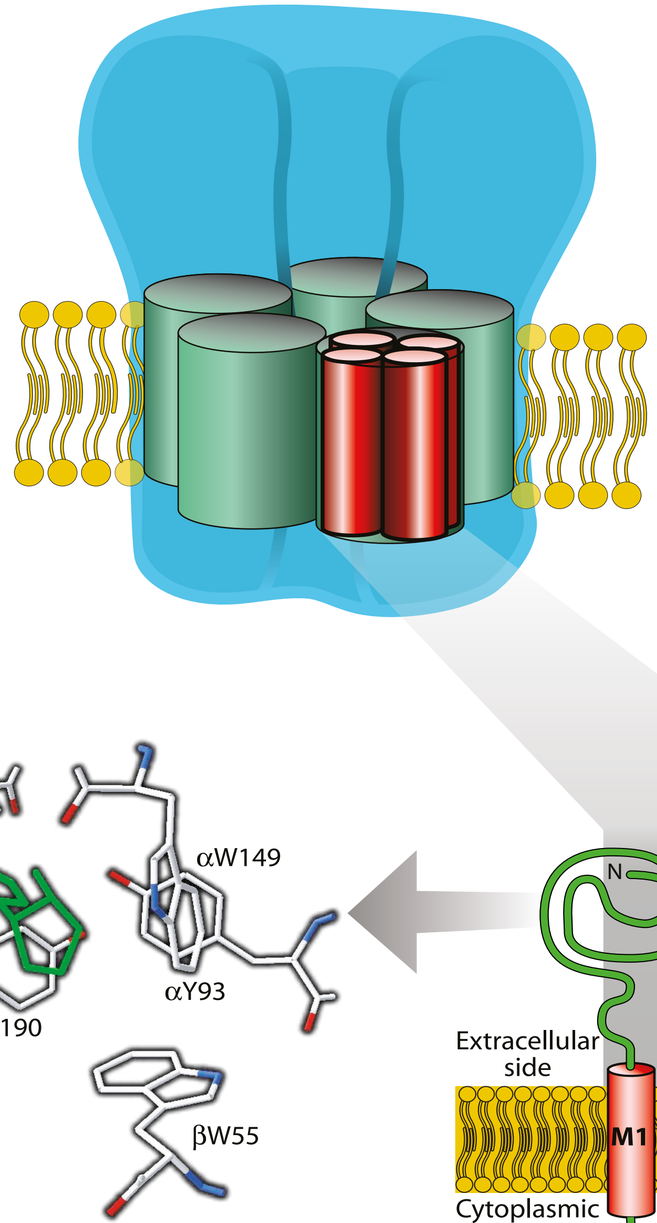
Selected Publications
Personnel

The nicotinic acetylcholine receptor is widely distributed in the central and peripheral nervous systems. Important functions and pathologies specific to the nervous 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 to regulate receptor biogenesis and function. Synthesis, assembly and localization of nicotinic receptors are complex processes that need the action of specific proteins. At present we characterize the interaction of some proteins with specific nicotinic receptor subtypes.

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



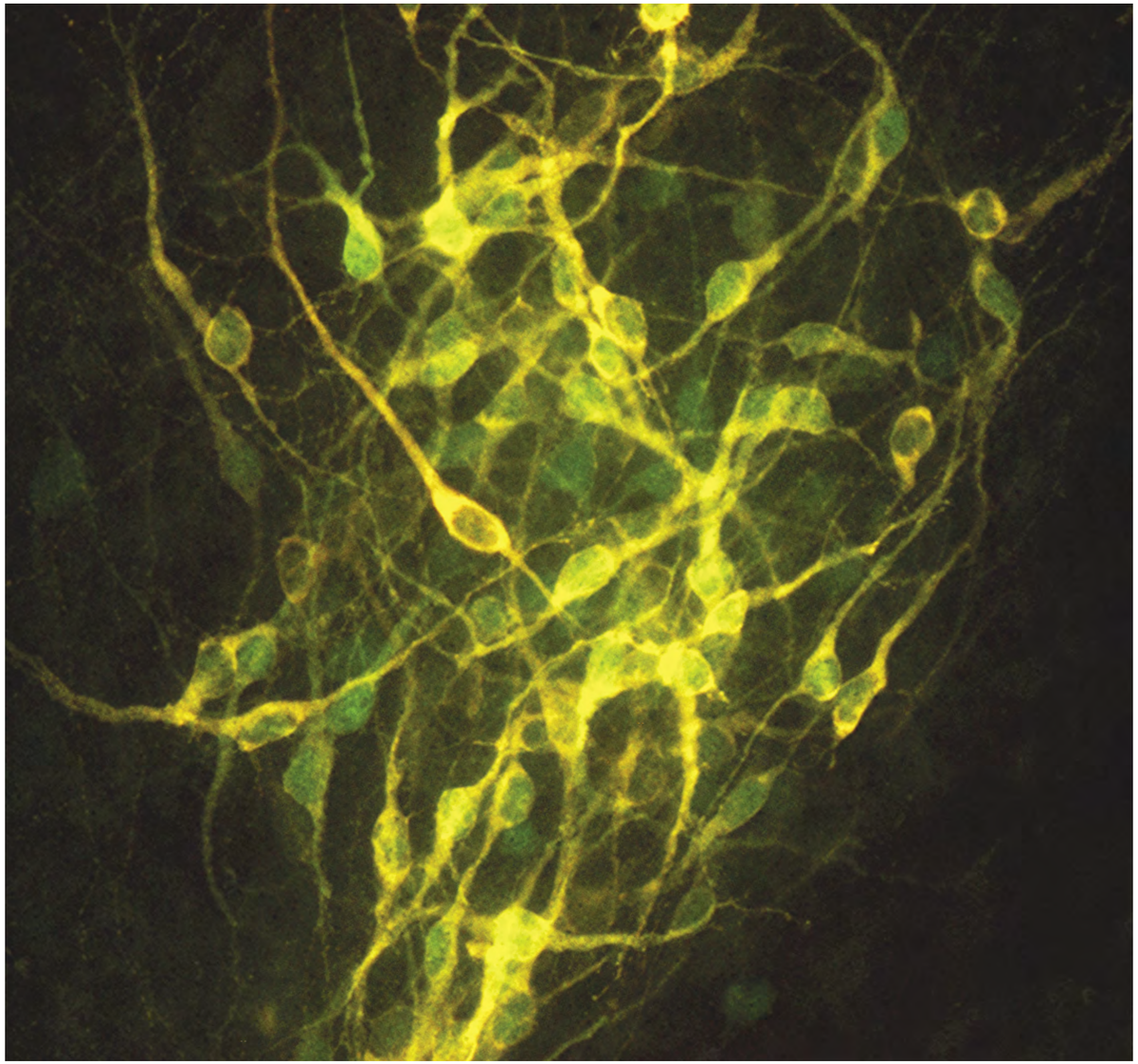
09 Cellular and conductual neuroscience

Carmen de Felipe UMH

Selected Publications
Personnel

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.



10 Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

Selected Publications
Personnel

Our studies are focused on four research projects:

Control of growth and tumorigenesis using *Drosophila*: Correct organ formation requires the balanced activation of a limited number of conserved developmental pathways (e.g. the Notch, Hedgehog, Wnt, JAK/STAT, AKT/PI3K and EGFR / Ras pathways), the disruption of which participates in the formation of most cancers. Our group has a general interest in understanding how these developmental pathways control organ formation (specification, proliferation, and differentiation) and how their dysregulation can lead to cancer.

Control of growth by organizing signals: Our group and others have shown that the Notch and Hedgehog signal transduction pathways play critical roles in creating and regulating specialized regions known as "organizers" that promote growth, patterning and retinal differentiation of the eye in *Drosophila melanogaster*. 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 specificity is achieved. Using the powerful genetic tools available in *Drosophila*, we have recently shown that specificity is achieved through the activation of the organ-specific transcription factor, eyegone and the secreted factor four-jointed. We have shown that eyegone is necessary and sufficient to mediate the specific growth response of Notch in the eye. Eyegone encodes a member of the PAX-family of oncogenes, but it differs from the canonical members in that eyegone protein has a truncated paired domain —a conserved DNA-binding domain that is presumed to be essential for PAX-associated oncogenic activity. Strikingly, we found that overexpression of human PAX6 (5a), which is structurally related to eyegone, induces tumours *in vivo*, whilst the canonical and previously presumed oncogenic PAX6 variant hardly affects growth in vivo. Our findings also redefine the process of organizer formation and function, and they identify four-jointed as a regulatory node integrating global growth control Notch pathway and the cell-autonomous tumor suppressor pathway Hippo/MST.

Genetic screens for novel tumour-inducing genes: Over seven years ago, we started complementary high-throughput genetic screens for mutations that both interact with the Notch pathway and that influence tissue growth or tumours. 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 hyper activation, 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. These data linked, 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. Recently, we have have identified, in colaboration with Dr. Borggrefe at the Max Planck Institut in Frieburg, the histone demethylase Lid/KDM5A as 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.

Drosophila models of tumour 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 epigenetic analysis of tumour metastasis has only recently been realised. We use 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*.

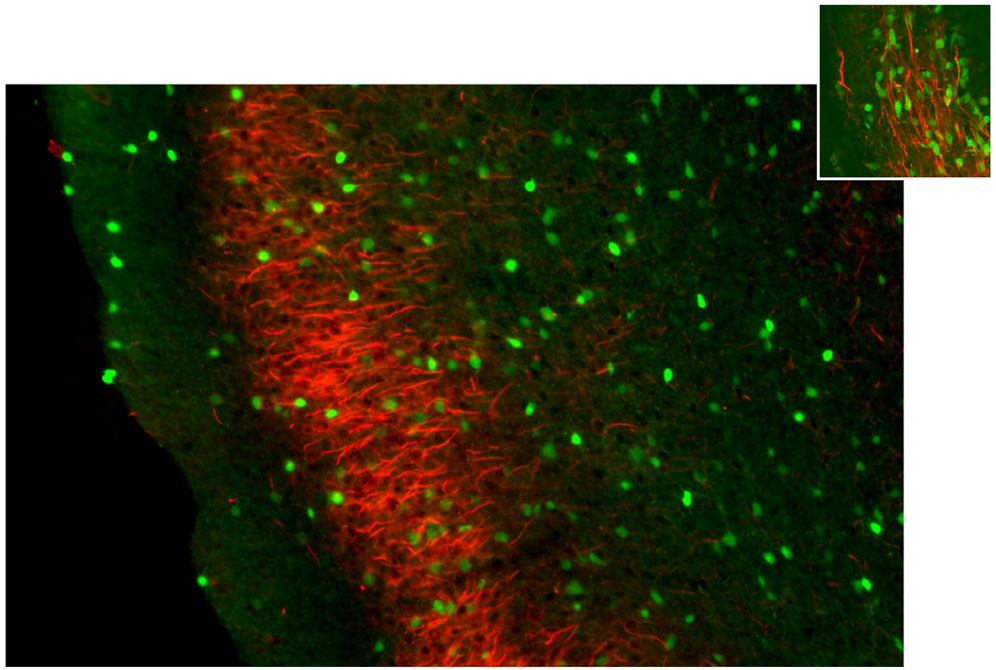
11 Cortical development

Alfonso Fairén CSIC

Selected Publications
Personnel

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.



12 Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH

Selected Publications
Personnel

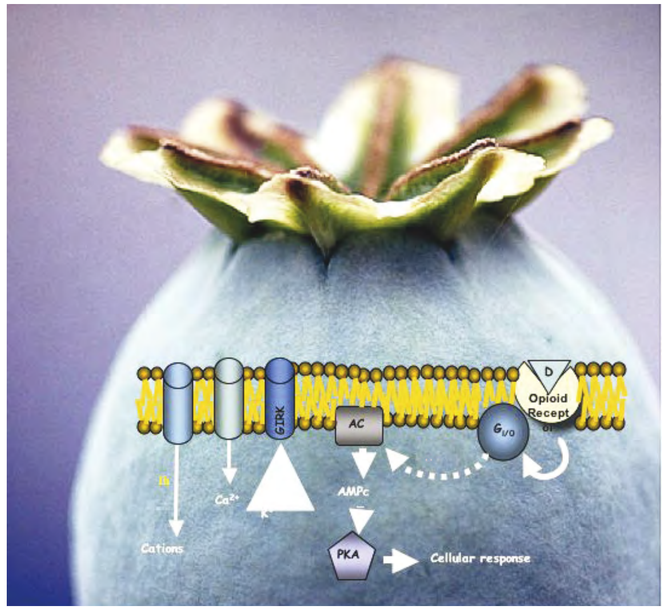
The improvement in the benefit–risk ratio for analgesic therapies is a relevant issue. Opioids are still the most potent and prescribed analgesic drugs. However, their clinical and non-clinical uses still have serious problems such as variability in the analgesic response, tolerance, dependence, addiction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



13 Ocular Neurobiology

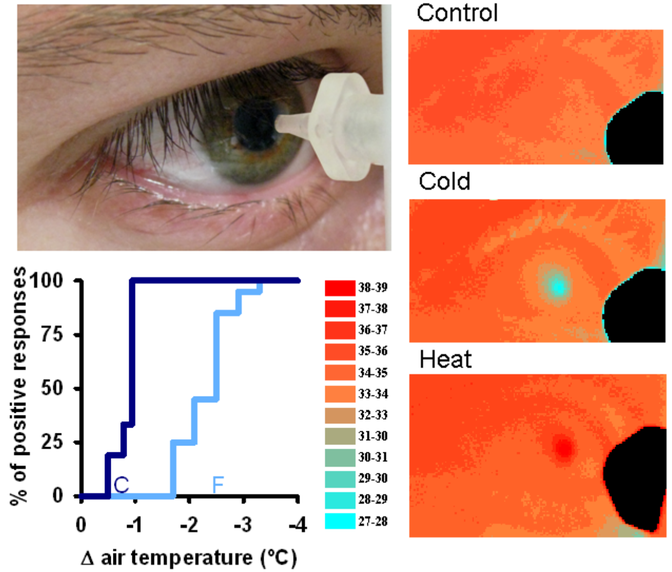
Juana Gallar UMH
Mª Carmen Acosta UMH

Selected Publications
Personnel

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.



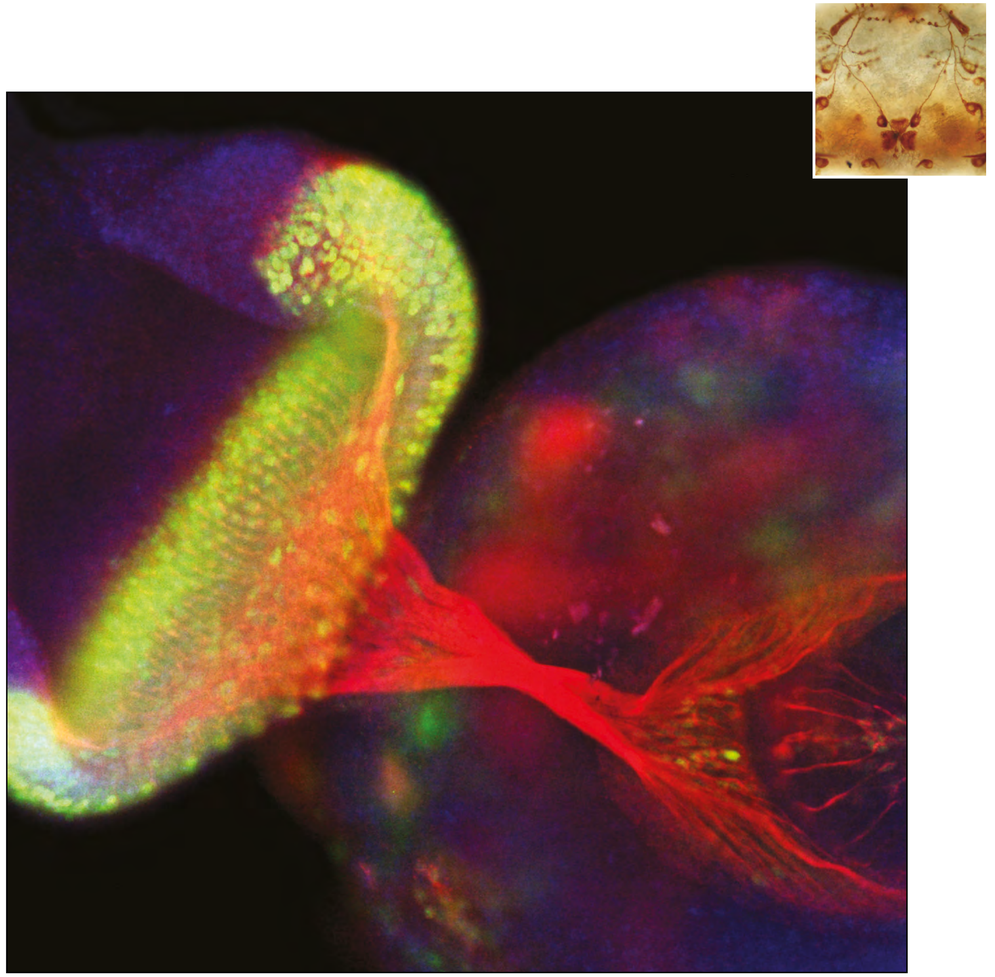
14 Developmental Neurogenetics

Luis García-Alonso CSIC

Selected Publications
Personnel

Nervous System function 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 established in three steps: growth and neurogenesis, to generate an organ with a characteristic size, shape and a species specific neural pattern, stereotyped guidance of each axon and dendrite, and synaptogenesis with the specific target cells. 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 molecules 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 EGF receptors. Our work reveals that the specificity of both L1- and NCAM-type proteins as modulators of FGF- and EGF-receptor function 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 function on the control of Notch signaling can be revealed in transgenic Drosophila.

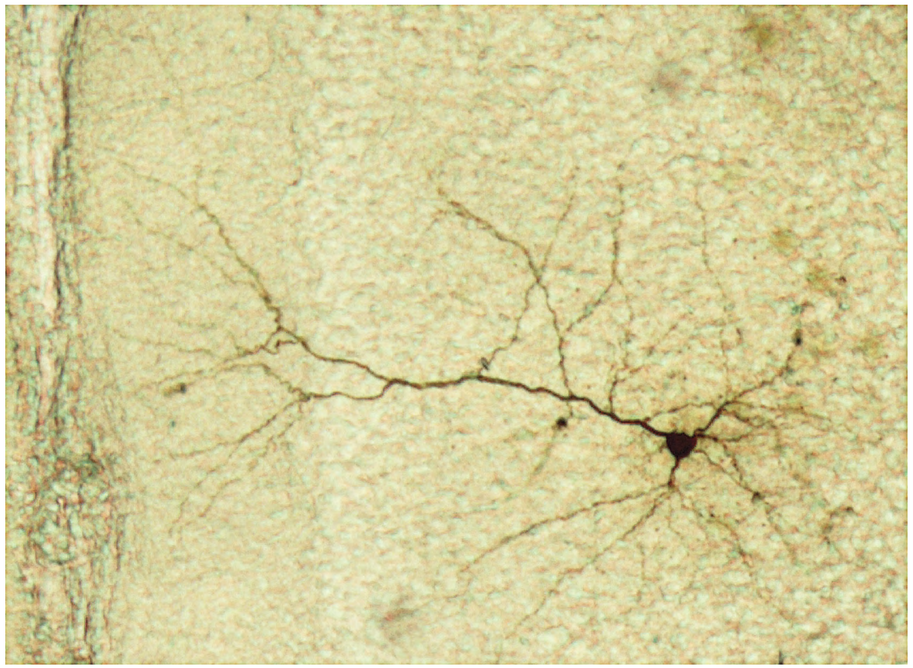


15 Physiology of the cerebral cortex

Emilio Geijo UMH

Selected Publications
Personnel

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.

16 Mechanotransduction in mammals

Ana Gomis CSIC

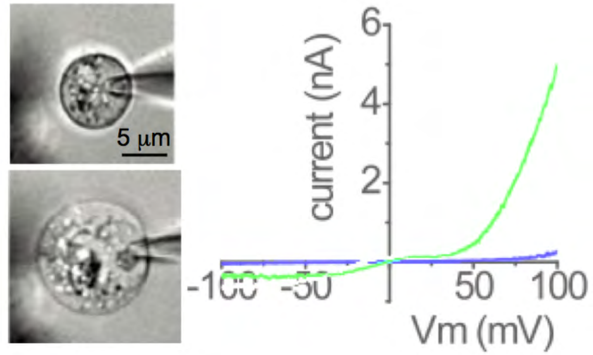
Selected Publications
Personnel

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

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

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

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



17 Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH

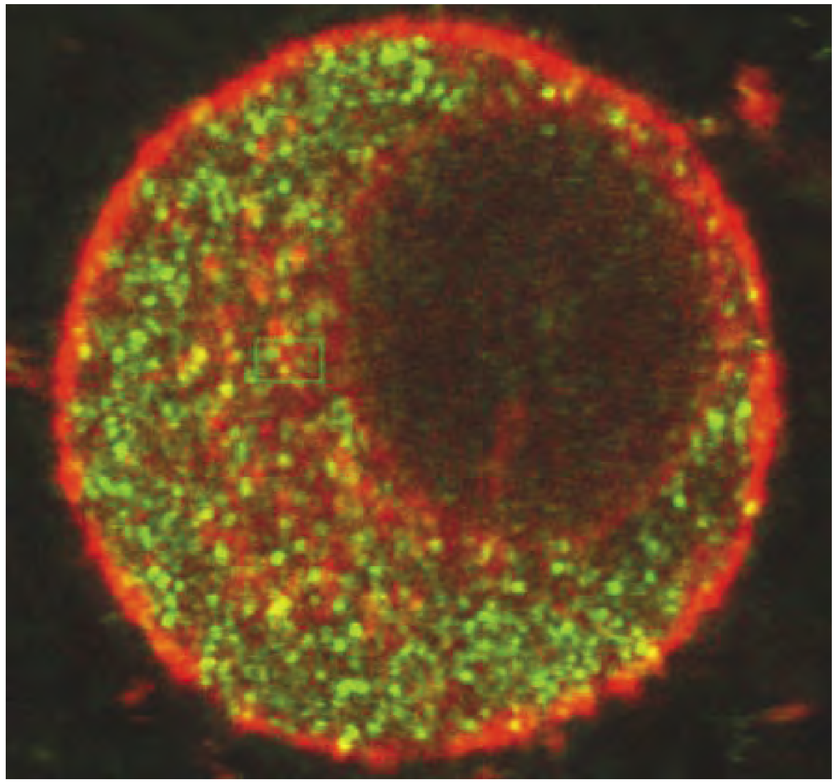
Selected Publications
Personnel

Adrenomedullary chromaffin cells have been used as an excellent experimental model to study the exocytosis and therefore the molecular mechanisms of neurotransmission. 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 molecular motors such a myosin-actin in vesicle transport during neurosecretion and the determination of essential aminoacids of synaptobrevin or SNAP-25 implicated 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.



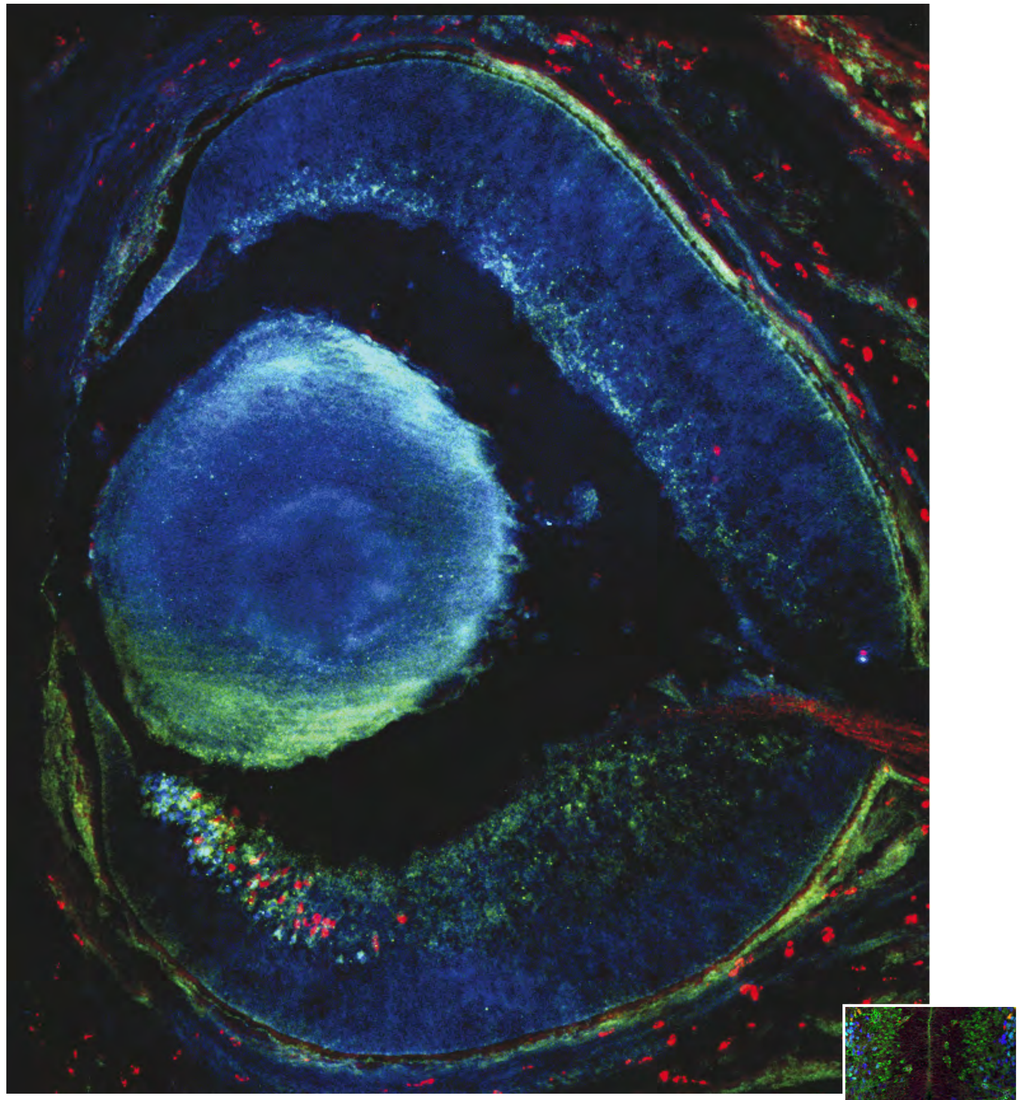
18 Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Selected Publications
Personnel

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.



19 Synaptic physiology

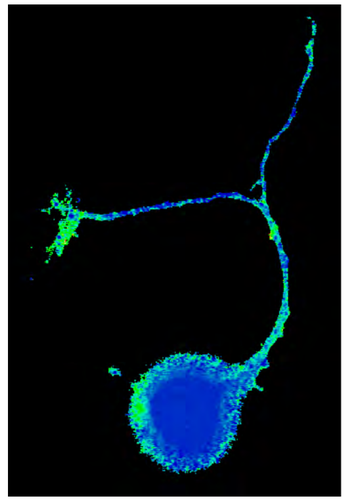
Juan Lerma CSIC

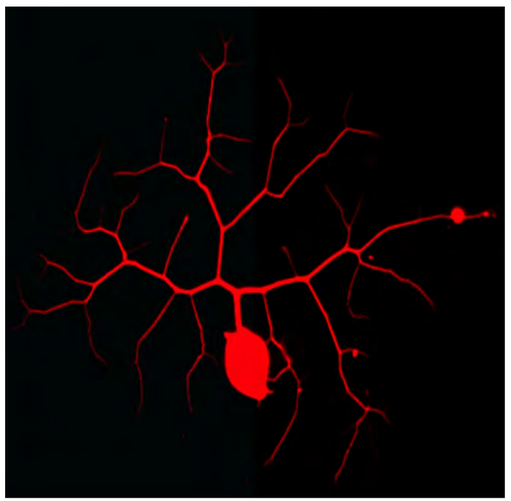
Selected Publications
Personnel

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

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

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





20 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications
Personnel

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.

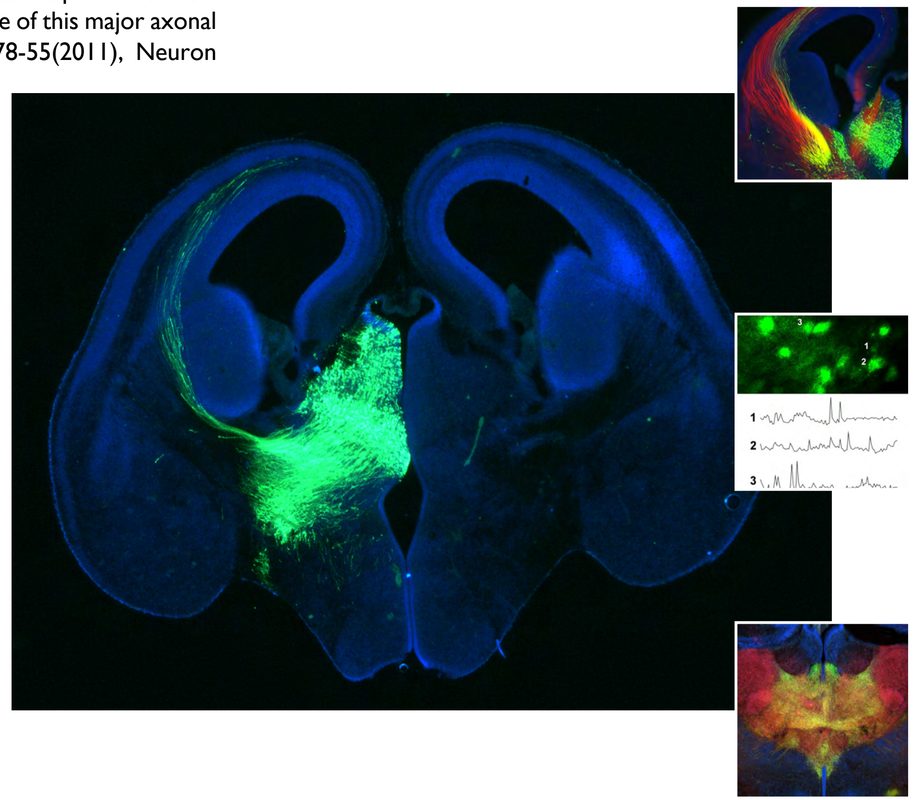
The development of the thalamocortical wiring requires a precise topographical sorting of its connections. Each thalamic nucleus receives specific sensory information from the environment and projects topographically to its corresponding cortical. A second level of organization is achieved within each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



21 Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

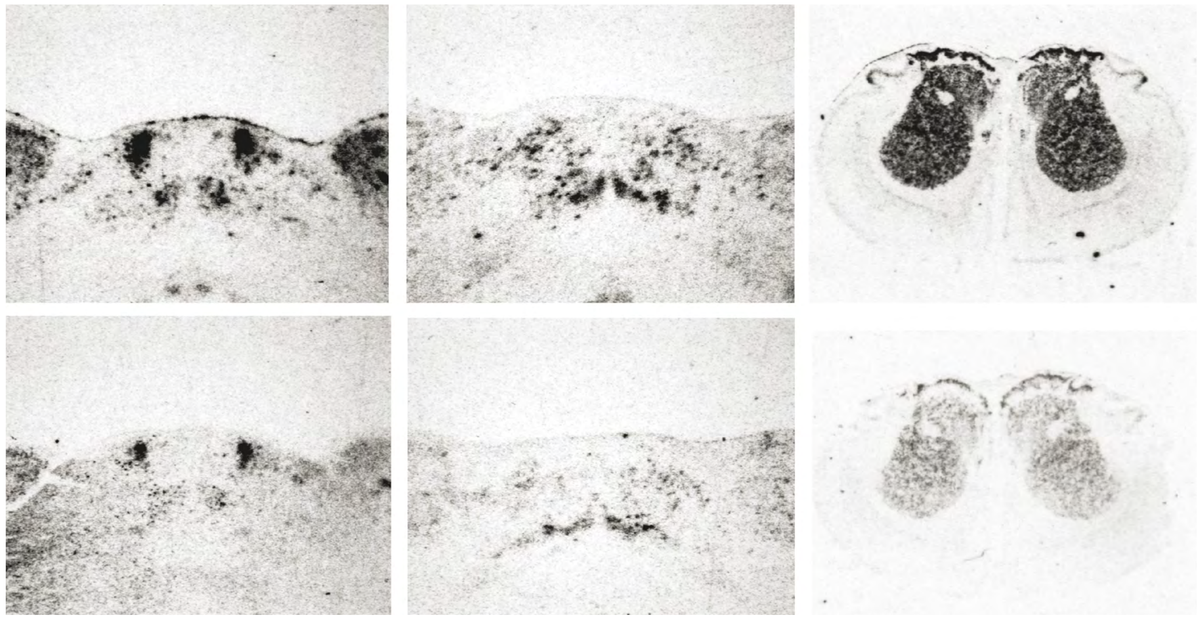
Selected Publications
Personnel

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.



22 Dynamics and plasticity of cortical sensory responses

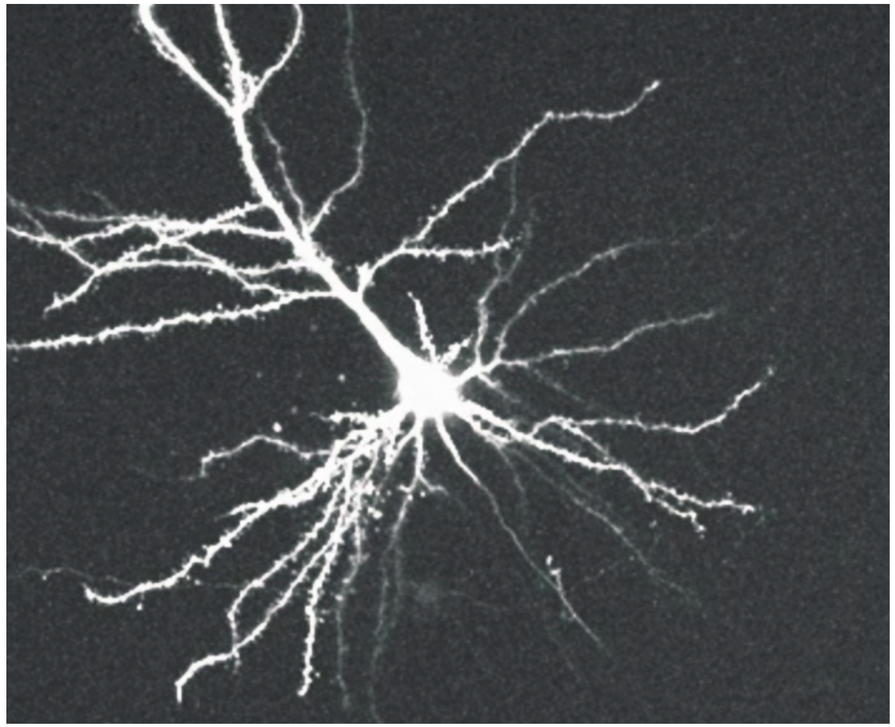
Miguel Maravall CSIC

Selected Publications
Personnel

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.



23 Neuronal specification and migration

Oscar Marín CSIC

Selected Publications
Personnel

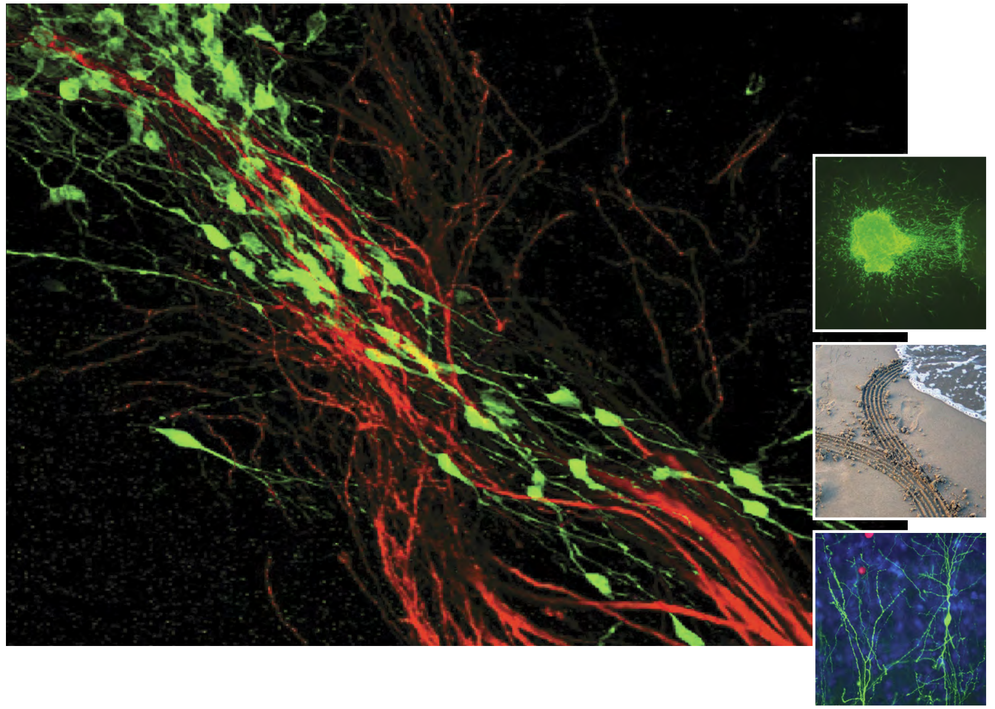
The main aim of our laboratory is to understand the molecular and cellular mechanisms controlling the development of the most anterior region of the brain, the telencephalon. The telencephalon contains key structures for the function of the mammalian brain, such as the basal ganglia and the cerebral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

In humans, mutations in genes that control the specification or migration of neurons in the cerebral cortex cause severe mental impairment or epilepsy, emphasizing the relevance of the search for other genes implicated in these processes.

In this context, our group focuses most of its efforts in the identification of novel genes controlling the development of cortical interneurons, a type of cortical cell which dysfunction underlies the aetiology of neurological and psychiatric disorders such as epilepsy or schizophrenia. To this aim, we are generating mouse strains to study the origin and fate of the different populations of cortical interneurons. Moreover, we are also in the process of generating mouse models of cortical interneuron deficiency, which we hope may contribute to understand the function of cortical interneurons.

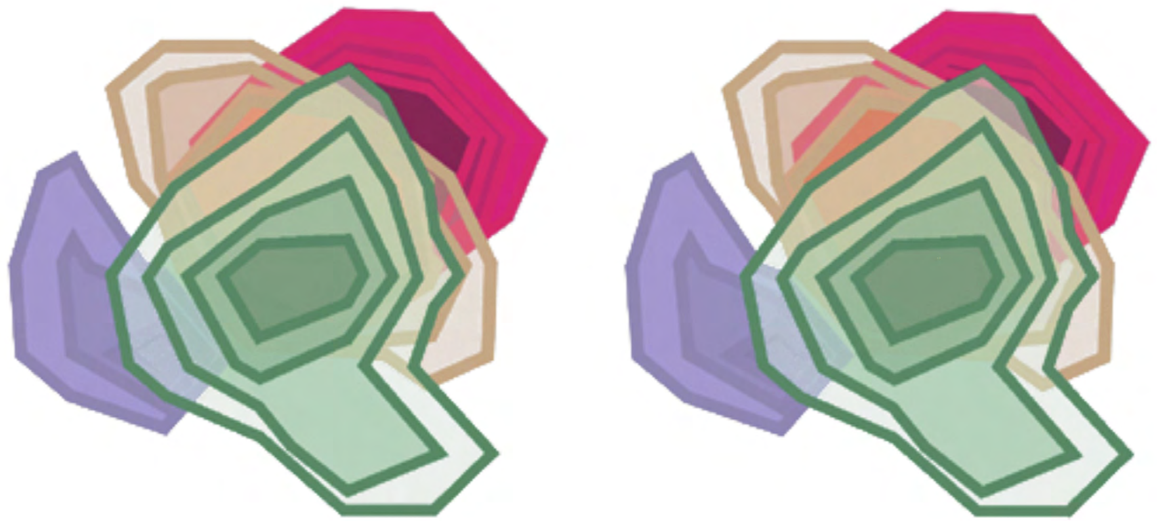


24 Visual Neuroscience Laboratory

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.



25 Experimental Embryology

Salvador Martínez UMH
Constantino Sotelo UMH

Selected Publications
Personnel

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).

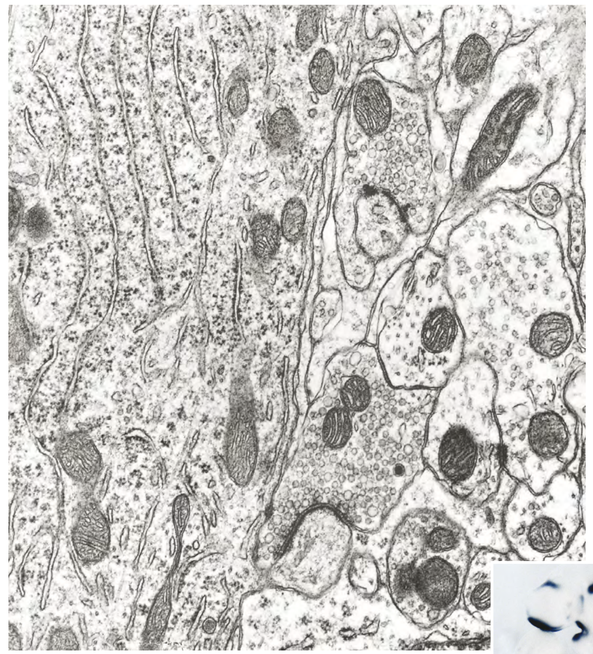
Experimental methodology: (i) Interspecific transplants of neural tissue between quail and chick embryonic brain areas. (ii) Explant cultures of mouse anterior neural tube will permit to make experimental embryological techniques on genetically altered mouse models.

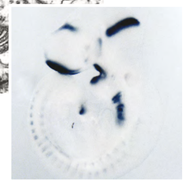
Neurogenetics: We are studying expression patterns of important genes related to the structural organization of the brain through its development. This research line is part of an EU Grant in which we pretend in a large scale manner to analyse the expression pattern of 16.000 genes at several embryonic 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 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: 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 fibres. 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.

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.





26 Cell movements in development and disease

M. Angela Nieto CSIC

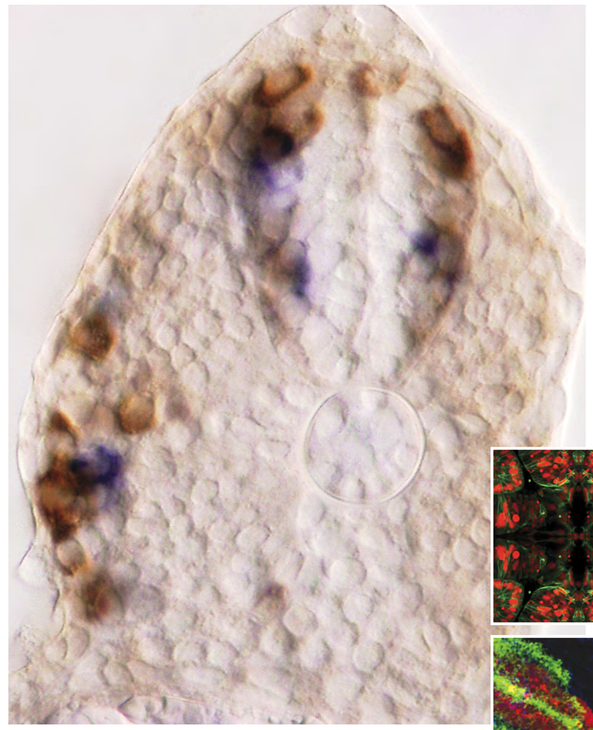
Selected Publications
Personnel

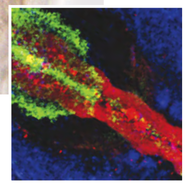
Our main interest is the study of cell behaviour in development and disease, in particular associated with cell movements. We have been working on the functional analysis of the Snail gene family, and have shown its implication in different processes during embryonic development in vertebrates, including the formation of the mesoderm and the neural crest both involving massive cell migration. We have also found that its pathological activation either during development or, in particular, in the adult leads to several prominent pathologies. As such, its 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 fulfils 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 found that the interplay between Snail and another transcription factor (Sox3) determines embryonic territories at gastrulation, ensuring the formation of the nervous system (2011).

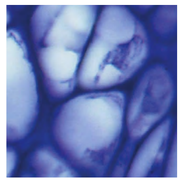
Snail activity is regulated by multiple mechanisms, from the gene transcriptional control to protein availability in the nucleus or postranslational modifications. We had previoulsy characterized the nuclear import pathways (2009) and now we have participated in a study that defines a novel phosphorylation of the Snail protein, promoting its nuclear retention and therefore, its activity (2011).

A phylogenetic analysis of this family has allowed us to conclude that the Snail genes constitute, along with the Scratch genes, a subgroup of the C2H2 zinc-finger transcription factors. We have traced back the origin of the superfamily to a protoSnail gene that underwent tandem duplication in the last common ancestor of the Diploblasts and Bilateria (2009). These studies favour the analyses of ancestral and acquired functions. We have found that 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 colonize distant territories both during embryonic development and during cancer progression, allowing cells to form different tissues and organs or distant metastasis, respectively.

We use mouse, chick and zebrafish as experimental models for loss or gain and function studies together with cultured cells and the analysis of samples from patients with the associated pathologies.







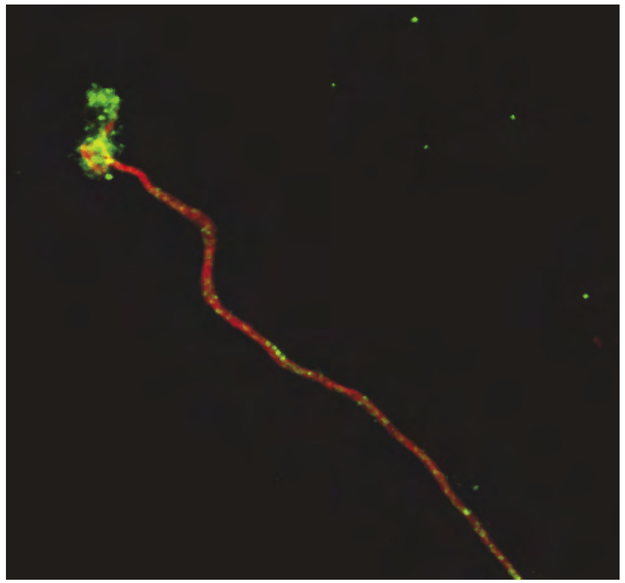
27 Neural circuit formation and remodeling

Beatriz Rico CSIC

Selected Publications
Personnel

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 ne



28 Altered molecular mechanism in Alzheimer's disease and dementia

Javier Sáez Valero UMH

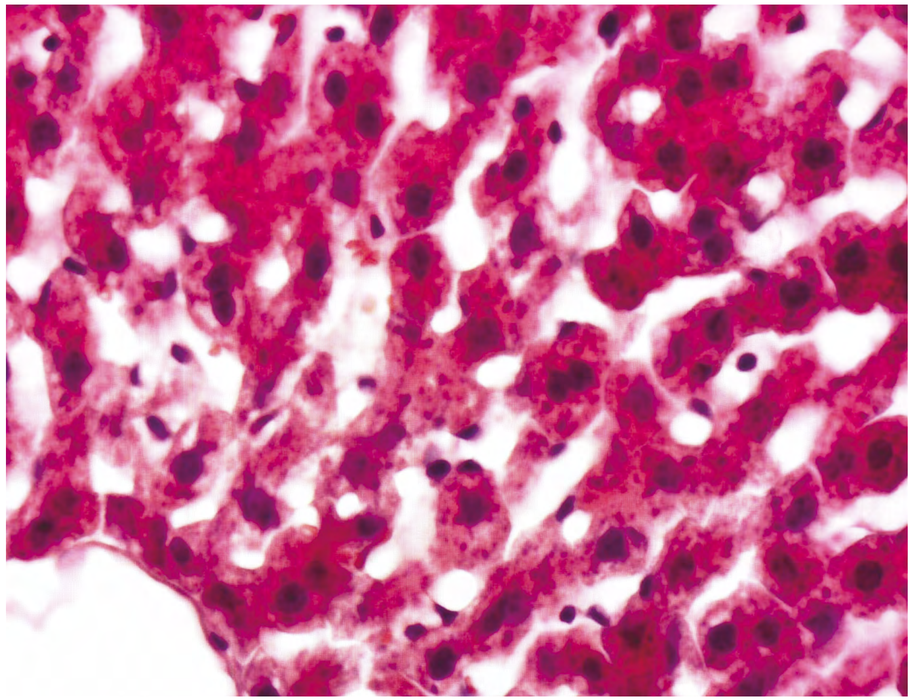
Selected Publications
Personnel

Our aim in the IN was 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 the glycoprotein 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 pattern of the proteoglycan Reelin in AD. Reelin is a glycoprotein 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 signalling 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.



29 Biophysics and pharmacology of ionic channels

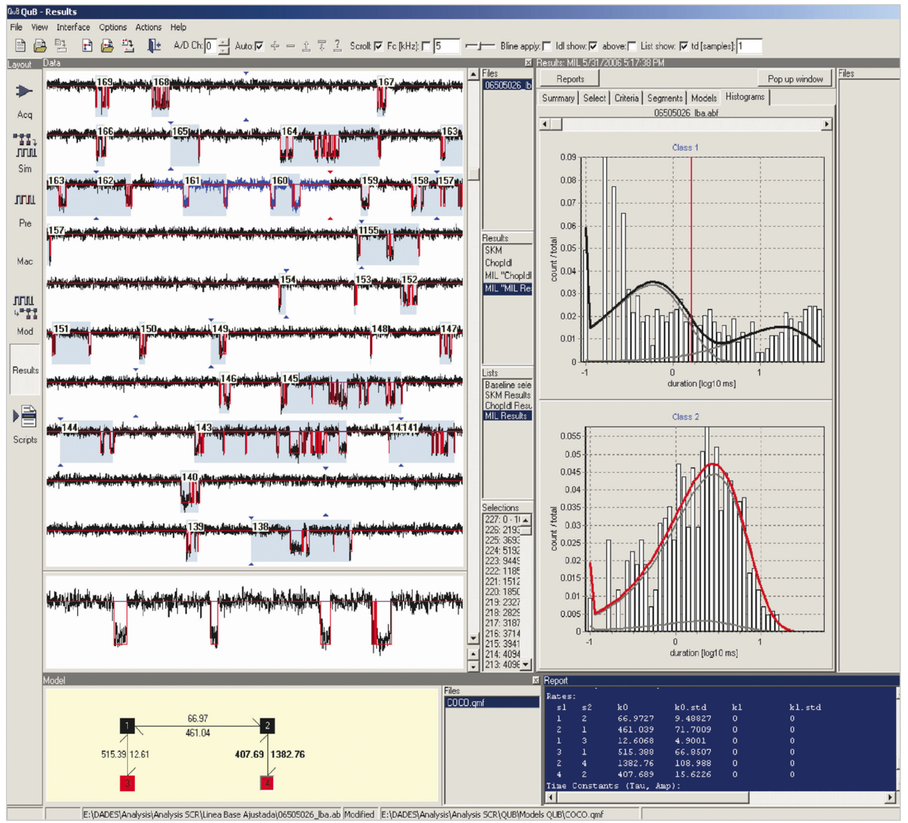
Francisco Sala UMH
Salvador Sala UMH

Selected Publications
Personnel

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 electrophysiological techniques described above.



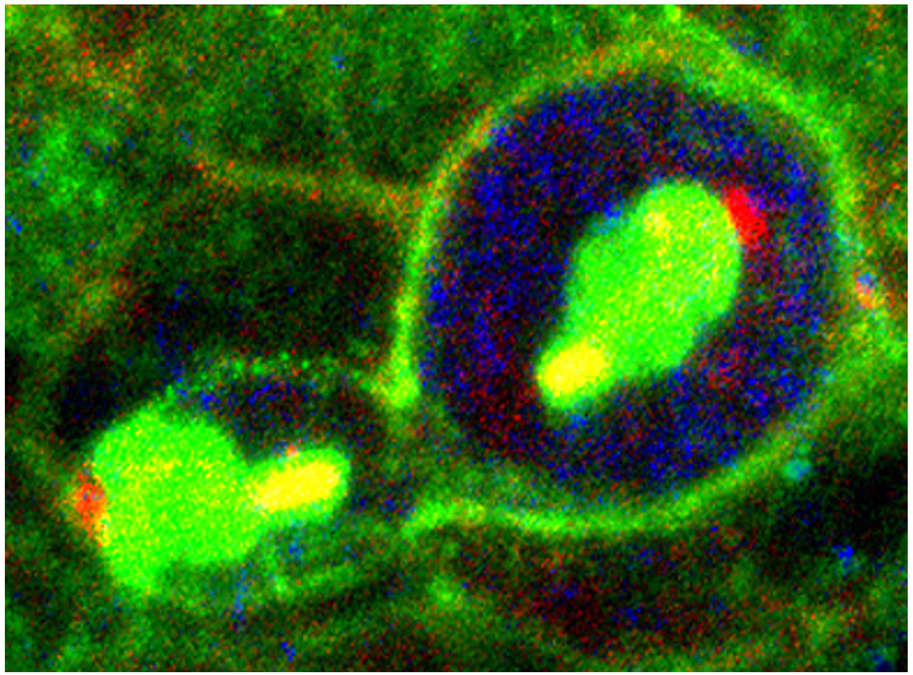
30 Molecular neurogenetics

Francisco Tejedor CSIC

Selected Publications
Personnel

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.



31 Cell signalling during neuronal migration

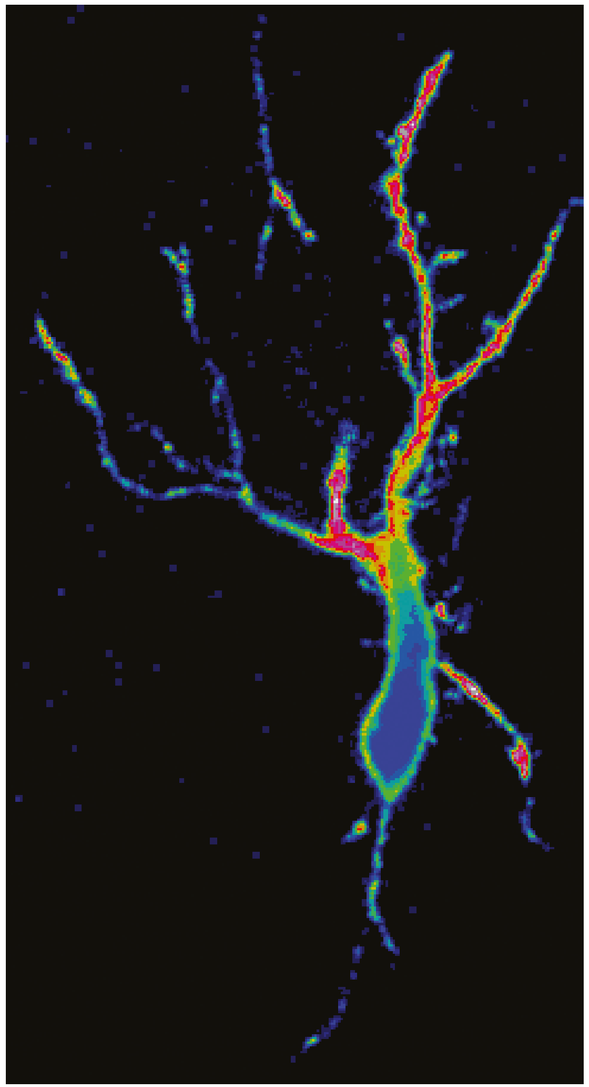
Miguel Valdeolmillos UMH
Fernando Moya UMH

Selected Publications
Personnel

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.



11 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 2010 - Jan 2011)
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 2011)
Module 1C: Neurogenesis
Module 2C: Synaptic function
Module 3C: Information processing
Module 4C: Neuropathology

12 COLLABORATIONS AND 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 de Desarrollo, Prof. Remedios Caro Almela

Asociación Española Contra el Cáncer

The Allen Institute for Brain Science

European Network of Neuroscience Institutes

Network of European Neuroscience Institutes

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

COLLABORATIONS AND AGREEMENTS

Neurobiology
Research Professorship
Remedios Caro Almela"

In collaboration with the Instituto de Neurociencias, the Martínez-Caro family sponsors the "Remedios Caro Almela" Developmental Neurobiology Chair. Professor Remedios Caro Almela was born in Murcia, on May of 1937 and she died sixty years later in Alicante, victim of a cancerous process. 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 Remedios Caro Almela Chair of Developmental Neurobiology, was created in the year 2000 as a result of a philanthropic initiative by Fernando Martínez Ramos, to honor the memory of his deceased wife Remedios Caro Almela.

The Chair was established at the Institute of Neurosciences, joint centre of the Spanish Scientific Research Council and the Miguel Hernández University, 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.

Since 2006, the Remedios Caro Almela Chair has sponsored an international prize in Developmental Neurobiology. This has been so far awarded to Barry Dickson (2006), François Guillemot (2007), Rüdiguer Klein (2008, Steve Wilson (2009) and Christine Holt (2011).

Dr Barry J. Dickson
2006

Dr François Guillemot
2007

Dr Rüdiger Klein
2008

Dr Stephen Wilson
2009

COLLABORATIONS AND AGREEMENTS

The Remedios Caro Almela Prize for Research in Developmental Neurobiology

The Remedios Caro Almela Prize in Developmental Neurobiology was created in 2006 as part of the Chair's activities, and consisted of an unrestricted award of 20.000€. 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.

On June 29th, the international Scientific Committee commissioned to award the fifth Remedios Caro Almela Prize for research in developemntal neurobiology, met to asses the work of talented and active European researchers in the field of nervous system development, looking for particularly outstanding work in this field carried out over the past few years.

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; Constantiono Sotelo, current holder of the Remedios Caro Almela Chair; 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 Cambriidge University (U.K.).

Christine Holt has made important 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 degrade at a local level in the growth cone, and in a convincing manner, she demonstrated that this process is necessary for a response to the orientation signals released 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 lecture 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.

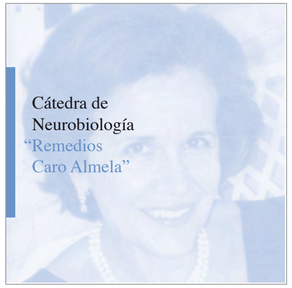
Professor Holt was born in Wylam (U.K.) in 1954, She graduated in Biological Sciences from Sussex's University and read her thesis in Zoology at the MRC, Kings College, London. After postdoctoral stays in the United States and Germany, she continued her research in the Cambridge University, where in 2003 she was appointed Professor in Developmetal 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 scientific journals.

in it's fifth edition awarded to

Dr Christine E. Holt

of the University of Cambridge

12 COLLABORATIONS AND AGREEMENTS



The Instituto de Neurociencias awarded their gold medal to Fernando Martinez Ramos, sponsor of the Remedios Caro Almela Chair. The ceremony, chaired by the Rector of the UMH - Jesús Tadeo Pastor Ciurana - and by the President of the CSIC - Rafael Rodrigo Montero - took place prior to the award ceremony of the Vth Remedios Caro Almela Prize in Developmental Neurobiology.

The gold medal is the highest award of the Instituto de Neurociencias. It was granted by unanimous agreement of its Board of Directors on December 14, 2009 to Fernando Martinez Ramos to express the IN's appreciation and admiration for his great activity of patronage. Fernando Martinez Ramos, who unfortunately passed away on May 2011, was a person with great cultural and social interests, which was reflected by different philanthropic activities. The Remedios Caro Almela Chair was created as a tribute to his deceased wife, which also gives name to the international award.

SERVICES AND FACILITIES

MOLECULAR BIOLOGY AND 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.

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.

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.

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

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.

SERVICES AND FACILITIES

ANIMAL HOUSE

The service for animal experimentation holds approximately 8000 mice in a pathogen free environment.

Its 2000m^2 facility is divided into several areas: breeding and maintanence of genetically modified mouse lines; breeding and maintanence of wild type mice and provision of females at defined gestational periods; quarentine; transgenics laboratory; experimental proceedures, and wash and sterilization facilities.

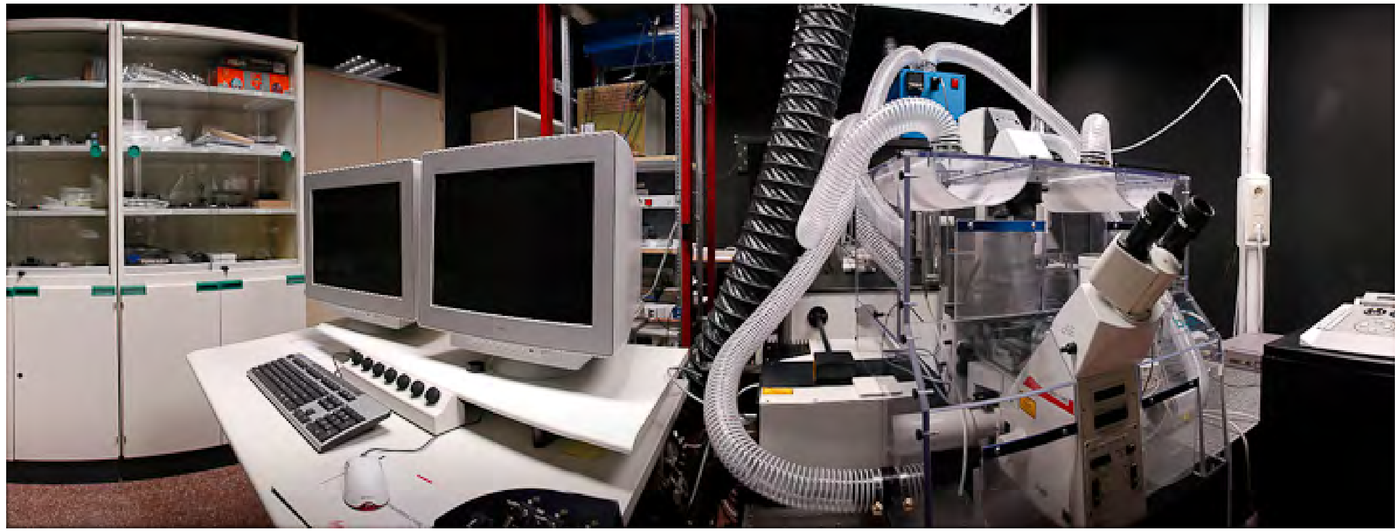
PURCHASING AND STORES

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 200 m2 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.

BEHAVIOURAL STUDIES AREA

(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



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.

DROSOPHILA COMMON SERVICE

The common facility for Drosophila research at the Institute includes a lab for culture media preparation, washing and sterilization of Drosophila lab material. There are two incubator rooms at 25°C and 18°C for the maintenance of mutant stocks and genetic combinations (more than three thousand at present time). In addition, there are two high precission incubator chambers at 18°C and 25°C for experimental purposes. Drosophila labs at the IN continuously serve stocks and mutant combinations to other labs in Europe and the US.

SERVICES AND FACILITIES

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.

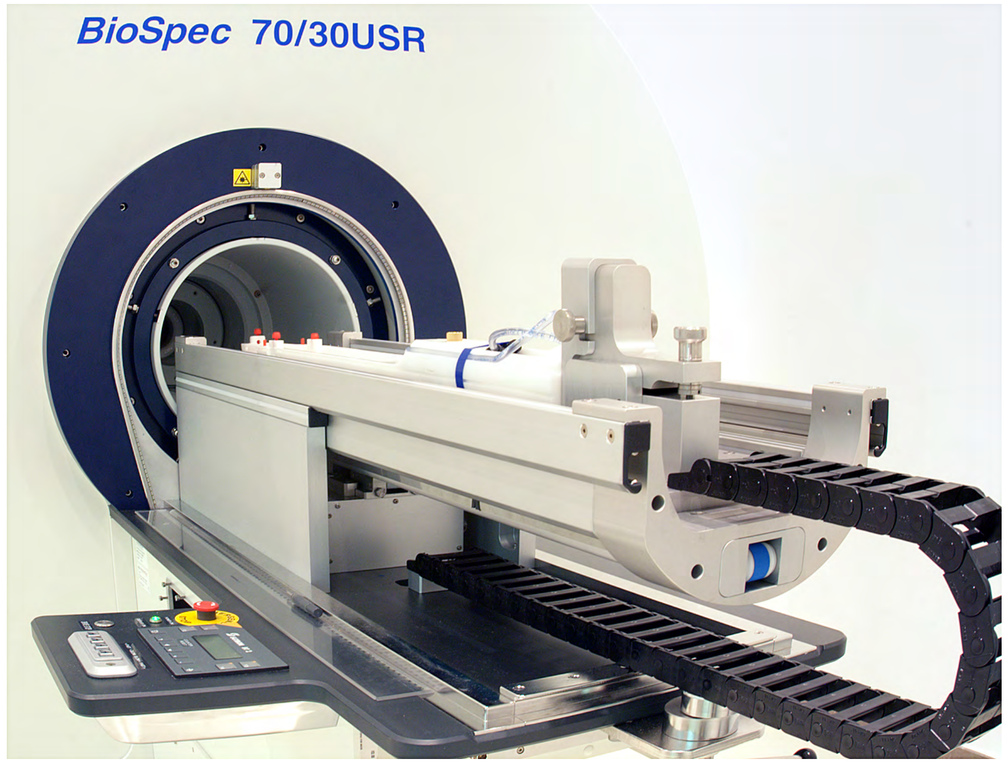
-Organotypic culture room: is equipped to carry out animal tissue explant cultures (microscope, vibrating microtome and tissue electroporator).

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.



13 SERVICES AND FACILITIES

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Mª Teresa García Hedo

ADMINISTRATION

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Mª Jesús Arencibia Rojas
Angelines Barrios Fernández
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Isabel Romero García
Ruth Rubio Sánchez
Mª Luisa Sánchez Vázquez


MTGH


ABF


AMLM


MRGL


EMB


IMP


MLSV


IRG MTPV RLC

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Stuart Bailey Ingham

ELECTRONIC WORKSHOP
Alfonso Pérez Vegara
Manuel Bonilla García

CELL CULTURE
Sara Carratalá Gosálbez
Rosa García Velasco

GLASSWARE & AUTOCLAVING
Trinidad Guillén Carrillo

BRAIN IMAGING SERVICE
Jesús Pacheco Torres


IOC

LGG


JCR


JER


SBI


JPT


TGC


SCG


RGV


APV

SERVICES AND FACILITIES

VETERINARY STAFF

Mª Jesús Molina Cimadevilla
Gonzalo Moreno del Val

ANIMAL HOUSE

Alejandro Botella García
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

Abolafia, JM; Vergara, R; Arnold, MM; Reig, R; Sanchez-Vives, MV
Cortical Auditory Adaptation in the Awake Rat and the Role of Potassium Currents
Cerebral Cortex 21 (5) 977-990 6,84

Acloque, H; Ocana, OH; Matheu, A; Rizzoti, K; Wise, C; Lovell-Badge, R; Nieto, MA
Reciprocal Repression between Sox3 and Snail Transcription Factors Defines Embryonic Territories at Gastrulation
Developmental Cell 21 (3) 546-558 13,95

Alfonso, JP; Caracuel, A; Delgado-Pastor, LC; Verdejo-Garcia, A
Combined goal management training and mindfulness meditation improve executive functions and decision-making performance in abstinent polysubstance abusers
Drug And Alcohol Dependence 117 (1) 78-81 3,37

Alves, DS; Castello-Banyuls, J; Faura, CC; Ballesta, JJ
An extracellular RRR motif flanking the M1 transmembrane domain governs the biogenesis of homomeric neuronal nicotinic acetylcholine receptors
Febs Letters 585 (8) 1169-1174 3,60

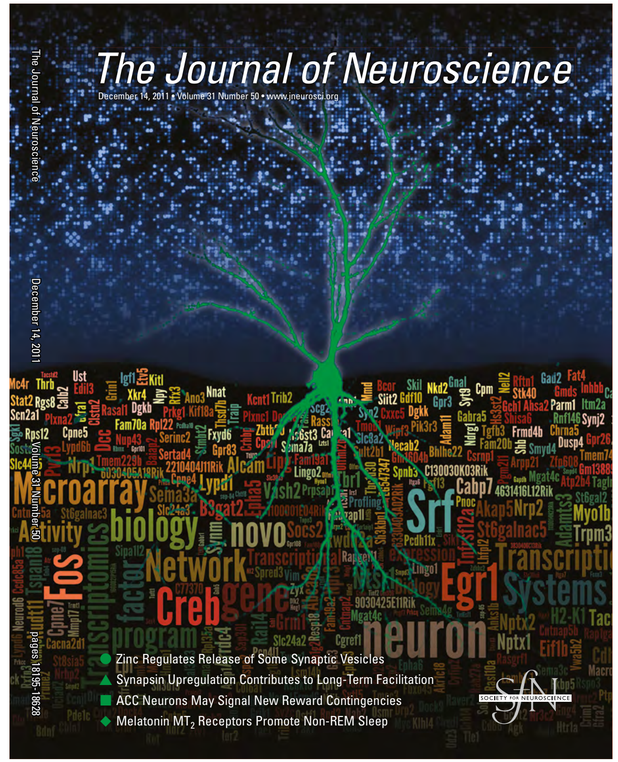
Barco, A; Marie, H
Genetic Approaches to Investigate the Role of CREB in Neuronal Plasticity and Memory
Molecular Neurobiology 44 (3) 330-349 6,07

Belmonte, C; Gallar, J
Cold Thermoreceptors, Unexpected Players in Ocular Dryness
Investigative Ophthalmology And Visual Science 52 (6) 3888-3892 3,47

Benito, E; Valor, LM; Jimenez-Minchan, M; Huber, W; Barco, A
cAMP Response Element-Binding Protein Is a Primary Hub of Activity-Driven Neuronal Gene Expression
Journal Of Neuroscience 31 (50) 18237-18250 7,27

Bielle, F; Marcos-Mondejar, P; Keita, M; Mailhes, C; Verney, C; Ba-Charvet, KN; Tessier-Lavigne, M; Lopez-Bendito, G; Garel, S
Slit2 Activity in the Migration of Guidepost Neurons Shapes Thalamic Projections during Development and Evolution
Neuron 69 (6) 1085-1098 14,03

Bielle, F; Marcos-Mondejar, P; Leyva-Diaz, E; Lokmane, L; Mire, E; Mailhes, C; Keita, M; Garcia, N; Tessier-Lavigne, M; Garel, S; Lopez-Bendito, G
Emergent Growth Cone Responses to Combinations of Slit1 and Netrin 1 in Thalamocortical Axon Topography
Current Biology 21 (20) 1748-1755 10,03



Callaway, EM; Borrell, V
Developmental Sculpting of Dendritic Morphology of Layer 4 Neurons in Visual Cortex: Influence of Retinal Input
Journal Of Neuroscience 31 (20) 7456-7470 7,27

Carmena, A; Makarova, A; Speicher, S
The Rap1-Rgl-Ral signaling network regulates neuroblast cortical polarity and spindle orientation
Journal Of Cell Biology 195 (4) 553-562 9,92

Carreres, MI; Escalante, A; Murillo, B; Chauvin, G; Gaspar, P; Vegar, C; Herrera, E
Transcription Factor Foxd1 Is Required for the Specification of the Temporal Retina in Mammals
Journal Of Neuroscience 31 (15) 5673-5681 7,27

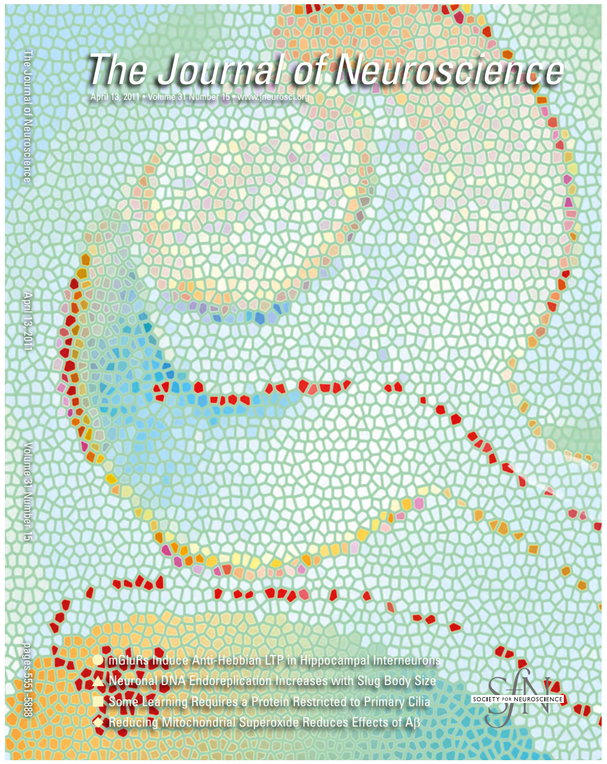
Colonques, J; Ceron, J; Reichert, H; Tejedor, FJ
A Transient Expression of Prospero Promotes Cell Cycle Exit of Drosophila Postembryonic Neurons through the Regulation of Dacapo
Plos One 6 (4) 4,41

Criado, M; Mulet, J; Gerber, S; Sala, S; Sala, F
Mutants of beta-strand beta 3 and the loop B in the interface between alpha 7 subunits of a homomeric acetylcholine receptor show functional and pharmacological alterations
Journal Of Neurochemistry 118 (6) 968-978 4,34

Criado, M; Mulet, J; Gerber, S; Sala, S; Sala, F
A small cytoplasmic region adjacent to the fourth transmembrane segment of the alpha 7 nicotinic receptor is essential for its biogenesis
Febs Letters 585 (15) 2477-2480 3,60

Criado, M; Svobodova, L; Mulet, J; Sala, F; Sala, S
Substitutions of amino acids in the pore domain of homomeric alpha 7 nicotinic receptors for analogous residues present in heteromeric receptors modify gating, rectification and binding properties
Journal Of Neurochemistry 119 (1) 40-49 4,34

Diez-Roux, G; Banfi, S; Sultan, M; Geffers, L; Anand, S; Rozado, D; Magen, A; Canidio, E; Pagani, M; Peluso, I; Lin-Marq, N; Koch, M; Bilio, M; Cantiello, I; Verde, R; De Masi, C; Bianchi, SA; Cicchini, J; Perroud, E; Mehmeti, S; Dagand, E; Schrinner, S; Nurnberger, A; Schmidt, K; Metz, K; Zwingmann, C; Brieske, N; Springer, C; Hernandez, AM; Herzog, S; Grabbe, F; Sieverding, C; Fischer, B; Schrader, K; Brockmeyer, M; Dettmer, S; Helbig, C; Alunni, V; Battaini, MA; Mura, C; Henrichsen, CN; Garcia-Lopez, R; Echevarria, D; Puelles, E; Garcia-Calero, E; Kruse, S; Uhr, M; Kauck, C; Feng, GJ; Milyaev, N; Ong, CK; Kumar, L; Lam, M; Semple, CA; Gyenesei, A; Mundlos, S; Radelof, U; Lehrach, H; Sarmientos, P; Reymond, A; Davidson, DR; Dolle, P; Antonarakis, SE; Yaspo, ML; Martinez, S; Baldock, RA; Eichele, G; Ballabio, A
A High-Resolution Anatomical Atlas of the Transcriptome in the Mouse Embryo
Plos Biology 9 (1) 12,47



Encinas, JL; Garcia-Cabezas, MA; Barkovich, J; Fontecha, CG; Peiro, JL; Soto, GMC; Borrell, V; Reillo, I; Lopez-Santamaria, M; Tovar, JA; Farmer, DL
Maldevelopment of the cerebral cortex in the surgically induced model of myelomeningocele: implications for fetal neurosurgery
Journal Of Pediatric Surgery 46 (4) 713-722 1,31

Femenia, T; Perez-Rial, S; Uriguen, L; Manzanares, J
Prodynorphin gene deletion increased anxiety-like behaviours, impaired the anxiolytic effect of bromazepam and altered GABA(A) receptor subunits gene expression in the amygdala
Journal Of Psychopharmacology 25 (1) 87-96 3,80

García-Ayllón MS, Small DH, Avila J, Sáez-Valero J
Revisiting the role of acetylcholinesterase in Alzheimer's disease: cross-talk with P-tau and _-amyloid
Front. Mol. Neurosci. 4 (22)

Garcia-Gutierrez, MS; Manzanares, J
Overexpression of CB2 cannabinoid receptors decreased vulnerability to anxiety and impaired anxiolytic action of alprazolam in mice
Journal Of Psychopharmacology 25 (1) 111-120 3,80

Gelman, D; Griveau, A; Dehorter, N; Teissier, A; Varela, C; Pla, R; Pierani, A; Marin, O
A Wide Diversity of Cortical GABAergic Interneurons Derives from the Embryonic Preoptic Area
Journal Of Neuroscience 31 (46) 16570-16580 7,27

Gontijo, AM; Miguela, V; Whiting, MF; Woodruff, RC; Dominguez, M
Intron retention in the Drosophila melanogaster Rieske iron sulphur protein gene generated a new protein
Nature Communications 2

Gutierrez LM, and Gil, A.
Modeling F-actin cortex influence on the secretory properties of neuroendocrine cells.
Commun. Integr Biol. 4 411-415-

Gutierrez-Martin, Y; Bustillo, D; Gomez-Villafuertes, R; Sanchez-Nogueiro, J; Torregrosa-Hetland, C; Binz, T; Gutierrez, LM; Miras-Portugal, MT; Artalejo, AR
P2X7 Receptors Trigger ATP Exocytosis and Modify Secretory Vesicle Dynamics in Neuroblastoma Cells
Journal Of Biological Chemistry 286 (13) 11370-11381 5,33

Hammerle, B; Ulin, E; Guimera, J; Becker, W; Guillemot, F; Tejedor, FJ
Transient expression of Mnb/Dyrk1a couples cell cycle exit and differentiation of neuronal precursors by inducing p27(KIP1) expression and suppressing NOTCH signaling
Development 138 (12) 2543-2554 6,90

Heredia, F. and Nieto, M.A.
An epigenetic mark to protect the epithelial phenotype in health and disease.
Cell Stem Cell 8 462-463 25,94

Lakoma, J; Garcia-Alonso, L; Luque, JM
Reelin sets the pace of neocortical neurogenesis
Development 138 (23) 5223-5234 6,90

Lerma J
Net(o) excitement for kainate receptors
Nature Neuroscience 14 (7) 808-810 14,19

Lonjon, N; Boniface, G; Feifel, R; Endres, R; Ribotta, MGY; Privat, A; Perrin, FE
Potential adverse effects of cyclosporin A on kidneys after spinal cord injury
Spinal Cord 49 (3) 472-479 1,83

Lopez-Atalaya, JP; Ciccarelli, A; Viosca, J; Valor, LM; Jimenez-Minchan, M; Canals, S; Giustetto, M; Barco, A
CBP is required for environmental enrichment-induced neurogenesis and cognitive enhancement
Embo Journal 30 (20) 4287-4298 10,12

Malkia, A; Morenilla-Palao, C; Viana, F
The Emerging Pharmacology of TRPM8 Channels: Hidden Therapeutic Potential Underneath a Cold Surface
Current Pharmaceutical Biotechnology 12 (1) 54-67 3,46

Marco, EM; Garcia-Gutierrez, MS; Bermudez-Silva, FJ; Moreira, FA; Guimaraes, F; Manzanares, J; Viveros, MP
Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects
Frontiers In Behavioral Neuroscience 5

Marín O, Gleeson JG.
Function follows form: understanding brain function from a genetic perspective.
Curr Opin Genet Dev. 21 (3) 237-239 9,38

Marín O.
A postnatal function for Nkx2-1 in basal forebrain integrity (Commentary on Magno et al.).
Eur J Neurosci. 34 (11) 1766- 3,66

Martinez-Frias, ML; Egues, X; Puras, A; Hualde, J; de Frutos, CA; Bermejo, E; Nieto, MA; Martinez, S
Thanatophoric Dysplasia Type II With Encephalocele and Semilobar Holoprosencephaly: Insights Into Its Pathogenesis
American Journal Of Medical Genetics Part A 155 (1) 197-202 2,51

McCabe, MJ; Gaston-Massuet, C; Tziaferi, V; Gregory, LC; Alatzoglou, KS; Signore, M; Puelles, E; Gerrelli, D; Farooqi, IS; Raza, J; Walker, J; Kavanaugh, SI; Tsai, PS; Pitteloud, N; Martinez-Barbera, JP; Dattani, MT
Novel FGF8 Mutations Associated with Recessive Holoprosencephaly, Craniofacial Defects, and Hypothalamo-Pituitary Dysfunction
Journal Of Clinical Endocrinology & Metabolism 96 (10) E1709-E1718 6,50

Mecklenburg, N; Garcia-Lopez, R; Puelles, E; Sotelo, C; Martinez, S
Cerebellar Oligodendroglial Cells have a Mesencephalic Origin
Glia 59 (12) 1946-1957 5,19

Meseguer, VM; Denlinger, BL; Talavera, K
Methodological Considerations to Understand the Sensory Function of TRP Channels
Current Pharmaceutical Biotechnology 12 (1) 3-11 3,46

Mishra, A; Schuz, A; Engelmann, J; Beyerlein, M; Logothetis, NK; Canals, S
Biocytin-Derived MRI Contrast Agent for Longitudinal Brain Connectivity Studies
Acs Chemical Neuroscience 2 (10) 578-587-

Moldrich, RX; Mezzera, C; Holmes, WM; Goda, S; Brookfield, SJ; Rankin, AJ; Barr, E; Kurniawan, N; Dewar, D; Richards, LJ; Lopez-Bendito, G; Iwata, T
Fgfr3 Regulates Development of the Caudal Telencephalon
Developmental Dynamics 240 (6) 1586-1599 2,86

Morante, J; Erclik, T; Desplan, C
Cell migration in Drosophila optic lobe neurons is controlled by eyeless/Pax6
Development 138 (4) 687-693 6,90

Neira-Zalentein, W; Holopainen, JM; Tervo, TMT; Borras, F; Acosta, MC; Belmonte, C; Gallar, J
Corneal Sensitivity in Diabetic Patients Subjected to Retinal Laser Photocoagulation
Investigative Ophthalmology & Visual Science 52 (8) 6043-6049 3,47

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 14,08

Ortega-Alvaro, A; Aracil-Fernandez, A; Garcia-Gutierrez, MS; Navarrete, F; Manzanares, J
Deletion of CB(2) Cannabinoid Receptor Induces Schizophrenia-Related Behaviors in Mice
Neuropsychopharmacology 36 (7) 1489-1504 6,69

Pastor D, Viso-León MC, Jones J, Jaramillo-Merchán J, Toledo-Aral JJ, Moraleda JM, Martínez S.
Comparative Effects between Bone Marrow and Mesenchymal Stem Cell Transplantation in GDNF Expression and Motor Function Recovery in a Motorneuron Degenerative Mouse Model.
Stem Cell Rev. 6,77

Perez-Rial, S; Garcia-Gutierrez, MS; Molina, JA; Perez-Nievas, BG; Ledent, C; Leiva, C; Leza, JC; Manzanares, J
Increased vulnerability to 6-hydroxydopamine lesion and reduced development of dyskinesias in mice lacking CB1 cannabinoid receptors
Neurobiology Of Aging 32 (4) 631-645 6,63

Pombero, A; Bueno, C; Saglietti, L; Rodenas, M; Guimera, J; Bulfone, A; Martinez, S
Pallial origin of basal forebrain cholinergic neurons in the nucleus basalis of Meynert and horizontal limb of the diagonal band nucleus
Development 138 (19) 4315-4326 6,90

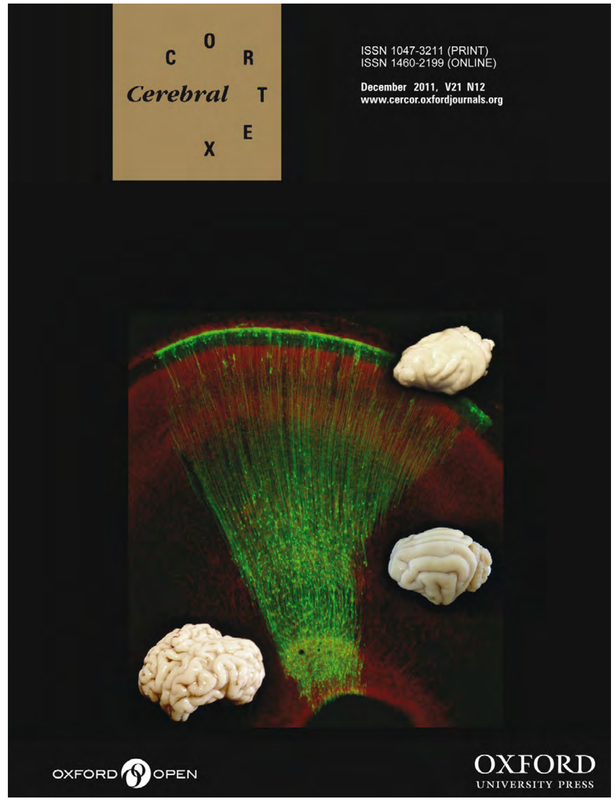
Reillo, I; Romero, CD; Garcia-Cabezas, MA; Borrell, V
A Role for Intermediate Radial Glia in the Tangential Expansion of the Mammalian Cerebral Cortex
Cerebral Cortex 21 (7) 1674-1694 6,84

Ricano-Cornejo, I; Altick, AL; Garcia-Pena, CM; Nural, HF; Echevarria, D; Miquelajauregui, A; Mastick, GS; Varela-Echavarria, A
Slit-Robo Signals Regulate Pioneer Axon Pathfinding of the Tract of the Postoptic Commissure in the Mammalian Forebrain
Journal Of Neuroscience Research 89 (10) 1531-1541 2,96

Rico, B; Marin, O
Neuregulin signaling, cortical circuitry development and schizophrenia
Current Opinion In Genetics & Development 21 (3) 262-270 9,38

Rodriguez-Aznar, E; Nieto, MA
Repression of Puma by Scratch2 is required for neuronal survival during embryonic development
Cell Death And Differentiation 18 (7) 1196-1207 9,05

Rodriguez-Lozano, FJ; Bueno, C; Insausti, CL; Meseguer, L; Ramirez, MC; Blanquer, M; Marin, N; Martinez, S; Moraleda, JM
Mesenchymal stem cells derived from dental tissues
International Endodontic Journal 44 (9) 800-806 2,38



Rosa, JM; Torregrosa-Hetland, CJ; Colmena, I; Gutierrez, LM; Garcia, AG; Gandia, L
Calcium entry through slow-inactivating L-type calcium channels preferentially triggers endocytosis rather than exocytosis in bovine chromaffin cells
American Journal Of Physiology-Cell Physiology 301 (1) C86-C98 3,82

Sanchez-Alcaniz, JA; Haege, S; Mueller, W; Pla, R; Mackay, F; Schulz, S; Lopez-Bendito, G; Stumm, R; Marin,
OCxcr7 Controls Neuronal Migration by Regulating Chemokine Responsiveness
Neuron 69 (1) 77-90 14,03

Sanchez-Huertas, C; Rico, B
CREB-Dependent Regulation of GAD65 Transcription by BDNF/TrkB in Cortical Interneurons
Cerebral Cortex 21 (4) 777-788 6,84

Schmid, D; Messlinger, K; Belmonte, C; Fischer, MJM
Altered thermal sensitivity in neurons injured by infraorbital nerve lesion
Neuroscience Letters 488 (2) 168-172 2,06

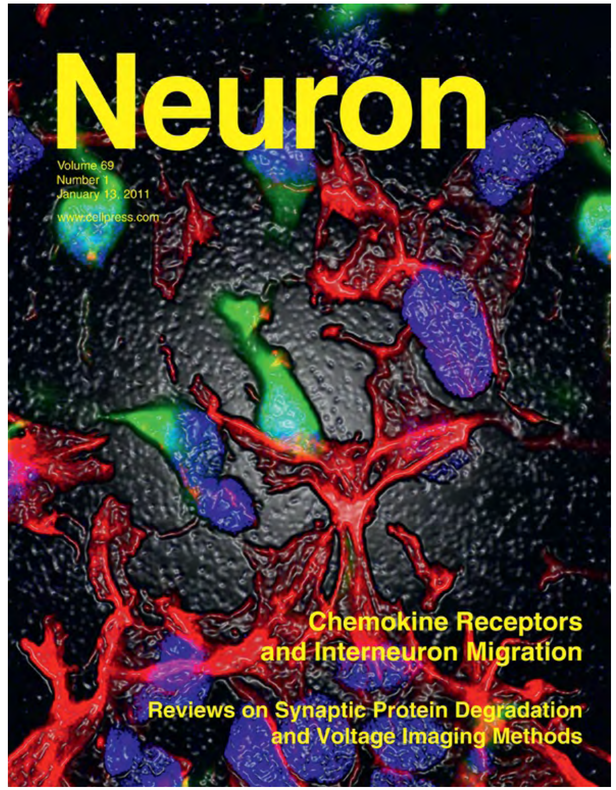
Simeone, A; Puelles, E; Omodei, D; Acampora, D; Di Giovannantonio, LG; Di Salvio, M; Mancuso, P; Tomasetti, C
Otx Genes in Neurogenesis of Mesencephalic Dopaminergic Neurons
Developmental Neurobiology 71 (8) 665-679 2,86

Slovakova, J; Carmena, A
Canoe functions at the CNS midline glia in a complex with Shotgun and Wrapper-Nrx-IV during neuron-glia interactions
Development 138 (8) 1563-1571 6,90

Sotelo, C
Camillo Golgi and Santiago Ramon y Cajal: The anatomical organization of the cortex of the cerebellum.
Can the neuron doctrine still support our actual knowledge on the cerebellar structural arrangement?
Brain Research Reviews 66 16-34 8,84

Szczepanski, J; Arnold, M; Wajnryb, E; Amigo, JM; Sanchez-Vives, MV
Mutual information and redundancy in spontaneous communication between cortical neurons
Biological Cybernetics 104 (3) 161-174 1,67

Tabares-Seisdedos, R; Dumont, N; Baudot, A; Valderas, JM; Climent, J; Valencia, A; Crespo-Facorro, B; Vieta, E; Gomez-Beneyto, M; Martinez, S; Rubenstein, JL
No paradox, no progress: inverse cancer comorbidity in people with other complex diseases
Lancet Oncology 12 (6) 604-608 17,76



Tejedor, FJ; Hammerle, B
MNB/DYRK1A as a multiple regulator of neuronal development
Febs Journal 278 (2) 223-235 3,13

Torregrosa-Hetland, CJ; Villanueva, J; Giner, D; Lopez-Font, I; Nadal, A; Quesada, I; Viniegra, S; Exposito-Romero, G; Gil, A; Gonzalez-Velez, V; Segura, J; Gutierrez, LM
The F-actin cortical network is a major factor influencing the organization of the secretory machinery in chromaffin cells
Journal Of Cell Science 124 (5) 727-734 6,29

Uriguen, L; Garcia-Gutierrez, MS; Manzanares, J
Decreased GABA(A) and GABA(B) receptor functional activity in cannabinoid CB(1) receptor knockout mice
Journal Of Psychopharmacology 25 (1) 105-110 3,80

Valente, P; Fernandez-Carvajal, A; Camprubi-Robles, M; Gomis, A; Quirce, S; Viana, F; Fernandez-Ballester, G; Gonzalez-Ros, JM; Belmonte, C; Planells-Cases, R; Ferrer-Montiel, A
Membrane-tethered peptides patterned after the TRP domain (TRPducins) selectively inhibit TRPV1 channel activity
Faseb Journal 25 (5) 1628-1640 6,52

Valero, M; Morenilla-Palao, C; Belmonte, C; Viana, F
Pharmacological and functional properties of TRPM8 channels in prostate tumor cells
Pflugers Archiv-European Journal Of Physiology 461 (1) 99-114 3,35

Valiente, M; Ciceri, G; Rico, B; Marin, O
Focal Adhesion Kinase Modulates Radial Glia-Dependent Neuronal Migration through Connexin-26
Journal Of Neuroscience 31 (32) 11678-11691 7,27

Vallejo, DM; Caparros, E; Dominguez, M
Targeting Notch signalling by the conserved miR-8/200 microRNA family in development and cancer cells
Embo Journal 30 (4) 756-769 10,12

Valor, LM; Pulopulos, MM; Jimenez-Minchan, M; Olivares, R; Lutz, B; Barco, A
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
Journal Of Neuroscience 31 (5) 1652-1663 7,27

Viana, F
Chemosensory Properties of the Trigeminal System
ACS Chemical Neuroscience 2 (1) 38-50-

Westerlund, N; Zdrojewska, J; Padzik, A; Komulainen, E; Bjorkblom, B; Rannikko, E; Tararuk, T; Garcia-Frigola, C; Sandholm, J; Nguyen, L; Kallunki, T; Courtney, MJ; Coffey, ET
Phosphorylation of SCG10/stathmin-2 determines multipolar stage exit and neuronal migration rate
Nature Neuroscience 14 (3) 305-313 14,19

Yu, TA; Yaguchi, Y; Echevarria, D; Martinez, S; Basson, MA
Sprouty genes prevent excessive FGF signalling in multiple cell types throughout development of the cerebellum
Development 138 (14) 2957-2968 6,90

Zoppi, S; Nievas, BGP; Madrigal, JLM; Manzanares, J; Leza, JC; Garcia-Bueno, B
Regulatory Role of Cannabinoid Receptor 1 in Stress-Induced Excitotoxicity and Neuroinflammation
Neuropsychopharmacology 36 (4) 805-818 6,69

20/12/2011

Case-Based Reasoning: A Computational Approach to Memory-Based Problem Solving

Josep-Lluis Arcos

Artificial Intelligence Research Institute (IIIA). CSIC. Barcelona

Programa doctorado

16/12/2011

Transsynaptic regulation of synaptic strength by N-cadherin and beta-catenin

Yukiko Goda

RIKEN Brain Science Institute, Wako, Saitama, Japan.

Programa doctorado

02/12/2011

Multiple Origins of Telencephalic Structures

Juan A. de Carlos

Dept. of Molecular, Cellular and Developmental Neurobiology, Instituto Cajal CSIC, Madrid

Programa doctorado

25/11/2011

Reading and Writing Activity Patterns by Light to Analyze Olfactory Computations in Zebrafish

Rainer Friedrich

Friedrich Miescher Institute for Biomedical Research. Basel. Switzerland

Programa doctorado

18/11/2011

Pallio-pallial Cell Migrations: Possible Impact on the Evolution of the Mammalian Neocortex

Luis Puelles

Universidad de Murcia

Programa doctorado

04/11/2011

Axon guidance at choice points

Esther Stoeckli

Institute of Molecular Life Sciences, University of Zurich, Switzerland

Programa doctorado

21/10/2011

Pharmacological Strategies to Modulate Ion Channel Activity

Antonio Ferrer Montiel

Universidad Miguel Hernández

Programa doctorado

14/10/2011

Molecular Lessons Learned from an Extremophile Mammal

Gary Lewin

Max Delbrúck Center for Molecular Medicine. Berlin-Buch. Germany

Programa doctorado

17/06/2011

Axon-glia interactions in myelination

Elior Peles

Department of Molecular Cell Biology, The Weizmann Institute of Science, Israel

Programa doctorado

10/06/2011

Activity-dependent transcriptional regulation in Alzheimer's disease

Carlos Saura

Institut de Neurociencies. Universitat Autrnoma de Barcelona.

Programa doctorado

03/06/2011

Distinct voltage-gated ion channels show unique, subcellular compartment-specific distribution patterns

Zoltan Nusser

Institute of Experimental Medicine. Hungarian Academy of Sciences. Budapest, Hungary.

Programa doctorado

27/05/2011

Genetic and pharmacological modulations of the pain system revealed by non-invasive functional Magnetic Resonance Imaging in transgenic mice

Andreas Hess

FAU Erlangen-Núrenberg, I.f. Experimental Pharmacology, Pharmacological Imaging and Image Analysis. Erlangen, Germany

Programa doctorado

20/05/2011

The orchestration of chromatin access in hormonal gene regulation

Miguel Beato

Center for Genomic Regulation (CRG), Barcelona

Programa doctorado

13/05/2011

Grid cells and the entorhinal space circuit (Dr. May-Britt Moser) / Transition states in hippocampal memory networks (Dr. Edvard Moser)

Edvard and May-Britt Moser

Kavli Institute for Systems Neuroscience, Faculty of Medicine, Trondheim, Norway.

Programa doctorado

29/04/2011

ALS, mitochondria and neurodegeneration

Hugo Bellen

HHMI-Baylor College of Medicine, Houston, Texas, USA

Programa doctorado

11/04/2011

Presentaciyn del libro "The Human Brain, Prenatal Development and Structure", del Dr. Miguel Marín Padilla

Dr. Miguel Marín Padilla

IN

Científico

08/04/2011

The Amyloid Precursor Protein alpha secreatse cleaving enzyme ADAM10: new functions for an old player

Monica Di Luca

Department of Pharmacological Sciences. University of Milan. Milano - Italy.

Programa doctorado

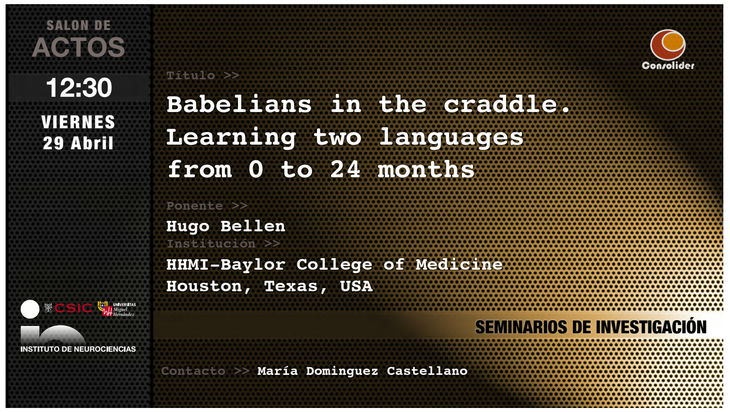
01/04/2011

Role of Reelin in adult plasticity

Eduardo Soriano

Laboratorio Neurobiología y Regeneraciyn, IRB Barcelona

Programa doctorado



25/03/2011

Mapping the face in the somatosensory brainstem

Filippo Rijli

Friedrich Miescher Institute for Biomedical Research, Switzerland

Programa doctorado

18/03/2011

Gene regulatory analysis of neural crest formation and EMT

Marianne Bronner

Albert Billings Ruddock Professor of Biology, California Institute of Technology, Pasadena CA

Programa doctorado

11/03/2011

Cortical malformations and vulnerability of the microtubule cytoskeleton

Fiona Francis

Equipe Avenir 'Cytoskeleton and neuronal migration disorders'. Institut du Fer a Moulin, Paris.

Programa doctorado

07/03/2011

From ion channels to behavior: in vivo dissection of circuits controlling pain and addiction

Inés Ibánez-Tallyn

Max-Delbruck-Center for Molecular Medicine, Berlin

Programa doctorado

25/02/2011

Sodium channels as targets for analgesia

Eija Kalso

Institute of Clinical Medicine, University of Helsinki, Finland

Programa doctorado

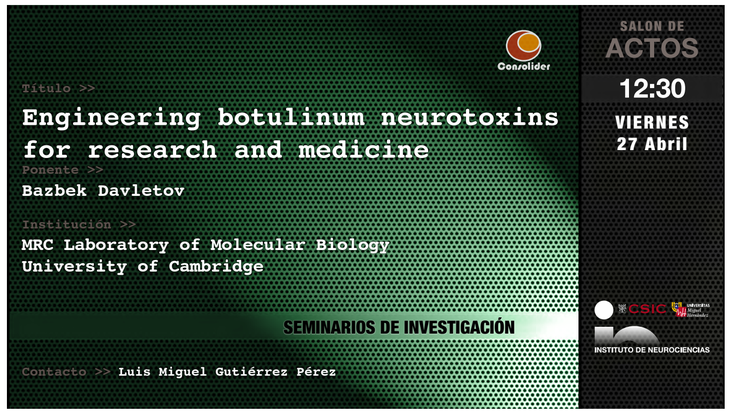
18/02/2011

Synaptic Mechanisms of Sensory Perception

Carl Petersen

Laboratory of Sensory Processing, SV-BMI-LSENS, EPFL, Lausanne, Switzerland

Programa doctorado



11/02/2011

Tripartite Synapse: communication between astrocytes and neurons

Alfonso Araque

Departamento de Neurobiología Funcional y de Sistemas, Instituto Cajal, CSIC, Madrid

Programa doctorado

04/02/2011

Chemokine signaling in neuronal migration

Yscar Marín

Unidad de Biología del Desarrollo, Instituto de Neurociencias de Alicante CSIC-UMH

Programa doctorado

28/01/2011

Neural circuit formation and function

Klas Kullander

Unit of Developmental Genetics, Department of Neuroscience, Uppsala University, Sweden

Programa doctorado

21/01/2011

Engineering botulinum neurotoxins for research and medicine

Bazbek Davletov

MRC Laboratory of Molecular Biology, University of Cambridge

Programa doctorado

14/01/2011

Sensory experience and the development of local inhibitory and excitatory circuits in layer 4 barrel cortex

Jonh Isaac

Lilly laboratories

Traslacional

Consolider

Cooperación de la vía de señalización de AKT y NOTCH en el desarrollo de tumores

María Cortina Andrada

María Dominguez Castellano (Director)

Papel fisiológico y utilidad terapéutica del receptor cannabinoide CB2 en modelos animales de ansiedad y depresión

Mª Salud García Gutiérrez

Jorge Manzanares Robles (Director)

Potencialidad in vitro de muestras de tejido nervioso sano y tumoral de pacientes adultos

Esther Mancheco Maciá

Minerva Giménez-Ribotta (Director)

A comparative transcriptomics approach for unveiling gene expression networks of activity-driven neuronal stimulation and plasticity

Eva Benito Garagorri

Angel L. Barco Guerrero (Director)

Diferenciación de las poblaciones basales en ausencia de SHH; estudio de las interacciones genéticas en la placa basal mesencefálica

Ariadna Pérez Balaguer

Salvador Martínez Pérez (Director)

OTHER ACITIVITIES

8th Christmas Meeting of the Instituto de Neurociencias

2nd Congress of 5P Sindrome and rare diseases

III Simposium PROMETEO NEC$_2$. Anomalias genéticas del desarrollo cortical y disfunci ón cerebral

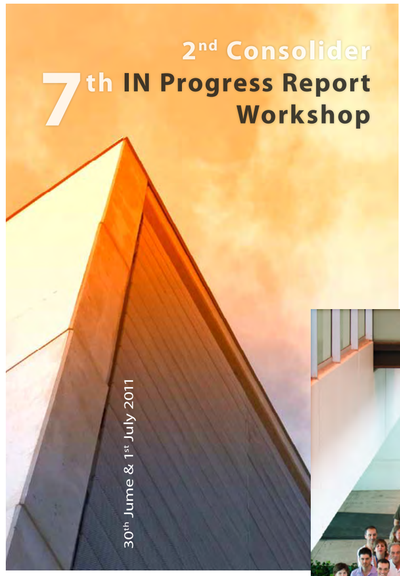
7th IN & 2nd Consolider Progress Report of the Instituto de Neurociencias.

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

"Células madre y cáncer: avances y retos" Course directed by Dr María Domínguez Castellano

"Brain Week 2011" activities.

"The Human Brain, Prenatal Development and Structure", Book presentation by Dr. Miguel MarÍn Padilla



Promega Prize to the best talk

15 Physiology of the cerebral cortex

Emilio Geijo UMH

Principal Investigator
Emilio Geijo

PhD Student
Víctor Rovira
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

EG

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

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

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

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

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

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

Geijo-Barrientos E., González O., Pastore-Olmedo C. (2011). Presence of repeater F-waves in the early stage of Guillain Barre Syndrome. **Journal of the Peripheral Nervous System**, in press.

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.

01 Mechanisms and receptors involved in analgesia and addiction

Juan J. Ballesta UMH

Principal Investigator
Juan J. Ballesta

Clinical Colaborator
Carlos del Pozo

JJB

CdP

01 Mechanisms and receptors involved in analgesia and addiction

Juan J. Ballesta UMH

Selected Publications
Personnel

Nowadays, the most potent clinically used analgesics are the opioids. However, their clinical use is limited by their problems, such as tolerance, dependence and addiction. Neuronal nicotinic receptors are also involved in antinociceptive mechanisms, being some nicotinic

ii. (1) the tolerance to the analgesic effects of nicotinic agonists, and (2) the dependence and addiction to nicotine. To assess these issues we use a variety of biochemical approaches and behavioural tests.

Ballesta, JJ. García, AG. Gutierrez, LM. Hidalgo, MJ. Palmero, M. Reig, JA. Viniegra, S. (1990). Separate [3H]-nitrendipine binding sites in mitochondria and plasma membranes of bovine adrenal medulla. **British Journal of Pharmacology**, 101: 21-26.

Anand, R. Peng, X. Ballesta, JJ. Lindstrom, J. (1993). Pharmacological characterization of a-bungarotoxin-sensitive acetycholine receptors immunoisolated from chick retina: contrasting properties of a7 and a8 subunit-containing subtypes. **Molecular Pharmacology**, 44: 1046-1050.

Críado, M. Domínguez del Toro, E. Carrasco-Serrano, C. Smillie, FI. Juíz, JM. Viniegra, S. Ballesta, JJ. (1997). Differential expression of a-bungarotoxin neuronal nicotinic receptors in adrenergic chromaffin cells: a role for transcription factor Egr-1. **The Journal of Neuroscience**, 17: 6554-6564.

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

Alves DS, Castello-Banyuls J, Faura CC , Ballesta, J.J. (2011). An extracellular RRR motif flanking the M1 transmembrane domain governs the biogenesis of homomeric neuronal nicotinic receptors **FEBS Lett** 585: 1169-1174

02 Transcriptional and epigenetic mechanisms of neuronal plasticity

Angel Barco CSIC

Principal Investigator
Angel Barco

PhD Investigator
Eva Benito
Satomi Ito
José P. López-Atalaya
Luis M. Valor

PhD Student
Anna Fiorenza
Deisy Guiretti
Pierrick Jego

Technical Staff
Francisca Almagro
María Jiménez Minchan
Román Olivares


AB


LV


EB


FA


DG


PJ


MJM


SI


J L-A


AF


RO

02 Transcriptional and epigenetic mechanisms of neuronal plasticity

Angel Barco CSIC

Barco, A, Alarcon, JM, 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.

Alarcon, JM, Malleret, G, Touzani, K, Vronskaya, S, Ishii, S, Kandel, ER, 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, Patterson, S, Alarcon, JM, Gromova, P, Mata-Roig, M, Morozov, A, 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.

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): 13909-13918.

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.

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.

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

Lopez-Atalaya JP, Gervasini C, Mottadelli F, Spena S, Piccione M, Gioacchino S, Selicorni A, Barco A and Larizza L. Histone acetylation deficits in lymphoblastoid cell lines from Rubinstein-Taybi syndrome patients. **J Med Genet** Oct 7, 2011. [Epub ahead of print].

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).

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.

03 Sensory transduction and nociception

Carlos Belmonte UMH
Roberto Gallego UMH
Félix Viana CSIC

Selected Publications
Personnel

Principal Investigator
Carlos Belmonte
Roberto Gallego
Félix Viana
Laura Almaraz

PhD Investigator
Laura Almaraz
Elvira de la Peña
Victor Meseguer
Cruz Morenilla
Hugo Vara

PhD Student
Bristol Denlinger
Carlos Fernández-Peña
Omar Fernández
Maria José López
Enoch Luis Baltazar
Jan-Albert Manenschijn
Andrés Parra
Susana Quirce

Technical Staff
Eva Quintero
Ana Miralles
Mireille Torá

03 Sensory transduction and nociception

Carlos Belmonte UMH
Roberto Gallego UMH
Félix Viana CSIC

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

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

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

Morenilla-Palao C*, Pertusa M*, Meseguer V, Viana F Lipid raft segregation modulates TRPM8 channel activity. **Journal of Biological Chemistry** (2009) 284:9215-9224 (* co-authors).

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

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

Orio, P., Madrid, R., de la Peña, E., Parra, A., Meseguer, V., Bayliss, D., Belmonte, C., Viana, F. Characteristics and physiological role of hyperpolarization activated currents in mouse cold thermoreceptors. **Journal of Physiology** (2009) 587:1961-1976.

Sánchez-Vives, M.V., Descalzo, V.F., Reig, R., Figueroa, N.A., Compte A. & Gallego, R. Rhythmic spontaneous activity in the piriform cortex. **Cerebral Cortex** (2008) 18:1179-1192.

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

Fajardo O, Meseguer V, Belmonte C, Viana F. TRPA1 channels mediate cold temperature sensing in mammalian vagal sensory neurons: pharmacological and genetic evidence. **Journal of Neuroscience** (2008) 28:7863-7875.

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

Madrid, R., Donovan-Rodríguez, T. Meseguer, V., Acosta, M.C., Belmonte C, Viana, F. Contribution of TRPM8 channels to cold transduction in primary sensory neurons and peripheral nerve terminals. **Journal of Neuroscience** (2006) 26:12512-12525.

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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

04 Neurogenesis and cortical expansion

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CV


VB

04 Neurogenesis and cortical expansion

Víctor Borrell CSIC

Borrell V, Marin O (2006) "Meninges control tangential migration of hem-derived Cajal-Retzius cells via CXCL12/CXCR4 signaling". **Nature Neuroscience** 9:1284-1293.

Borrell V (2010) "In vivo gene delivery to the postnatal ferret cerebral cortex by DNA electroporation". **J Neurosci Methods** 186:186-195.

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.

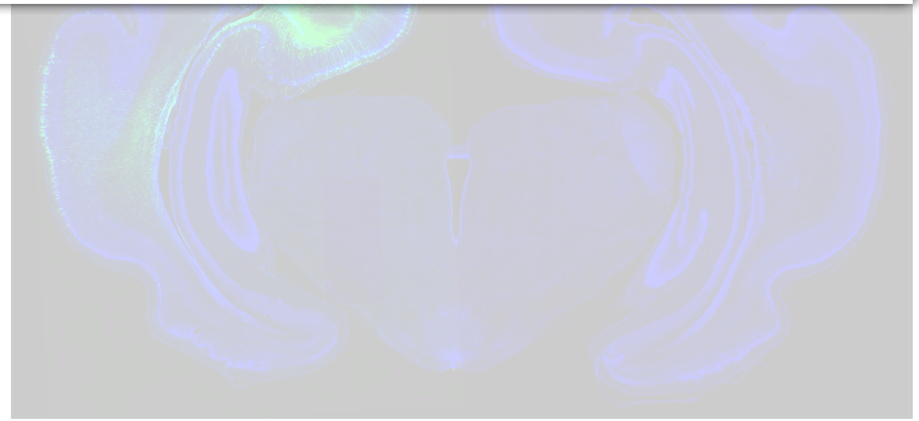
Reillo I, De Juan C, García-Cabezas MÁ, Borrell V (2011) "A role for Intermediate Radial Glia in the tangential expansion of the mammalian cerebral cortex". **Cerebral Cortex** 21:1674-1694.

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

Reillo I, Borrell V (2012) "Germinal zones in the developing cerebral cortex of ferret: ontogeny, cell cycle kinetics and diversity of progenitors". **Cerebral Cortex** (Advance Online doi:10.1093/cercor/ bhr284).

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 analysis of the cellular and molecular mechanisms involved in the normal expansion and folding of the mammalian cerebral cortex. 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 these processes.



05 Molecular control of axonal myelination

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05 Molecular control of axonal myelination

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Selected Publications
Personnel

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

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

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

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

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

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

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

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

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

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

06 Plasticity of brain networks

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BFN

EAS

CQG

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06 Plasticity of brain networks

Santiago Canals Gamoneda CSIC

Canals, S., Casarejos, M.J., de Bernardo, S., Rodríguez-Martín, E and Mena, M.A. (2003). Nitric oxide triggers the toxicity due to glutathione depletion in midbrain cultures through 12-lipoxygenase. **J. Biol. Chem.** 278(24): 21542-9.

Canals, S., López-Aguado, L., Herreras, O. Synaptically recruited apical currents are required to initiate axonal and apical spikes in hippocampal pyramidal cells: modulation by inhibition. **J. Neurophysiol**. 93(2):909-18. (2005)

Canals, S., Makarova, I., Lopez-Aguado, L., Largo, C., Ibarz, JM., Herreras, O. Longitudinal depolarization gradients along the somatodendritic axis of CA1 pyramidal cells: a novel feature of spreading depression. **J. Neurophysiol**. 94(2):943-51. (2005)

Canals, S.*, Larrosa, B., Pintor, J., Mena, M.A. and Herreras O. Metabolic challenge to glia activates an adenosine-mediated safety mechanism that promotes neuronal survival by delaying the onset of spreading depression waves. **J. Cereb. Blood Flow Metab.** 28(11):1835-44. (2008) (* Corresponding author)

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

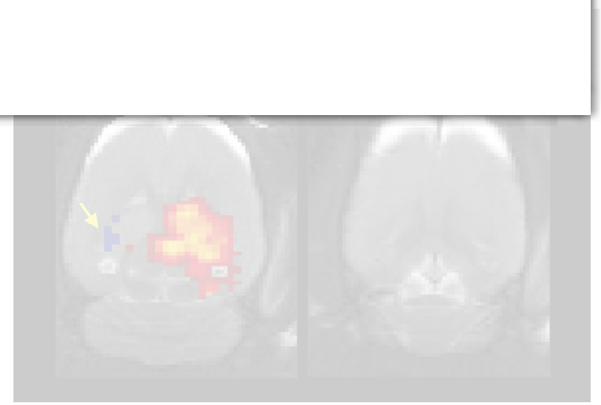
Angelovski, G., Fouskova, P., Mamedov, I., Canals, S., Toth, E., Logothetis, N.K. Smart MRI agents sensing extracellular calcium fluctuations. **Chem. Bio. Chem.** 9(11):1729-1734. (2008)

Canals, S.*, Beyerlein, M., Murayama Y. and Logothetis, N.K. Electric stimulation fMRI of the perforant pathway to the rat hippocampus. **Magn. Reson. Imaging**. 26(7):978-86. (2008) (*Corresponding author)

Canals, S.*, Beyerlein, M. and Logothetis, N.K. Functional MRI evidence for LTP-induced neural network reorganization. **Curr. Biol.** 19(5):398-403. (2009). (Highlighted in Faculty of 1000, Nat. Rev. Neurosci. and Curr. Biol.) (* Corresponding author)

Eschenko, O., Canals, S., Simanova, I., Beyerlein, M., Murayama, Y. and Logothetis, N.K. Mapping of functional brain activity in freely behaving rats during voluntary running using manganese-enhanced MRI: implications for longitudinal studies. **Neuroimage** 49:2544-2555 (2010)

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.



07 PDZ proteins and signaling networks during the specification of neuronal identities

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Selected Publications
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RPG


JS


SS


AC

07 PDZ proteins and signaling networks during the specification of neuronal identities

Ana Carmena CSIC

Carmena, A., Bate, M., Jiménez, F. (1995). Lethal of scute, a proneural gene, participates in the specification of muscle progenitors during Drosophila embryogenesis. **Genes Dev.** 9: 2373- 2383.

Carmena, A., Gisselbrecht, S., Harrison, J., Jiménez, F., Michelson, AM. (1998). Combinatorial Signalling Codes for the Progressive Determination of Cell Fates in the Drosophila Embryonic Mesoderm. **Genes Dev.** 12: 3910- 3922.

Carmena, A., Murugasu-Oei, B., Menon, D., Jiménez, F., Chia, W. (1998). Inscuteable and numb mediate asymmetric muscle progenitor cell divisions during Drosophila myogenesis. **Genes Dev.** 12: 304- 315.

Speicher, S., García-Alonso, L., Carmena, A., Martín-Bermudo, MD., de la Escalera S., Jiménez F. (1998). Neurotactin Functions in Concert with Other Identified CAMs in Growth Cone Guidance in Drosophila. **Neuron**, 20: 221- 233.

Halfon, MS., Carmena, A., Gisselbrecht, S., Sackerson, CM., Jiménez, F., Baylies, MK., Michelson, AM. (2000). Ras pathway specificity is determined by the integration of multiple signal-activated and tissue-restricted transcription factors. **Cell**, 103: 63-74.

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

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

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

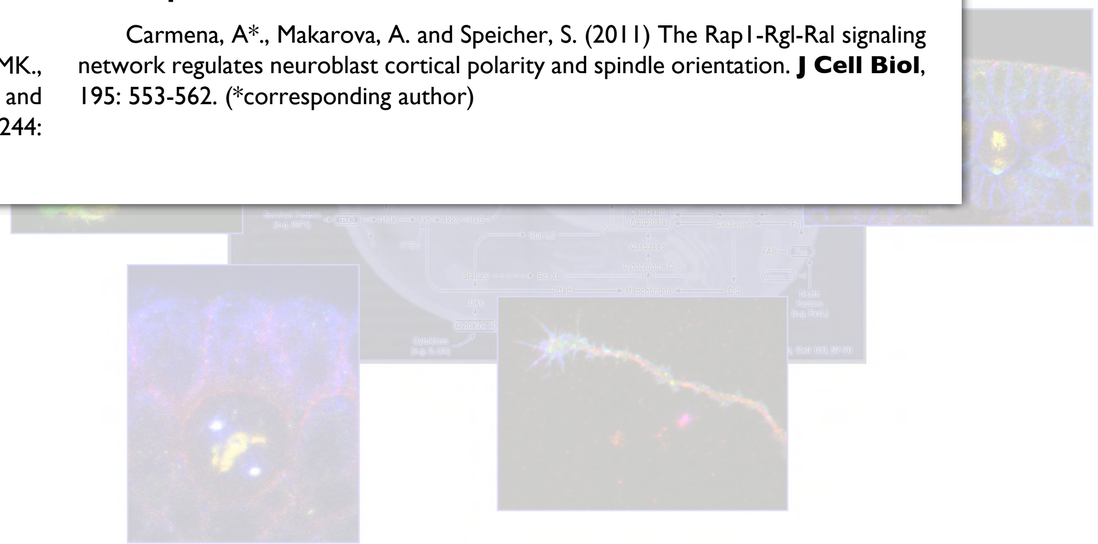
Carmena, A. (2008) Signaling networks during development: the case of asymmetric cell division in the Drosophila nervous system. **Dev. Biol.** 321: 1-17.

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

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

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

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



07 PDZ proteins and signaling networks during the specification of neuronal identities

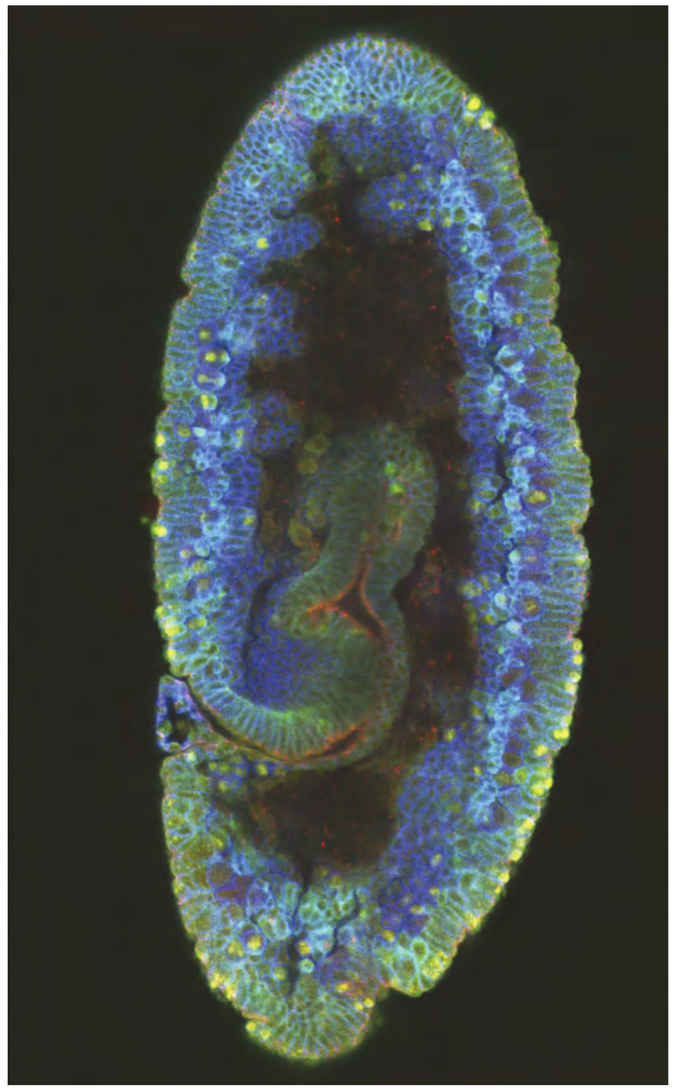
Ana Carmena CSIC

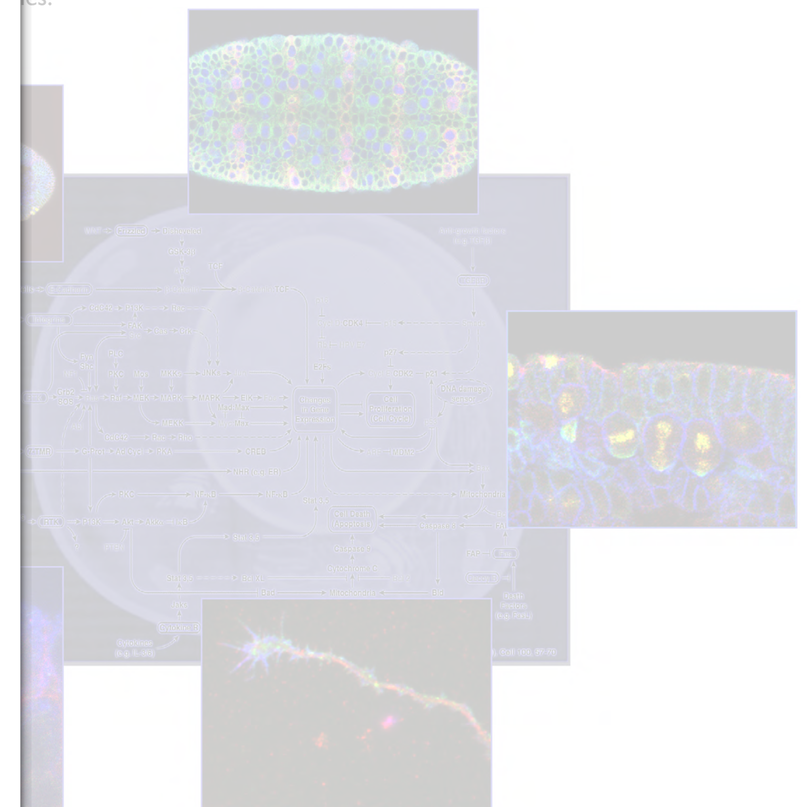
Selected Publications
Personnel

During the development of the n a great diversity of neuronal types fact, the human brain has more than 10 neurons, most of them specified during development. Unravelling the molecular underlie the acquisition of neuronal iden objective of our group.

Specifically, we are interested in analy mechanisms of cross talk between the sig pathways involved in the generation of This will allow us to discover the fun networks established within the cell an within the networks required for thei regulation. In this context, PDZ (PSD- domain-containing proteins have a specia PDZ proteins are usually associated to th at particular sub membrane locations, junctions and synapses. It is frequent t supramolecular complexes around PDZ Indeed, numerous PDZ proteins co anchoring of proteins to the membrane, of receptor and channels, and also to incr and fidelity of signal transduction pathw proteins are excellent candidates as communication between signalling pathw

Our group analyzes the function of including the PDZ protein Cano fundamental biological processes for th neural identities, such as asymmetric neural differentiation. To implement t use a multidisciplinary approach that co





08 Molecular neurobiology of neuronal nicotinic receptors

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08 Molecular neurobiology of neuronal nicotinic receptors

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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 interaction with the N-terminal alpha-helix is essential for biogenesis of alpha7 nicotinic receptors. **J. Neurochem.** 112, 103-111.

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

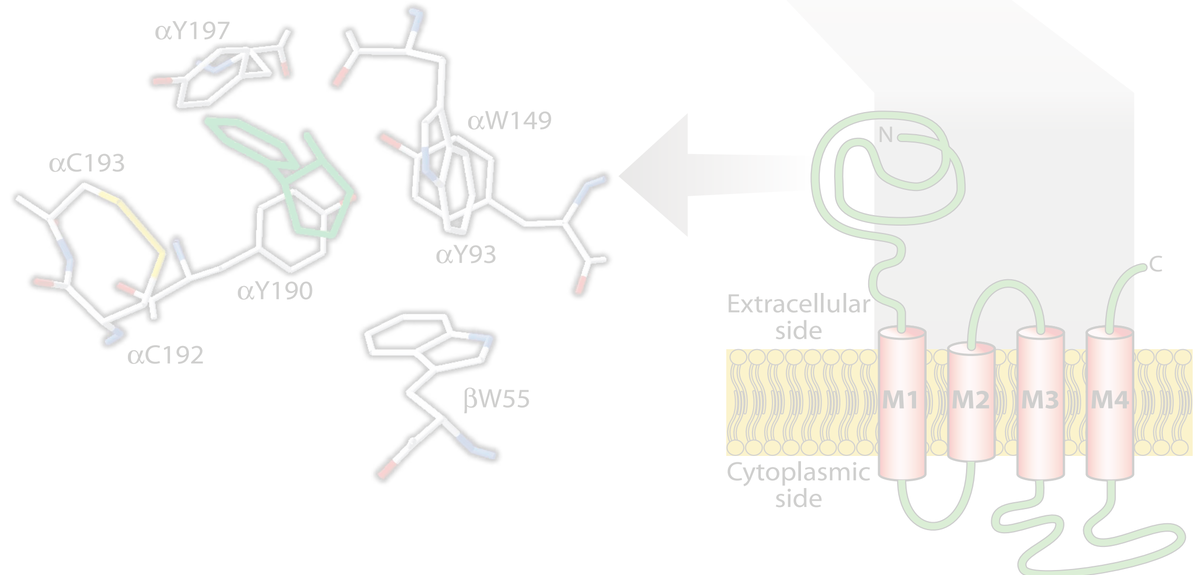
Criado, M., Mulet, J., Gerber, S., Sala, S., Sala, F. (2011) A small cytoplasmic region adjacent to the fourth transmembrane segment of the alpha7 nicotinic receptor is essential for its biogenesis. **FEBS Lett.** 585, 2477-2480.

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

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

the interaction of some proteins with specific nicotinic receptor subtypes.

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



09 Cellular and conductual neuroscience

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09 Cellular and conductual neuroscience

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

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

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

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

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

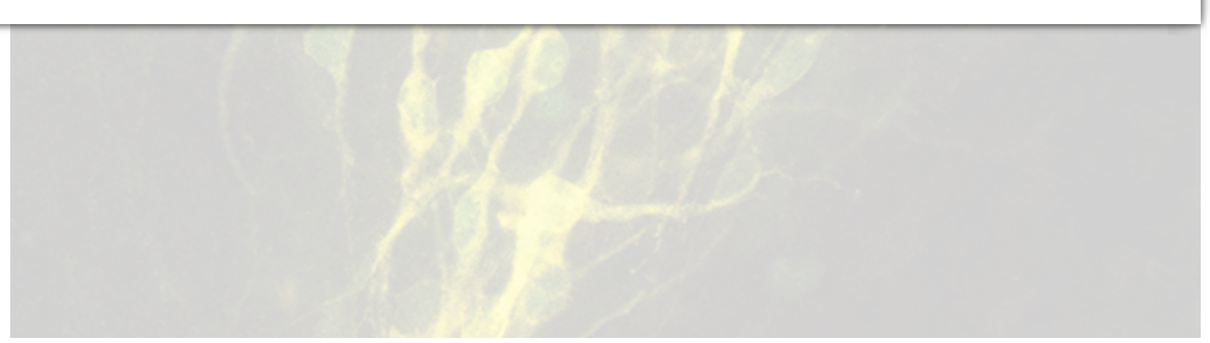
Gadd, CA; Murtra, P; De Felipe, C; Hunt, SP. (2003). Neurokinin-1 receptor-expressing neurons in the amygdala modulate morphine reward and anxiety behaviors in the mouse. **J.Neurosci.**, 23 (23): 8271-8280.

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

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

Tebar, LA et al Deletion of the mouse RegIIIbeta (Reg2) gene disrupts ciliary neurotrophic factor signaling and delays myelination of mouse cranial motor neurons. **PNAS**, 105(32):11400-5, AUG 12 2008.

Gad, Monika, Pedersen, Anders Elm, Kristensen, Nanna Ny, de Felipe, Carmen, Claesson, Mogens H. 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 AUG 2009



10 Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

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Almudena Ortiz España


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IGC
DFM
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ZAAB
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10 Mechanisms of growth control and cancer in *Drosophila*

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Mollereau, B*., Dominguez, M*., Webel,R., Colley, NJ., Keung, B., de Celis, JF., Desplan, C. (2001). Two-step process for photoreceptor formation in Drosophila. **Nature**, 412: 911-913. (* Equally contributing authors).

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.

Dominguez, M*., Ferrés-Marcó, D., Gutierréz-Aviñó, FJ., Speicher, SA., Beneyto, M. (2004). Growth and specification of the eye are controlled independently by eyegone and eyeless in Drosophila melanogaster. **Nature Genetics**, 36:10-11. (* Author for correspondence).

Dominguez, M., Casares, F. (2005). The Organ Specification-Growth connection: new in-sights from the eye-antennal disc. **Developmental Dynamics**, 232 (3):673-84.

Ferres-Marco, D., Gutierrez-Garcia I., Vallejo, DM., Bolivar, J., Gutierrez-Avino, FJ., and Dominguez, M. (2006). Epigenetic silencers and Notch collaborate to promote malignant tumours by Rb silencing. **Nature** 439/7075, 430-436.

Dominguez, M. (2006). Interplay between Notch and epigenetic silencers in cancer. **Cancer Res.** 66 (18) Sep 15;66(18):8931-4

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).

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

Palomero T., Dominguez M. and A.A. Ferrando. (2008). The role of the PTEN/AKT Pathway in NOTCH1-induced leukemia. **Cell Cycle** 7(8):965-70.

Gutierrez-Aviño, FJ, Ferres-Marco, D and Dominguez, M. (2009). The position and function of the Notch-mediated eye growth organizar: The roles of JAK/STAT and Four-jointed. **EMBO Reports** 10(9):1051-8.

Liefke R., Oswald F., Alvarado C., Ferres-Marco D., Mittler G., Rodriguez P., Dominguez M., and T. Borggrefe (2010). Histone demethylase KDM5A is an integral part of the core Notch-RBP-J repressor complex. **Genes Dev.** 2010 24 (6)

Vallejo D., Caparros E., Dominguez M. (2011). Targeting Notch signalling by the conserved miR8/200 microRNA family in development and cancer cells. **EMBO J.** Feb 16;30(4):756-69. Epub 2011 Jan 11.

Gontijo A.M., Miguela V., Whiting M.F., Woodruff R. C, Dominguez M (2011). Intron retention in the Drosophila melanogaster Rieske iron sulphur protein gene generated a new protein. **Nature Communications** 2011 2 (323) doi:10.1038/ncomms1328 Published 24 May 2011

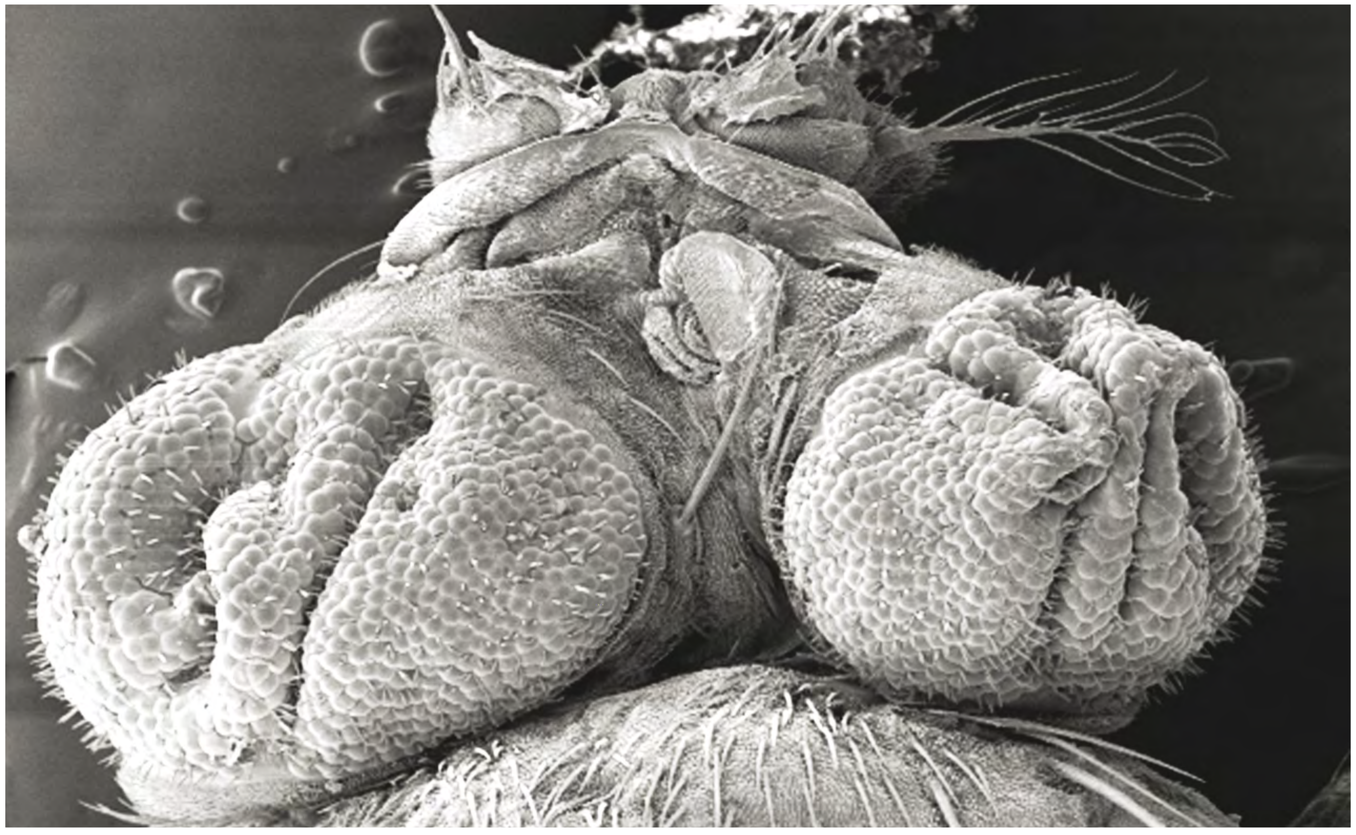
canonical members in that eyegone protein has a truncated paired domain —a conserved DNA-binding domain that is presumed to be essential for PAX-associated oncogenic activity. Strikingly, we found that overexpression of human PAX6 (5a), which is structurally related to eyegone,

of tumorigenesis. Recently, we have have identified, in colaboration with Dr. Borggrefe at the Max Planck Institut in Frieburg, the histone demethylase Lid/KDM5A as a core component of Notch silencing complex in tissue growth and tumroigenesis and the conserved microRNA miR-

10 Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

Selected Publications
Personnel



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canonical members in that eyegone protein has a truncated paired domain —a conserved DNA-binding domain that is presumed to be essential for PAX-associated oncogenic activity. Strikingly, we found that overexpression of human PAX6 (5a), which is structurally related to eyegone,

of tumorigenesis. Recently, we have have identified, in colaboration with Dr. Borggrefe at the Max Planck Institut in Frieburg, the histone demethylase Lid/KDM5A as a core component of Notch silencing complex in tissue growth and tumroigenesis and the conserved microRNA miR-

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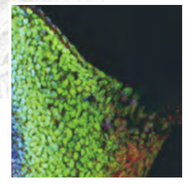

10 Mechanisms of growth control and cancer in *Drosophila*

Maria Domínguez CSIC

Selected Publications
Personnel

Our studies are focused on four research projects:

Control of growth and tumorigenesis using *Dr*

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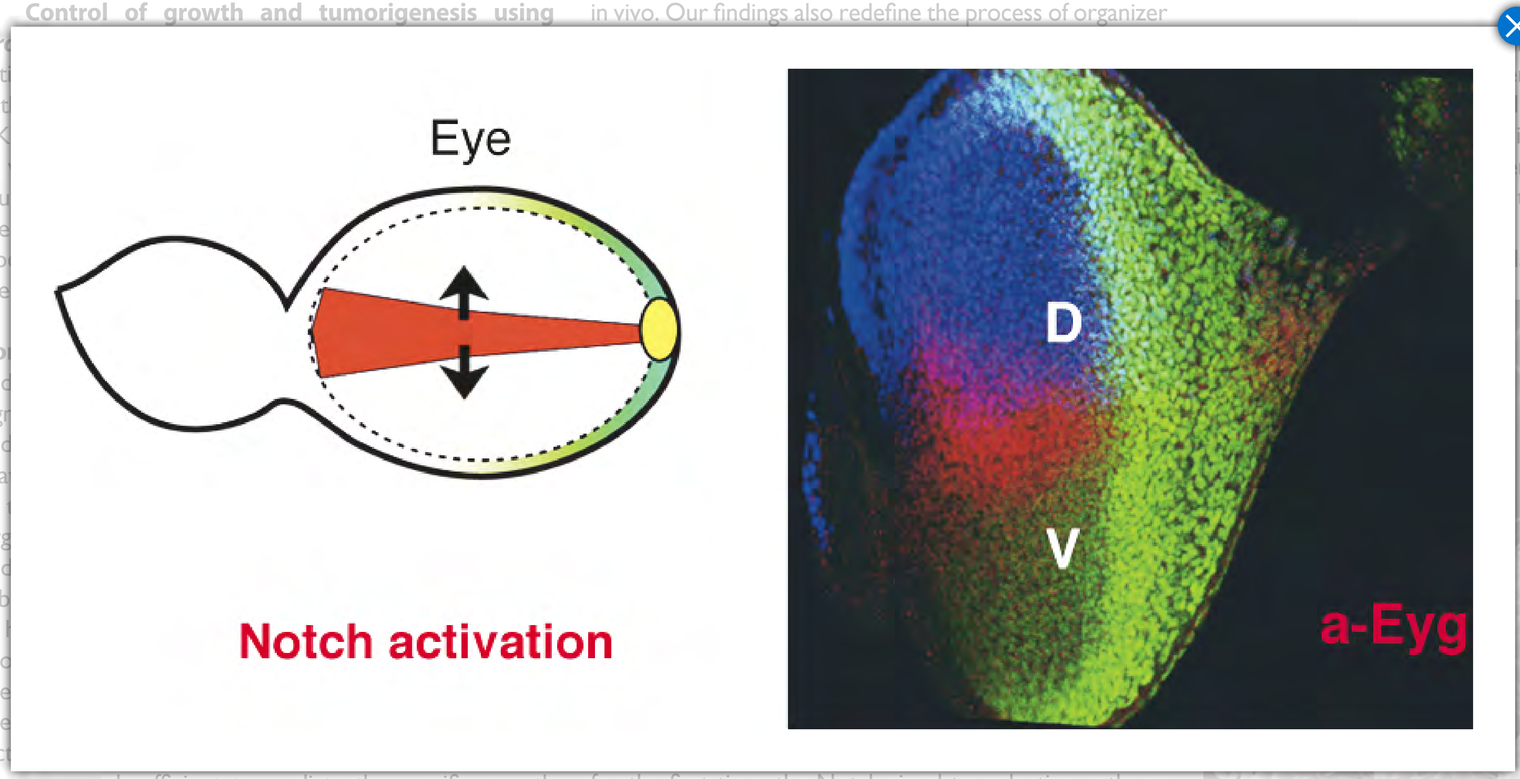

necessary and sufficient to mediate the specific growth response of Notch in the eye. Eyegone encodes a member of the PAX-family of oncogenes, but it differs from the canonical members in that eyegone protein has a truncated paired domain —a conserved DNA-binding domain that is presumed to be essential for PAX-associated oncogenic activity. Strikingly, we found that overexpression of human PAX6 (5a), which is structurally related to eyegone, induces tumours *in vivo*, whilst the canonical and previously presumed oncogenic PAX6 variant hardly affects growth in vivo. Our findings also redefine the process of organizer

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. Recently, we have have identified, in colaboration with Dr. Borggrefe at the Max Planck Institut in Frieburg, the histone demethylase Lid/KDM5A as 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.

metastasis: The fruit fly
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11 Cortical development

Alfonso Fairén CSIC

Fairén, A., Peters, A., Saldanha, J. (1977). A new procedure for examining Golgi impregnated neurons by light and electron microscopy. **J. Neurocytol**, .6: 311-337.

Fairén, A., De Felipe, J., Regidor, J. (1984). Nonpyramidal cells: general account. In A. Peters and E.G. Jones (eds): **Cerebral Cortex**, Vol. I. New York: Plenum, pp. 201-253.

Fairén, A., Cobas, A., Fonseca, M. (1986). Times of generation of glutamic acid decarboxylase immunoreactive neurons in mouse somatosensory cortex. **J. Comp. Neurol.**, 251: 67-83.

DeDiego, A., Smith-Fernández, A., Fairén, A. (1994). Cortical cells that migrate beyond area boundaries: Characterization of an early neuronal population in the lower intermediate zone. **Eur. J. Neurosci.** 6: 983-997.

Meyer, G., Soria, JM., Martínez-Galán, JR., Martín-Clemente, B., Fairén, A. (1998). Different origins and developmental histories of transient neurons in the marginal zone of the fetal and neonatal rat cortex. **J. Comp. Neurol.**, 397: 493-518.

G. López-Bendito, G., Shigemoto, R., Fairén, A., Luján, R. (2002). Differential distribution of Group I metabotropic glutamate receptors during rat cortical development. **Cerebral Cortex**, 12:625-638.

Morante-Oria, J., Carleton, A., Ortino, B., Kremer, EJ., Fairén, A., Lledo, PM. (2003). Subpallial origin of a novel population of Reelin-negative, projecting pioneer neurons of the neocortical marginal zone. **PNAS**, 100:12468-12473.

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.

Gil-Sanz, C., Delgado-García, J.M., Fairén, A., Gruart, A. (2008). Involvement of the mGluR1 receptor in hippocampal synaptic plasticity and associative learning in behaving mice. **Cerebral Cortex**, 18:1653-1663.

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.

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.

11 Cortical development

Alfonso Fairén CSIC

Principal Investigator
Alfonso Fairén

PhD Student
Cecilia Palazzetti
Nuria Ruiz Reig (hasta noviembre de 2010).

Technical Staff
Belén Andrés Bayón

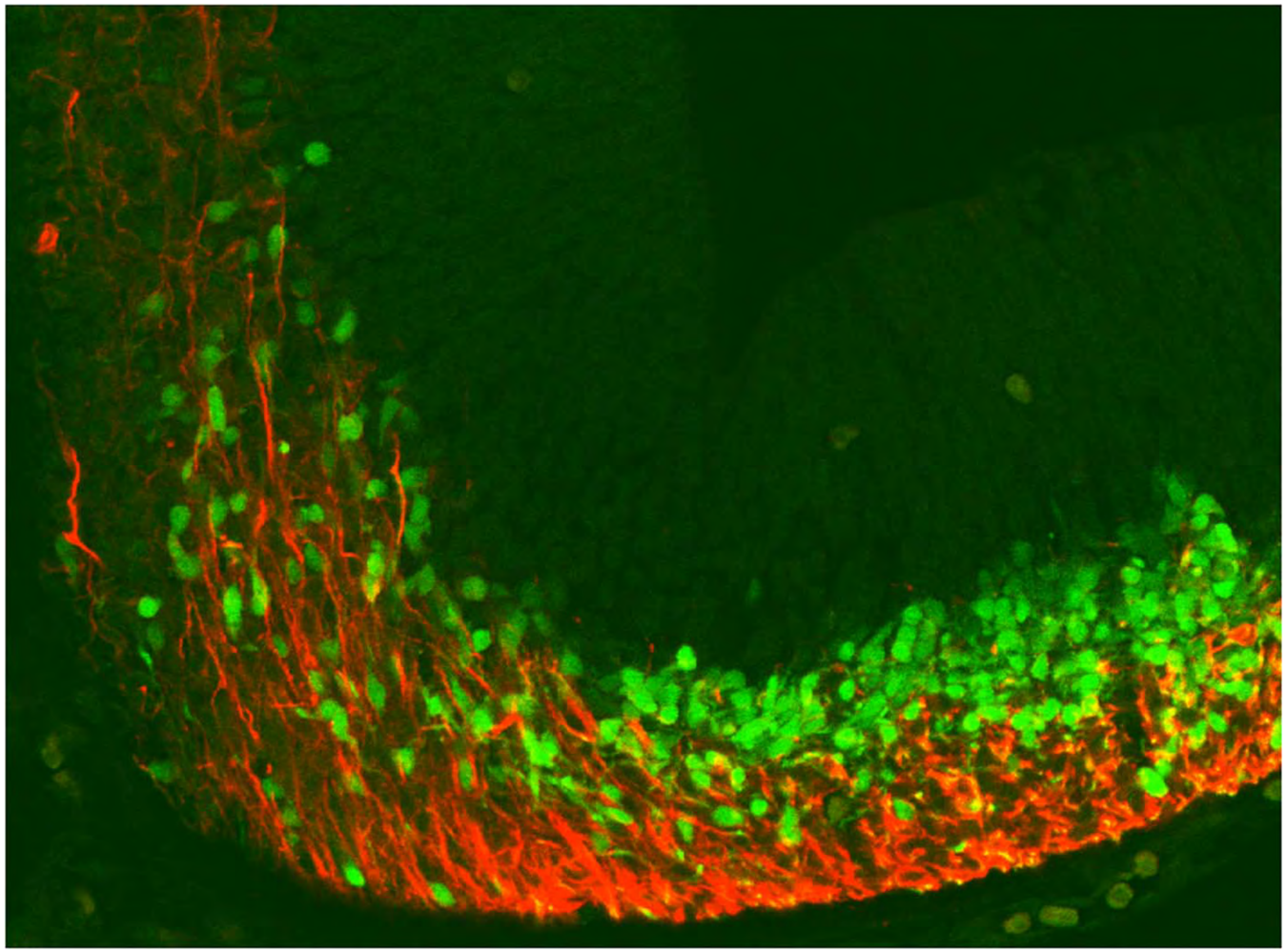
AF

GFG NRR BAB MCP CP

11 Cortical development

Alfonso Fairén CSIC

Selected Publications
Personnel



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12 Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH

Principal Investigator
Clara C. Faura Giner

PhD Investigator
Carlos del Pozo

PhD Student
Luis Gómez Salinas
Yolanda Sastre Peris

Student
Anja Balk

CF

12 Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH

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

Faura, CC., Olaso, MJ., Horga, JF. (1996). Morphine-3-glucuronide behaves as a functional antagonist of morphine-6-glucuronide, but not of morphine analgesia in tolerant and non tolerant mice. **Pain**, 65: 25-30.

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

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

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

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

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S. Single dose dipyrone for acute postoperative pain. **Cochrane Database Syst Rev.** 2010 Sep 8;(9):CD003227.

Berbel P, Navarro D, Ausó E, Varea E, Rodríguez AE, Ballesta JJ, Salinas M, Flores E, Faura CC, de Escobar GM. Role of late maternal thyroid hormones in cerebral cortex development: an experimental model for human prematurity. **Cereb Cortex.** 2010 Jun;20(6):1462-75

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

J J Ballesta, J Cremades, M Rodríguez-Muñoz, J Garzón C C Faura. Sensitivity to μ Opioid Receptor Mediated Antinociception is Determined by Cross−regulation Between μ and δ Opioid Receptors at Supraspinal level. **Br J Pharmacol** DOI: 10.1111/j.1476-5381.2011.01750.x

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.

13 Ocular Neurobiology

Juana Gallar UMH
Mª Carmen Acosta UMH

Principal Investigator
Juana Gallar
Mª Carmen Acosta

PhD Student
Adolfo Aracil
Susana Quirce
Kamila Mizerska

Technical Staff
Carolina L. Luna

Scientific Colaborator
José Belmonte
(Depto. Cirugía UMH y Hospital General Universitario de Alicante)
Timo Tervo
(Ophthalmology, University of Helsinki, Helsinki, Finlandia)
Waldir Neira
(Ophthalmology, University of Helsinki, Helsinki, Finlandia)
Javier Belmonte
(Hospital General Universitario de Alicante)

MCA

JG

13 Ocular Neurobiology

Juana Gallar UMH
Mª Carmen Acosta UMH

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

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

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

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

Gallar J, Morales C, Freire V, Acosta MC, Belmonte C, Duran JA (2009) Decreased corneal sensitivity and tear production in fibromyalgia. **Invest. Ophthalmol. Vis. Sci.** 50: 4129–4134.

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

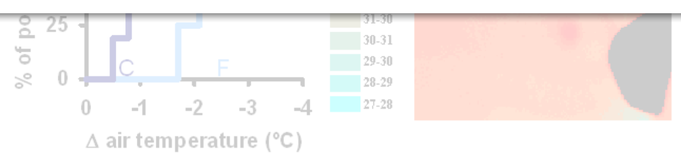
Parra A, Madrid R, Echevarria D, Del Olmo S, Morenilla-Palao C, Acosta MC, Gallar J, Dhaka A, Viana F, Belmonte C (2010). Ocular surface wetness is regulated by TRPM8-dependent cold thermoreceptors of the cornea. **Nat Med** 16: 1396-1399.

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

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

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.



14 Developmental Neurogenetics

Luis García-Alonso CSIC

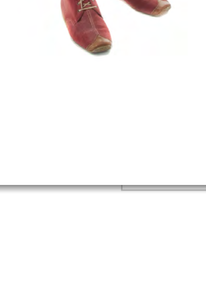
Selected Publications
Personnel

Principal Investigator
Luis García-Alonso

PhD Student
Jarmila Lakomà
Emma Velásquez

Technical Staff
Sigrid Baars
Anna Carboncino


LG-A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14 Developmental Neurogenetics

Luis García-Alonso CSIC

García-Alonso, L., vanBerkum, M., Grenningloh, G., Schuster, C., Goodman, C. (1995). Fasciclin II Controls Proneural Gene Expression in Drosphila. **PNAS**, 92: 10501-10505.

García-Alonso, L., Fetter, R., Goodman, C. (1996). Genetic Analysis of Laminin A in Drosophila: Extracellular Matrix Containing Laminin A is Required for Ocellar Axon Pathfinding. **Development**, 122: 2611-2621.

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

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

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

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

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 molecules 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 EGF receptors. Our work reveals that the specificity of both L1- and NCAM-type proteins as modulators of FGF- and EGF-receptor function 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 function on the control of Notch signaling can be revealed in transgenic Drosophila.

14 Developmental Neurogenetics

Luis García-Alonso CSIC

Selected Publications
Personnel

Nervous System function is determined by the number
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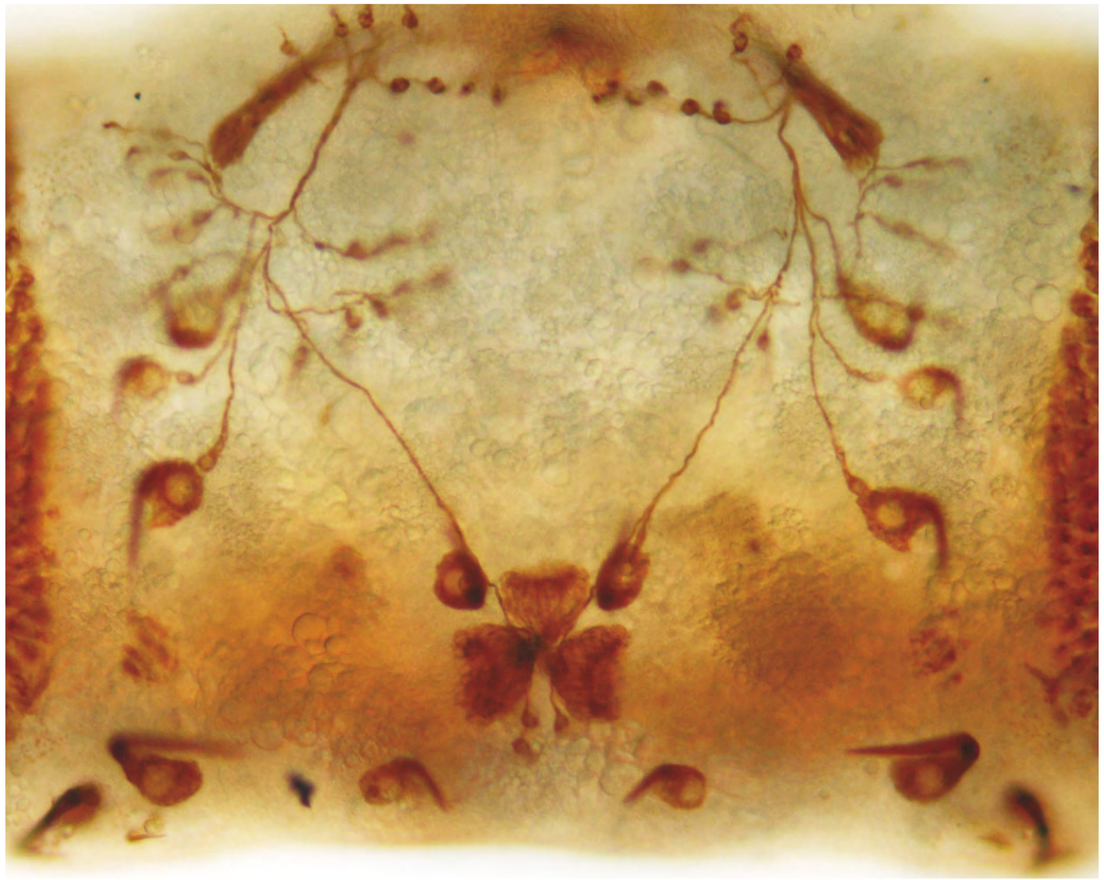


16 Mechanotransduction in mammals

Ana Gomis CSIC

Principal Investigator
Ana Gomis

PhD Student
Anna Lucia Conte
Danny Mauricio Florez

Technical Staff
Ana Miralles
Mireille Torá

16 Mechanotransduction in mammals

Ana Gomis CSIC

channels have been cloned recently and the TRP's channels are firm candidates to be sensory mechanotransducction channels. We use single cell electrophysiology and Ca2+ imaging at sensory neurones and after transfection of TRP channels in mechanically-insensitive HEK293 cells. Moreover, we use molecular biology approaches in collaboration with Dr. Hugo Cabedo's group at the IN.

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.

Ana Gomis, Matthias Pawlak, Endre A. Balazs, Robert F. Schmidt and Carlos Belmonte Effects of different molecular weight elastoviscous hyaluronan solutions on articular nociceptive afferents. **Artritis & Rheumatism** 50 :314-26 (2004)

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

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

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

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

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

Ana Gomis*, Ana Miralles, Robert F. Schmidt and Carlos Belmonte. 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. (2009) (*corresponding author)

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

17 Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH

Selected Publications
Personnel

Principal Investigator
Luis M. Gutiérrez
Salvador Viniegra

PhD Investigator
José Heliodoro Villanueva
Inmaculada López

PhD Student
Cristina Juana Torregrosa
Virginia Garcia

Technical Staff
María del Mar Francés


LMG


VG


CJT


JHV


IL


MdMF


SV

17 Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH

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.

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

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

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

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

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

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

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

18 Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Principal Investigator
Eloísa Herrera

PhD Investigator
Susana Ferreiro

PhD Student
Augusto Escalante
Blanca Murillo
Geraud Chauvin

Technical Staff
Celia Vegar
Yaiza Coca


EH


AE


BM


GC


CV

18 Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Selected Publications
Personnel

Most metazoans are bilaterally symmetric and many features of mature neural function including molecular mechanisms that govern axonal divergence at the midline and the assembly of bilateral circuits in the target tissues.

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).

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

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

García-Frigola C, Carreres MA, Vegar C, Mason CA and Herrera E. (2008). Zic2 promotes axonal divergence at the optic chiasm midline by EphB1-dependent and –independent mechanisms. **Development**. 135(10):1833-41

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. Comment in EMBO Journal 15;29(18):3037-8.

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).

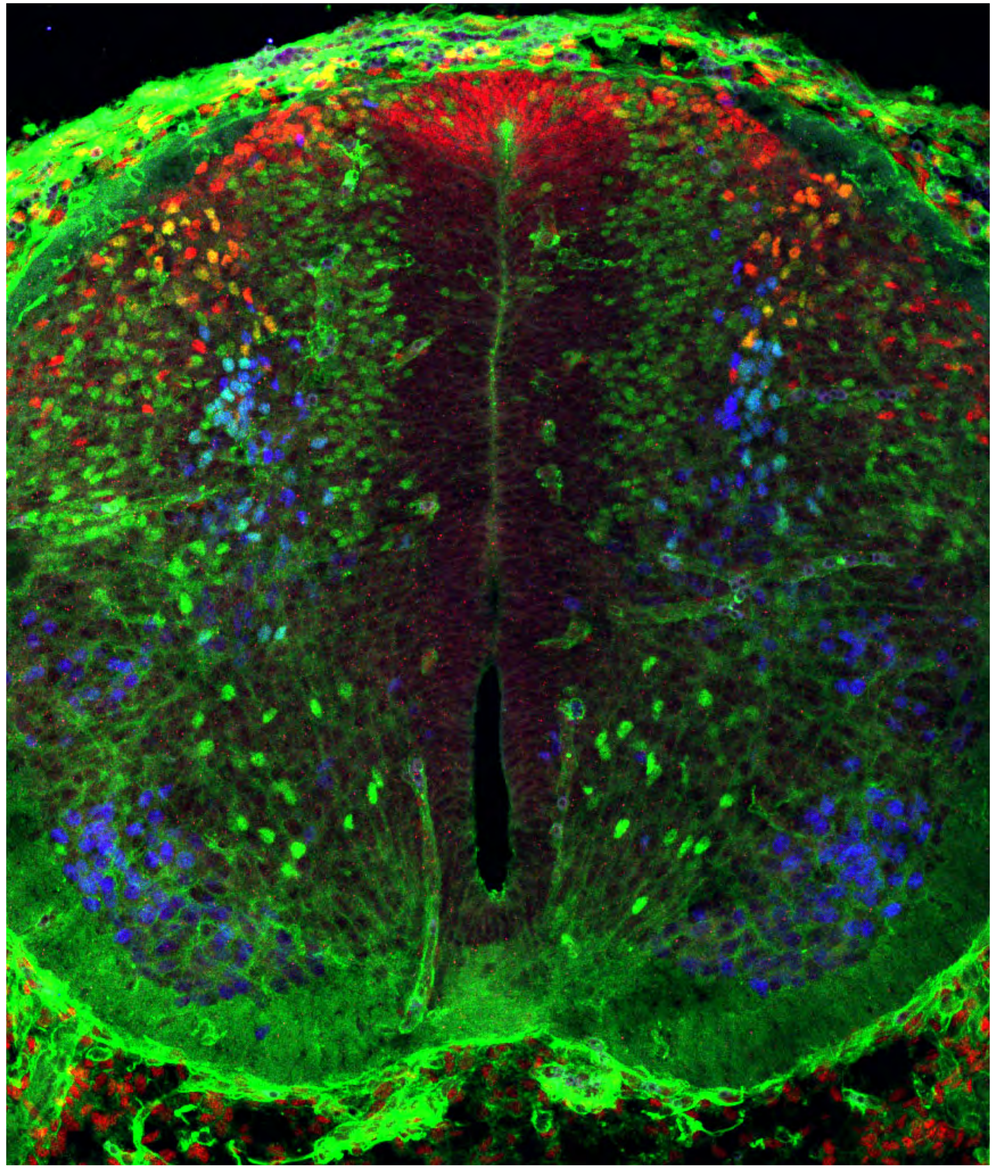
Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Selected Publications
Personnel

Most metazoans many features of the interpretation o coordination of locor communication betwe order to integrate sen of the body and then e the nervous system re midline and axons re the brain. Alterations the midline or in the brain may perturb the in the nervous syste to pathological cons coordination.

We use the develop the spinal cord in mam molecular mechanisms the midline and the as target tissues.



19 Synaptic physiology

Juan Lerma CSIC

Selected Publications
Personnel

Principal Investigator
Juan Lerma

PhD Investigator
M. Isabel Aller
Ana V. Paternain
Ricardo J. Rodrigues
Izabela Rutkovska

PhD Student
Joana M. Marques
Jon Palacios

Technical Staff
Mónica Llinares
Esther Picó

JL

ML
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IR
JMM
JP
AVP

19 Synaptic physiology

Juan Lerma CSIC

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

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

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

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

Rivera R, Rozas JL and Lerma J (2007) PKC-dependent Autoregulation of Membrane Kainate Receptors. **EMBO Journal** 26, 4359-67

Priel A, Selak S, Lerma J, and Stern-Bach Y (2006) Block of kainate receptor desensitization uncovers a key trafficking checkpoint. **Neuron** 52, 1037-1046

Lerma J. (2006) Kainate Receptor Physiology, **Curr. Op. Pharmacol.** 6, 89-97

Lerma, J. (2003). Roles and rules of kainate receptors in synaptic transmission. **Nature Rev Neurosci** 4:481-95.

Rozas, J.L., Paternain A.V. and Lerma J. (2003) Non-canonical signaling by ionotropic kainate receptors. **Neuron** 39: 543–553.

Lerma, J., Paternain, A.V., Rodríguez-Moreno, A., and López-García, J.C (2001) Molecular Physiology of Kainate Receptors. **Physiologial Reviews**. 81: 971-998.

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

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-

20 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications
Personnel

GLB

Principal Investigator
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Technical Staff
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Administration
Helena Campos Martín

20 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

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

Moldrich RX, Mezzera C, Holmes WM, Goda S, Brookfield SJ, Rankin AJ, Barr E, Kurniawan N, Dewar D, Richards LJ, López-Bendito G, Iwata T. (2011) Fgfr3 regulates development of the caudal telencephalon. **Dev. Dyn.** vol.240(6) pp. 1586-99

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.

López-Bendito G, Arlotta P (2011) Cell replacement therapies for nervous system regeneration. **Developmental Neurobiology** pp.

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

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

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

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

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

Molnár Z*, López-Bendito G*, Small J, Partridge LD, Blakemore C, Wilson MC (2002) Normal development of embryonic thalamocortical connectivity in the absence of evoked synaptic activity. **Journal of Neuroscience** 22:10313-10323.

Jones L,* López-Bendito G*, Gruss P, Stoykova A, Molnár Z (2002) Pax6 is required for the normal development of the forebrain axonal connections. **Development** 129:5041-5052

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.

20 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications
Personnel

Our research team run
studying the cellular a
involved in the development
brain. In particular, our aim i
underlying thalamocortical a
and ultimately the rewiring
integrated and innovative exp

The development of t
requires a precise topo
connections. Each thalamic
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level of organization is achiev
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topographical organization,
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area. Therefore, the level of
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than other projection systen
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influences and maintains the fu
brain. We also believe that re
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thalamus.

Three major questions a
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Within these projects
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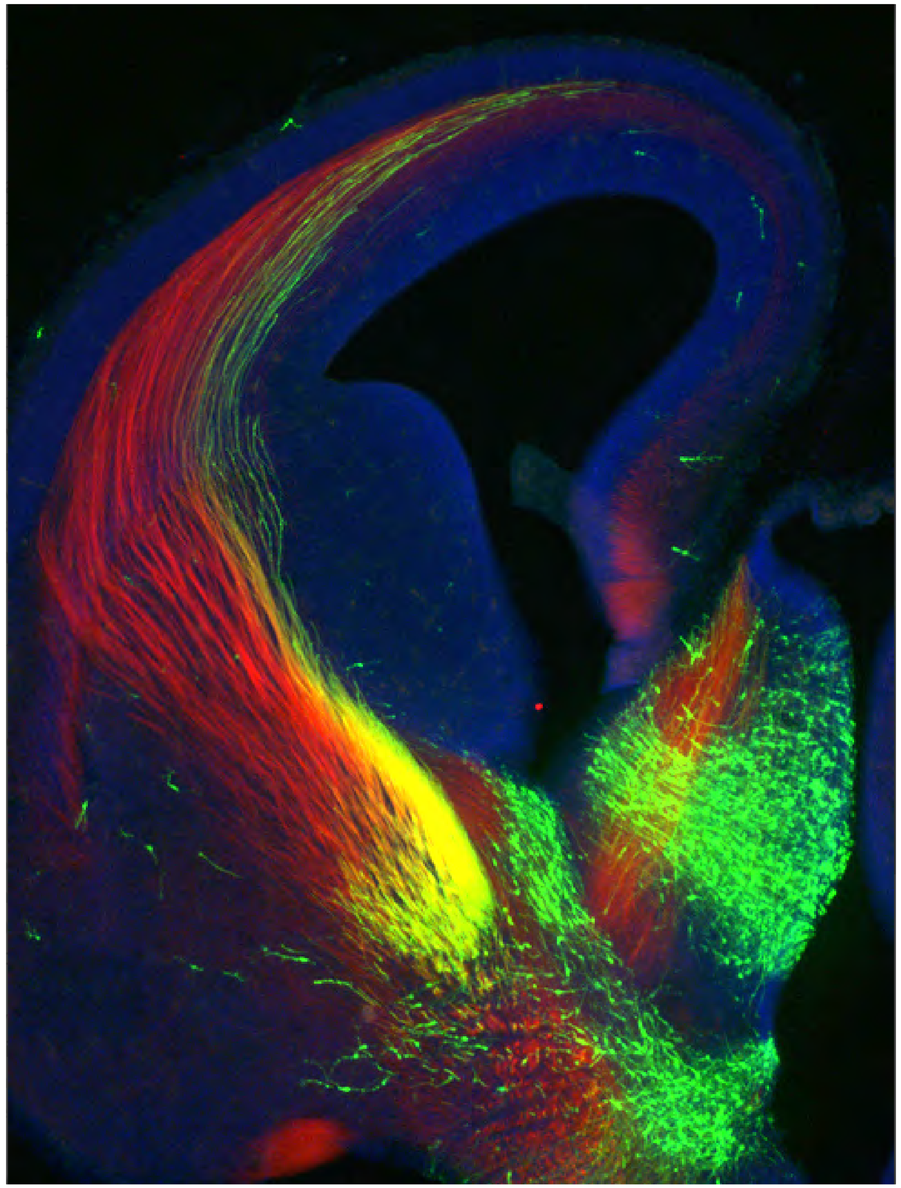
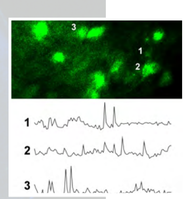
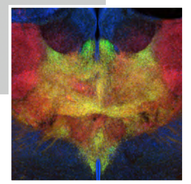






20 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

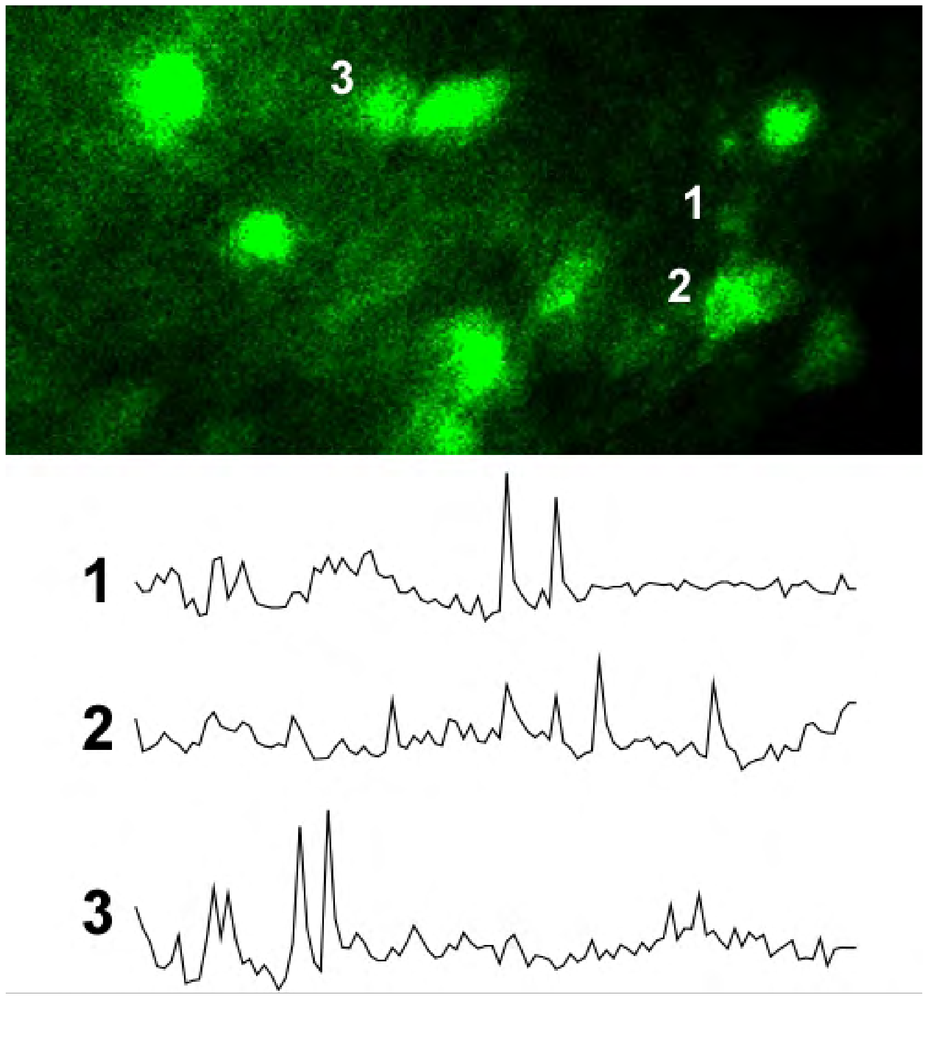
Selected Publications
Personnel

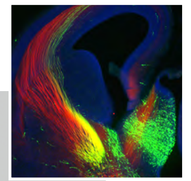
Our research team studying the cellula involved in the developme brain. In particular, our a underlying thalamocortic and ultimately the rewiri integrated and innovative

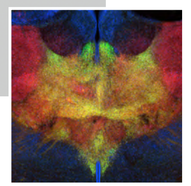
The development c requires a precise t connections. Each thala sensory information from topographically to its co level of organization is ac thalamocortical connec topographical organizatio accurate spatial represe area. Therefore, the leve of the thalamocortical pro than other projection sy hypothesis of our laborato influences and maintains t brain. We also believe tha can be triggered by activit thalamus.

Three major question laboratory: i) the transcrip topography; ii) integration thalamocortical behaviou mechanisms involved in wiring.

Within these proj experimental programme manipulation of gene expr biology, biochemistry, cel



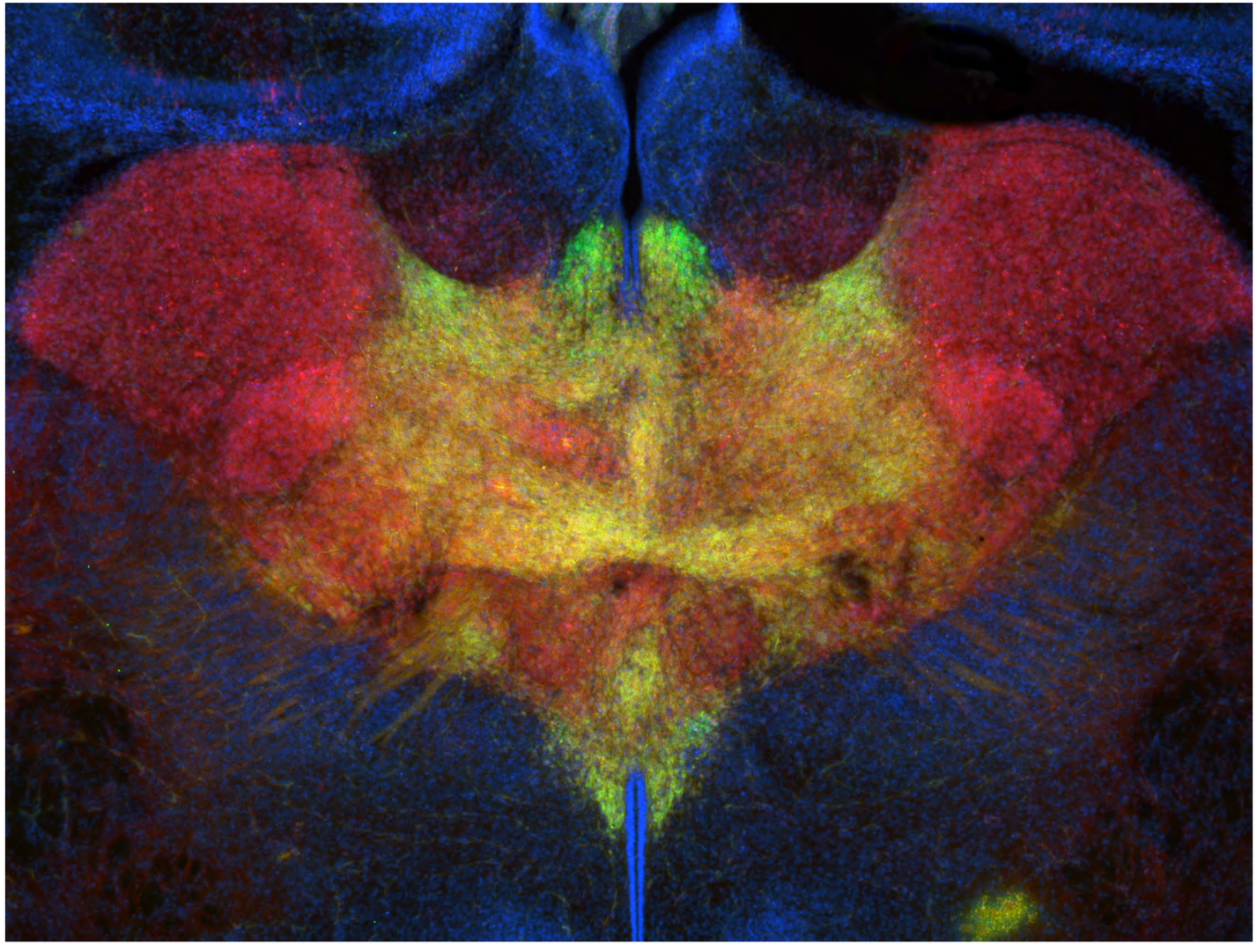


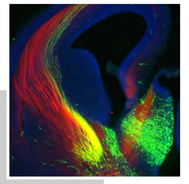


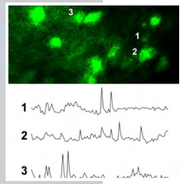
20 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications
Personnel







21 Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

Selected Publications
Personnel

Principal Investigator
Jorge Manzanares

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ARR


FNR


MSGG


MAAF


JM

21 Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

García-Gutiérrez, MS, Manzanares, J. Overexpression of CB2 cannabinoid receptor gene expression results in decreased vulnerability to anxiety and impaired action of alprazolam in mice. **Journal of Psychopharmacology**, 25(1): 111-120 (2011).

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

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

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

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

Navarrete, F., Pérez-Ortiz, J.M., Manzanares, J. CB2 cannabinoid receptor-mediated regulation of impulsive-like behavior in DBA/2 mice. **British Journal of Pharmacology** 165 260–273 (2012).

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

García-Gutiérrez MS, García-Bueno B, Zoppi S, Leza JC, Manzanares J. 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 (2012).

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. CB2R activation down-regulates stroke-induced classic and alternative brain macrophage/microglial activation concomitant to neuroprotection. **Stroke** 43(1):211-219 (2012).

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. Endogenous cannabinoid system regulates intestinal barrier function in vivo through cannabinoid type 1 receptor activation. **Am J Physiol Gastrointest Liver Physiol** 302: G565–G571 (2012).

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.

22 Dynamics and plasticity of cortical sensory responses

Miguel Maravall CSIC

Selected Publications
Personnel

Principal Investigator
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Giovanni Ferrati

Technical Staff
Anna Pitas

ALA

FM

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MM

22 Dynamics and plasticity of cortical sensory responses

Miguel Maravall CSIC

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.

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

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

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

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

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

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

Puccini, GD; Compte, A; Maravall, M. (2006). Stimulus dependence of barrel cortex directional selectivity. **PLoS ONE 1**: e137. doi: 10.1371/journal.pone.0000137.

23 Neuronal specification and migration

Oscar Marín CSIC

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Oscar Marín

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Cristina García-Frigola (with Beatriz Rico)
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S. Ricardo Scott Barrios
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Ángeles Casillas Bajo
María Antonia Fernández Otero (con CONSOLIDER SP2 groups)
Trinidad Gil García
María Pérez Sanjuan

Administration
Virtudes García

23 Neuronal specification and migration

Oscar Marín CSIC

Flames, N; Long, JE; Garratt, AN; Fischer, TM; Gassmann, M; Birchmeier, C; Lai, C; Rubenstein, JL; Marín, O. (2004). Short- and long-range attraction of cortical GABAergic interneurons by Neuregulin-1. **Neuron**, 44: 251-61.

López-Bendito, G; Cautinat, A; Sánchez, JA; Bielle, F; Flames, N; Garratt, AN; Talmage, DA; Role, L; Charnay, P; Marín, O; Garel, S. (2006). Tangential neuronal migration controls axon guidance: a role for Neuregulin-1 on thalamocortical axon navigation. **Cell**, 125: 127-42.

Borrell, V; Marín, O (2006) Meninges control tangential migration of hem-derived Cajal-Retzius cells via CXCL12/CXCR4 signaling. **Nature Neuroscience**, 9: 1284-93.

Flames N, Pla R, Gelman DM, Rubenstein JL, Puelles L, Marín O (2007) Delineation of multiple subpallial progenitor domains by the combinatorial expression of transcriptional codes. **Journal of Neuroscience** 27:9682-95.

López-Bendito G, Sánchez-Alcaniz JA, Pla R, Borrell V, Pico E, Valdeolmilos M, Marín O (2008). Chemokine signaling controls intracortical migration and final distribution of GABAergic interneurons. **Journal of Neuroscience** 28:1613-24.

Nóbrega-Pereira S, Kessaris N, Du T, Kimura S, Anderson S.A, Marín O (2008) Postmitotic Nkx2-1 controls the migration of telencephalic interneurons by direct repression of guidance receptors. **Neuron** 59:733-45.

Martini FJ, Valiente M, López-Bendito G, Szabó G, Moya F, Valdeolmillos M, Marín O (2009) Biased selection of leading process branches mediates chemotaxis during tangential neuronal migration. **Development** 136:41-50.

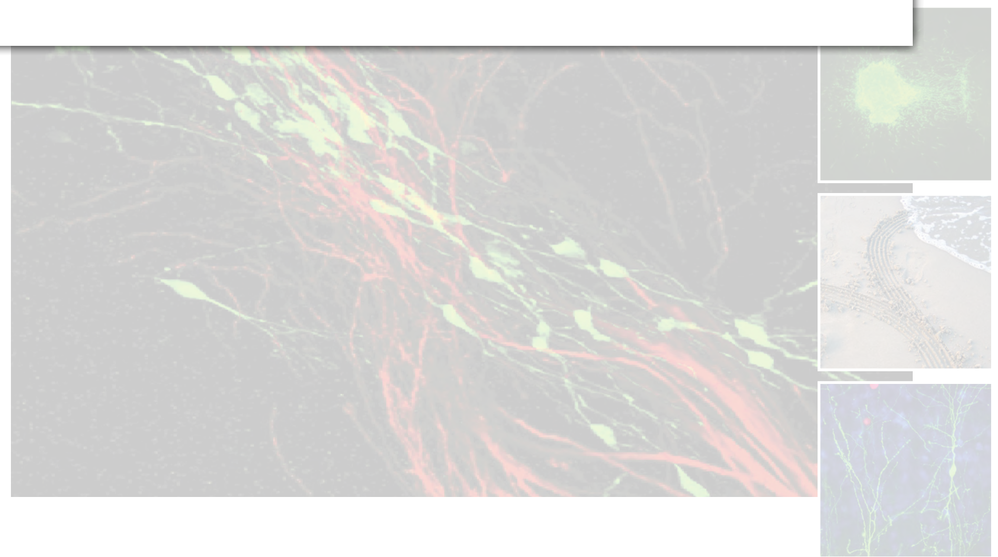
Gelman DM, Martini FJ, Nóbrega-Pereira S, Pierani A, Kessaris N, Marín O (2009) The embryonic preoptic area is a novel source of cortical GABAergic interneurons. **Journal of Neuroscience** 29:9380-89.

Fazzari P, Paternain AV, Valiente M, Pla R, Lujan R, Lloyd K, Lerma J, Marin O, Rico B (2010) Control of cortical GABA circuitry development by Nrg1 and ErbB4 signalling. **Nature** 464:1376-1380.

Sánchez-Alcañiz JA, Haege S, Mueller E, Pla R, Mackay F, Schulz S, López-Bendito G, Stumm R, Marín O (2011) Cxcr7 controls neuronal migration by regulating chemokine responsiveness. **Neuron** 69(1) 77-90.

factors determine how the different types of neuronal precursors decide their fate.

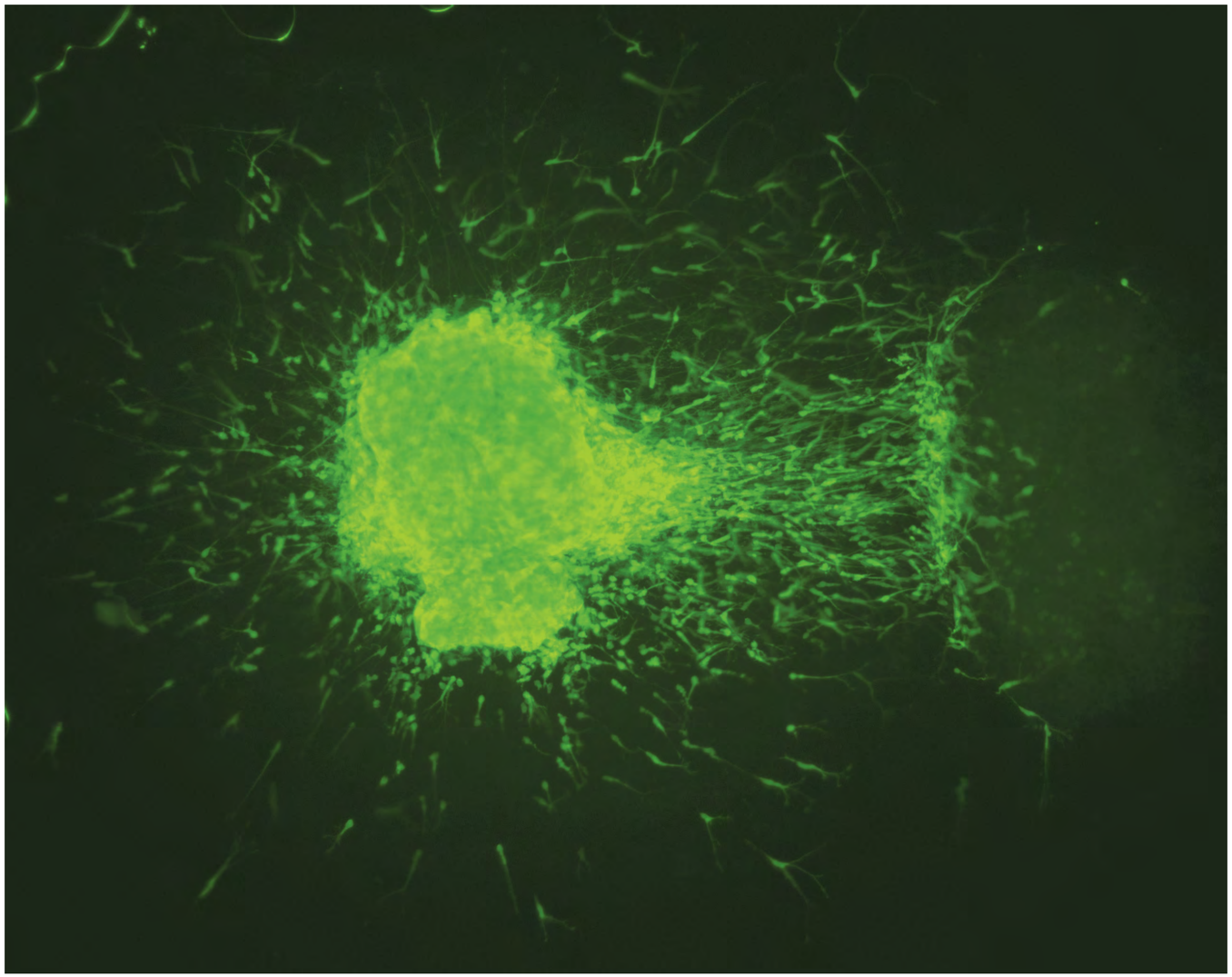
In addition, since proliferative regions are normally located at a distance from the place where neurons finally reside and function, new neurons have to move to reach their final position in the telencephalon. The process of neuronal migration is particularly complex in the cerebral cortex, where neurons 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



23 Neuronal specification and migration

Oscar Marín CSIC

Selected Publications
Personnel



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disorders such as epilepsy
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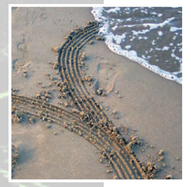
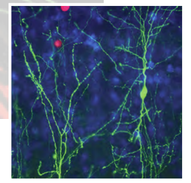
ng mouse models of cortical
h we hope may contribute
f cortical interneurons.





23 Neuronal specification and migration

Oscar Marín CSIC

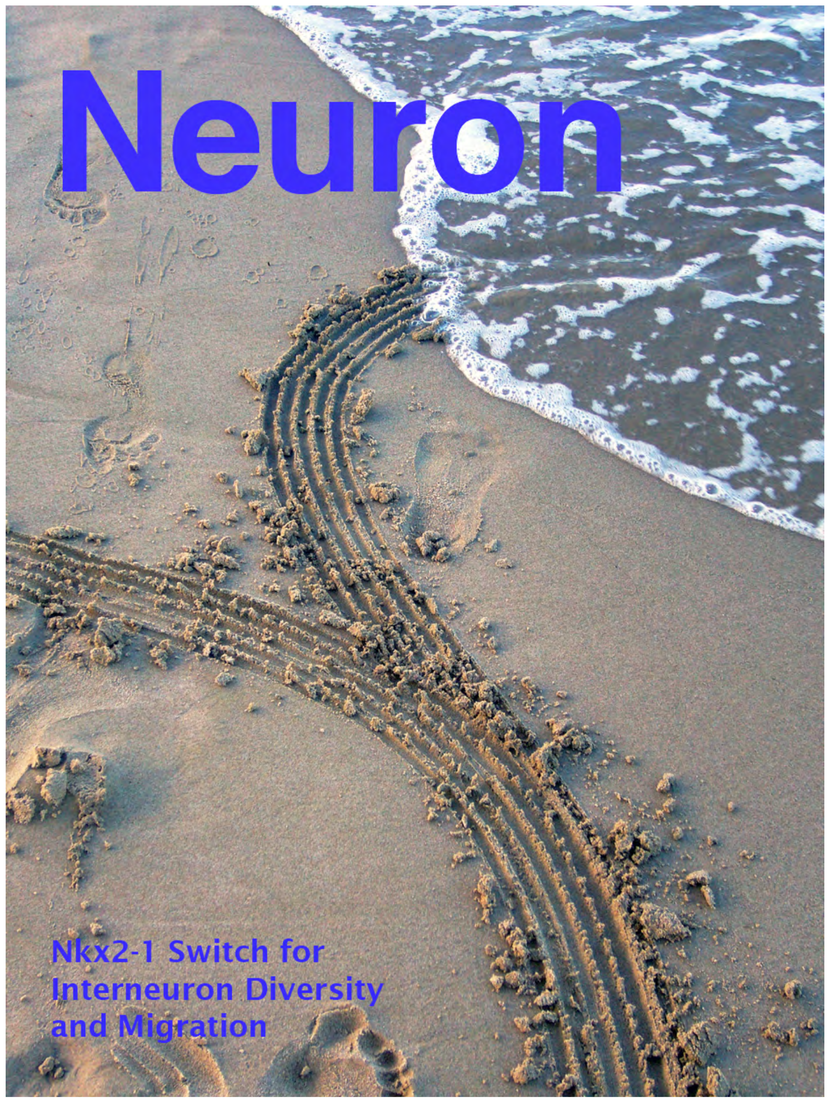
Selected Publications
Personnel

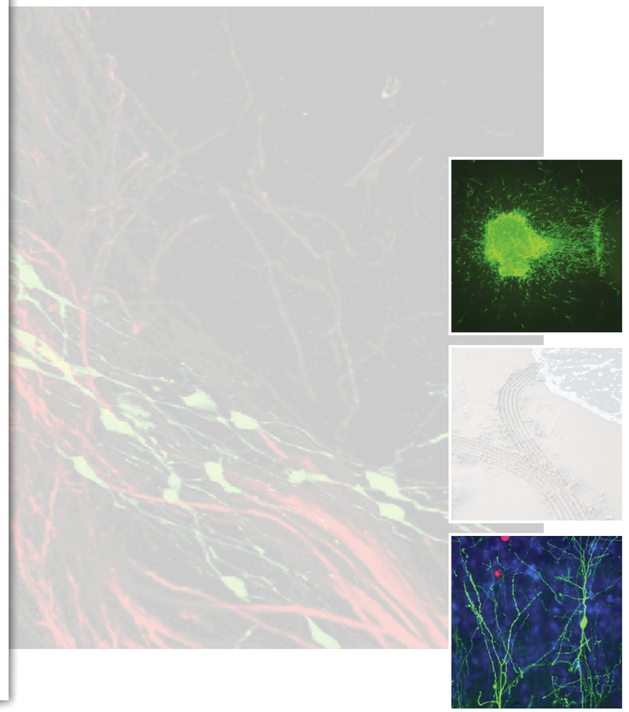
The main aim of our lab the molecular and cellul the development of the mo brain, the telencephalon. Th key structures for the functio such as the basal ganglia and cerebral cortex, for example central nervous system and is functions that distinguish us a

As in other regions of th most telencephalic neuron development from precursor areas, named "proliferative z place and time of birth of a fundamental characteristics (s content, for example). How limited knowledge of the facto called "neuronal specification in understanding the molecul the specification of different telencephalon. In other word factors determine how the c precursors decide their fate.

In addition, since prolifera located at a distance from finally reside and function, n to reach their final position process of neuronal migrati in the cerebral cortex, wher very long distances to reac of the main research inter to understand the cellular a controlling the migration of combining multiple experim

In this context, our group focuses most of its ts in the identification of novel genes controlling development of cortical interneurons, a type of ical cell which dysfunction underlies the aetiology of rological and psychiatric disorders such as epilepsy chizophrenia. To this aim, we are generating mouse ns to study the origin and fate of the different ulations of cortical interneurons. Moreover, we are in the process of generating mouse models of cortical rneuron deficiency, which we hope may contribute nderstand the function of cortical interneurons.

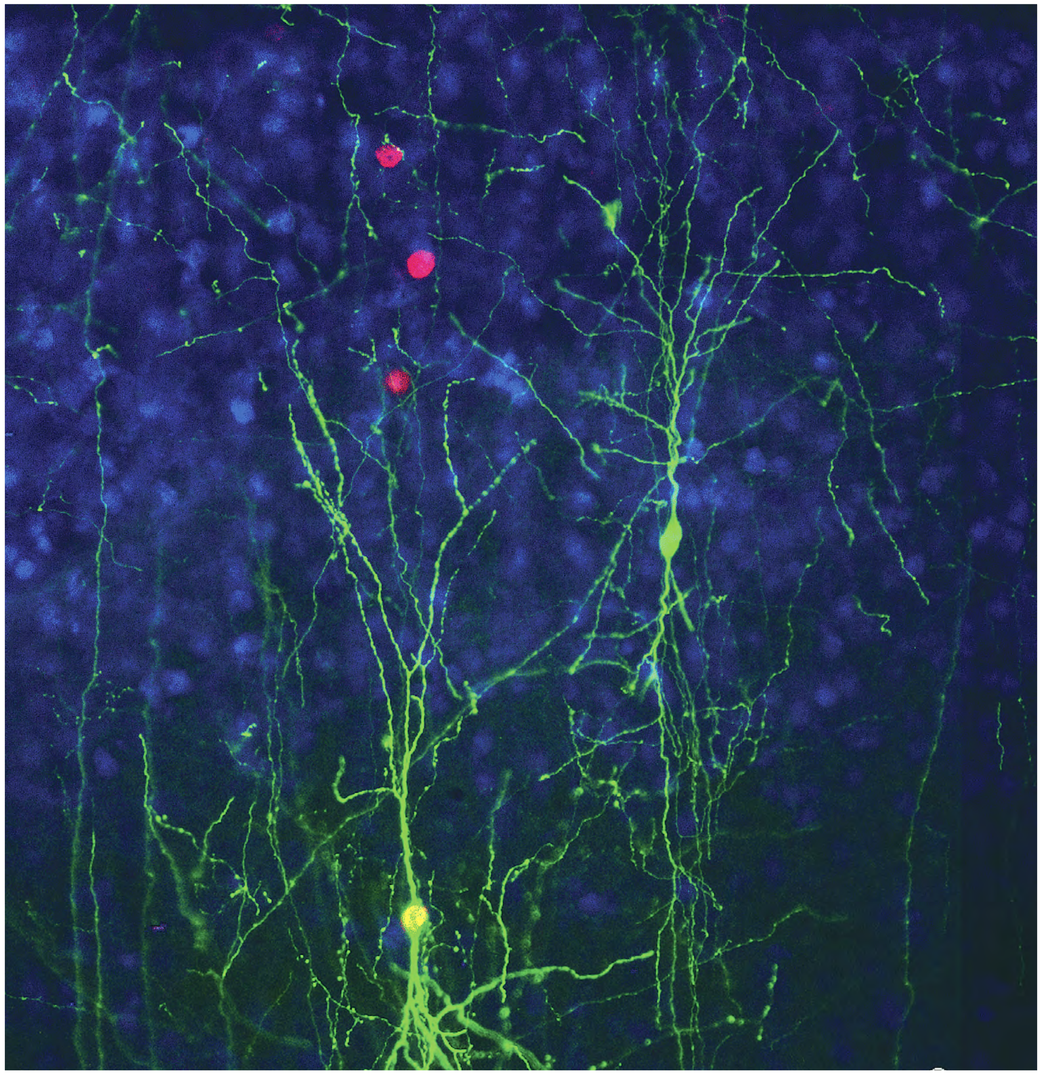




23 Neuronal specification and migration

Oscar Marín CSIC

Selected Publications
Personnel

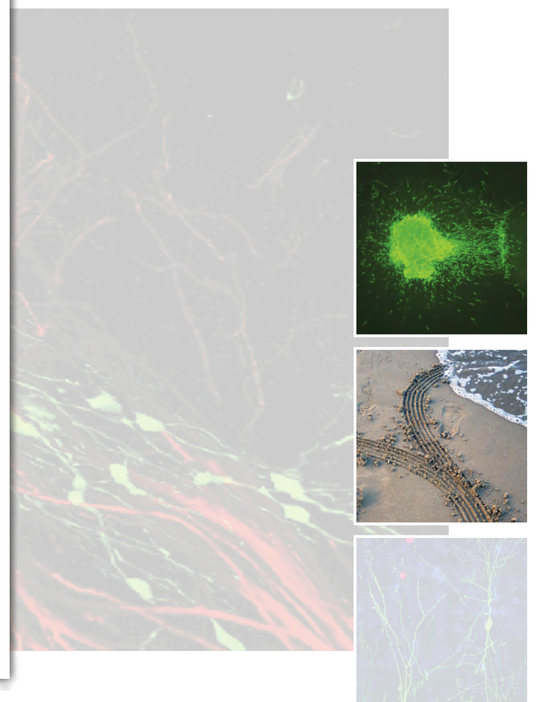


The main aim o the molecular a the development o brain, the telencep key structures for t such as the basal g cerebral cortex, for central nervous syst functions that disting

As in other reg most telencephalic development from p areas, named "proli place and time of b fundamental charact content, for examp limited knowledge o called "neuronal spe in understanding th the specification of telencephalon. In ot factors determine h precursors decide t

In addition, since located at a distan finally reside and fu to reach their final process of neurona in the cerebral cort very long distance of the main resea to understand the controlling the mig combining multiple

context, our group focuses most of its identification of novel genes controlling nent of cortical interneurons, a type of which dysfunction underlies the aetiology of and psychiatric disorders such as epilepsy nia. To this aim, we are generating mouse udy the origin and fate of the different f cortical interneurons. Moreover, we are cess of generating mouse models of cortical deficiency, which we hope may contribute the function of cortical interneurons.



24 Visual Neuroscience Laboratory

Luis M. Martínez CSIC

Principal Investigator
Luis M. Martínez.

PhD Student
Diego Alonso Pablos
Isabel Benjumeda Wijnhoven
Manuel Molano Mazón (with Miguel Maravall)

Technical Staff
Joaquín Márquez Bugella

LMM

JMB

DAP

IBW

MMM

24 Visual Neuroscience Laboratory

Luis M. Martínez CSIC

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

Martinez LM* & Alonso JM* (2001) "Construction of complex receptive fields in primary visual cortex." **Neuron**. 32:515-525. * Co-author

Hirsch JA, Martinez LM, Pillai C, Alonso JM, Wang Q & Sommer FT (2003) "Functionally distinct inhibitory neurons at the first stage of visual cortical processing." Nature Neuroscience. 6:1300-1308.

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

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

Martinez LM (2006) "The generation of visual cortical receptive fields." Progress in Brain Research. 154:73-92.

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

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

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

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.

25 Experimental Embryology

Salvador Martínez UMH
Constantino Sotelo UMH

Selected Publications
Personnel

Principal Investigator
Salvador Martínez
Constantino Sotelo
Eduardo de Puelles
Diego Echevarria

PhD Investigator
Arancha Botella
Carlos Bueno
Elisabetta Caspani
Philip Crossley
Teresa Escamez
Raquel Garcia
Jonathan Jones
Almudena Martinez
Ana Isabel Pombero
Carolina Redondo
Mari Carmen Viso
Diego Pastor

PhD Student
Ivan Crespo
Valentina Cuccioli
Jesus Jaramillo
Jesus Martínez López
Nora Mecklenburg
Juan Antonio Moreno
Maria Navarro
Ariadna Perez
Carmina Ramirez

Administration
Maria Jesús Arencibia

Technical Staff
Olga Bahamonde
Paloma Gomez Morgan
Mónica Rodenas
Alicia Estirado
Francisca Almagro


SM


JJ AM RG AIP CR IC CB VC PGM AB EdP DE OB AT AE MR JML MJA PB MN NM JAM CS

Experimental Embryology

Salvador Martínez UMH
Constantino Sotelo UMH

M.L. Martínez-Frias, X. Egües, J. Hualde, C.A. de Frutos, E. Bermejo, M.A. Nieto, & S. Martínez. "Thanatophoric Dysplasia Type II with encephalocele and semilobar Holoprosencephaly: Insights into its pathogenesis" **American Journal of medical genetics**; 155: 197-202 (2011).

C. Sotelo and A. Chedotal. Hindbrain tangential migration.In: **Comprehensive Developmental Neuroscience**. Pasko Rakic and John Rubenstein (Eds.), New York: Oxford University Press (in press).

C. Sotelo and F. Rossi. Purkinje cell migration and differentiation. In: **Handbook of Cerebellum and Cerebellar Disorders**. Mario Manto, Donna Gruol, Jeremy Schmahmann, Nori Koibuchi and Ferdinando Rossi (Eds). Heidelberg: Springer Verlag (in press).

Graciana Diez-Roux, et al. A High-Resolution Anatomical Atlas of the Transcriptome in the Mouse Embryo **PLoS Biol.** January 18; 9(1): e 1000582 (2011).

Rafael Tabaré-Seisdedos, Nancy Dumont, Anaïs Baudot, Jose M Valderas, Joan Climent, Alfonso Valencia, Benedicto Crespo-Facorro, Eduard Vieta, Manuel Gómez Beneyto, Salvador Martinez, John L. Rubenstein. No paradox, no progress: inverse cáncer comorbidity in people with other complex diseases. Personal view, **Lancet** Oncology; 12: 604-608 (2011).

Itzel Ricaño-Cornejo, Amy L. Altick, Claudia M. Garcia-Peña, Hikmet Feyza Nural, Diego Echevarria, Amaya Miquelajáuregui, Grant S. Mastick & Alfredo Varela-Echevarria. Slit-Robo signals regulate pioneer TPOC axón pathfinding in the mammalian forebrain. **Journal of Neuroscience Research** 89: 1531-1541 (2011)

Tian Yu, Yuichiro Yaguchi, Diego Echevarria, Salvador Martinez & M. Albert Basson. Sprouty genes prevent excessive FGF signalling in multiple cell types throughout development of the cerebellum. **Development** 138: 2957-2968 (2011).

Nora Mecklenburg, Raquel Garcia-Lopez, Eduardo Puelles, Constantino Sotelo & Salvador Martinez. Cerebellar oligodendroglial cells have a mesencephalic origin. **GLIA** 59: 1946-1957 (2011).

Maria-Ximena Silveyra, Maria-Salud Garcia.Ayllón, Elena Gómez de Barreda, David H. Small, Salvador Martinez, Jesus Avila & Javier Sáez-Valero. Altered expression of brain acetylcholinesterase in FTDP-17 human tau transgenic mice **Neurobiology of Aging** 2011 Apr 27. [Epub ahead of print] (in press).

Diego Pastor, Mari Carmen Viso-León, Jonathan Jones, Jesus Jaramillo-Merchán, Juan Jose Toledo-Arál, José Maria Moraleda, Salvador Martinez. Comparative effects between bone marrow and mesenchymal stem cell transplantation in GDNF expression and motor function recovery in a motorneuron degenerative mouse model. **Stem Cell Reviews and Reports** DOI 10.1007/s12015-011-9295; (2011).

Ana Pombero, Carlos Buenos, Laura Saglietti, Monica Rodenas, Jordi Guimera, Alexandro Bulfone & Salvador Martinez. Pallial origin of basal forebrain cholinergic neurons in the nucleus basalis of Meynert and horizontal limb of the diagonal band nucleus. **Development** 138: 4315-4326; (2011).

C. Sotelo Camillo Golgi and Santiago Ramon y Cajal: The anatomical organization of the cortex of the cerebellum. Can the neuron doctrine still support our actual knowledge on the cerebellar structural arrangement? **Brain Research Reviews**. 66: 16-34; (2011).

S. Martinez. **El Sindrome de Down**. Colección ¿Qué sabemos de? Ed. Los libros de la Catarata. 2011

McCabe MJ, Gaston-Massuet C, Tziaferi V, Gregory LC, Alatzoglou KS, Signore M, Puelles E, Gerrelli D, Farooqi IS, Raza J, Walker J, Kavanaugh SI, Tsai PS,Pitteloud N, Martinez-Barbera JP, Dattani MT. Novel FGF8 mutations associated with recessive holoprosencephaly, craniofacial defects, and hypothalamo-pituitary dysfunction. **J Clin Endocrinol Metab**. 96: E1709-1718 (2011).

Simeone A, Puelles E, Omodei D, Acampora D, Di Giovannantonio LG, Di Salvio M, Mancuso P, Tomasetti C. Otx genes in neurogenesis of mesencephalic dopaminergic neurons. **Dev Neurobiol**; 71(8): 665-679 (2011).

Salvador Martinez & Eduardo Puelles. Chapter 1 "Functional anatomy of the oromotor system" **Oromotor Disorder in Childhood**. Editors: Manuel Roig-Quilis & Lindsay Pennington.

Salvador Martínez, Eduardo Puelles, Luis Puelles, & Diego Echevarria. Chapter 1 "Molecular Regionalization of the Developing Neural Tube" **The Mouse Nervous System**. Edited by Charles Watson, George Paxino & Luis Puelles.

25 Experimental Embryology

Salvador Martínez UMH
Constantino Sotelo UMH

Selected Publications
Personnel

Our studies are focused

Experimental Embryology and chick embryos allow molecular factors that co segmentation, proliferation, migration processes of the C concentrate our research wo the molecular factors that co morphogenetic activity of the anterior neural tube of verte particularly the molecular ac like SHH, WNTs and FGFs i zona limitans intrathalamic (Z ridge (ANR).

Experimental method transplants of neural tissue embryonic brain areas. (ii) anterior neural tube will pe embryological techniques on models.

Neurogenetics: We are stud important genes related to th the brain through its develop part of an EU Grant in which manner to analyse the expres at several embryonic stages org/ee/). The further genetic m recombination will help us to of these genes. Currently we important of human neuropa created a line of research i of lisencephaly, several cort

26 Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications
Personnel


MAN

Principal Investigator
M. Angela Nieto

Associated Investigator
Joan Galcerán

PhD Investigator
Jose Manuel Mingot
Fabiana Heredia de Oliveira
María Teresa Grande
Elisa Guida
Oscar Ocaña
Eva Rodriguez-Aznar
Sonia Vega

PhD Student
Juan Manuel Fons
Rebeca Córcoles

Technical Staff
Diana Abad
Josepa Chuliá
Cristina López
Mireille Tora

Administration
Sonia Martin


SM JMF RC MT JC DA CL


JG JMM FHdO MTG EG OO ER-A SV

26 Cell movements in development and disease

M. Angela Nieto CSIC

Boutet, A., De Frutos, C.A., Maxwell, P.H., Mayol, M.J., Romero, J. and Nieto, M.A. (2006). Snail activation disrupts tissue homeostasis and induces fibrosis in the adult kidney. **EMBO J.** 25, 5603-5613

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.

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.

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.

Zhang, K., Rodriguez-Aznar, E., Yabuta, N., Owen, R.J., Mingot, J.M., Nojima, H., Nieto, M.A. and Longmore, G.D. (2011) . Lats2 kinase potentiates Snail1 activity by promoting nuclear retention upon phosphorylation. **EMBO J.** 31, 29-43.

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 found that the interplay between Snail 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 previoulsy 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 (2011).

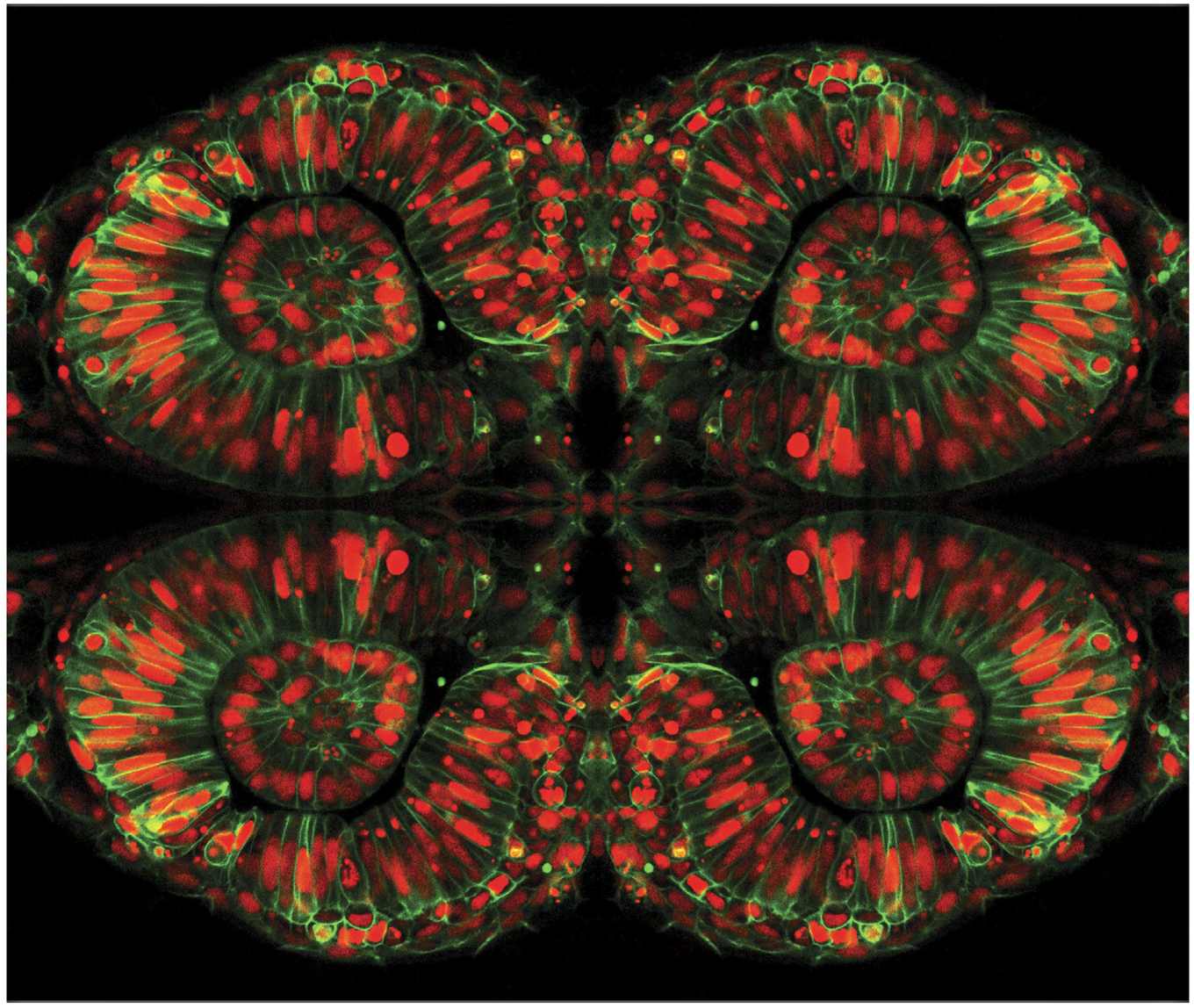
advantage to colonize distant territories both during embryonic development and during cancer progression, allowing cells to form different tissues and organs or distant metastasis, respectively.

We use mouse, chick and zebrafish as experimental models for loss or gain and function studies together with cultured cells and the analysis of samples from patients with the associated pathologies.

26 Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications
Personnel



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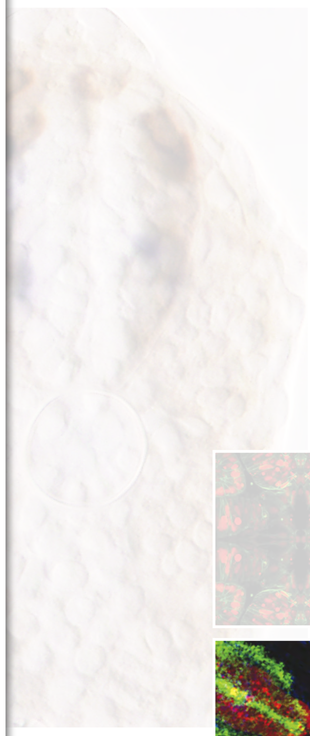

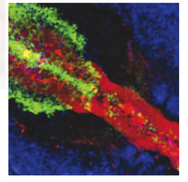

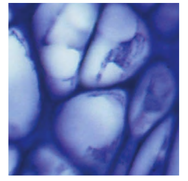

26 Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications
Personnel

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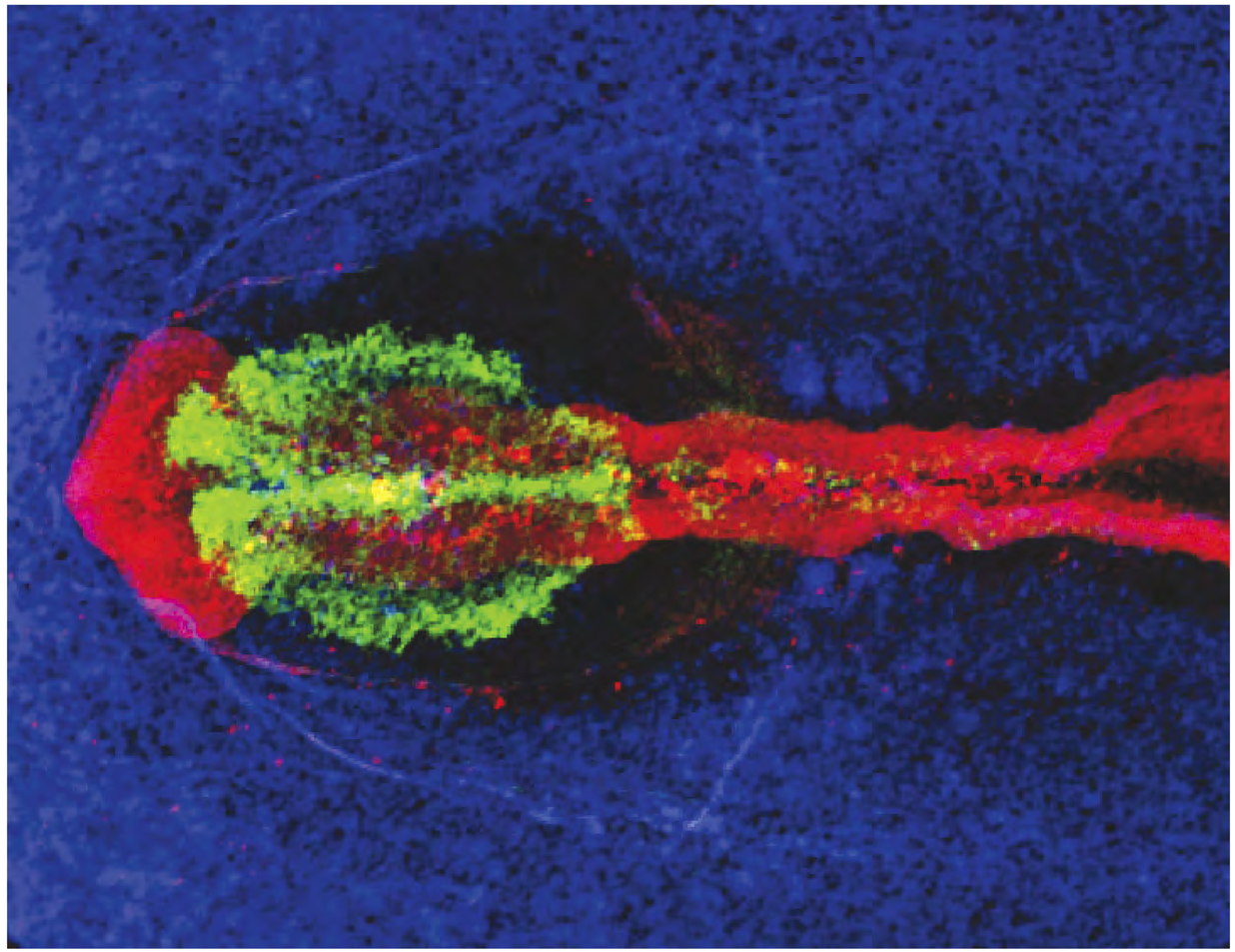
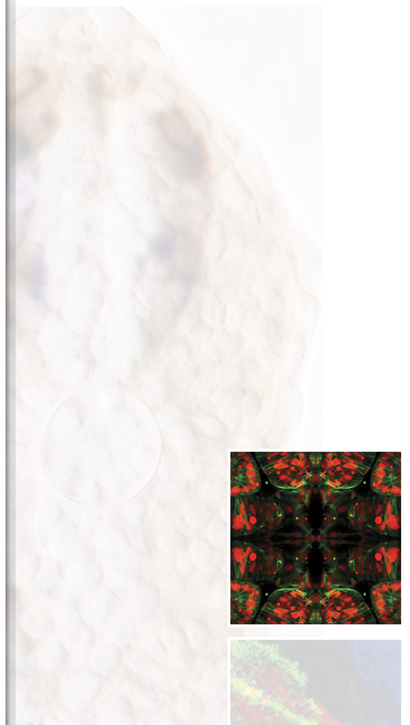
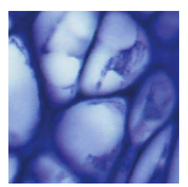


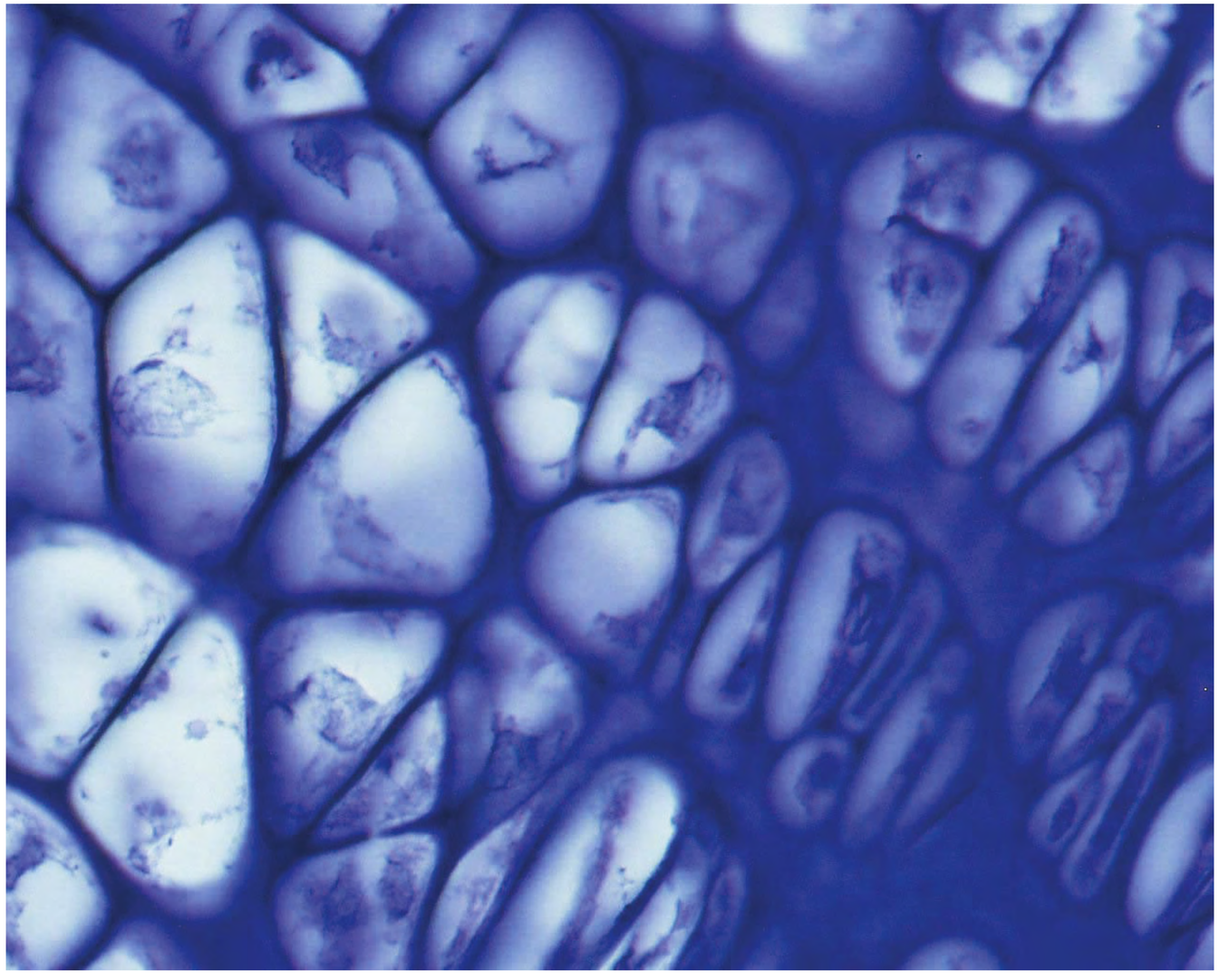




26 Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications
Personnel



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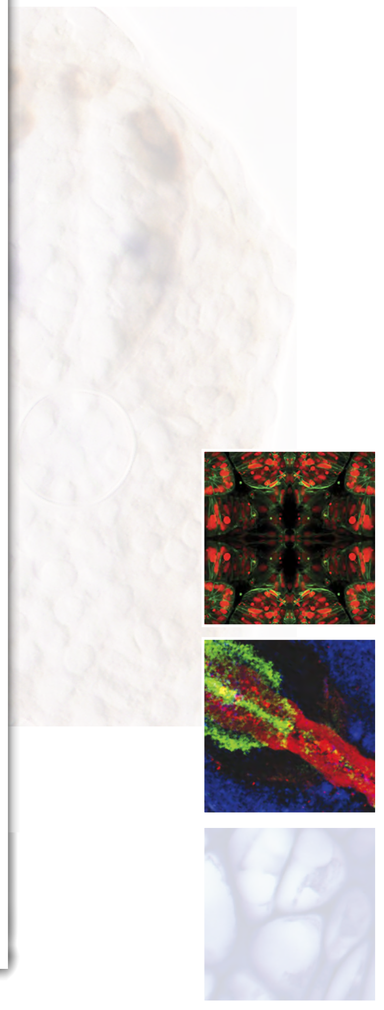


27 Neural circuit formation and remodeling

Beatriz Rico CSIC

Selected Publications
Personnel

Principal Investigator
Beatriz Rico

PhD Investigator
Isabel Del Pino (with Oscar Marín)
Cristina García Frigola (with Oscar Marín)

PhD Student
Emilia Favuzzi
Antonio Jesús Hinojosa
Ana Navarro

Technical Staff
Diana Baeza


BR


AN


DB


CGF

27 Neural circuit formation and remodeling

Beatriz Rico CSIC

Rico, B*., Beggs, H., Schahin, D., Kimes, N., Schmidt, A., Reichardt, LF*. (2004). Control of axonal branching and synapse formation by focal adhesion kinase. **Nature Neuroscience**, 7(10): 1059-1069. (* corresponding authors).

Sánchez-Huertas and Rico B*. BDNF/TrkB signaling controls the maturation of the GABAergic synapses via transcriptional regulation of GAD65. **Cerebral Cortex**. on line, August 25, doi:10-1093 (2010). * corresponding author.

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

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

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.

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 ne

28 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

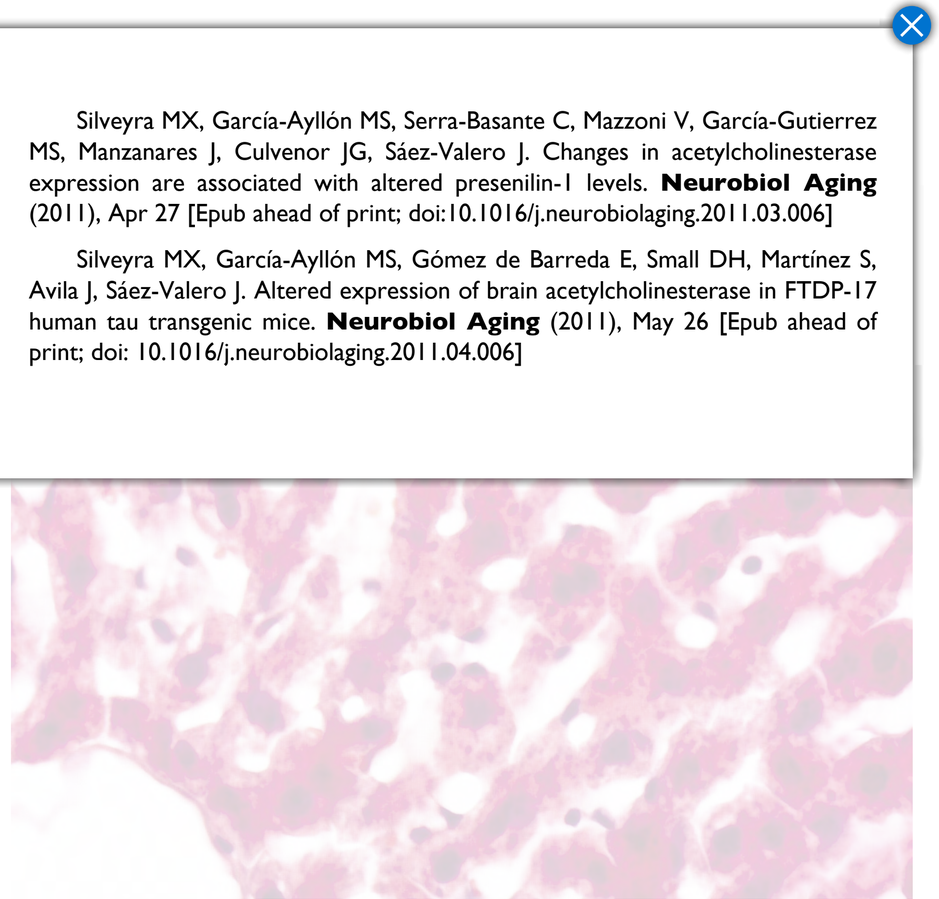
28 Altered molecular mechanism in Alzheimer's disease and dementia

Javier Sáez Valero UMH

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 pattern of the proteoglycan Reelin in AD. Reelin is a glycoprotein 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 signalling 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.



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. "Reelin expression and glycosylation patterns are altered in Alzheimer's disease." **Proc. Natl Acad. Sci.** USA. 103, 5573-5578 (2006)

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

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

Silveyra MX, García-Ayllón MS, Serra-Basante C, Mazzoni V, García-Gutierrez MS, Manzanares J, Culvenor JG, Sáez-Valero J. Changes in acetylcholinesterase expression are associated with altered presenilin-1 levels. **Neurobiol Aging** (2011), Apr 27 [Epub ahead of print; doi:10.1016/j.neurobiolaging.2011.03.006]

Silveyra MX, García-Ayllón MS, Gómez de Barreda E, Small DH, Martínez S, Avila J, Sáez-Valero J. Altered expression of brain acetylcholinesterase in FTDP-17 human tau transgenic mice. **Neurobiol Aging** (2011), May 26 [Epub ahead of print; doi: 10.1016/j.neurobiolaging.2011.04.006]

Biophysics and pharmacology of ionic channels

Francisco Sala UMH
Salvador Sala UMH

Principal Investigator
Francisco Sala
Salvador Sala

Technical Staff
José Mulet

JM

SS

FS

Biophysics and pharmacology of ionic channels

Francisco Sala UMH
Salvador Sala UMH

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 electrophysiological techniques described above.

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

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

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

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

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

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

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

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 β-strand β3 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.

30 Molecular neurogenetics

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Selected Publications
Personnel

Principal Investigator
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30 Molecular neurogenetics

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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.

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.

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.

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

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

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.

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

evolutionary conserved family of protein-kinases, which play several functions through brain development. We are focusing on its role in proliferation, neurogenesis, and neuronal differentiation. Mnb 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.

31 Cell signalling during neuronal migration

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31 Cell signalling during neuronal migration

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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.

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

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

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

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.

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.

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.

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.