INSTITUTO DE NEUROCIENCIAS

ANNUAL REPORT

2010

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INDEX

CSIC
Consejo Superior de Investigaciones Científicas

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

01 SALUTATION

JUAN LERMA : Director

This report covers just one year of activity at the Neurosciences Institute (IN), 2010, in contrast to previous reports which used to include two years. In addition, we join the campaign to minimize the use of paper launched by the institutions to which the IN is a part, and have adopted a purely digital format. In 2010, our Institute has continued to develop neuroscience research of outstanding quality in Spain. Over recent years, the IN has increased the number of components, reaching a relatively stable population. The review of scientific productivity indicates that we have achieved quality values higher than the national average and over other comparable centers in Europe.

In the last year, Elvira de la Peña has reached the status of tenured Assistant Professors from their previous contracted position. Emilio Geijo has been promoted to full professor, while Javier Morante, Ricardo Scott and Luis Miguel Valor have been awarded with a Ramón y Cajal long-term contract. In the field of personnel classification, we maintain a stable proportion of about 60% women and 40% men and over 20% of our personnel come from other countries.

In the scientific realm, an important milestone for the IN has been the beginning of its 2010-2013 action plan, which encloses the lines of research to be developed over four years. In this sense, the IN continues to make progress in both fundraising and productivity, following the path set in the previous strategic plan. Notable is that more than ¾ of the staff corresponds to contracts externally funded by grants obtained by IN researchers on a competitive basis. This determines that the scientific output and international impact of IN continue to increase, reflecting the high dedication of its staff. This past year has been full of relevant findings, widely fulfilling the mission of generating significant knowledge around the brain and its mechanisms. We are sure that the reader of this memory will be interested to review the selection of these milestones listed in a specific section.

The comparative of 2000-03 and 2007-10 periods, shows the evolution of IN scientific impact on an international scientific landscape. While we have increased the number of articles in more than 60%, their impact, as measured by citations in the period, has been more than doubled.

Indeed, we feel proud of this past year, in which several IN members have achieved significant recognition to their research. On the one hand, Salvador Martinez received the Research Award from the Foundation Diogenes, Carlos Belmonte was reelected as the President of IBRO and appointed member of the Royal Academy of Medicine of Murcia and honorary member of the Barraquer Institute and the undersigned was elected to the Academia Europaea (The Academy of Europe) and received the Highest Academic Distinction for Lifetime Achievements from the Universidad Mayor de San Marcos in Lima. Angela Nieto was appointed as president of the Spanish Society of Developmental Biology, president of the Academic Council of the Universidad Internacional Menéndez Pelayo (UIMP), Spanish delegate and Vicechair of European Molecular Biology Laboratory and Conference (EMBL-C) and a member of the EMBO Publications Advisory Board. In addition, Oscar Marin was elected to the editorial board of Science and Beatriz Rico entered the prestigious EMBO Young Investigator Program (YIP).

Science and neuroscience in particular are called to change the way of social thinking and behavior

With this, the IN and its members strengthen its international presence.

In 2010 we started our action plan 2010-2013, which was assessed by an international panel of experts and approved with great remarks. We started new lines of research that define the IN's activity for the next 4 years. In this way, we intend to pursue incorporation of most modern techniques that enable our researchers to conduct experiments under the same conditions of our European or American colleagues. In this regard, in 2010 we have incorporated state-of-the-art techniques such as magnetic resonance imaging (fMRI) and fluorescence-assisted cell sorting (FACS). This represents an investment in scientific equipment of € 2.2 million, achieved thanks to the support received from MICINN, the Generalitat Valenciana, CSIC and UMH. These technologies will allow us to image the working brain with a spatial resolution of tenths of a millimeter, and secondly, to select and isolate cells according to the expression of specific markers. This technique will be crucial in the search for molecules involved in tumor development, neuropsychiatric and degenerative diseases as well as in the design of cellular therapies.

Science and neuroscience in particular are called to change the way of social thinking and behavior. It is destined to change human attitudes and habits radically. I thank everyone at the IN, in one or another position, for their effort this latter year for contributing to the INs' mission. They have definitively been instrumental in positioning the IN at a high scientific level. I, finally, also thank the Institutions that we belong to for their continuing support of our research.

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.

The founding Director of the IN, Carlos Belmonte, retired in 2007, when the present Director, Juan Lerma was elected by the Council of the Institute.

03 WHERE WE ARE

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

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

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

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

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

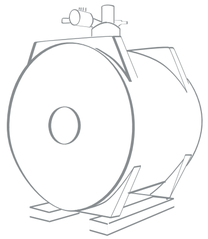
There is a second level of organization based on research lines. These lines constitute a horizontal organisation grouping members of different research units around more specific research subjects. This horizontal-vertical structure facilitates greater interactions between institute members, through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

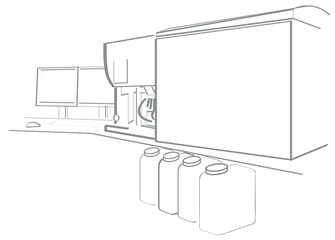
The IN undertakes an important training activity through its International PhD Programme in Neuroscience, which has been awarded with a mention as "Programme of Excellence" by the Ministry of Education. It also strives to be a centre of reference in terms of both national and international collaborations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

The years following the relocation of the IN to its new building have seen an important period of expansion, resulting in the IN becoming the largest Spanish institute monographically dedicated to the study of the nervous system and its pathologies. The significant increase in personnel has been in both young to senior researchers, several of them of recognized international prestige. The IN currently has 41 tenured researchers (22 from the UMH and 19 from the CSIC), 6 non-tenure scientists, 144 doctoral and postdoctoral researchers and 105 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 2010 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 has begun implementing 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

Discovery that TRPM8 ion channel is essential for excitability and thermosensitivity of corneal cold receptors and for maintaining normal basal secretion of tears.
Parra et al., Nature Medicine 2010.

Identified neuropathological processes associated with malfunctions in the intracellular signaling pathway triggered by CREB
Valor et al. Cell Death Differ 2010

Demonstration that mice deficient in both protein CBP and its paralogue p300 acquire phenotypes reminiscent of Rubinstein-Taybi syndrome symptoms
Viosca et al. Neurobiol Dis.2010

Demostration of FAK Focal Adhesion Kinase as a regulator of axons refinement in response to Sema3A by regulating the subcellular localization of paxillin adhesion molecule in the growth cone.
Rodríguez-Chacón et al., Cell Molecular Neuroscience, 2010

Demonstration of a new molecular mechanism whereby BDNF/TrkB regulates the formation and functioning of inhibitory circuits.
Sanchez-Huertas and Rico, Cerebral Cortex, 2010.

Developed a new application of the neural information theory to analyze in vivo how sensory signals contained in different brain rhythms interact within a neuron.
Alenda et al., J Neuroscience, 2100.

Description of the potential biological function of alpha-synuclein, a molecule associated with neurodegenerative diseases, to interfere in the regulation of the secretory response mediated by SNARE proteins.
Darios et al., EMBO Reports, 2010.

Identification of a histone demethylase as a member of the Notch repressor complex in development and cancer.
Liefke Ret al., Genes Dev. 2010

First functional evaluation of sensory nerves regenerating into artificial corneal substitutes.
McLaughlin et al., Biomaterials 2010).

Discovered a new signaling pathway that regulates the formation of GABAergic synapses, representing the first demonstration of a ligand-receptor system that control the development of inhibitory circuits.
Fazzari et al., Nature, 2010.

Evidenced that the loss of CBP specifically in forebrain neurons and the consequent reduction in the level of acetylation of histones leads to neural defects in memory and activity-dependent gene expression, dissociating mental retardation from anatomical defects observed in this syndrome.
Valor et al. J. Neuroscience, 2011

Reported that the transcription factor Zic2 controls the expression of the serotonin transporter, which is essential for the eye-specific refinement of the optic fibers and for establishing binocular vision.
(García-Frigola and Herrera, EMBO Journal, 2010)

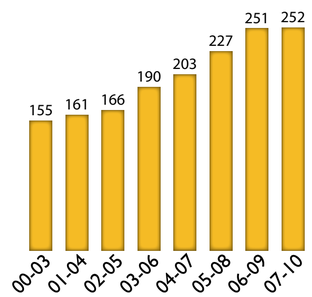
Established the contribution of different ion channels to the thermal sensitivity of the corneal recipient eye.
(Madrid et al. J. Neuroscience, 2010)

Discovering of a new cell type in the developing brain of higher mammals, named Intermediate Radial Glia Cell, which is shown to play fundamental roles in the expansion and folding of the cerebral cortex..
Reillo et al., Cerebral Cortex, 2010

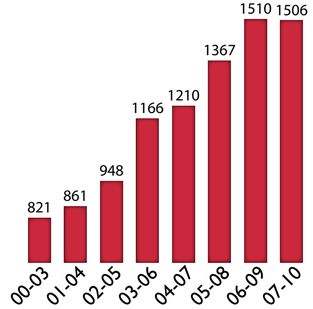
07 THE INSTITUTE IN NUMBERS

PUBLICATIONS AND IMPACT

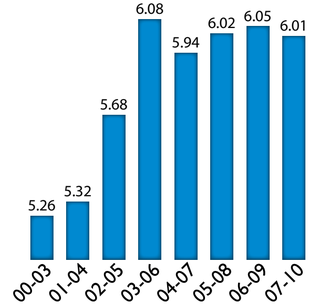
Number of Published Articles



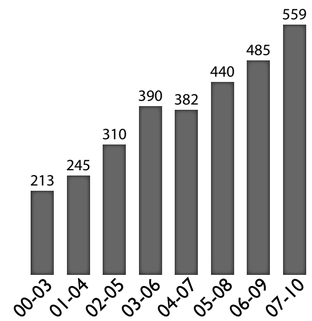
Cumulated Impact Factor



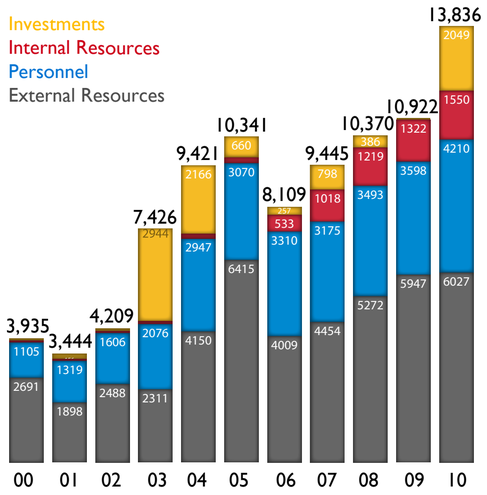
Average Impact Factor



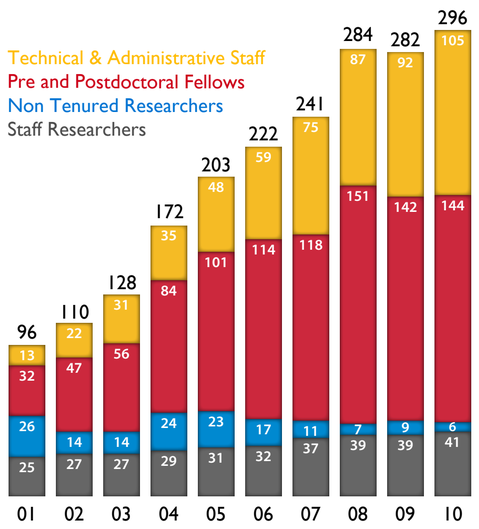
Citations



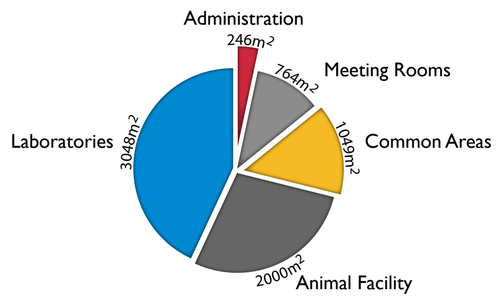
BUDGET GROWTH IN THOUSANDS OF EUROS



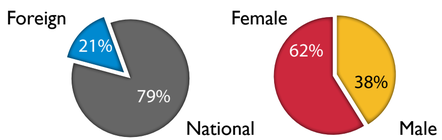
PERSONNEL BY CATEGORY



SURFACE DISTRIBUTION



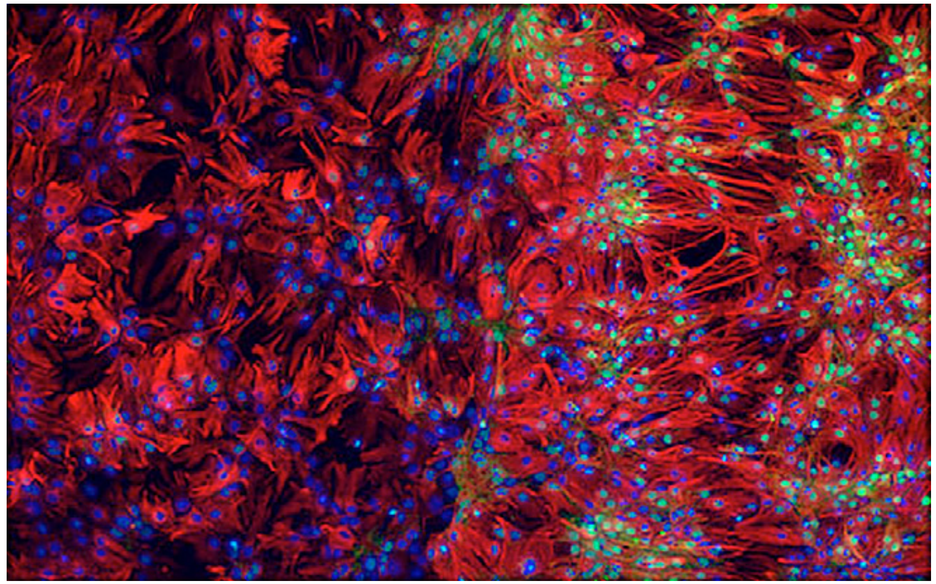
PERSONNEL BY ORIGIN & GENDER



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 a molecular approach. Towards this end, we use biochemistry, biophysics, pharmacology and molecular genetics and biology techniques (frequently combined with non molecular techniques such as electrophysiology or behavior). 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.

09 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 non-noxious and noxious thermal, mechanical and chemical stimuli by mammalian peripheral sensory neurons. We are particularly interested in the role played by different classes of ion channels in modulating the excitability of 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

1 **PHYSIOLOGY OF THE PREFRONTAL CORTEX & CAROTID BODY**
Laura Almaraz, Emilio Geijo

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

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

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

5 **THYROID HORMONES AND ORGANIZATION OF THE CEREBRAL CORTEX**
Pere Berbel

6 **NEUROGENESIS AND CORTICAL EXPANSION**
Víctor Borrell

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

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

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

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

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

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

13 **CORTICAL DEVELOPMENT**
Alfonso Fairén

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

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

16 **DEVELOPMENTAL NEUROGENETICS**
Luis García-Alonso

17 **MECHANOTRANSDUCTION IN MAMMALS**
Ana Gomis

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

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

20 **SYNAPTIC PHYSIOLOGY**
Juan Lerma

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

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

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

24 **NEURONAL SPECIFICATION AND MIGRATION**
Oscar Marín

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

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

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

28 **NEURAL PLASTICITY AND SYNAPTOGENESIS**
Beatriz Rico

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

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

31 **MOLECULAR NEUROGENETICS**
Francisco Tejedor

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

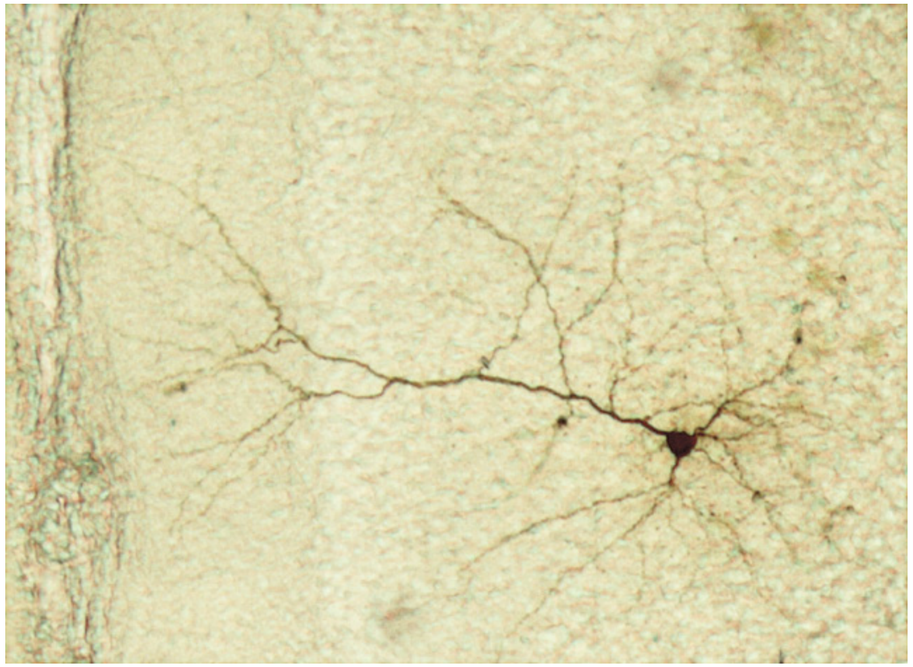
01 Physiology of the prefrontal cortex

Laura Almaraz UMH
Emilio Geijo UMH

Selected Publications
Personnel

Our group is interested in the physiology of the nervous system. We are developing two research lines:

The study of the basic physiological mechanisms of the cortical local microcircuits, in particular of the prefrontal cortex; This cortical region is implicated in cognitive functions and very specially in short term memory or working memory; also, it is 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 videomicroscopy and Nomarski optics; in these neurons we record membrane potential and currents and synaptic responses. The specific objectives of this line of 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 latter line of weork is carried out in collaboration with Dr. Salvador Martínez (Institute of Neurosciences).



In addition to the above lines 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: the study of the mechanisms of generation and the diagnostic value of the F-wave, which is a late component of the human electromyogram and that can be used to estimate some aspects of the excitability of spinal motor neurons.

02 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.

03 Transcriptional control of neural plasticity

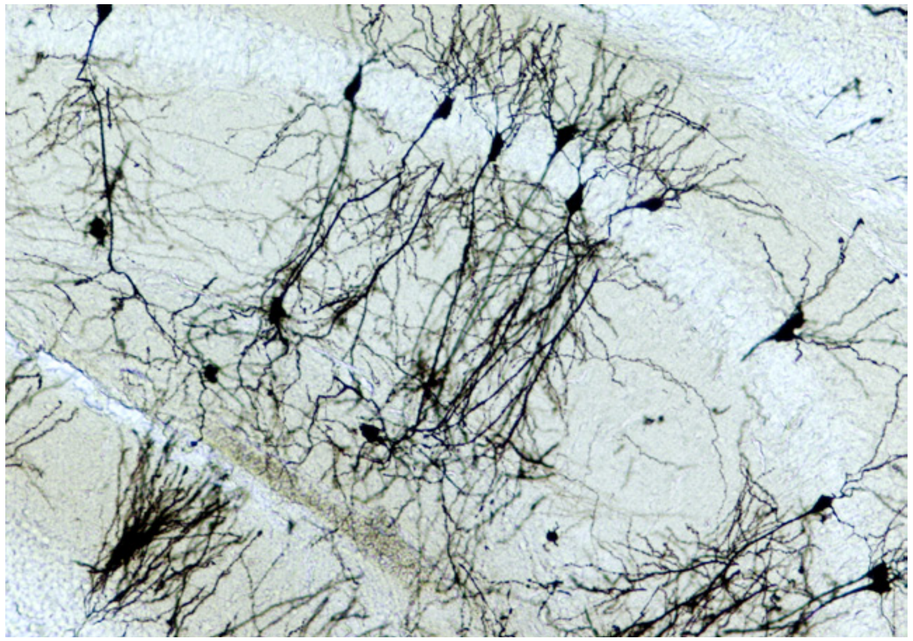
Angel Barco CSIC

Selected Publications
Personnel

We are interested in the molecular mechanisms underlying learning and memory storage, more precisely in their transcriptional control. We also investigate how the malfunction of these molecular cascades may lead to pathological situation 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 has 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 behavior. We also use genechips, chromatin immunoprecipitation and other techniques for the global analysis of gene expression to identify candidate genes important in these processes.

Chromatin remodeling and neural 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 marking of the chromatin that might well underlie the long-term transcriptional effects in specific loci required for the changes in gene expression underlying long-lasting modifications of synaptic function and behavior. We are interested in exploring the contribution of histone modifications to the perpetuation of synaptic changes and memory stability, both in the healthy brain and in mouse model for different neurological conditions, such as Huntington disease and diverse mental retardation syndromes.



04 Sensory transduction and nociception

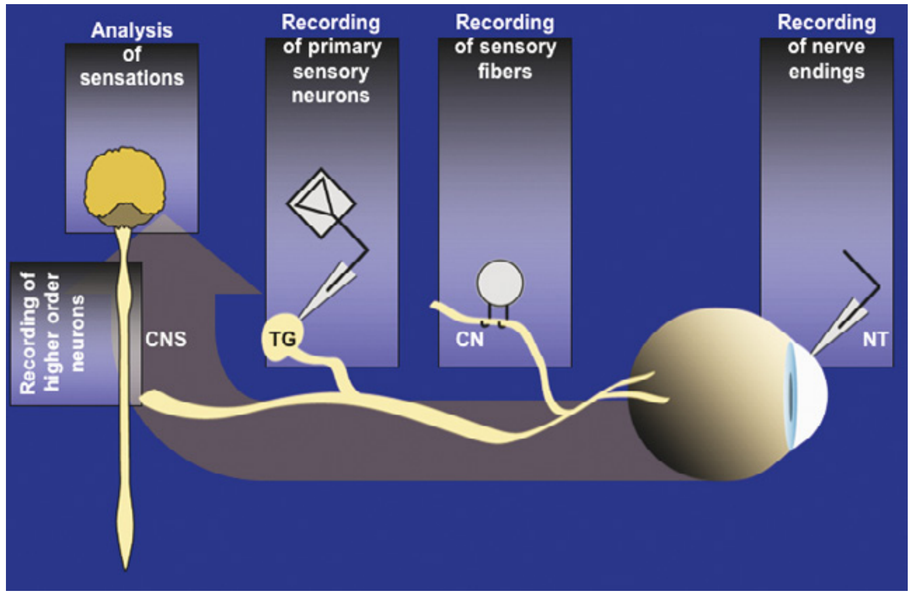
Carlos Belmonte UMH
Roberto Gallego UMH
Félix Viana CSIC

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.

05 Thyroid hormones and organization of the cerebral cortex

Pere Berbel UMH

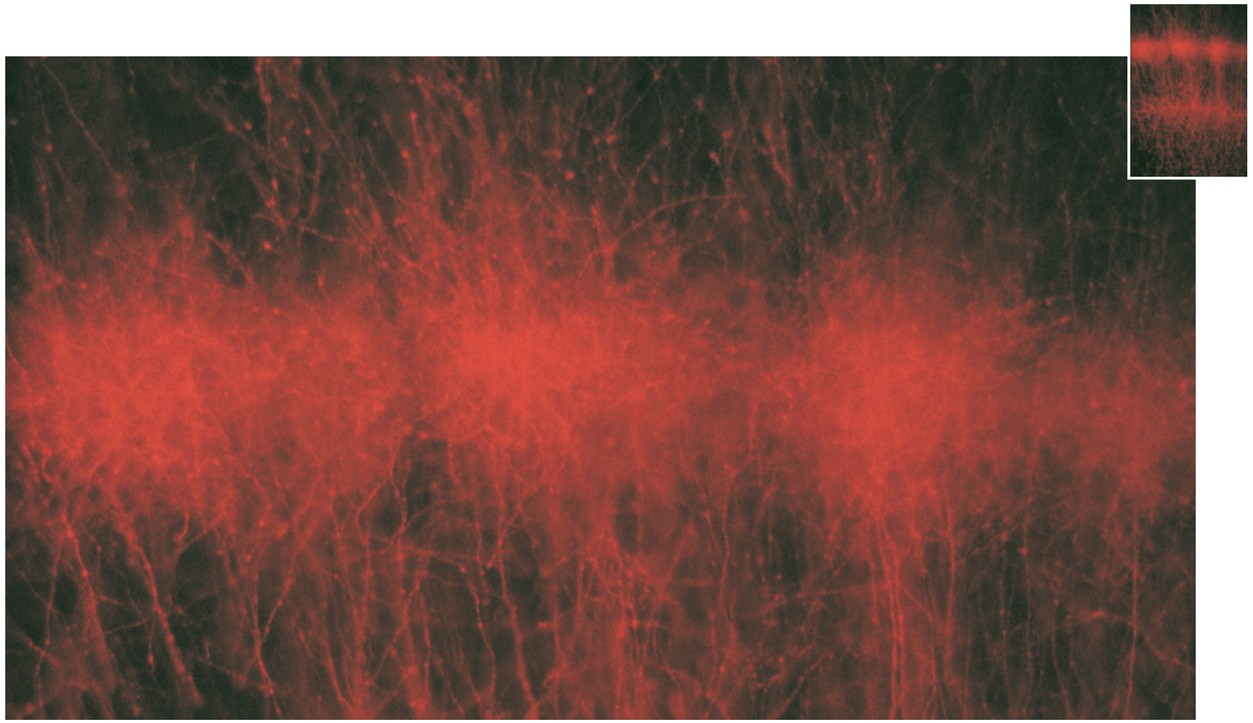
Selected Publications
Personnel

Maternal, foetal and neonatal thyroid hormones are fundamental for the development of the CNS, particularly that of the cerebral cortex. In humans, their deficit can produce severe neurological alterations such as hearing loss and speech abnormalities, motor alterations and mental retardation.

Using experimental models in animals and epidemiological studies in humans, we are studying behavioural and structural alterations produced by maternal, foetal and neonatal thyroid hormone deficiency, critical periods of their action during pregnancy and postnatal development, and the possibility of recovery following an adequate treatment.

We have observed that during pregnancy, low levels of thyroid hormones, produced by a low iodine diet or by goitrogen treatment, cause irreversible alterations in the CNS of their progeny, such as abnormal neuronal migration during corticogenesis and impaired maturation of connections. This deficiency can be not only severe and chronic, as observed in cretinism, but also milder as in maternal hypothyroxinemia which could be considered non-pathologic for non-pregnant women.

In developed countries such as Italy, the Netherlands, USA and Canada, maternal hypothyroxinemia affects 1 out of 10-20 children, at least half of them will have an IQ of 15 points under the normal mean, and will suffer severe neurological alterations such as ADHD. Our epidemiological data show that in Alicante the number of affected children is even higher. Children of hypothyroxinemic mothers will have impaired intellectual skills because maternal thyroid hormones levels were not assessed during pregnancy. In almost all the cases, low thyroid hormones levels can be corrected by an adequate iodine intake. An abnormal hormonal condition similar to the one found in foetuses from severe hypothyroxinemic mothers occurs in prematurely born children that in our country accounts for 10% of all births.



06 Neurogenesis and cortical expansion

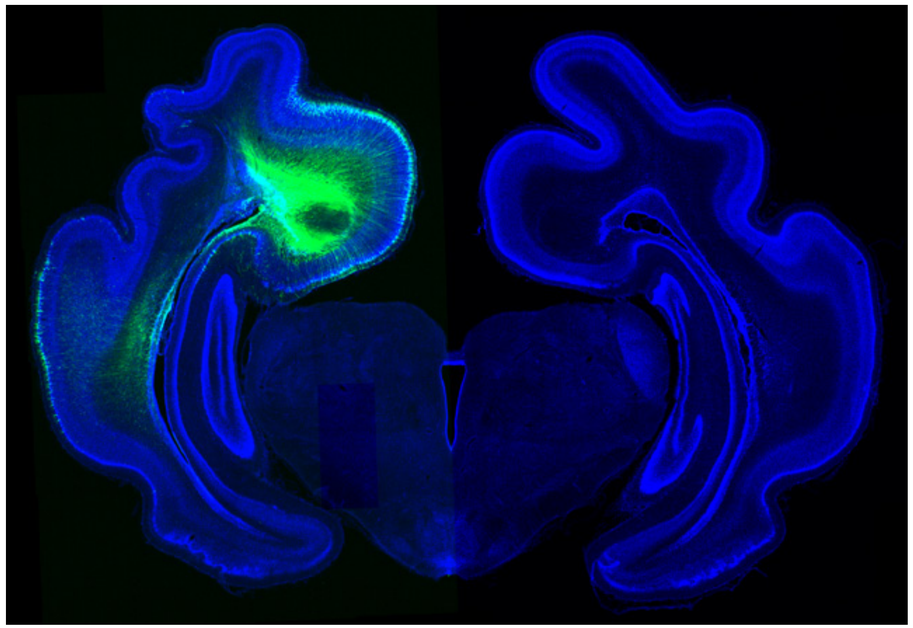
Víctor Borrell CSIC

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 neuron migration or of cortical folding.

We are interested in the identification and analysis of the basic mechanisms involved in the normal expansion and folding of the cerebral cortex in higher mammals. 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 of Cajal-Retzius cells and intermediate progenitors in the tangential vs. radial expansion of the cerebral cortex, and in the formation of folds and fissures at stereotypic locations in the cerebral cortex during development.



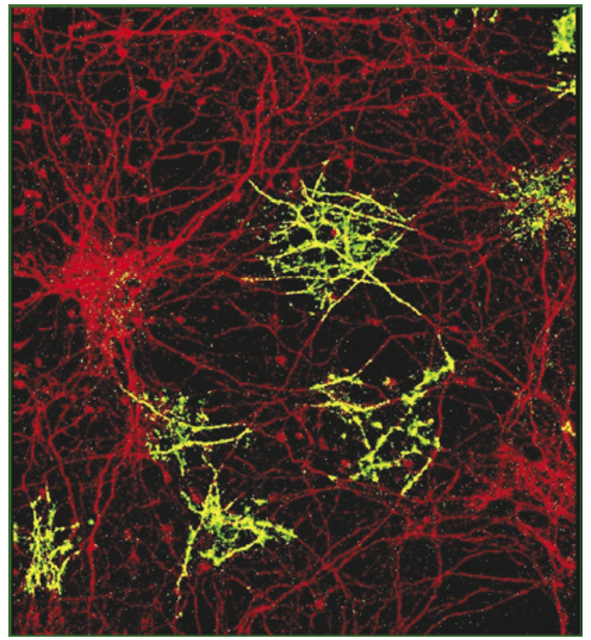
07 Molecular control of axonal myelination

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 signalling 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.



08 Plasticity of brain networks

Santiago Canals Gamoneda CSIC

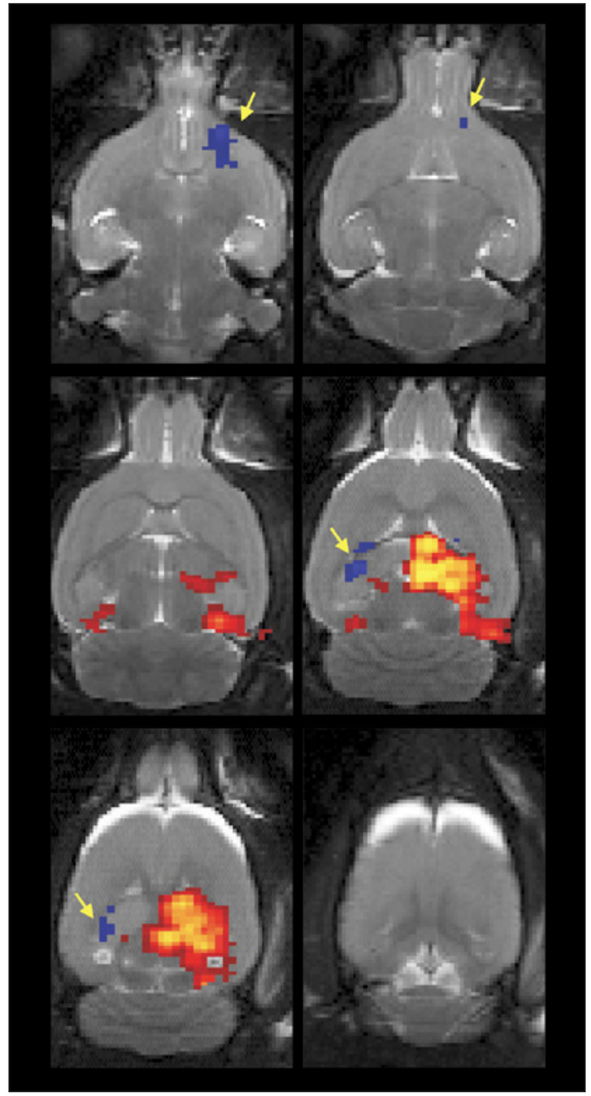
Selected Publications
Personnel

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.



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

Ana Carmena CSIC

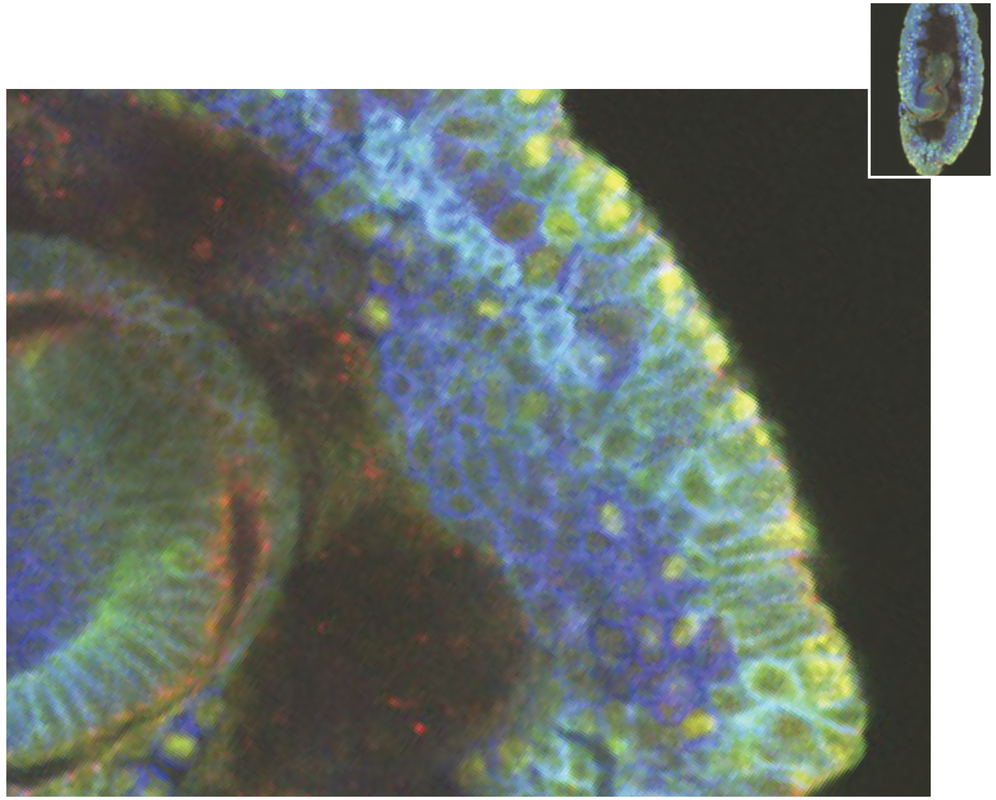
Selected Publications
Personnel

During the development of the nervous system a great diversity of neuronal types is generated. Indeed, the human brain has more than 100.000 millions of neurons, most of them specified during the embryonic development. Unraveling 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 cellular diversity. This will allow us to discover the functional signaling networks established within the cell and the key nodes within the networks required for their formation and regulation. In this context, PDZ domain-containing proteins (PSD-95, Dlg, ZO-1) have a special interest for us. PDZ proteins are usually associated to the cell membrane at particular submembrane 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 points of cross-communication between signaling pathways.

Our group analyzes the function of PDZ proteins, including the PDZ protein Canoe/AF-6, during fundamental biological processes for the generation of cellular identities, such as asymmetric cell divisions and morphogenesis. To implement this project, we use a multidisciplinary approach that combines different techniques of Genetics,Cellular Biology, Biochemistry and Molecular Biology. The embryonic 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.



10 Molecular neurobiology of neuronal nicotinic receptors

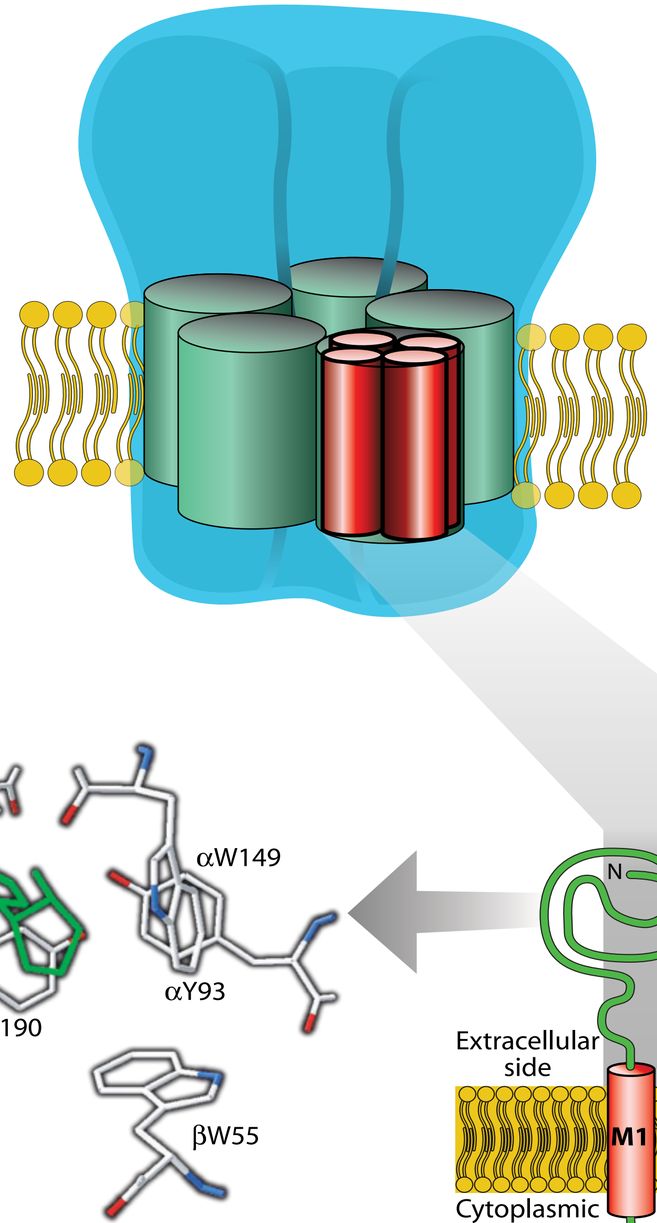
Manuel Criado UMH

The nicotinic acetylcholine receptor is widely distributed in the central and peripheral nervous systems. Important functions and pathologies specific 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.



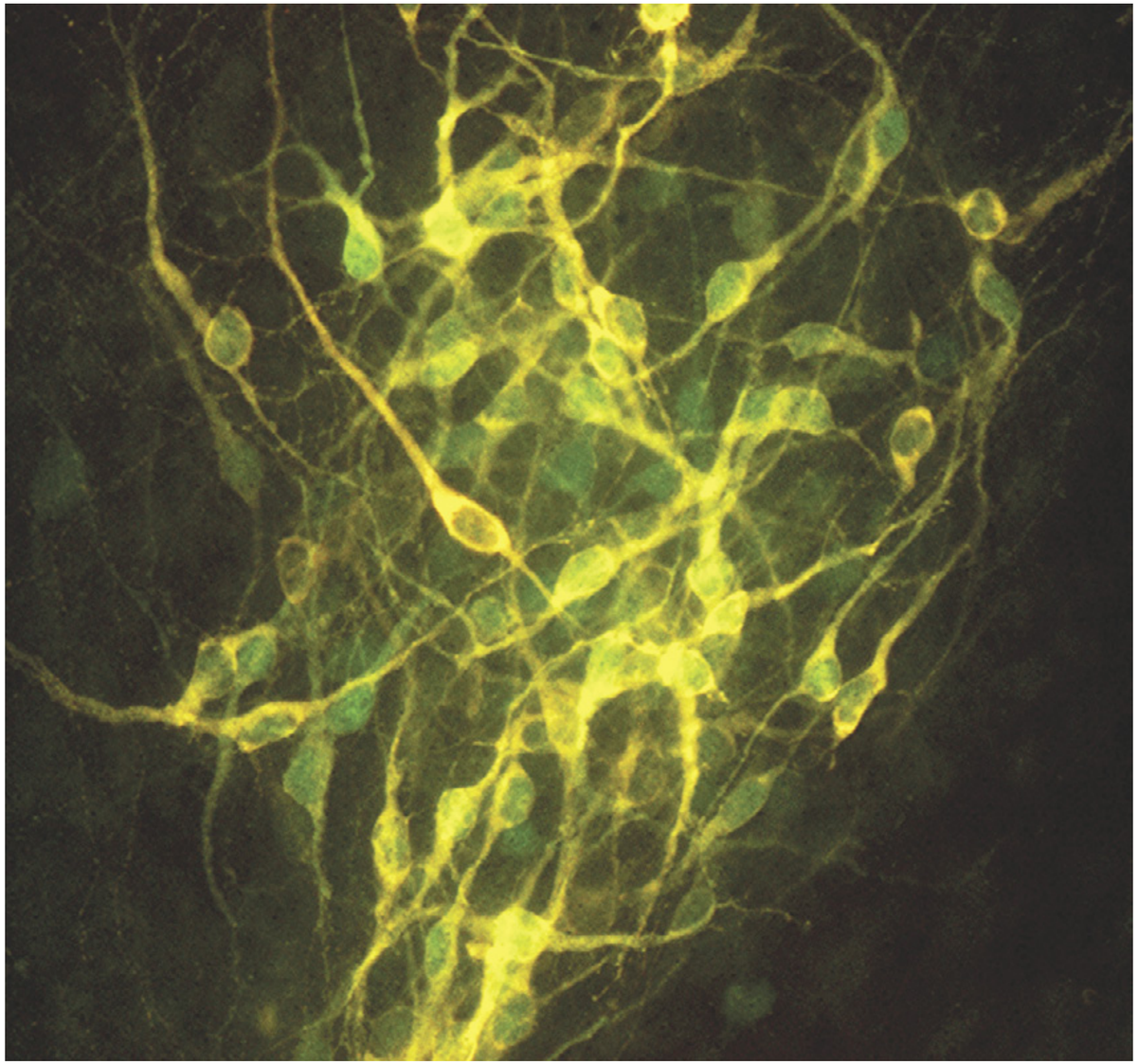
11 Cellular and conductual neuroscience

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.



12 Mechanisms of growth control and cancer in Drosophila

Maria Domínguez CSIC

Selected Publications
Personnel

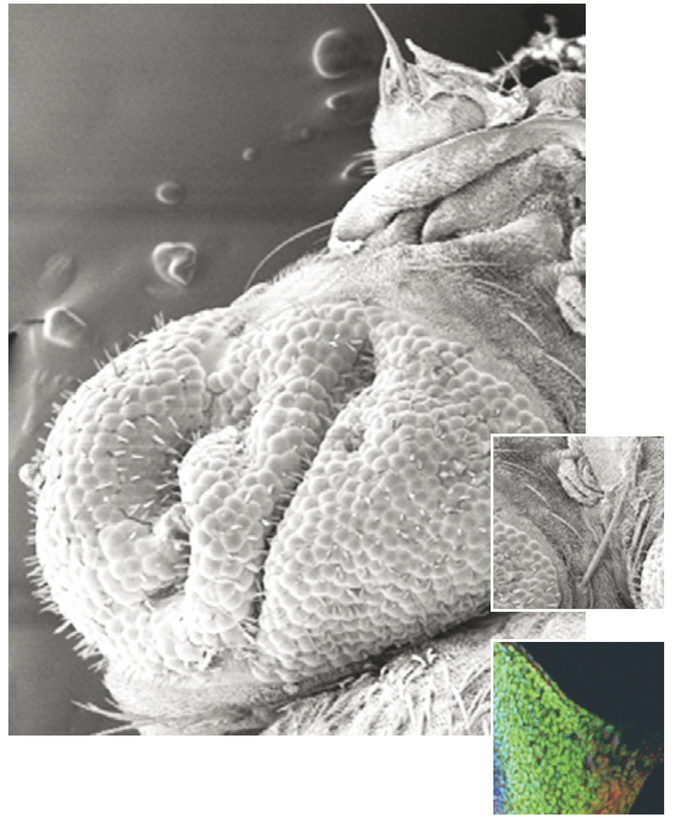
Our studies are focused on four research projects:

Control of growth and tumorigenesis using Drosophila eye: 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: In the past few years, 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 and patterning 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. 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.

Genetic screens for novel tumour-inducing genes: Over six years ago, we started two 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 recent publications). These included two novel epigenetic repressors, Pipsqueak and Lola, that when coupled with Notch hyperactivation, 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 resistence of T-cell acute lymphoblastic leukemic cells to inhibitors of the Notch pathway. All together, 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.

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 are using genetic, molecular and cellular methods to study the steps and key genes involved in the transformation of normal healthy cells into cancerous cells capable of metastasing.



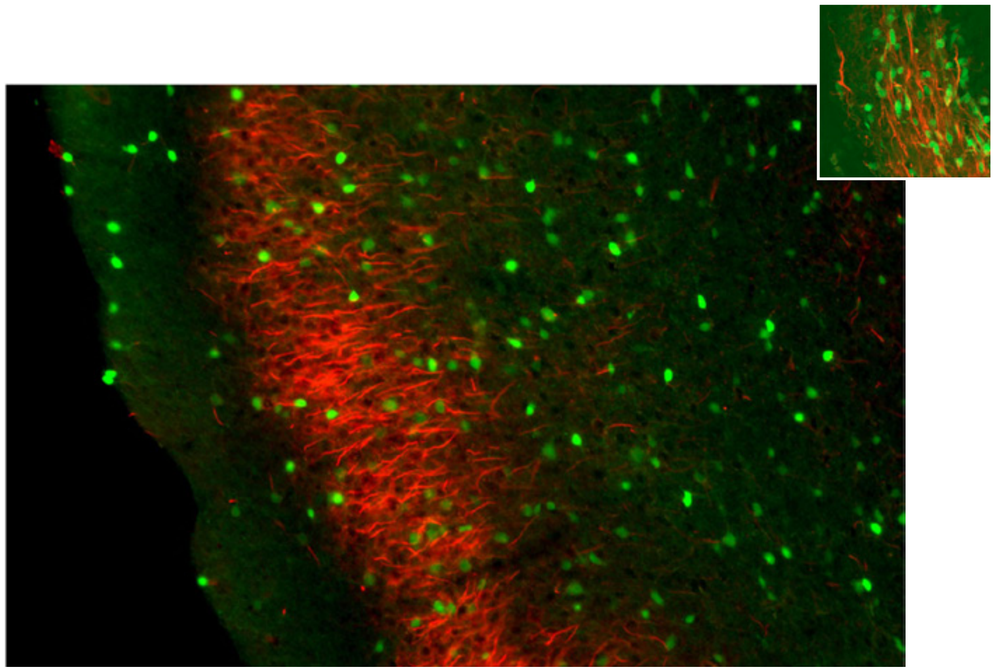
13 Cortical development

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.



14 Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH

Selected Publications
Personnel

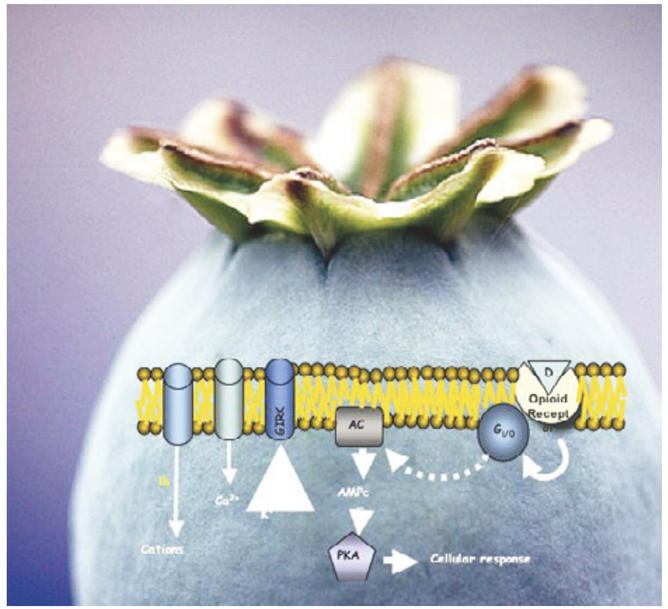
The improvement in the benefit–risk ratio for analgesic therapies is a relevant issue. Opioids are still the most potent and prescribed analgesic drugs. However, their clinical and non-clinical uses still have serious problems such as variability in the analgesic response, tolerance, dependence, addiction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



15 Ocular Neurobiology

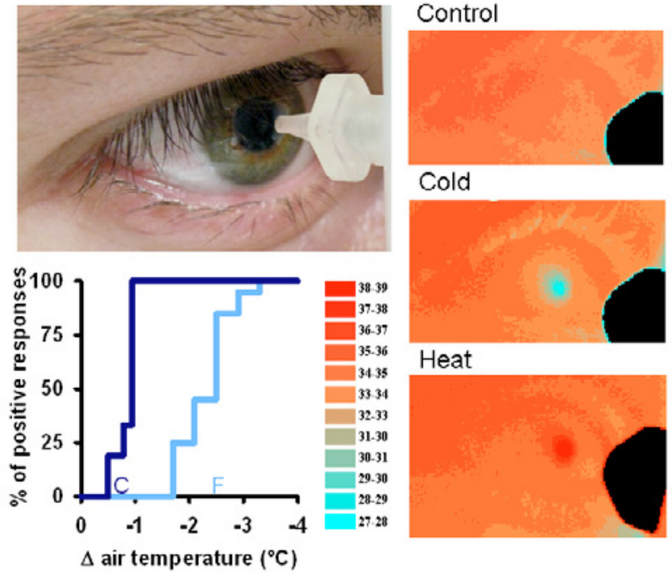
Juana Gallar UMH
Mª Carmen Acosta UMH

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 (analyzing 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 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 centers 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 discomfort and pain subsequent to nerve lesion.



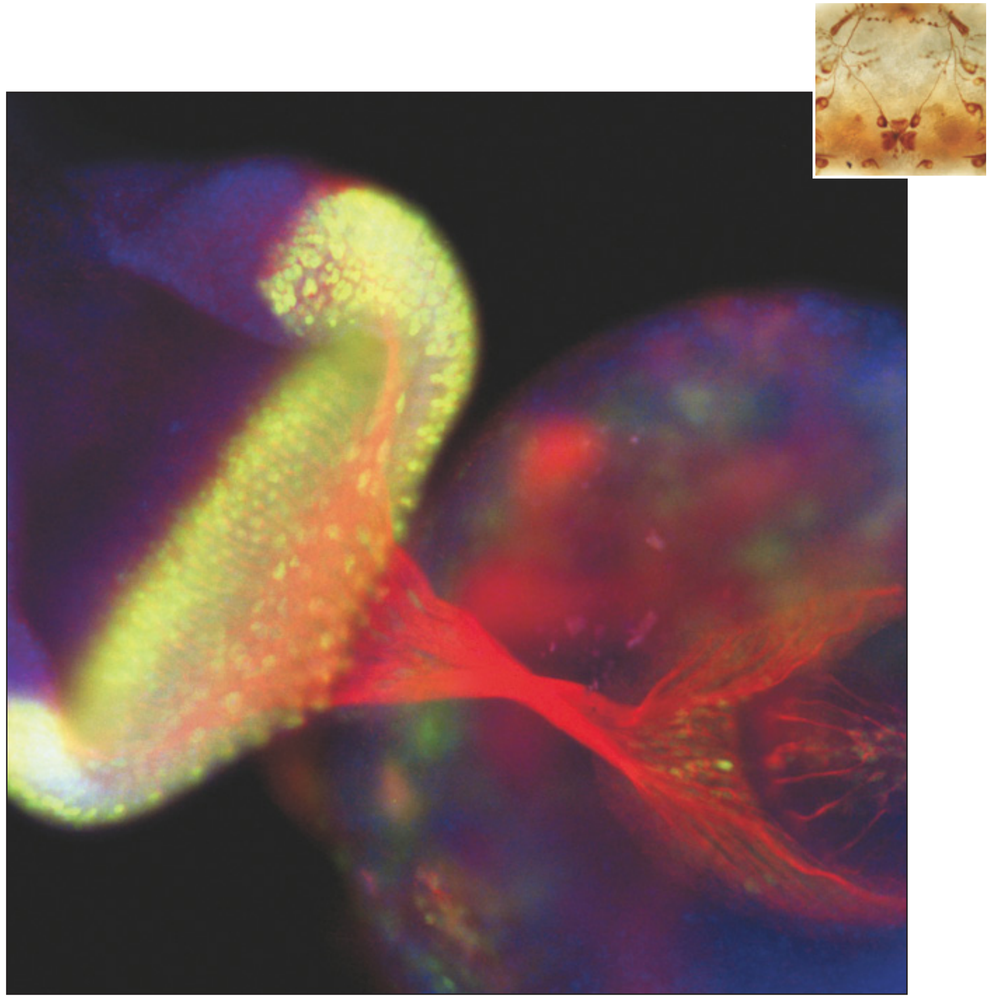
16 Developmental Neurogenetics

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 use *Drosophila* as transgenic model organism to study Reelin function, a vertebrate cell communication protein that was lost during invertebrate evolution.



17 Mechanotransduction in mammals

Ana Gomis CSIC

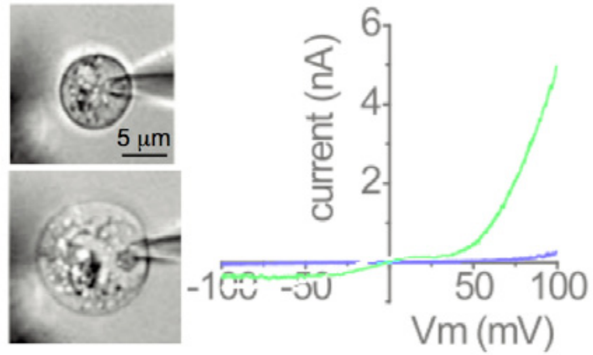
Selected Publications
Personnel

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.



18 Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH

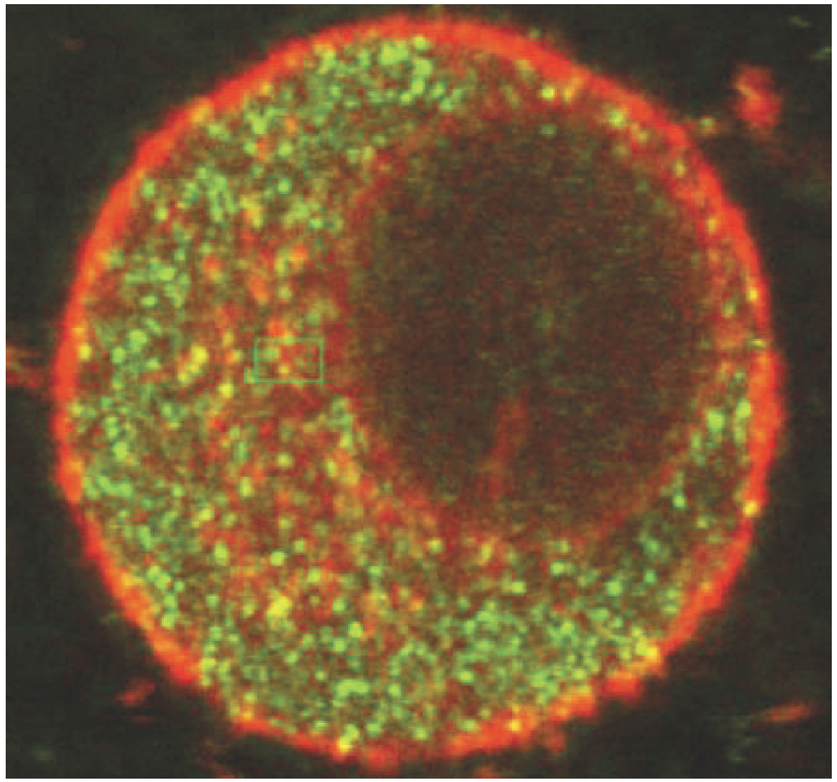
Selected Publications
Personnel

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.



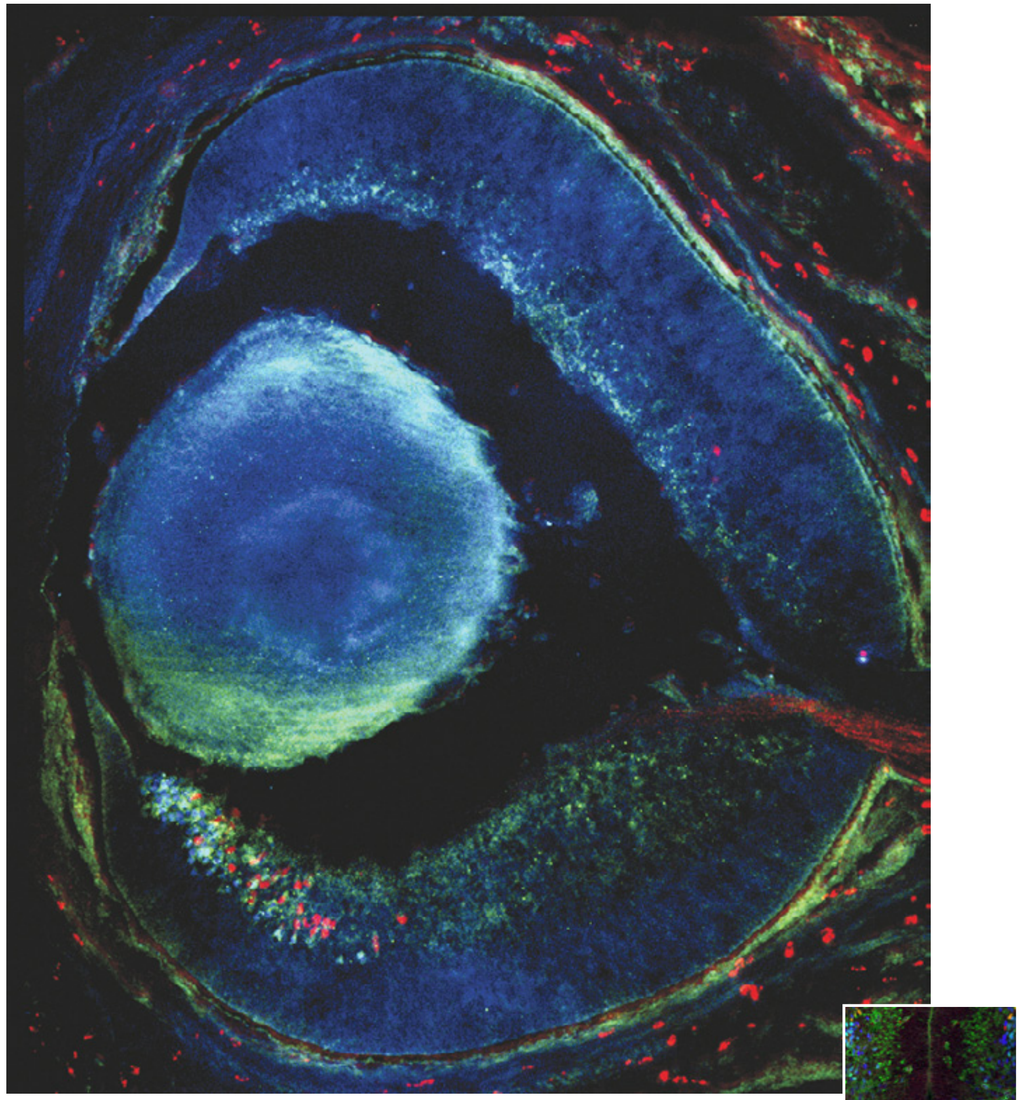
19 Development and assembly of bilateral neural circuits

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 to pathological consequences in vision or motor coordination for instance.

We use the development of the mammalian visual system as a model to understand the molecular mechanisms that generate retinal axon divergence at the midline as well as the assembly of bilateral circuits at the target tissues. We then investigate whether molecules and mechanisms newly identified in the visual system play similar functions in other bilateral pathways of the CNS such as the spinal cord.



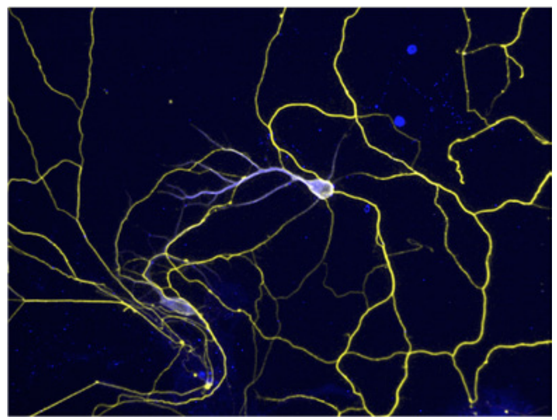
20 Synaptic physiology

Juan Lerma CSIC

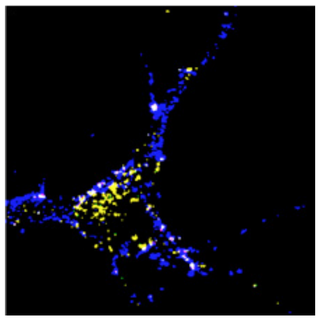
Selected Publications
Personnel

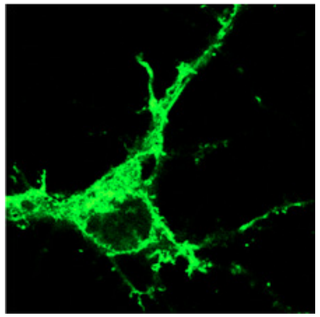
Neurons communicate with each other by means of releasing neuroactive substances that activate specific proteins situated at the postsynaptic membrane. This is a finely regulated process on which the correct performance of our brain depends, which is to say ourselves. One of the current goals of modern 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. We have identified already several proteins fulfilling this role. One of them is SNAP25, which was a surprise since this protein is well known to mediate the transmitter release process. The regulation of receptors by interacting proteins provide novel strategies to influence receptor function in an exquisite way and promote the idea that they may constitute an avenue to develop new drug targets to control excitability diseases, such as epilepsy.





21 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications
Personnel

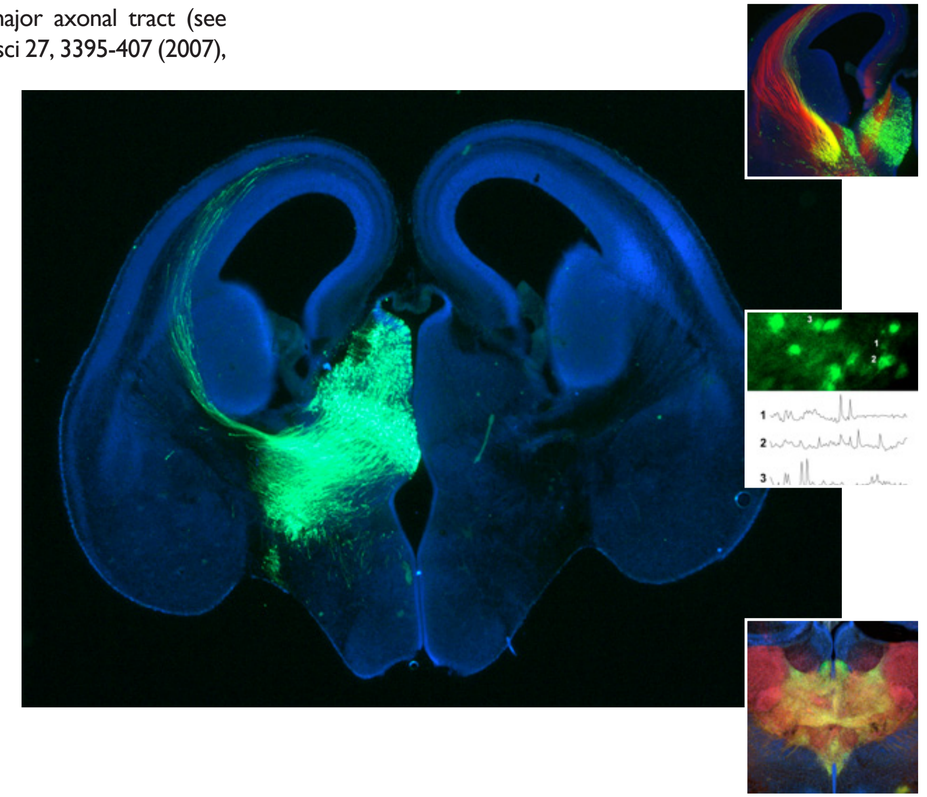
Our research team runs several related projects studying the cellular and molecular mechanisms involved in the development of axonal connections in the brain. In particular, our aim is to uncover the principles underlying thalamocortical axonal wiring, maintenance and ultimately the rewiring of connections,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



22 Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

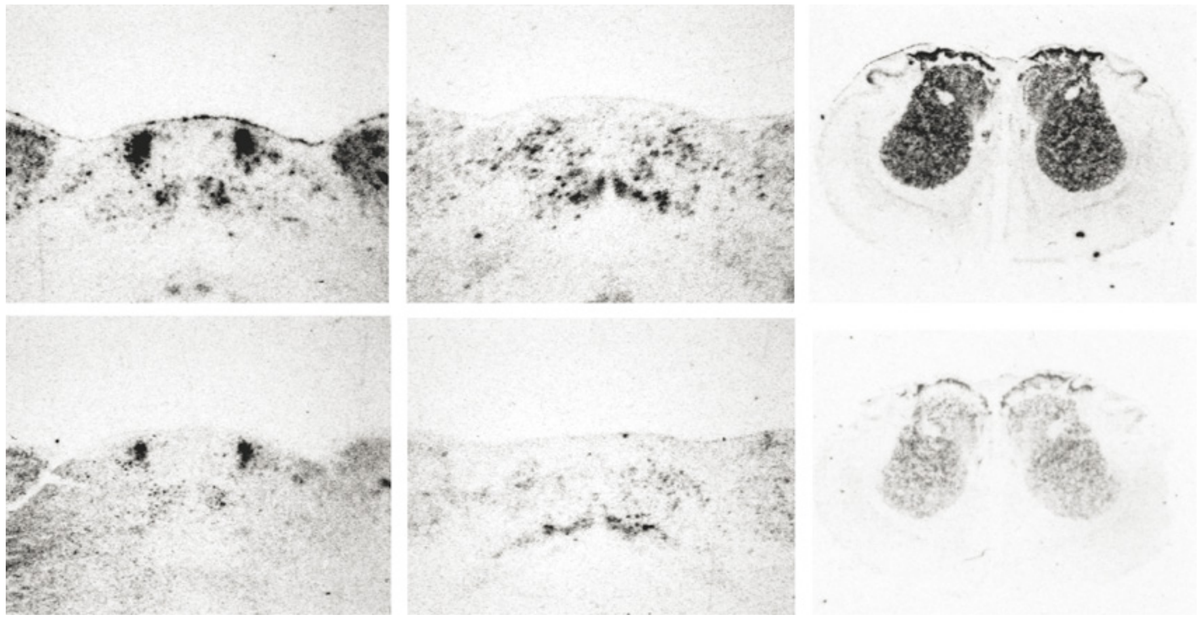
Selected Publications
Personnel

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.



23 Dynamics and plasticity of cortical sensory responses

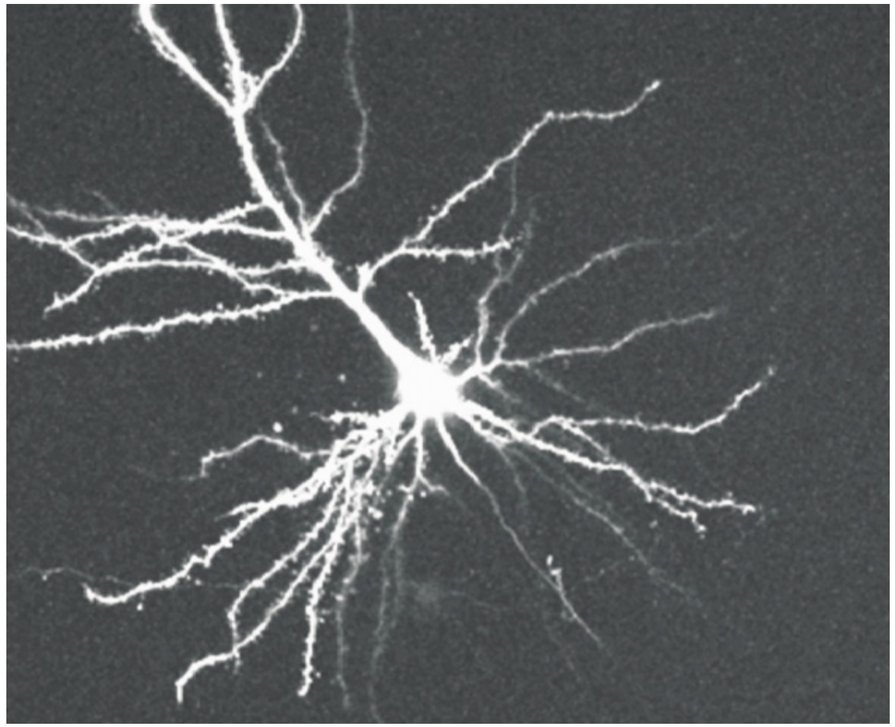
Miguel Maravall CSIC

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.



24 Neuronal specification and migration

Oscar Marín CSIC

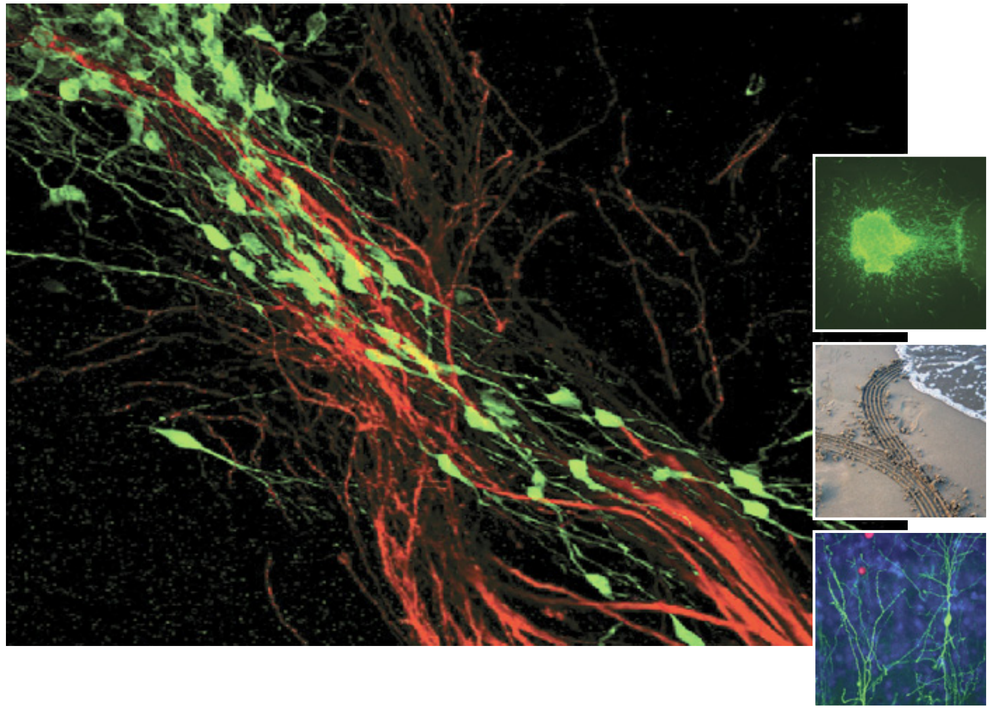
Selected Publications
Personnel

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 thetelencephalon. 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 etiology 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.



25 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.

26 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 signaling molecules like SHH, WNTs and FGFs in the Isthmic organizer, the zona limitans intrathalamic (ZLI) and the anterior neural ridge (ANR).

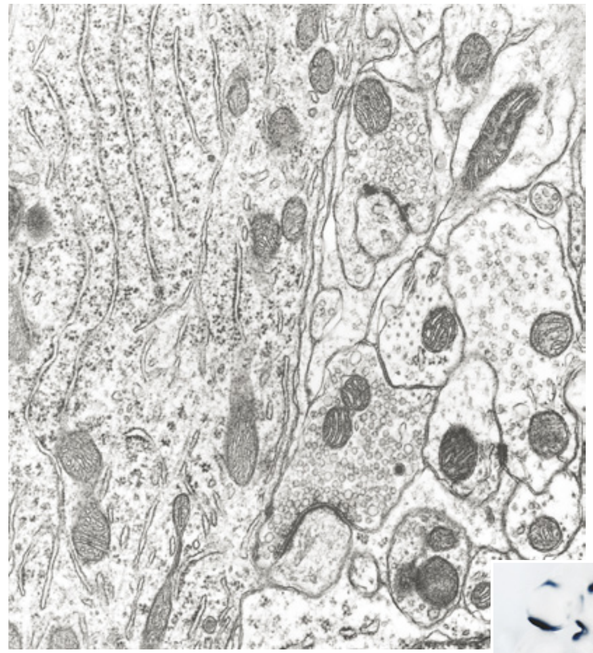
Experimental methodology: (i) Interspecific transplants of neural tissue between quail and chick embryonic brain areas. (ii) Explant cultures of mouse anterior neural tube will permit to make experimental embryological techniques on genetically altered mouse models.

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 analyze the expression pattern of 16.000 genes at several embryonic stages of mice (www.eurexpress.org/ee/). The further genetical manipulation by homologous recombiantion 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 peripheric senso-motoral neuropathologies as well as Down syndrome. Related to this research line we are analyzing the genetic alteration associated to functional psychosis (squizophrenia and bipolar disorder), particularly genes related to alteration in cortical arquitectural 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 (knock-outs); (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 fibers. Our studies are focused mainly on studying the molecular control of the decision adopted by these neurons of crossing or not to cross the ventral midline of the brain stem, during migration and axonal growth.

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.



27 Cell movements in development and disease

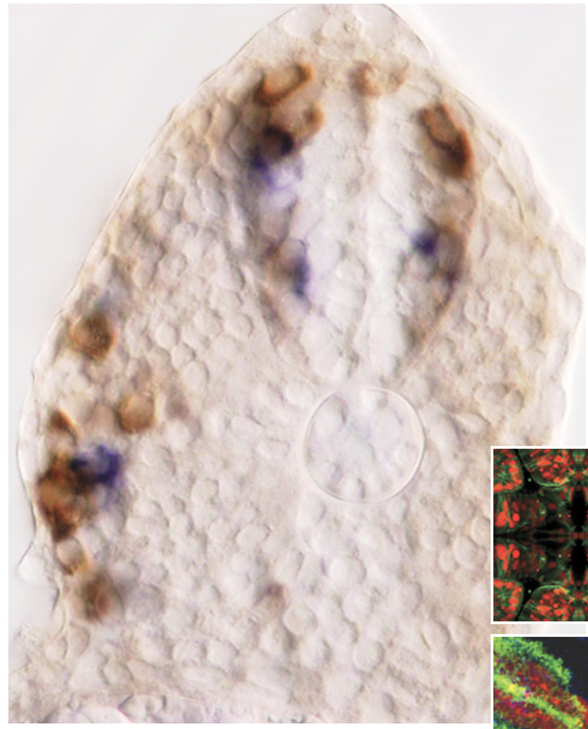
M. Angela Nieto CSIC

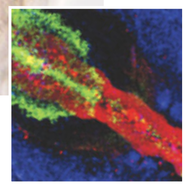
Selected Publications
Personnel

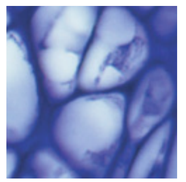
We have been interested in the analysis of cell behavior in development and disease for more than 15 years. We have been working on the functional analysis of the Snail gene family, and have shown its implication in different processes during embryonic development in vertebrates, including the formation of the mesoderm and the neural crest. 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 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 fetal 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).

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 a tandem duplication in the last common ancestor of the Diploblasts and Bilateria (2009). We have also characterized the nuclear import pathways that regulate the activity of Snail proteins as representatives of C2H2 zinc finger transcription factors (2009). These studies will favour the analyses of ancestral and acquired functions. We have found that Scrtach is not involved in the regulation of cell movements, but rather it is important for cell survival (2010), a role that we found associated with Snail in epitelial 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. Therefore, cell survival is an ancestral function of the Snail/Scrtach 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. The survival properties associated with Scratch expressing cells controls the number of spinal neurons during embryonic development (2010).

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.







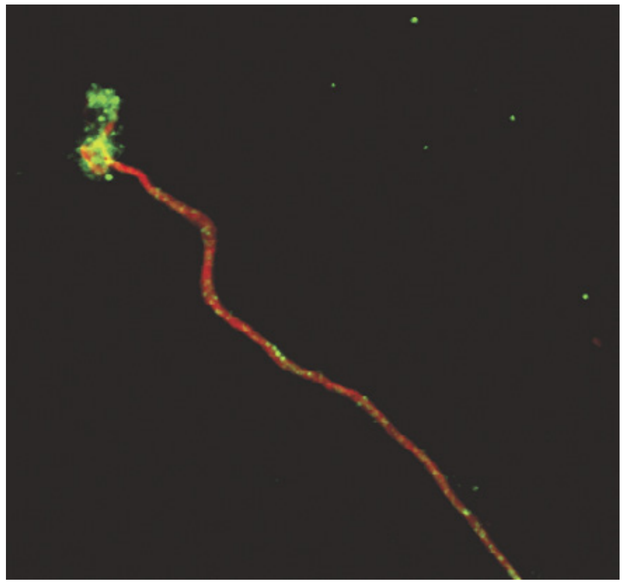
28 Neural circuit formation and remodeling

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 arborization. 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 which might be involved in the assembly of neural circuits.

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



29 Altered molecular mechanism in Alzheimer's disease and dementia

Javier Sáez Valero UMH

Selected Publications
Personnel

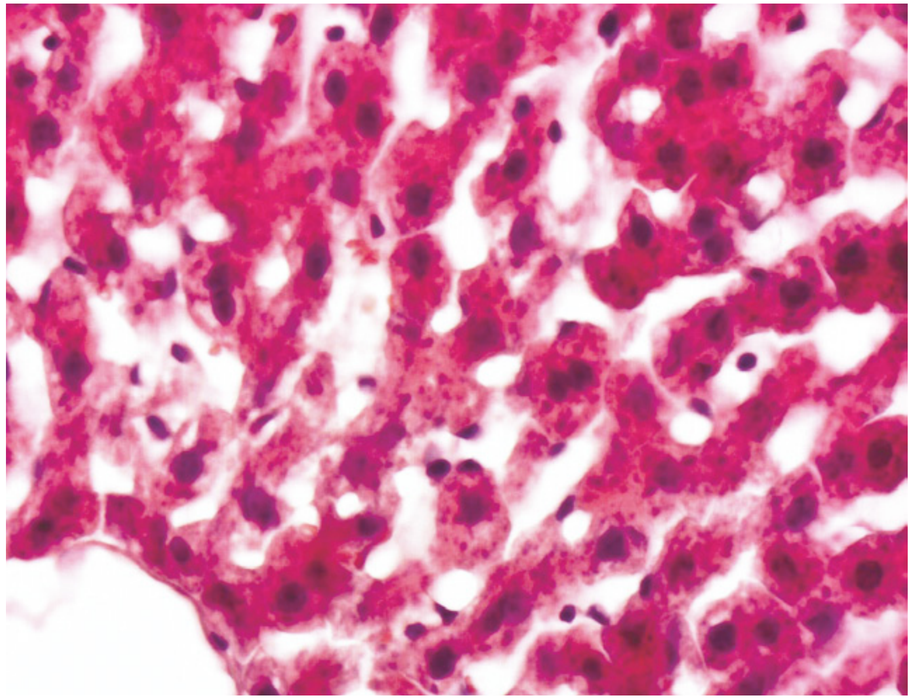
Our aim in the IN was to introduce a line of research into Alzheimer's disease (AD) and dementia that originated from a basic point of view but that was relevant to the development of clinical-diagnostic applications.

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 β-amyloid 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.

We also collaborate actively with clinicians and basic research in the study of liver cirrhosis and its most common neurological complication, hepatic encephalopathy.

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.



30 Biophysics and pharmacology of ionic channels

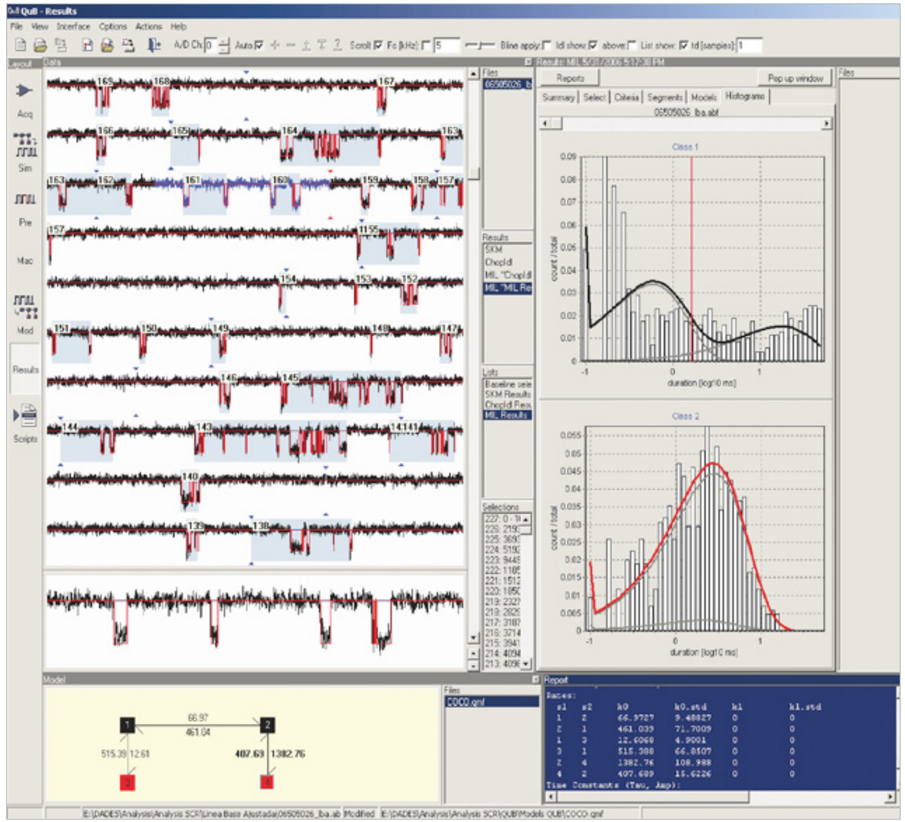
Francisco Sala UMH
Salvador Sala UMH

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.



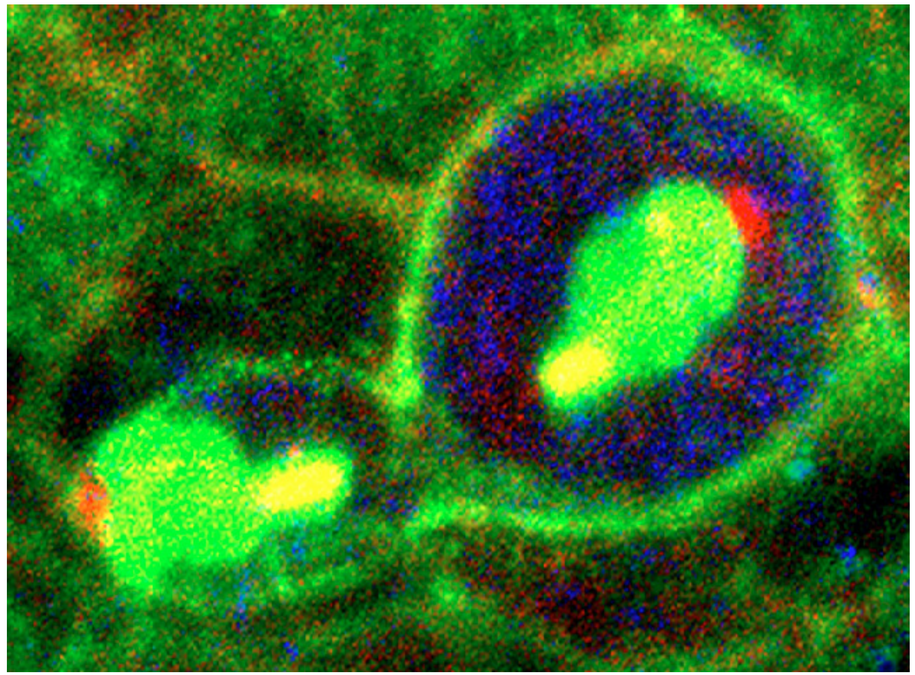
31 Molecular neurogenetics

Francisco Tejedor CSIC

Selected Publications
Personnel

One of the most important issues in developmental neurobiology is to elucidate how the large number and wide 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 proliferation and cell 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 centers 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.

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 encodes a very well 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.



32 Cell signalling during neuronal migration

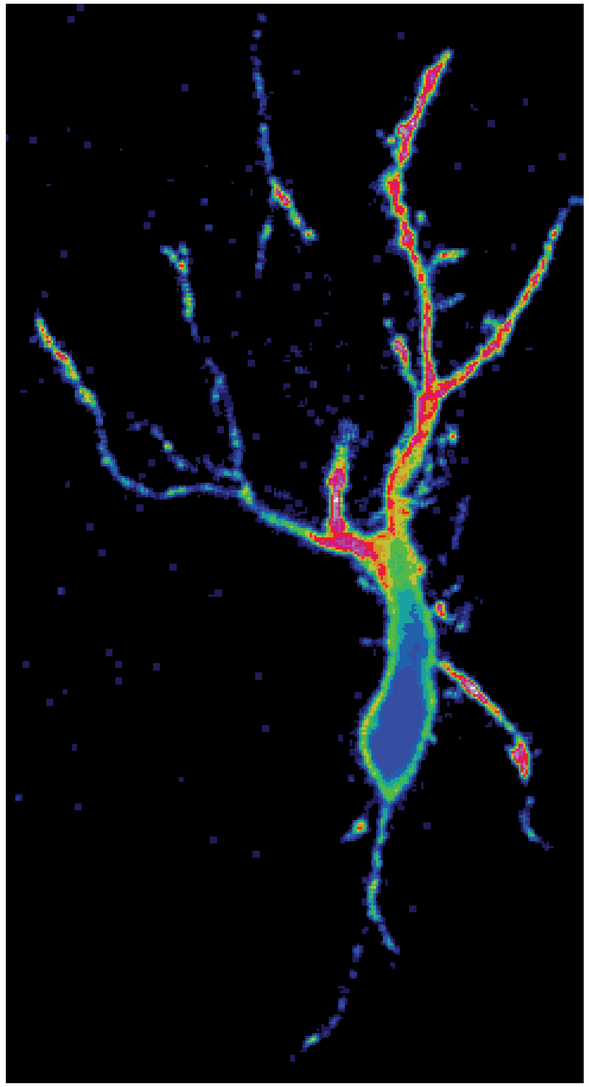
Miguel Valdeolmillos UMH
Fernando Moya UMH

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

Fondation Jérôme Lejeune

Fundacion Inocente Inocente

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.

Research Professorship of Developmental Biology "Remedios Caro Almela"

In 2000, in collaboration with the Instituto de Neurociencias the Martínez-Caro family started to sponsor 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.

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) and Steve Wilson (2009).

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

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

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

Confocal Electrophysiology Station with resonant scanner and high temporal resolution and electrophysiology equipment.

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

Neurolucida system for neuroanatomical analysis of brain and nervous system. Workstations for image processing and analysis that allow the extraction of statistical parameters and quantification of scientific results. Reconstructions 3D and 4D from image series.

SERVICES AND FACILITIES

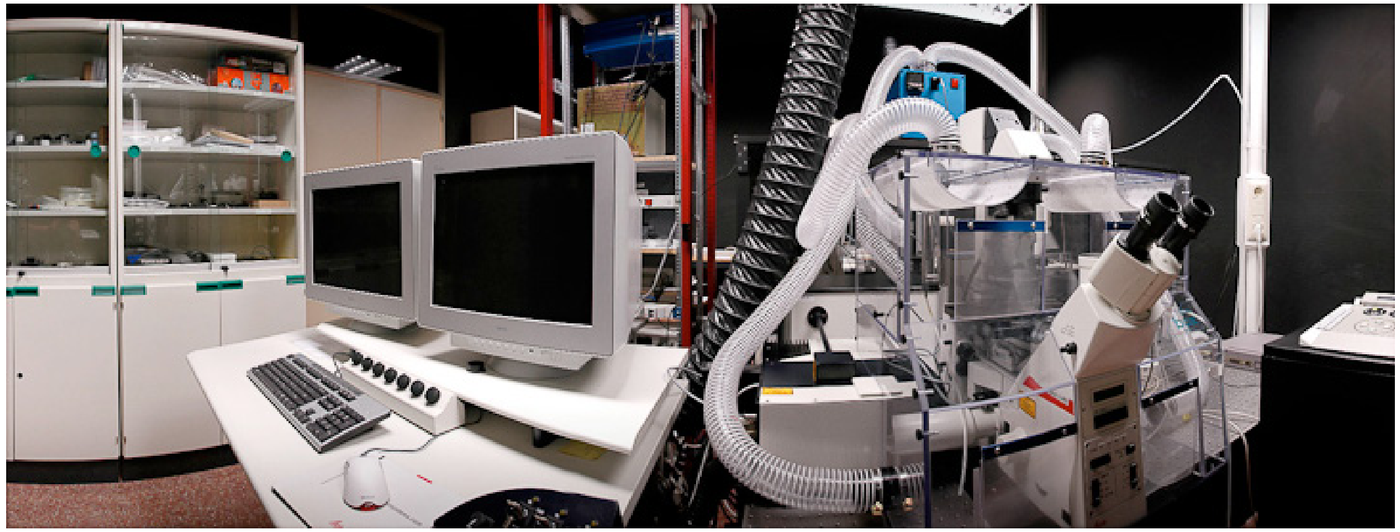
ELECTRONICS WORKSHOP

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.

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

The area for behavioural studies contains two units. The first one, bigger and with more equipment for analysis, is allocated in the mouse transgenic core in the IN building. In this common area there are 7 independent spaces and a common wharehouse and washing area. Equipment such as Skinner boxes, rotarod, treadmill, 8 arms maze, hot plate and water maze with tracking system allow researchers to study the behaviour of mice (motor function, memory, learning, 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. The second one, smaller and with more basic equipment, is located in the general animals facility of the UMH in the Campus of Sant Joan.

FLUORESCENCE ASSISTED CELL SORTING

The Institute runs the latest generation "Fluorescence Assisted Cell Sorting" (FACS) currently available. Our FACSAria is a digital analyzer/sorter of high precision and sensitivity for sorting and analysis of cell populations with differently tagged structures, used in studies such as: the search for molecules involved in neuronal development and plasticity, the search for molecules implicated in tumour development, neuropsychiatric and neurodegenerative disorders, and cell therapy: stem cell isolation for transplant in animal models for neuropsychiatric and neurodegenerative diseases.

SERVICES AND FACILITIES

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 purposses. Drosophila labs at the IN continuously serve stocks and mutant combinations to other labs in Europe and the US.

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.

SERVICES AND FACILITIES

MANAGER

Gloria Hoyos

ADMINISTRATION

Mª Luz Arce Fernández
Mª Jesús Arencibia Rojas
Angelines Barrios Fernández
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Ruth Rubio Sánchez
Mª Luisa Sánchez Vázquez


GH


ABF


AMLM


MRGL


EMB


IMP


MLSV


IRG MTPV RLC

SERVICES AND FACILITIES

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Joana Expósito Romero

COMPUTING
Maria Isabel Sánchez Febrero

RADIOACTIVITY CONTROL
Emilio Gutiérrez Flores

SCIENTIFIC ILLUSTRATION
Stuart Bailey Ingham

ELECTRONIC WORKSHOP
Alfonso Pérez Vegara
Manuel Bonilla García

CELL CULTURE
Sara Carratalá Gosálbez
Rosa García Velasco

GLASSWARE & AUTOCLAVING
Trinidad Guillén Carrillo


MTGH


IOC


LGG


JCR


JER


SBI


TGC


SCG


RGV


APV

SERVICES AND FACILITIES

VETERINARY STAFF

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ANIMAL HOUSE

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Mª Ángeles Soler Ripoll
Lucía Yuste Jiménez

DROSOPHILA SERVICE

Alicia Sánchez Rincón

ZEBRAFISH FACILITY

Diana Abad Bataller

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1/15

Abnormal protein phosphorylation and Parkinson´s disease: unexpected therapeutic opportunities

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1/22

Schwann cells and Myelination: Lessons from Development and Disease

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1/29

Efectos nicho y efectos comunidad en la regulación de la auto-renovación de células madre

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2/5

Sistema endocannabinoide y alteraciones cognitivas

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2/12

Chromogranins as regulators of the storage and exocytosis of neurotransmitters

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2/19

From genes to shape: notions from the study of the Drosophila tracheal system

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Nrg1/ErbB4 signalling controls the development of cortical GABAergic circuits: insights into the etiology of the Schizophrenia

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3/12

Signaling axonal regeneration in the adult CNS

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3/26

From epithelial cell polarity to retinal degeneration - lessons from Drosophila

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4/9

The Objectivity of Subjective Truths

Semir Zeki

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4/23

Signaling through gap junctions and hemichannels in the CNS: Golgi wasn't entirely wrong

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4/23

Epigenetic remodeling of synaptic AMPA receptors in neuronal death

Suzanne Zukin

Dominick P. Purpura Dept. of Neuroscience. Albert Einstein College of Medicine, New York, USA

5/7

Tumor invasion and metastasis: EMT and cancer stem cells

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5/14

Molecular control of cortico-fugal and cortico-cortical connections

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5/21

Morpho-functional plasticity of hippocampal mossy fiber synapses

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5/25

Seminario Laboratorio Neurogenética Molecular

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5/28

Color vision in Drosophila

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6/4

Using light to follow the maturation of functional GABAergic networks in the developing cortex

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6/11

Control of the cell cycle during neurogenesis: who plays the game?

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6/18

Workshop: La patentabilidad de las invenciones biotecnológicas, del descubrimiento a la patente.

Francisco Fernández y Branas

Biotechnology, European Patent Office. La Haya, Holanda.

6/18

Los glaciares retroceden, la vida avanza. Un proceso global desde los polos a las altas montañas tropicales.

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6/18

Cambio global y conservación de la biodiversidad.

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6/30

La Prevención de Riesgos Laborales en el Trabajo con Riesgo Ergonómico

Enrique Verdoy Sanz

Servicio de Prevención del CSIC

7/8

6th IN-PROGRESS REPORT

IN researchers

Instituto de Neurociencias

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6th IN-PROGRESS REPORT
IN researchers
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7/22
Investigating synaptic vesicle recycling by STED and electron microscopy
Silvio Rizzoli
European Neuroscience Institute STED Microscopy of Synaptic Function. Gottingen, Germany

9/24
A cortical map of vestibular representation in the rodent brain revealed by functional imaging and electrophysiology
Ede Rancz
Department Neuroscience, Physiology and Pharmacology. University College London Neuroscience, UK

10/8
Regeneration of the peripheral nervous system - links to tumourigenesis
Alison Lloyd
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Lighting up the Brain
Gero Miesenboeck
Dept. of Physiology, Anatomy and Genetics. Waynflete Professor of Physiology, University of Oxford, UK

10/22
Sara endosomes and asymmetric cell division
Marcos González Gaitán
Biochemistry Department, University of Geneva, Switzerland

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Dmitri Rusakov
Department of Clinical and Experimental Epilepsy, UCL, London

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Paola Bovolenta
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11/19

Tumor suppressors at the interface of cancer and aging

Manuel Serrano

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11/26

What can experience-dependent plasticity tell us about learning and memory?

Gerald Finnerty

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12/3

Neural mechanisms for olfactory decision-making

Zach Mainen

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12/17

Spectraplakins - cytoskeletal integrators with key roles in neuronal growth

Andreas Prokop

The Wellcome Trust Centre for Cell-Matrix Research, The University of Manchester

Díaz Quesada, Marta
Mechanisms underlying response dynamics in barrel cortex
Miguel Maravall Rodríguez (Director)

Femenía Cantó, Teresa
Papel de la dinorfina en los mecanismos que regulan la respuesta emocional y su implicación en la dependencia alcohólica. Un posible modelo animal de patología dual.
Jorge Manzanares Robles (Director)

Ferrés Marcó, Mª Dolores
Identificación de genes y mecanismos causativos de cáncer y metástasis en drosophila melanogaster
María Domínguez Castellano (Director)

Gómez Sánchez, Jose Antonio
Implicación de la vía NRG-ERBB en la mielinización del SNP, la neurofribromatosis y el desarrollo de tumores malignos del sistema nervioso periférico
Hugo Cabedo Martí (Director)

Martínez Ferre, Almudena
Morfogenetic role of FGF8 and WNT8B in diencephalic development of vertebrate brain. An experimental study in mouse and chick embryos
Salvador Martínez Pérez (Director)

Martini, Francisco José
Guía direccional y fuerzas propulsoras en la migración de las interneuronas corticales
Miguel A. Valdeolmillos (Director)

Pertusa Pastor, María
Biogénesis, tráfico y modulación de la función del canal iónico termosensible TRPM8
Félix Viana de la Iglesia (Director)

Rodríguez Chacón, Mariola
Función de la quinasa de adhesión focal (FAK) en el desarrollo axonal y en el cono de crecimiento
Beatriz Rico Gozalo (Director)

Sánchez Alcañiz, Juan Antonio
Analysis of the mechanisms regulating the intracortical dispersion of interneurons. A role for the CXCL12, CXCR4 and CXCR7 trio
Óscar Marín Parra & Guillermina López-Bendito (Director)

Sánchez Huertas, Carlos
Función de BDNF y TRKB en la maduración de las sinapsis gabaérgicas
Beatiz Rico Gozalo (Director)

01 Physiology of the prefrontal cortex

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01 Physiology of the prefrontal cortex

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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.

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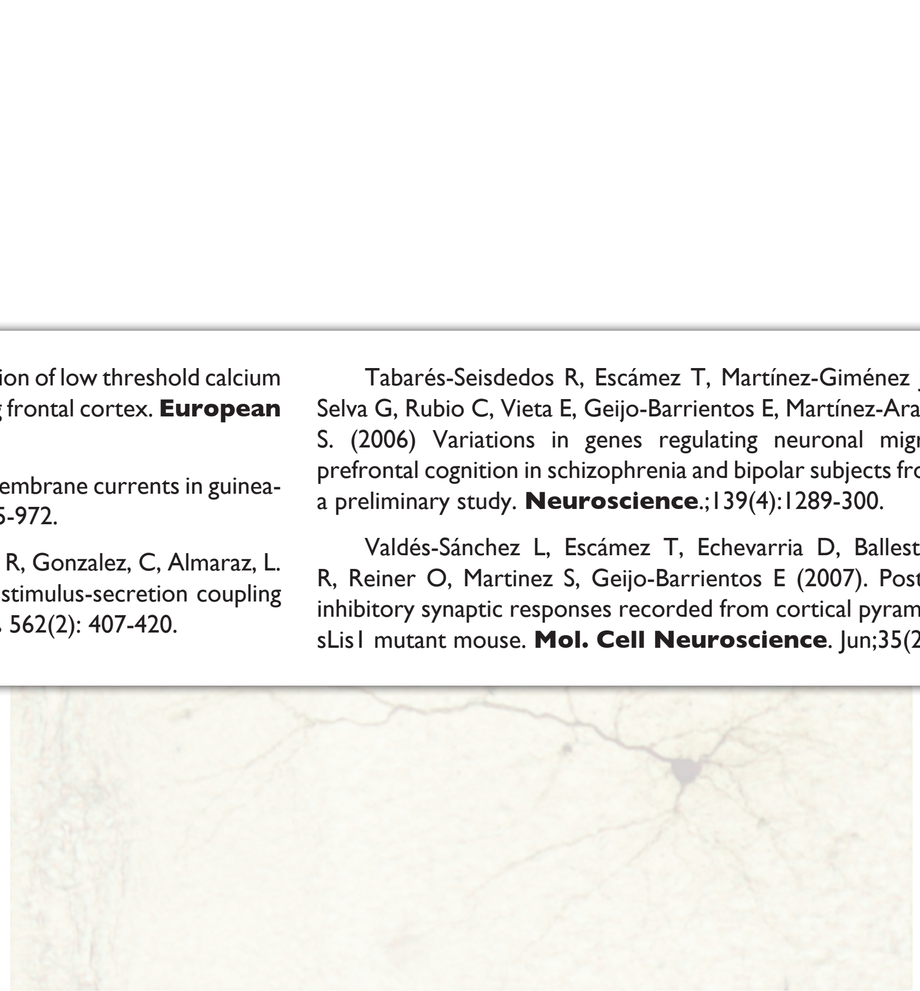
modulation of cortical functions. We use intracellular recording with patch electrodes and microelectrodes in pyramidal and non pyramidal cortical neurons visually identified with infrared videomicroscopy and Nomarski optics; in these neurons we record membrane potential and currents and synaptic responses. The specific objectives of this line of 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 latter line of weork is carried out in collaboration with Dr. Salvador Martínez (Institute of Neurosciences).



In addition to the above lines 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: the study of the mechanisms of generation and the diagnostic value of the F-wave, which is a late component of the human electromyogram and that can be used to estimate some aspects of the excitability of spinal motor neurons.

02 Mechanisms and receptors involved in analgesia and addiction

Juan J. Ballesta UMH

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02 Mechanisms and receptors involved in analgesia and addiction

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Selected Publications
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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

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.

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03 Transcriptional control of neural plasticity

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03 Transcriptional control of neural plasticity

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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.

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transcriptional effects in specific loci required for the changes in gene expression underlying long-lasting modifications of synaptic function and behavior. We are interested in exploring the contribution of histone modifications to the perpetuation of synaptic changes and memory stability, both in the healthy brain and in mouse model for different neurological conditions, such as Huntington disease and diverse mental retardation syndromes.

04 Sensory transduction and nociception

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04 Sensory transduction and nociception

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CLOSE

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.

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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.

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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.

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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.

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

05 Thyroid hormones and organization of the cerebral cortex

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Daniela Navarro

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Mª Concepción Núñez

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05 Thyroid hormones and organization of the cerebral cortex

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Lavado, R, Ausó, E, García-Velasco, JV, Escobar del Rey, F, Berbel, P, Morreale de Escobar, G. Maternal hypothyroxinemia early in development alters cell migration and cerebral cortex cytoarchitecture in the rat. **J. Clin. Invest.** (2003) 111: 1073-1082.

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Morte, B, Díez, D., Ausó, E., Belinchón, M.M., Gil, P., Grijota-Martínez, C., Navarro, D., Morreale de Escobar, G., Berbel, P. and Bernal, J. Thyroid hormone regulation of gene expression in the developing rat fetal cerebral cortex: Prominent role of the CaMKIV pathway. **Endocrinology** (2010) 151: 810-820.

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women.

In developed countries such as Italy, the Netherlands, USA and Canada, maternal hypothyroxinemia affects 1 out of 10-20 children, at least half of them will have an IQ of 15 points under the normal mean, and will suffer severe neurological alterations such as ADHD. Our epidemiological data show that in Alicante the number of affected children is even higher. Children of hypothyroxinemic mothers will have impaired intellectual skills because maternal thyroid hormones levels were not assessed during pregnancy. In almost all the cases, low thyroid hormones levels can be corrected by an adequate iodine intake. An abnormal hormonal condition similar to the one found in foetuses from severe hypothyroxinemic mothers occurs in prematurely born children that in our country accounts for 10% of all births.

05 Thyroid hormones and organization of the cerebral cortex

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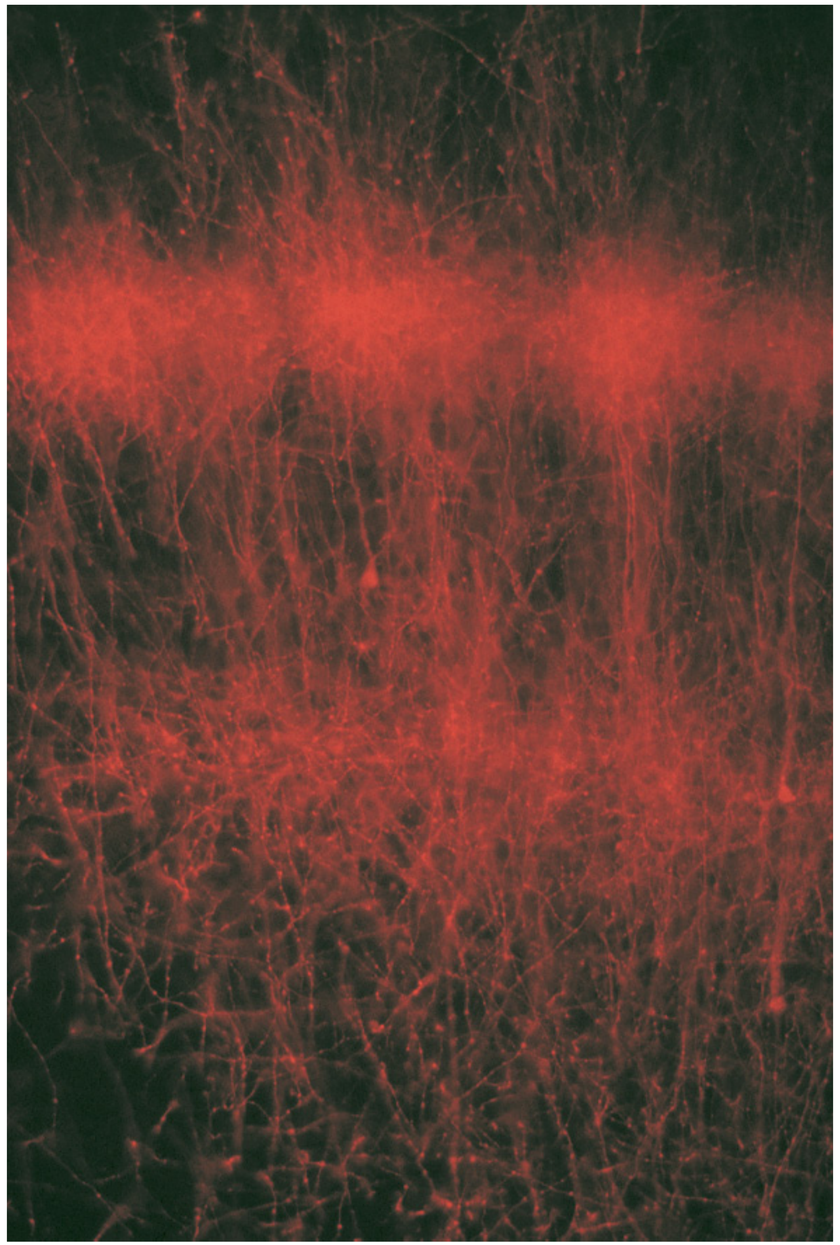
Selected Publications
Personnel



Maternal, foetal and neona
are fundamental for the d
particularly that of the cerebral cort
can produce severe neurological a
loss and speech abnormalities, mo
retardation.

Using experimental models in a
studies in humans, we are studying
alterations produced by maternal, f
hormone deficiency, critical perio
pregnancy and postnatal developm
recovery following an adequate tre

We have observed that dur
of thyroid hormones, produced b
goitrogen treatment, cause irrevers
of their progeny, such as abnormal
corticogenesis and impaired matur
deficiency can be not only severe
in cretinism, but also milder as in m
which could be considered non-pa
women.

In developed countries such as It
and Canada, maternal hypothyroxi
20 children, at least half of them w
under the normal mean, and will
alterations such as ADHD. Our e
that in Alicante the number of affec
Children of hypothyroxinemic mo
intellectual skills because maternal
were not assessed during pregnan
low thyroid hormones levels can be
iodine intake. An abnormal horm
the one found in foetuses from
mothers occurs in prematurely b
country accounts for 10% of all bir

06 Neurogenesis and cortical expansion

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Camino de Juan

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Maria Antonia Fernández


IR

MAM


MAF


CdJ


AC

CV


VB

06 Neurogenesis and cortical expansion

Víctor Borrell CSIC

development during embryogenesis, and functional studies in rodents have shown that these genes play essential roles in distinct aspects of cortical neuron migration or of cortical folding.

We are interested in the identification and analysis of the basic mechanisms involved in the normal expansion and folding of the cerebral cortex in higher mammals. 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 of Cajal-Retzius cells and intermediate progenitors in the tangential vs. radial expansion of the cerebral cortex, and in the formation of folds and fissures at stereotypic locations in the cerebral cortex during development.

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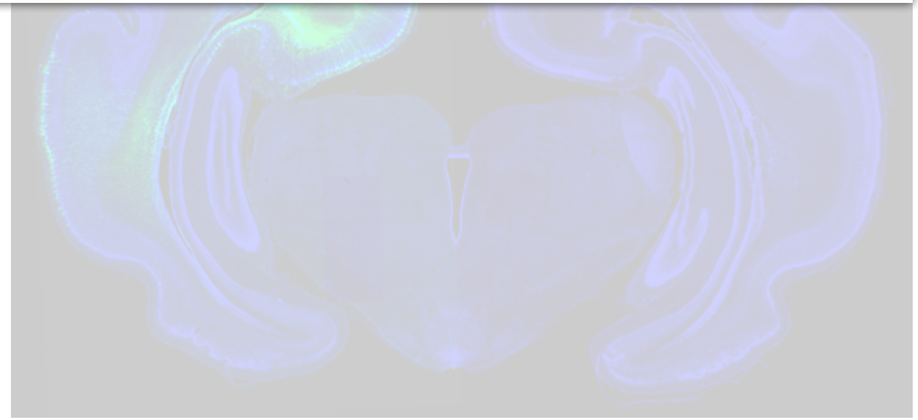

07 Molecular control of axonal myelination

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07 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.

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

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08 Plasticity of brain networks

Santiago Canals Gamoneda CSIC

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Carlos Quesada Granja
Efrén Álvarez Salvado

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EAS

CQG

BFN

SCG

08 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.

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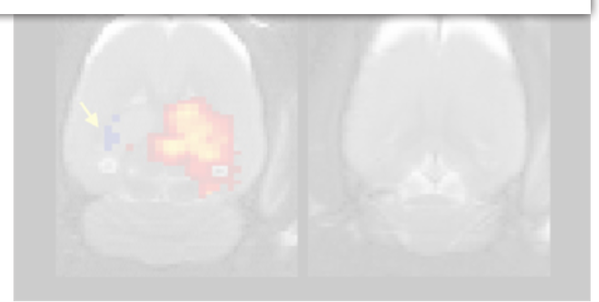
from, and react to, changes in the environment can also be activated by drugs of abuse. Human and animal studies indicate that the refractory nature of addiction results from drug-induced stimulation of reward-related learning networks. As a consequence, drug seeking behaviour becomes hard-wired in the addict's brain. By applying the same multidisciplinary approach, we are investigating the functional reorganization of brain networks supporting addiction and relapse.



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

Ana Carmena CSIC

Selected Publications
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Aljona Makarova

Technical Staff
Stephan Speicher


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RPG


JS


SS


AC

09 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.

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

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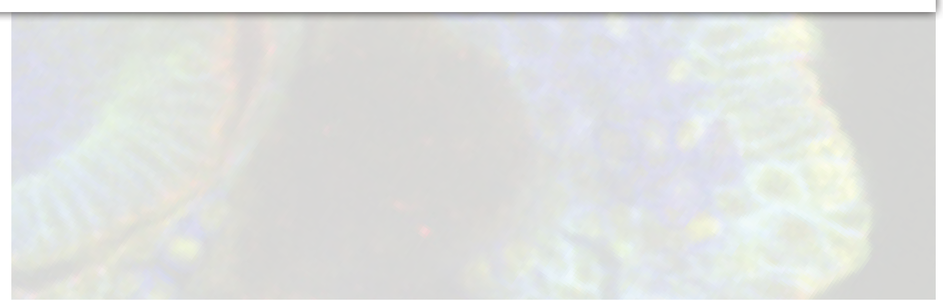
Our group analyzes the function of PDZ proteins, including the PDZ protein Canoe/AF-6, during fundamental biological processes for the generation of cellular identities, such as asymmetric cell divisions and morphogenesis. To implement this project, we use a multidisciplinary approach that combines different techniques of Genetics,Cellular Biology, Biochemistry and Molecular Biology. The embryonic development



09 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 type
Indeed, the human brain has more
millions of neurons, most of them spec
embryonic development. Unraveling
mechanisms that underlie the acquisiti
identities is the main objective of our g

Specifically, we are interested
vivo the mechanisms of cross-talk bet
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cellular diversity. This will allow us t
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PDZ domain-containing proteins (PSD
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submembrane locations, such as cellula
synapses. It is frequent the formation of
complexes around PDZ-based sca
numerous PDZ proteins contribute to
of proteins to the membrane, to th
receptor and channels, and also to incre
and fidelity of signal transduction pathw
proteins are excellent candidates as p
communication between signaling path

Our group analyzes the function of
including the PDZ protein Canoe
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of cellular identities, such as asymmetr
and morphogenesis. To implement this
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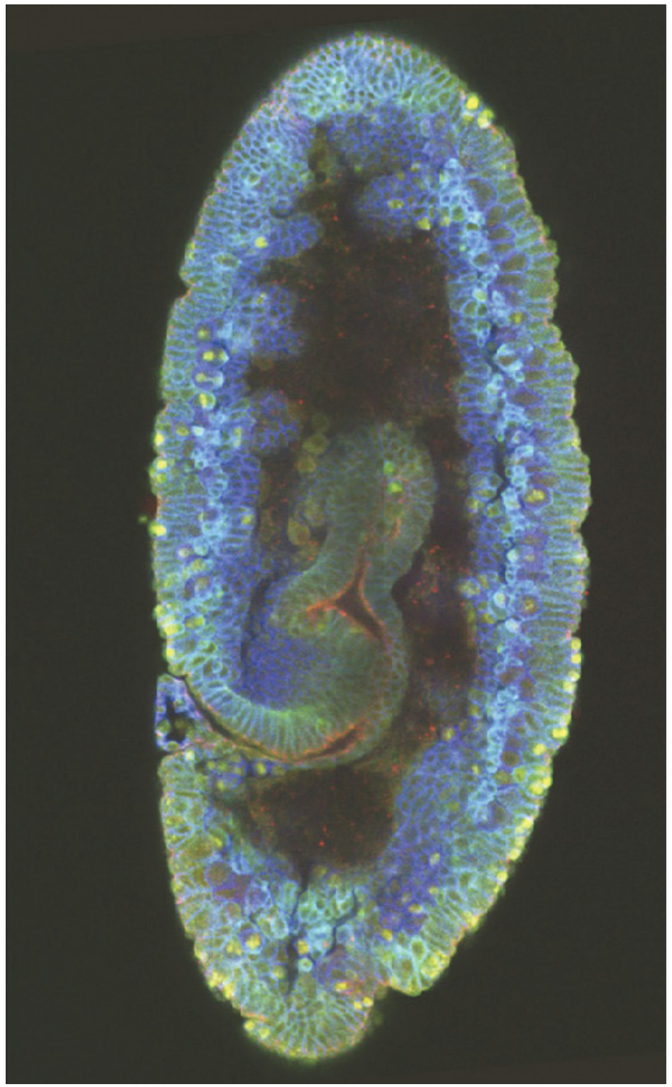

10 Molecular neurobiology of neuronal nicotinic receptors

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MC


LS

10 Molecular neurobiology of neuronal nicotinic receptors

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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. **J. Neurochem.** 104, 719-730.

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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.

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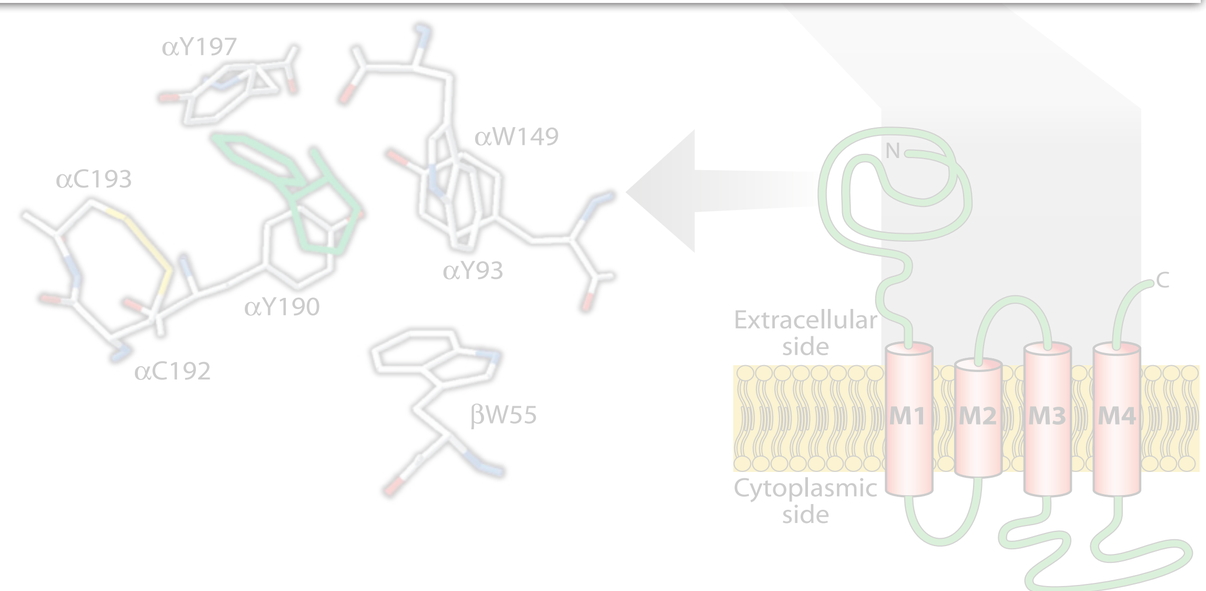
the interaction of some proteins with specific nicotinic receptor subtypes.

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



11 Cellular and conductual neuroscience

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11 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.

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12 Mechanisms of growth control and cancer in drosophila

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Almudena Ortiz España

12 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.

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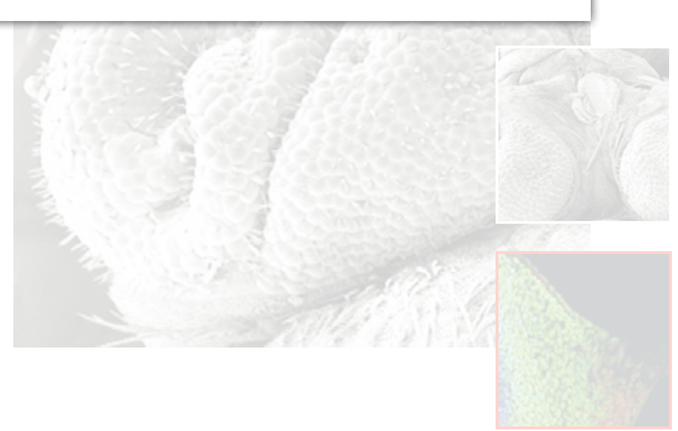
Liefke R., Oswald F., Alvarado C., Ferres-Marco D., Mittler G., Rodriguez P., Dominguez M., and T. Borggrefe (2010). Histone demethylase KDM5A is an integral part of the core Notch-RBP-J repressor complex. **Genes Dev.** 2010 24 (6)

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.

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 are using genetic, molecular and cellular methods to study the steps and key genes involved in the transformation of normal healthy cells into cancerous cells capable of metastasing.



12 Mechanisms of growth control and cancer in drosophila

Maria Domínguez CSIC

Selected Publications
Personnel

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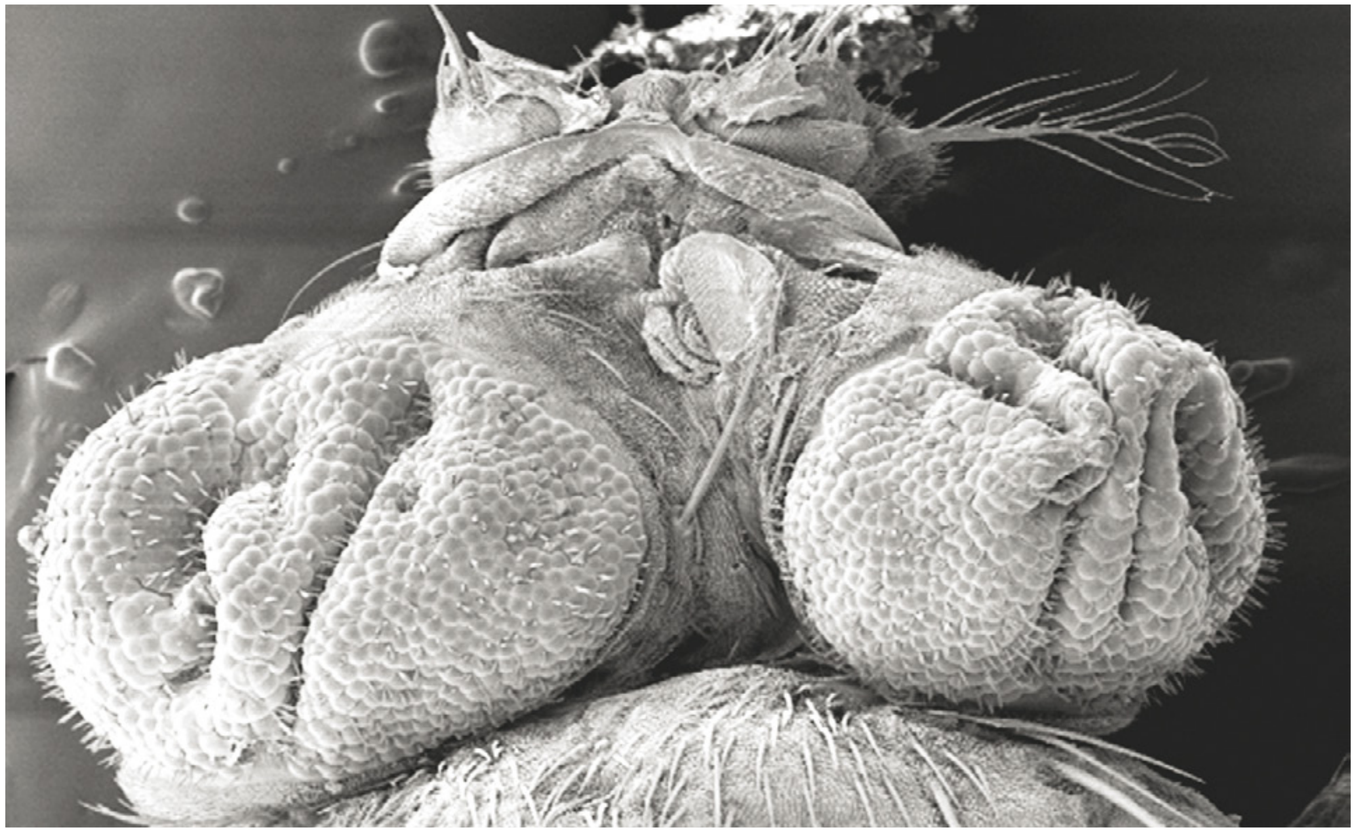
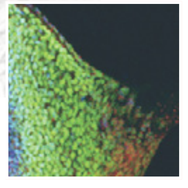
in the transformation of normal healthy cells into cancerous cells capable of metastasing.





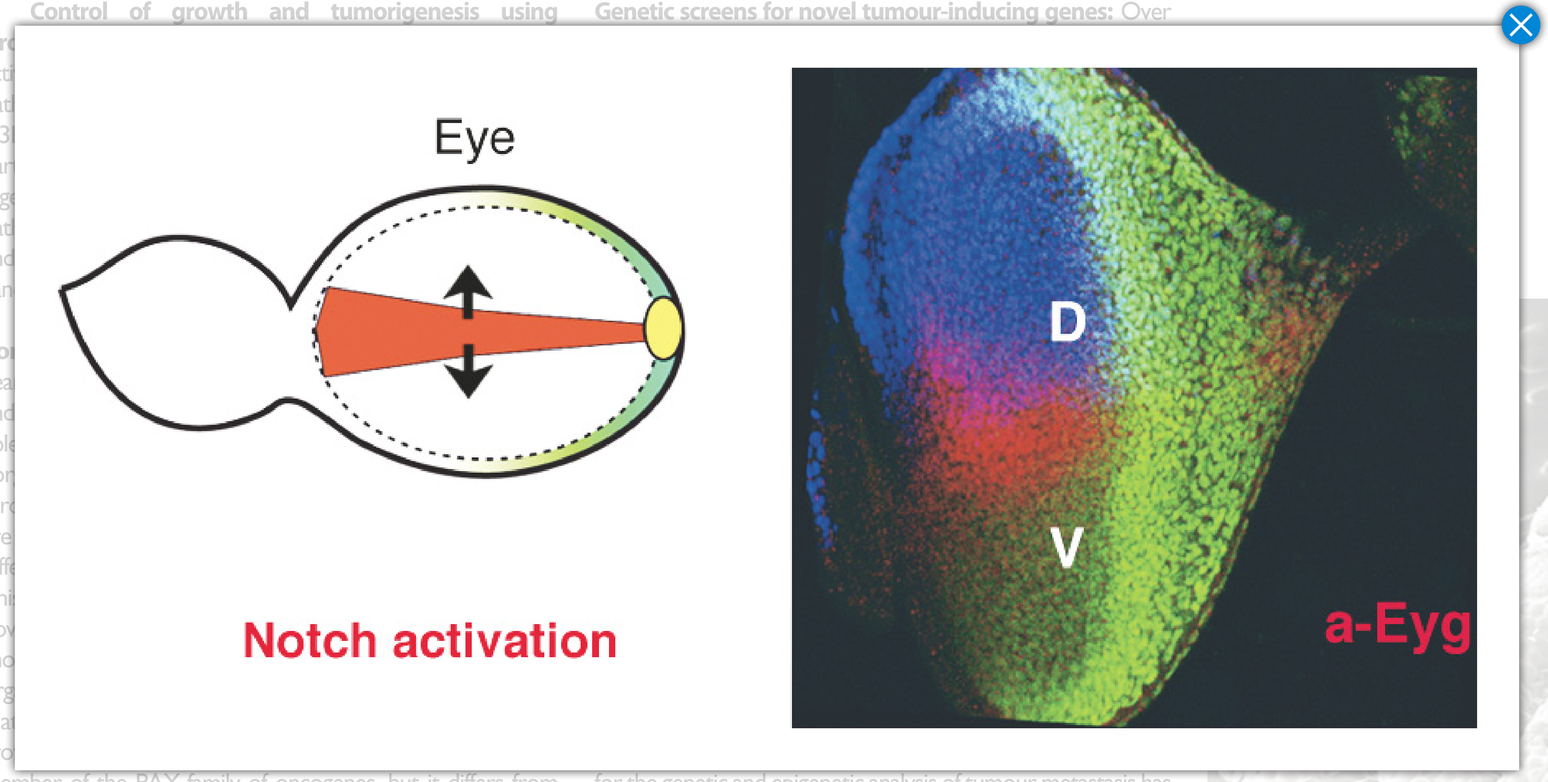
12 Mechanisms of growth control and cancer in drosophila

Maria Domínguez CSIC

Selected Publications
Personnel

Our studies are focused on four research projects:

Control of growth and tumorigenesis using **Genetic screens for novel tumour-inducing genes:** Over



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.

for the genetic and epigenetic analysis of tumour metastasis has only recently been realised. We are using genetic, molecular and cellular methods to study the steps and key genes involved in the transformation of normal healthy cells into cancerous cells capable of metastasing.

13 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.

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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.

13 Cortical development

Alfonso Fairén CSIC

AF

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

PhD Investigator
Ana Espinosa Martínez (hasta septiembre de 2010)

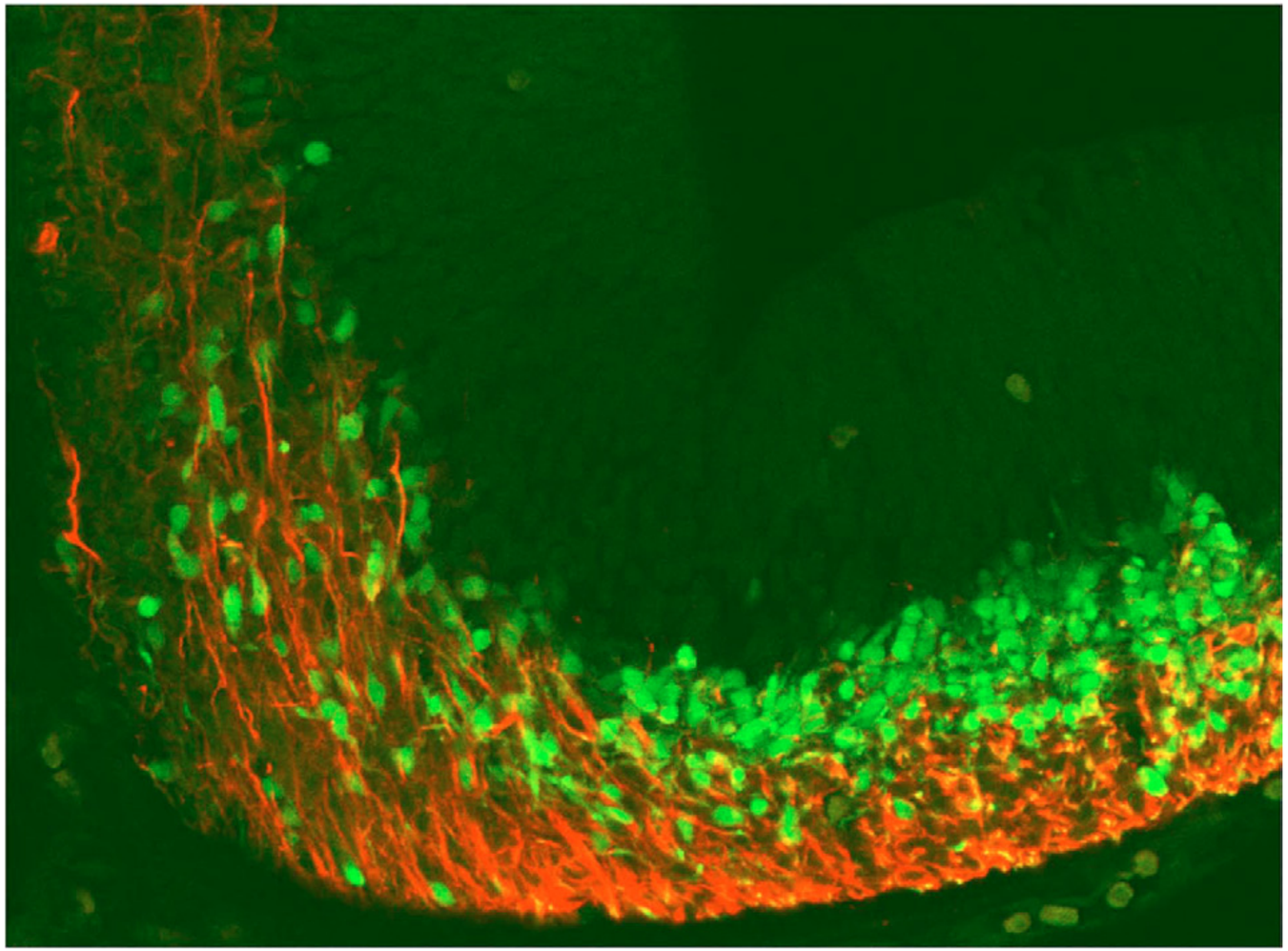
Technical Staff
Belén Andrés Bayón
Gloria Fernández García (desde junio de 2010).

GFG NRR BAB MCP CP

13 Cortical development

Alfonso Fairén CSIC

Selected Publications
Personnel



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14 Neurobiology and neuromodulation of the opioid actions

Clara C. Faura Giner UMH

Selected Publications
Personnel

Principal Investigator
Clara C. Faura Giner

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14 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

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 opiod 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)

15 Ocular Neurobiology

Juana Gallar UMH
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15 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.

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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., Acosta, MC., Gutierrez, AR., Belmonte, C (2007) Impulse activity in corneal sensory nerve fibers after photorefractive keratectomy. **Invest. Ophthalmol. Vis.** Sci. 48: 4033-4037.

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.

ophthalmic drugs, and the role of the ocular surface innervation in blinking and in basal and reflex tearing.

At the present time, the ONG centers 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 discomfort and pain subsequent to nerve lesion.

16 Developmental Neurogenetics

Luis García-Alonso CSIC

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Emma Velásquez

Technical Staff
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Alejandro Montoya
Anna Carboncino


LG-A


SB


AC


AM


JL

16 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.

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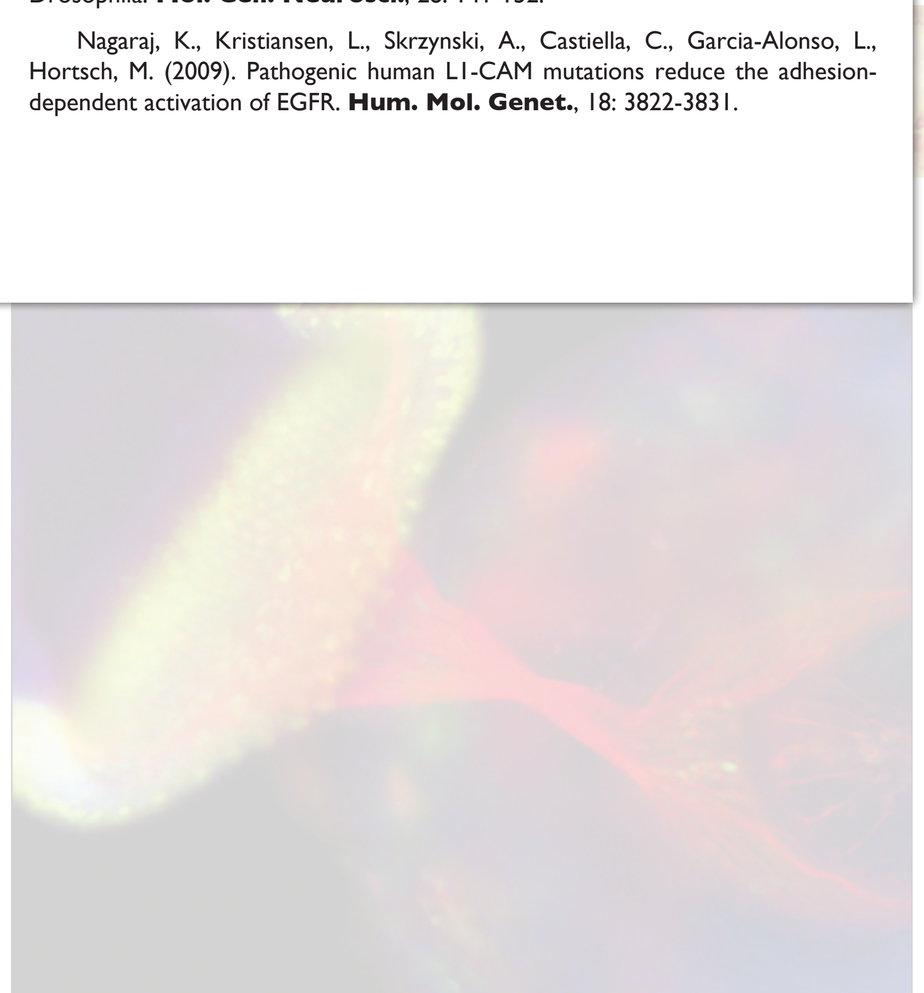
Kristiansen, L., Velasquez, E., Romani, S., Baars, S., Berezin, V., Bock, E., Hortsch, M., Garcia-Alonso, L. (2005). Genetic analysis of an overlapping functional requirement for L1- and NCAM-type proteins during sensory axon guidance in Drosophila. **Mol. Cell. Neurosci.**, 28: 141-152.

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.

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 use *Drosophila* as transgenic model organism to study Reelin function, a vertebrate cell communication protein that was lost during invertebrate evolution.



16 Developmental Neurogenetics

Luis García-Alonso CSIC

Selected Publications
Personnel

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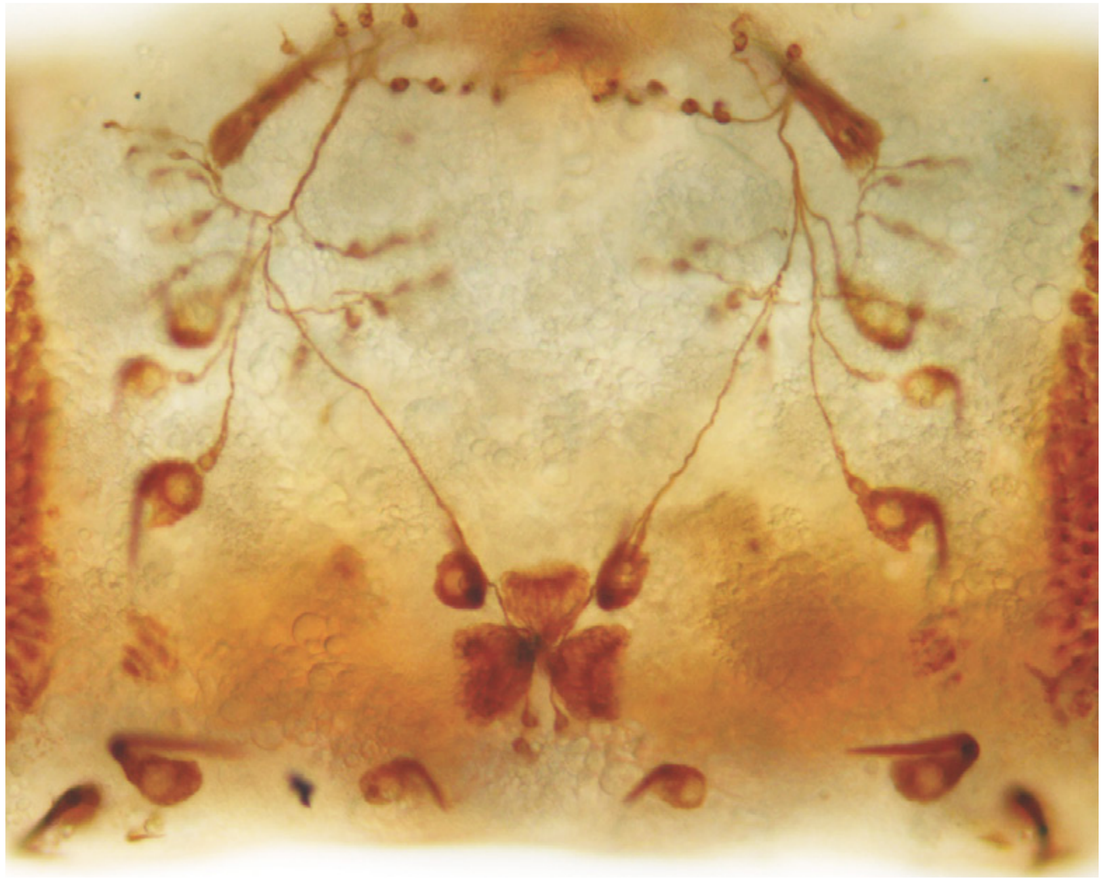

17 Mechanotransduction in mammals

Ana Gomis CSIC

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Danny Mauricio Florez

Technical Staff
Ana Miralles


AG


AM


DMF


ALC

17 Mechanotransduction in mammals

Ana Gomis CSIC

*Caprini M, *Gomis A, Cabedo H, Planells R, Belmonte C, Viana F and Ferrer-Montiel A.. GAP43 stimulates inositol-trisphosphate-mediated calcium release in response to hypotonicity. **EMBO Journal** 22 :3004-14 (2003) (*co-authors)

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)

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 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.

18 Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH

Selected Publications
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Inmaculada López

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Virginia Garcia

Technical Staff
María del Mar Francés


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VG


CJT


JHV


IL


MdMF


SV

18 Molecular mechanisms of neurosecretion

Luis M. Gutiérrez UMH
Salvador Viniegra UMH

Selected Publications
Personnel

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.

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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.

19 Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Principal Investigator
Eloísa Herrera

PhD Investigator
Cristina G. Frigola

PhD Student
Mª Isabel Carreres
Augusto Escalante
Blanca Murillo
Geraud Chauvin

Technical Staff
Celia Vegar

19 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 mechanisms that generate retinal axon divergence at the midline as well as the assembly of bilateral circuits at the target tissues. We then investigate whether molecules and mechanisms newly identified in the visual system play similar functions in other bilateral pathways of the CNS such as the spinal cord.

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).

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García-Frigola, C., Carreres MI., Vegar, C and Herrera, E. (2007). Gene delivery in retinal ganglion cells by in utero electroporation. **BMC Developmental Biology**. 7:103

E. Herrera and C. García-Frigola (2008). Genetics and development of the optic chiasm. **Frontiers in Bioscience**. 13:1646-1653

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.*

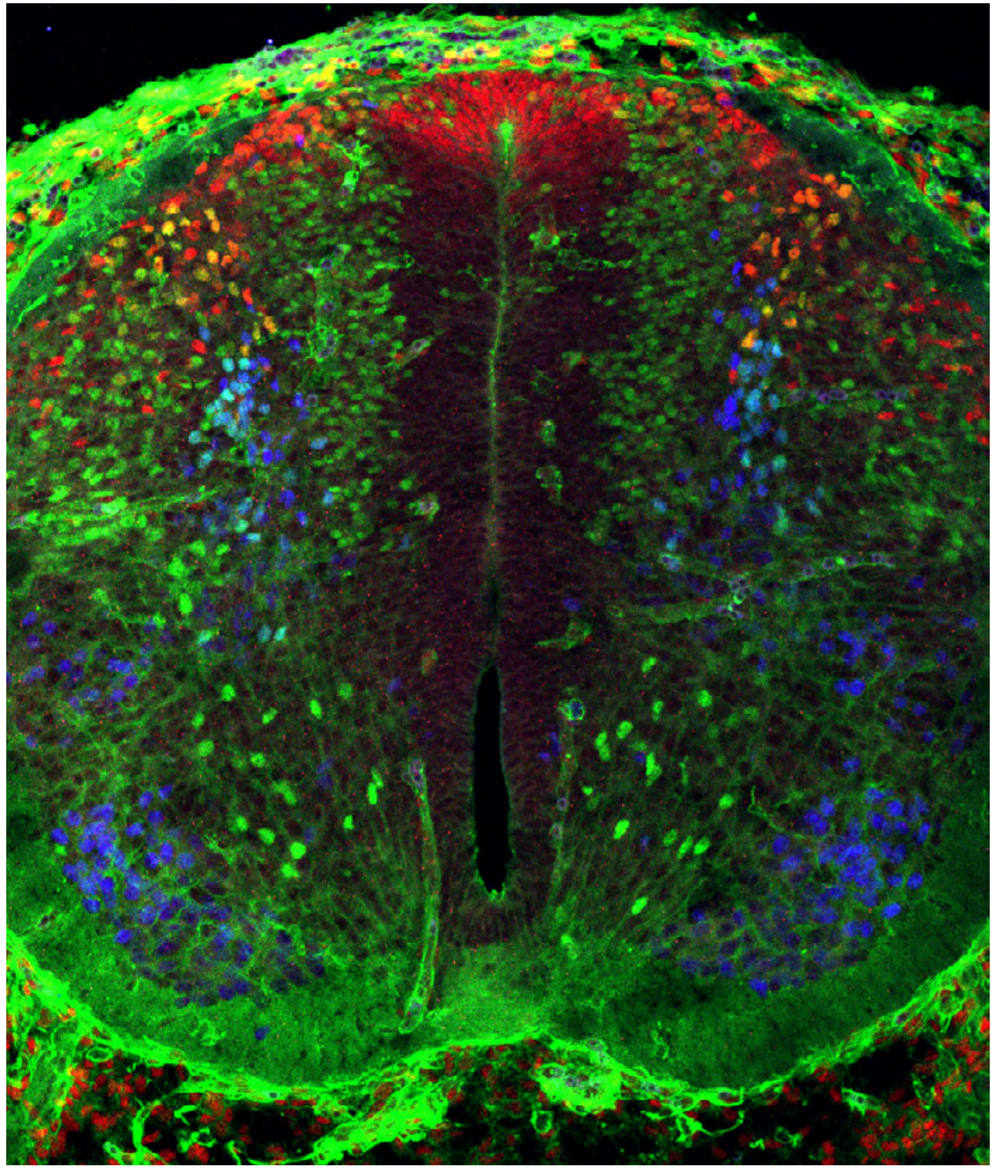
19 Development and assembly of bilateral neural circuits

Eloísa Herrera CSIC

Selected Publications
Personnel

Most metazoans many features of the interpretation of coordination of locom 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 system consequences in visi instance.

We use the develop system as a model mechanisms that gener midline as well as the a target tissues. We the and mechanisms newly similar functions in oth such as the spinal cord



20 Synaptic physiology

Juan Lerma CSIC

Selected Publications
Personnel

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

PhD Student
José Antonio Cano
Wilfrid Mazier
Joana M. Marques
Jon Palacios

Technical Staff
Mónica Llinares
Esther Picó


JL


WM ML RJR MIA EP IR JMM JP AVP

20 Synaptic physiology

Juan Lerma CSIC

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.

Gomes AR, Ferreira J, Paternain AV, Lerma J, Duarte CB, Carvalho AL (2008) Characterization of alternatively spliced isoform of AMPA receptor subunits encoding truncated receptors. **Mol Cell Neurosci.** 37:323-34.

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

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

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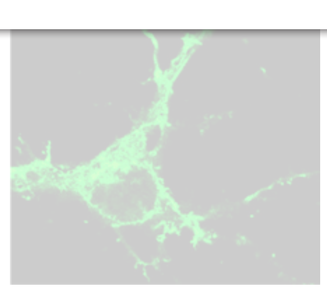
Lerma, J., Paternain, A.V., Rodríguez-Moreno, A., and López-García, J.C (2001) Molecular Physiology of Kainate Receptors. **Physiologial Reviews**. 81: 971-998.

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

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. We have identified already several proteins fulfilling this role. One of them is SNAP25, which was a surprise since this protein is well known to mediate the transmitter release process. The regulation of receptors by interacting proteins provide novel strategies to influence receptor function in an exquisite way and promote the idea that they may constitute an avenue to develop new drug targets to control excitability diseases, such as epilepsy.



21 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

GLB

Principal Investigator
Guillermina López-Bendito

PhD Investigator
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Henrik Gezelius
Erik Mire
Graciela Navarro Mora

PhD Student
Eduardo Leyva Díaz
Paula Marcos Mondéjar
Cecilia Mezzera

Technical Staff
Noelia García Lillo
Elka San Martín

21 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

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.

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.

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21 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
underlying thalamocortical a
and ultimately the rewiring
integrated and innovative exp

The development of t
requires a precise topo
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Three major questions a
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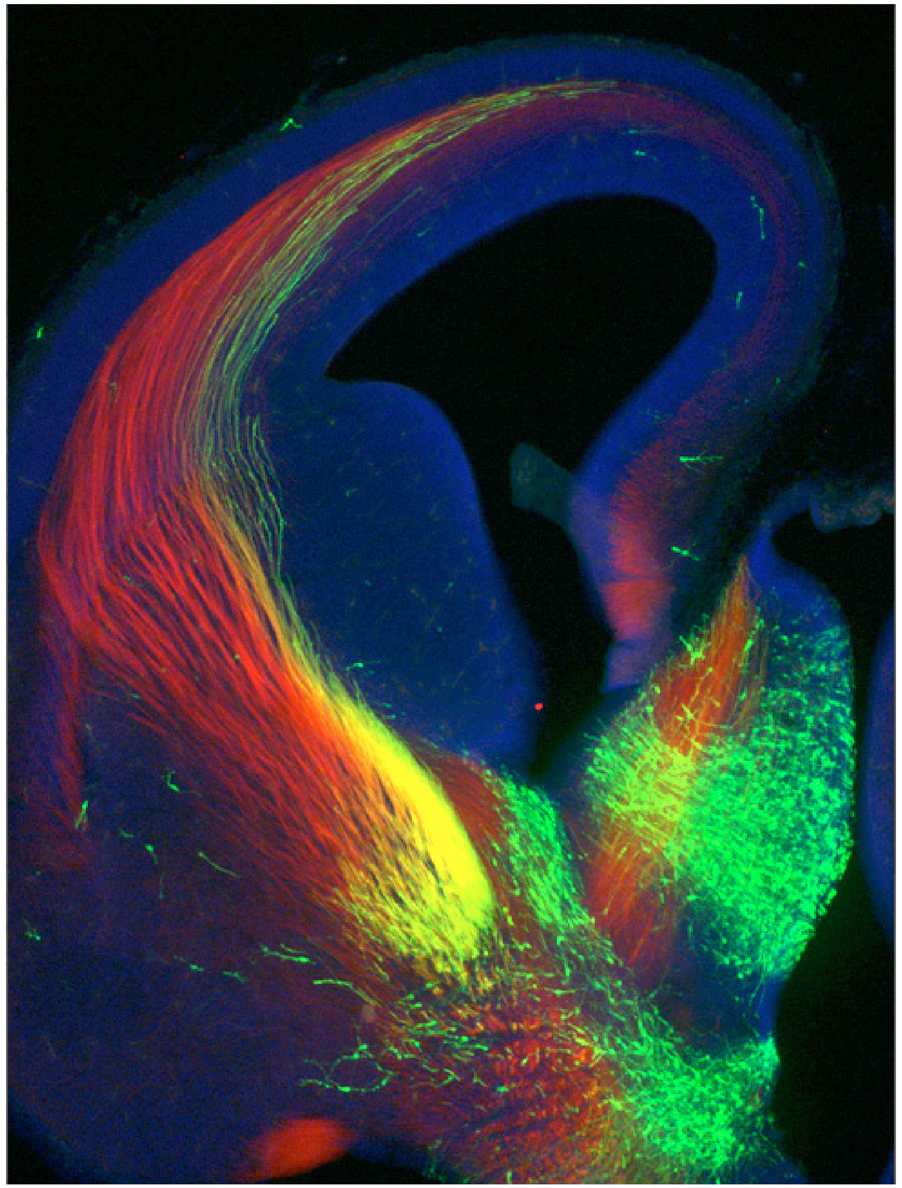

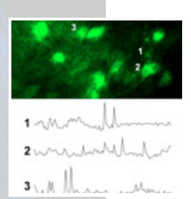

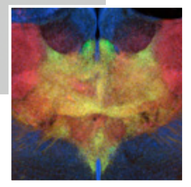

21 Cellular & molecular mechanisms of brain wiring

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.

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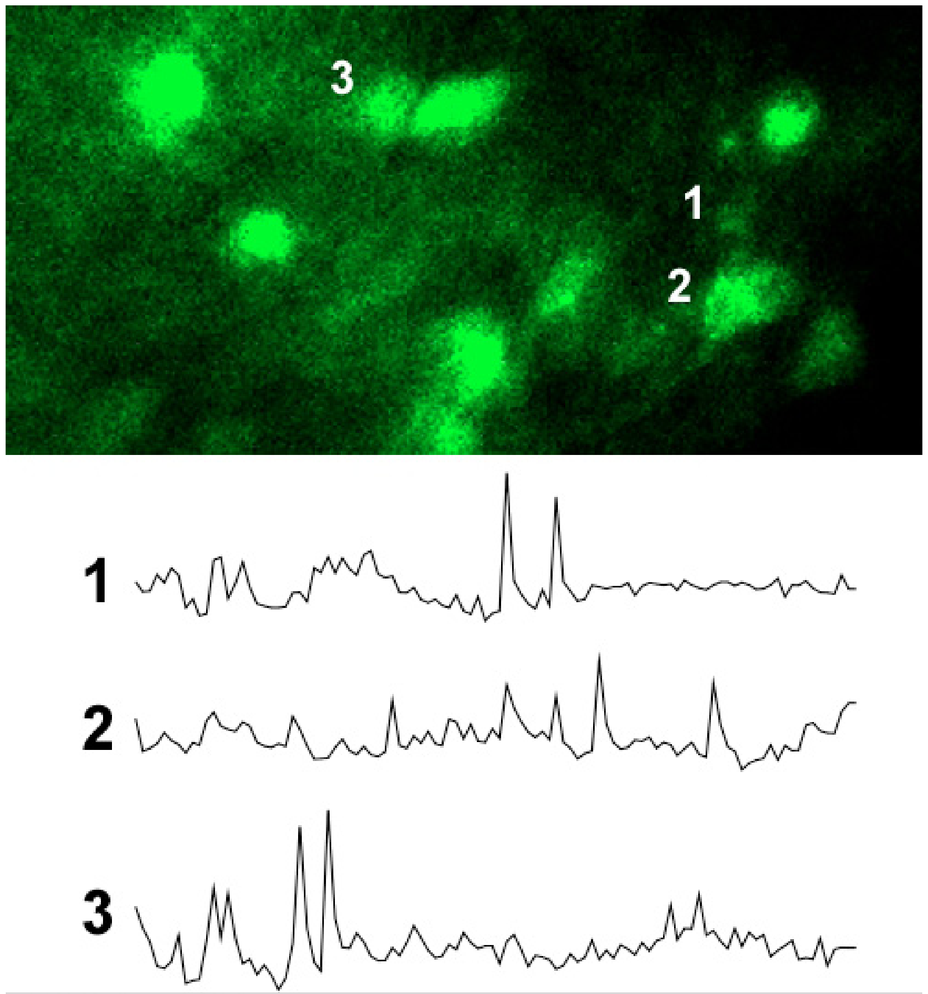
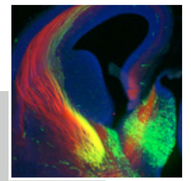
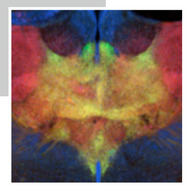


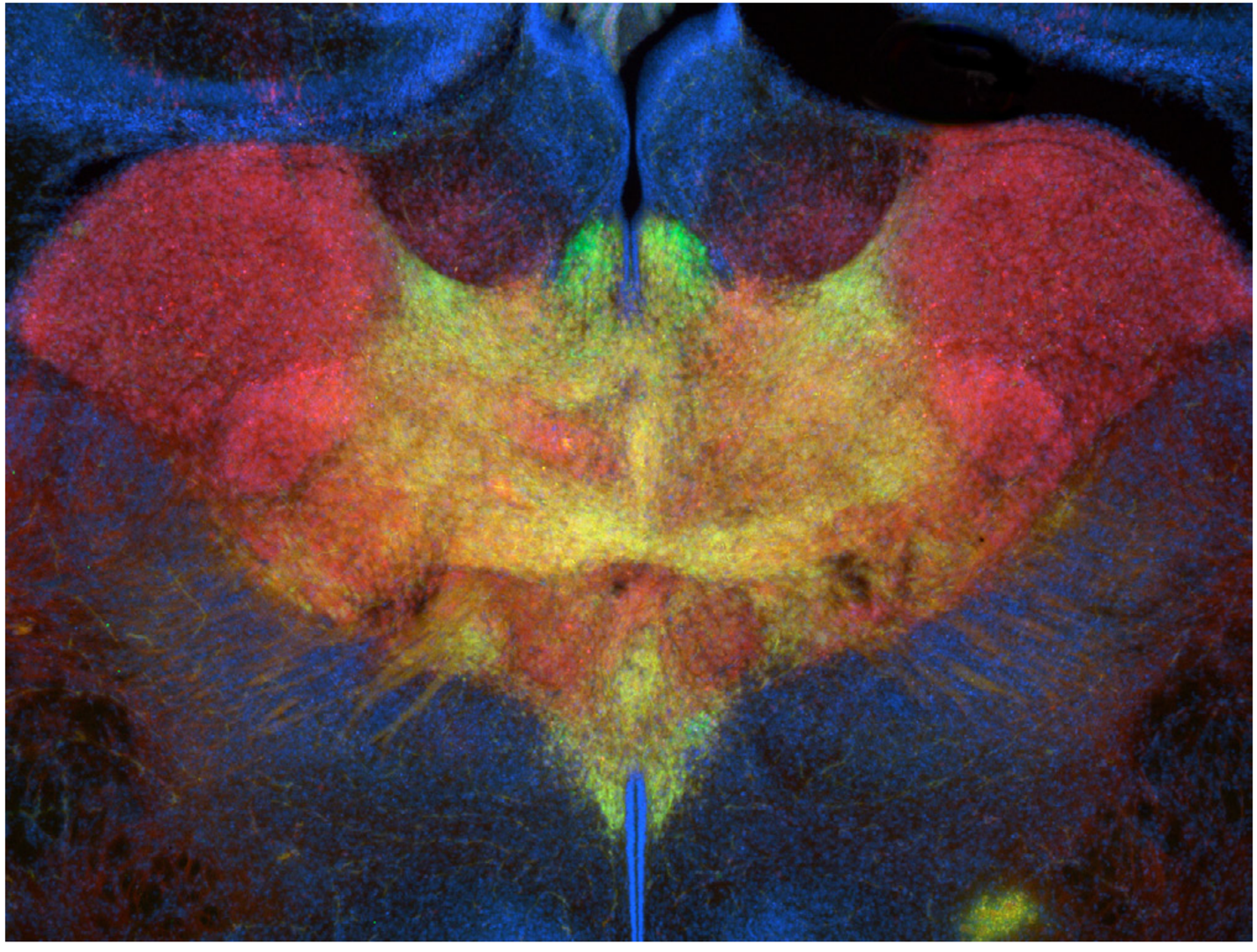


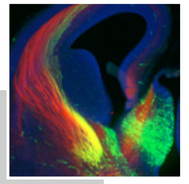


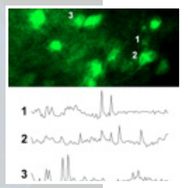
21 Cellular & molecular mechanisms of brain wiring

Guillermina López-Bendito CSIC

Selected Publications
Personnel







22 Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

Selected Publications
Personnel

Principal Investigator
Jorge Manzanares

PhD Investigator
Carlos Leiva Santana

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Francisco Navarrete Rueda
María Auxiliadora Aracil Fernández
María del Carmen Montesino Vázquez

Technical Staff
Patricia Rodríguez García
Analía Rico Rodríguez


ARR


FNR


MSGG


MAAF


JM

22 Translational neuropsychopharmacology of neurological and psychiatric diseases

Jorge Manzanares UMH

Oliva, J.M., Manzanares, J. Gene transcription alterations associated to decrease of ethanol intake induced by naltrexone in brain regions of Wistar rats. **Neuropsychopharmacology** 32(6): 1358-1369 (2007).

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Rubio, G, Martinez-Gras, I, Manzanares J Modulation of impulsivity by topiramate: Implications for the treatment of alcohol dependence **Journal of Clinical Psychopharmacology** 29(6): 584-589 (2009).

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García-Gutiérrez, MS, Pérez-Ortiz, JM Gutiérrez-Adan, A., Manzanares, J. Cannabinoid CB2 receptors overexpression results in a depression-resistant endophenotype **British Journal of Pharmacology** 160: 1773-1784 (2010).

Femenía, T., García-Gutiérrez, MS, Manzanares, J. CB1 receptor blockade decreases ethanol intake and associated neurochemical changes using Fawn-Hooded rats. **Alcohol Clinical and Experimental Research** 34(1): 131-141 (2010).

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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** (en prensa).

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.

23 Dynamics and plasticity of cortical sensory responses

Miguel Maravall CSIC

Selected Publications
Personnel

Principal Investigator
Miguel Maravall

PhD Investigator
Ana Lía Albarracín
Francisco Martini

PhD Student
Manuel Molano (with Luis Martínez)
Giovanni Ferrati

ALA

FM

MM

MM

23 Dynamics and plasticity of cortical sensory responses

Miguel Maravall CSIC

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.

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

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.

24 Neuronal specification and migration

Oscar Marín CSIC

Principal Investigator
Oscar Marín

PhD Investigator
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Cristina García-Frigola (with Beatriz Rico)
Diego M. Gelman
Cécile Jacques
Caroline Kappeler
Sandra Peregrín
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S. Ricardo Scott
Carolina Varela
Verona Villar

PhD Student
Juan A. Sánchez
Manuel Valiente
Gabriele Ciceri
Giorgia Bartolini

Technical Staff
Pedro Aracil (with Beatriz Rico)
Ángeles Casillas
María Antonio Fernández (with CONSOLIDER SP2)
Trinidad Gil
María Pérez

Administration
Virtudes García

24 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.

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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.

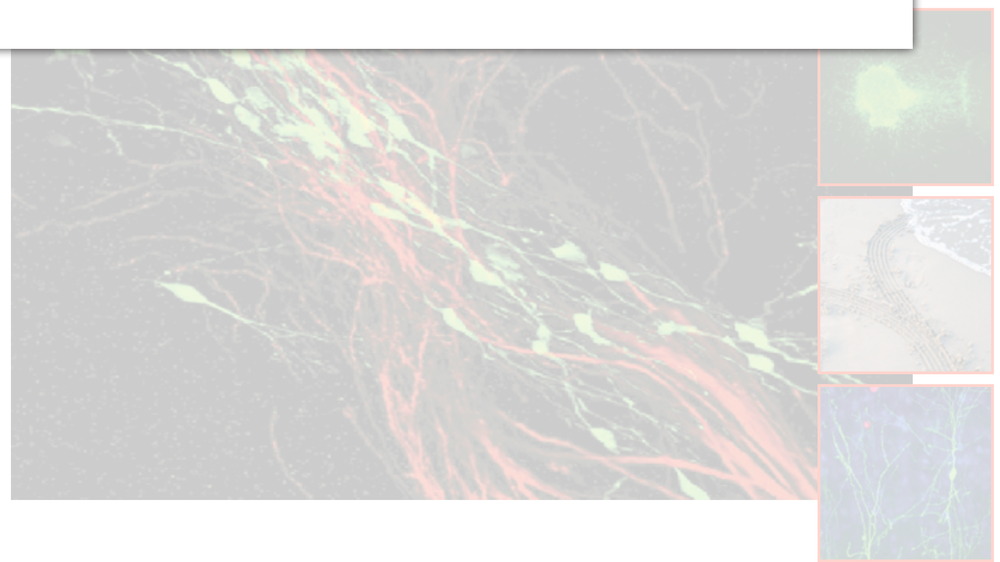
Gelman DM, Martini FJ, Nóbrega-Pereira S, Pierani A, Kessaris N, Marín O (2009) The embryonic preoptic area is a novel source of cortical GABAergic interneurons. **Journal of Neuroscience** 29:9380-89.

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 (2010) Cxcr7 controls neuronal migration by regulating chemokine responsiveness. **Neuron** 69(1) 77-90.

how the different types of neuronal precursors decide their fate.

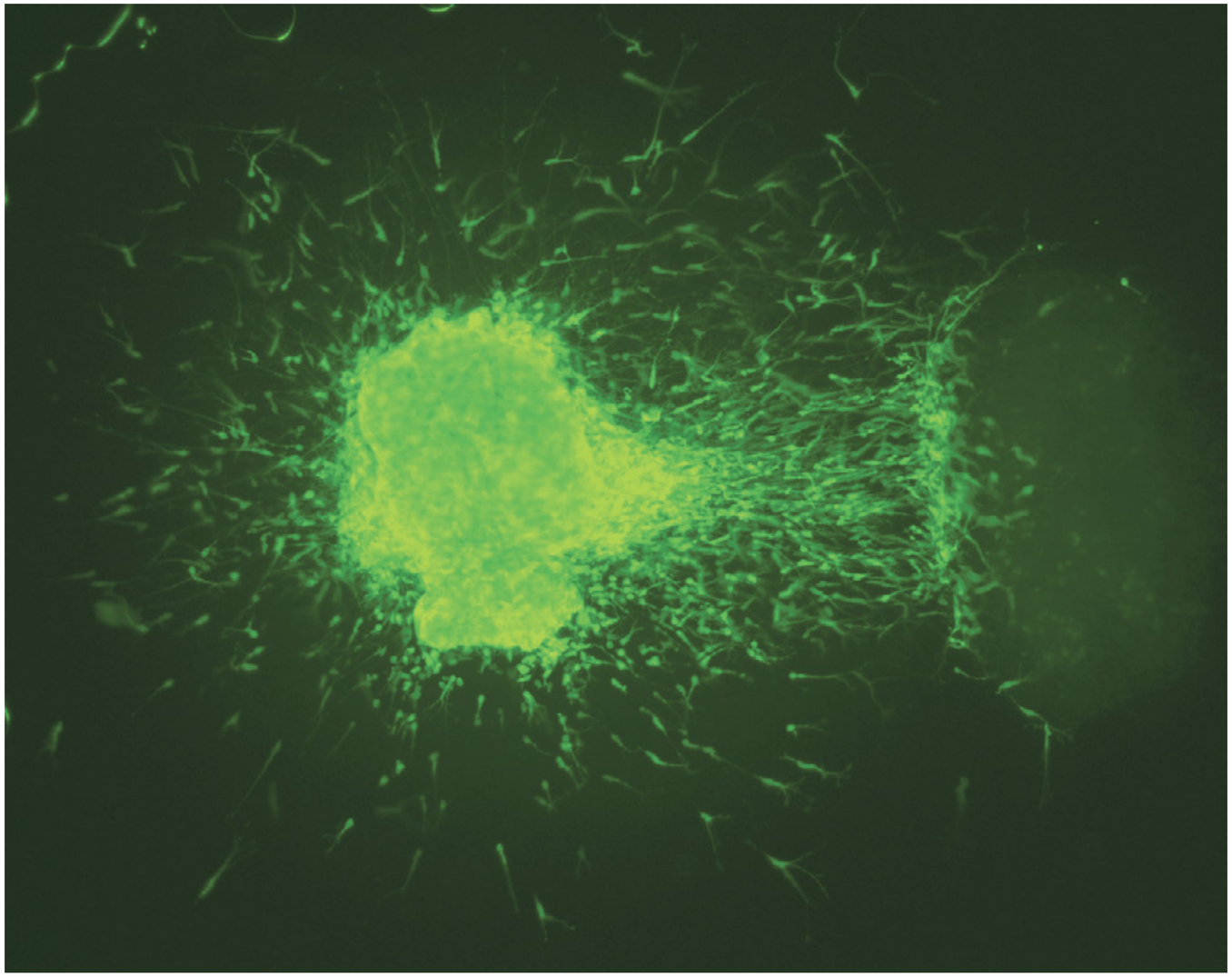
In addition, since proliferative regions are normally located at a distance from the place where neurons finally reside and function, new neurons have to move to reach their final position in the telencephalon. The process of neuronal migration is particularly complex in the cerebral cortex, where neurons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



[24] Neuronal specification and migration

Oscar Marín CSIC

Selected Publications
Personnel



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24 Neuronal specification and migration

Oscar Marín CSIC

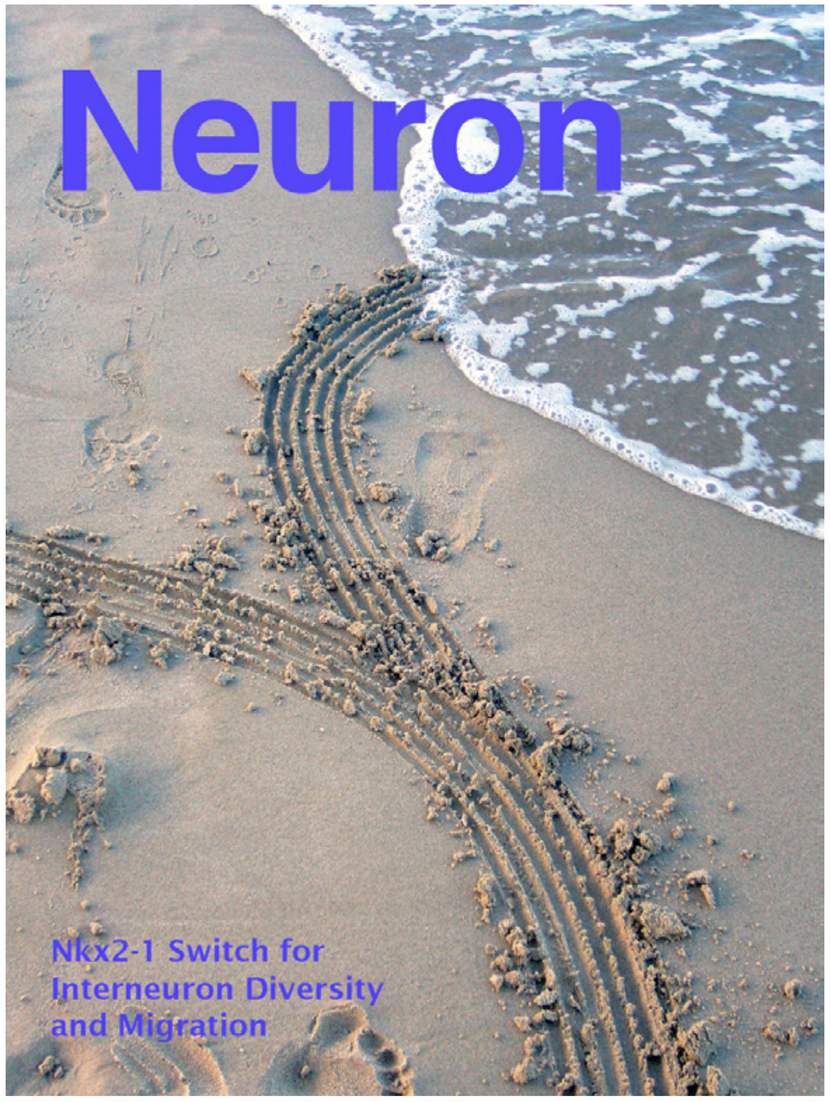
Selected Publications
Personnel

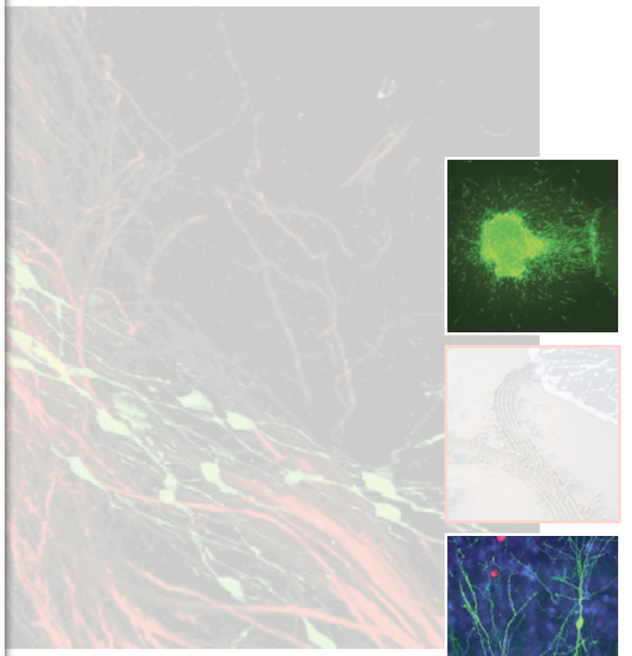
The main aim of our labo molecular and cellular m development of the most ante telencephalon. The telencepha for the function of the mamma ganglia and the cerebral co for example, is the larger str system and is essential for th distinguish us as humans.

As in other regions of the c telencephalic neurons are gen from precursor cells located i "proliferative zones". In most of birth of a neuron highly characteristics (such as its ne example). However, we still ha of the factors that control thi specification". Our group is i the molecular mechanisms c of different neuronal populati other words, we want to disc how the different types of n their fate.

In addition, since prolife located at a distance from finally reside and function, n to reach their final position process of neuronal migratio the cerebral cortex, where ne long distances to reach their d research interests of our la the cellular and molecular the migration of cortical ne multiple experimental metho embryology, time-lapse micro

t of its efforts in the identification of novel genes trolling the development of cortical interneurons, pe of cortical cell which dysfunction underlies the logy of neurological and psychiatric disorders such as epsy or schizophrenia. To this aim, we are generating se strains 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 neuron deficiency, which we hope may contribute nderstand the function of cortical interneurons.





24 Neuronal specification and migration

Oscar Marín CSIC

Selected Publications
Personnel

The main aim of molecular and
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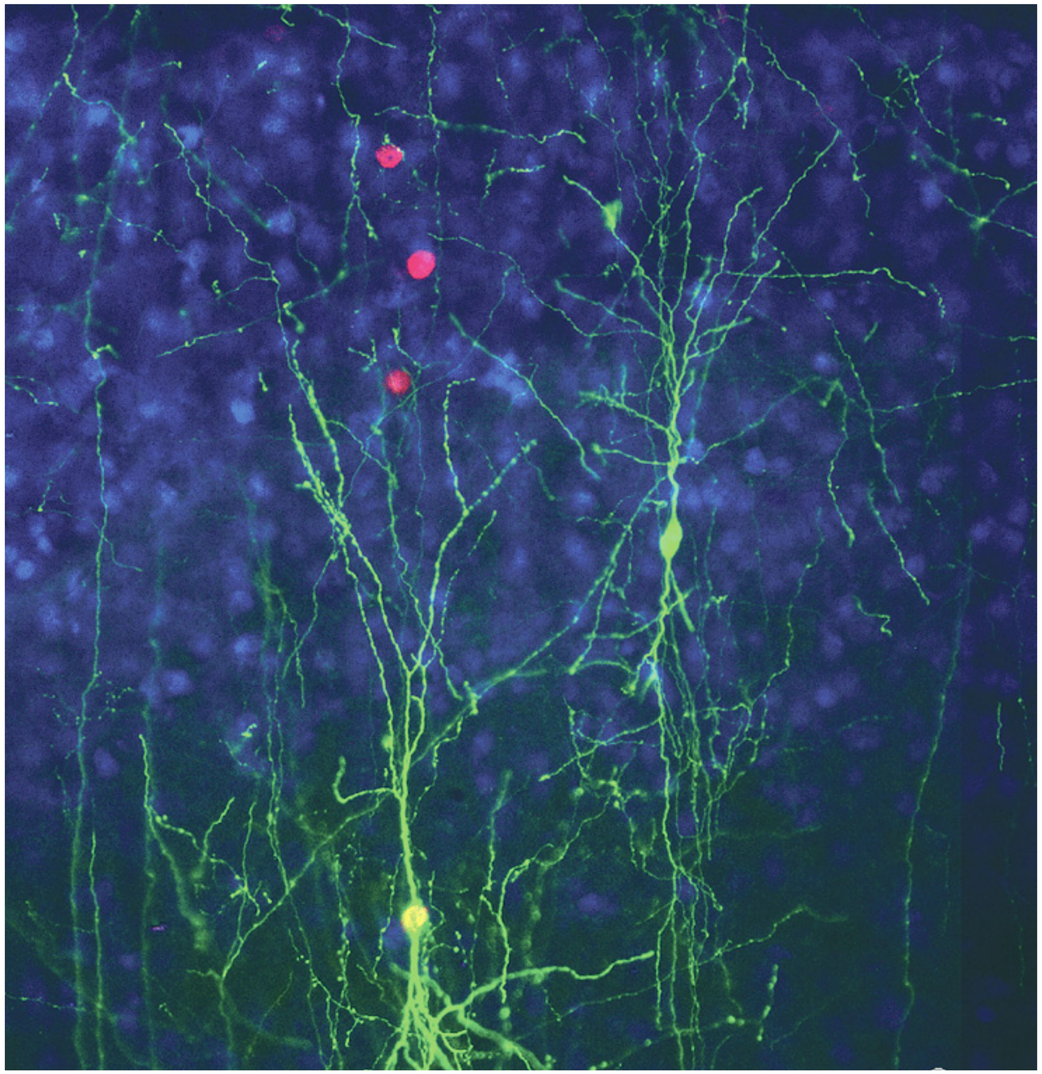

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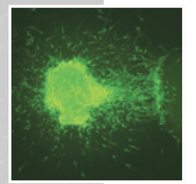

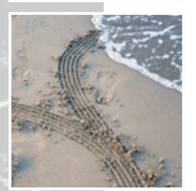

25 Visual Neuroscience Laboratory

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

25 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.

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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.

26 Experimental Embryology

Salvador Martínez UMH
Constantino Sotelo UMH

Principal Investigator
Salvador Martínez
Constantino Sotelo
Eduardo de Puelles
Diego Echevarria

PhD Investigator
Arancha Botella
Carlos Bueno
Elisabetta Caspani
Philip Crossley
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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
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Juan Antonio Moreno
Maria Navarro
Ariadna Perez
Carmina Ramirez

Administration
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Technical Staff
Olga Bahamonde
Paloma Gomez Morgan
Mónica Rodenas
Aurelia Torregrosa
Alicia Estirado


SM


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

26 Experimental Embryology

Salvador Martínez UMH
Constantino Sotelo UMH

Crossley, P.H., Martinez S. and Martin, G.R. (1996) Midbrain development induced by FGF8 in the chick embryo. **Nature**. Mar 7;380(6569):66-8.

Reiner, O., Cahana, A., Escámez T. and Martínez, S. (2002) "LIS1- no more no less". **Mol. Psychiatry**. Jan; 7 (1):12-6.

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Sotelo, C. (2008) "Development of "pinceaux" formations and dendritic translocation of climbing fibers during the acquisition of the balance between glutamatergic and gamma-aminobutyric acidergic inputs in developing Purkinje cells". **Journal of Comparative Neurology** 506: 240-262

Di Meglio, T., Nguyen-Ba-Charvet, K., Tessier-Lavigne, M., Sotelo, C. and Chedotal, A. (2008) "Molecular mechanisms controlling midline crossing by precerebellar neurons". **Journal of Neuroscience** 28: 6285-6294

Martínez-Ferre A & Martínez S (2009) "The development of the thalamic motor learning area is regulated by Fgf8 expression". **J. Neurosci.** 29(42): 13389-13400 (2009)

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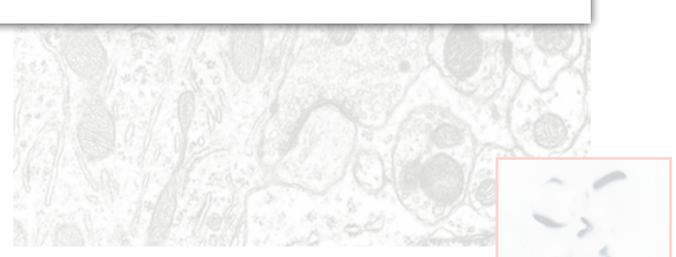
Mashimo, T., Hadjebi, O., Amair-Pinedo, F., Tsurumi, T., Langa, F., Serikawa, T., Sotelo, C., Guenet, J.L. and Rosa, J.L. (2009) "Progressive Purkinje cell degeneration in tambaleante mutant mice is a consequence of a missense mutation in HERC1 E3 ubiquitin ligase." **PLoS Genet.** 5(12):e1000784. Epub 2009 Dec 24.

Garcia-Lopez R, Martinez S. (2010) "Oligodendrocyte precursors originate in the parabasal band of the basal plate in prosomere 1 and migrate into the alar prosencephalon during chick development". **Glia**. 58:1437-50.

Jones J, Jaramillo-Merchán J, Bueno C, Pastor D, Viso-León M, Martínez S. (2010). "Mesenchymal stem cells rescue Purkinje cells and improve motor functions in a mouse model of cerebellar ataxia". **Neurobiol Dis.** 40:415-23.

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 analyze the expression pattern of 16.000 genes at several embryonic stages of mice (www.eurexpress.org/ee/). The further genetical manipulation by homologous recombiantion 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

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 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 analyze the expres at several embryonic stages of ee/). The further genetical m recombiantion will help us to of these genes. Currently we important of human neuropa created a line of research i of lisencephaly, several cort

27 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

Student
Rebeca Blázquez Durán

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

27 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

Blanco, M.J., Barrallo-Gimeno, A., Acloque, H., Reyes, A.E., Tada, M., Allende, M.L., Mayor, R. and Nieto, M.A. (2007). Snail 1a and 1b cooperate in the anterior migration of the axial mesendoderm in the zebrafish embryo. **Development** 134, 4073-4081.

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.

Morales, A.V., Acloque, H., Ocaña, O.H., De Frutos, C.A. and Nieto, M.A. (2007). Snail at the crossroads of symmetric and asymmetric processes in the developing mesoderm. **EMBO reports** 8, 104-109.

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

Mingot, J.M., Vega, S., Maestro, B., Sanz, J.M. and Nieto, M.A. (2009) Characterization of Snail nuclear import pathways as representatives of C2H2 zinc finger transcription factors. **J. Cell Sci.** 122, 1452-1460.

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.

Franco, D.L., Mainez, J., Vega, S., Sancho, P., Murillo, M.M., de Frutos, C.A., del Castillo, G., López-Blau, C., Fabregat, I. and Nieto, M.A. (2010) Snail1 suppresses TGF-b-induced apoptosis and is sufficient to trigger EMT in adult hepatocytes. **J. Cell Sci.** 123, 3467-3477.

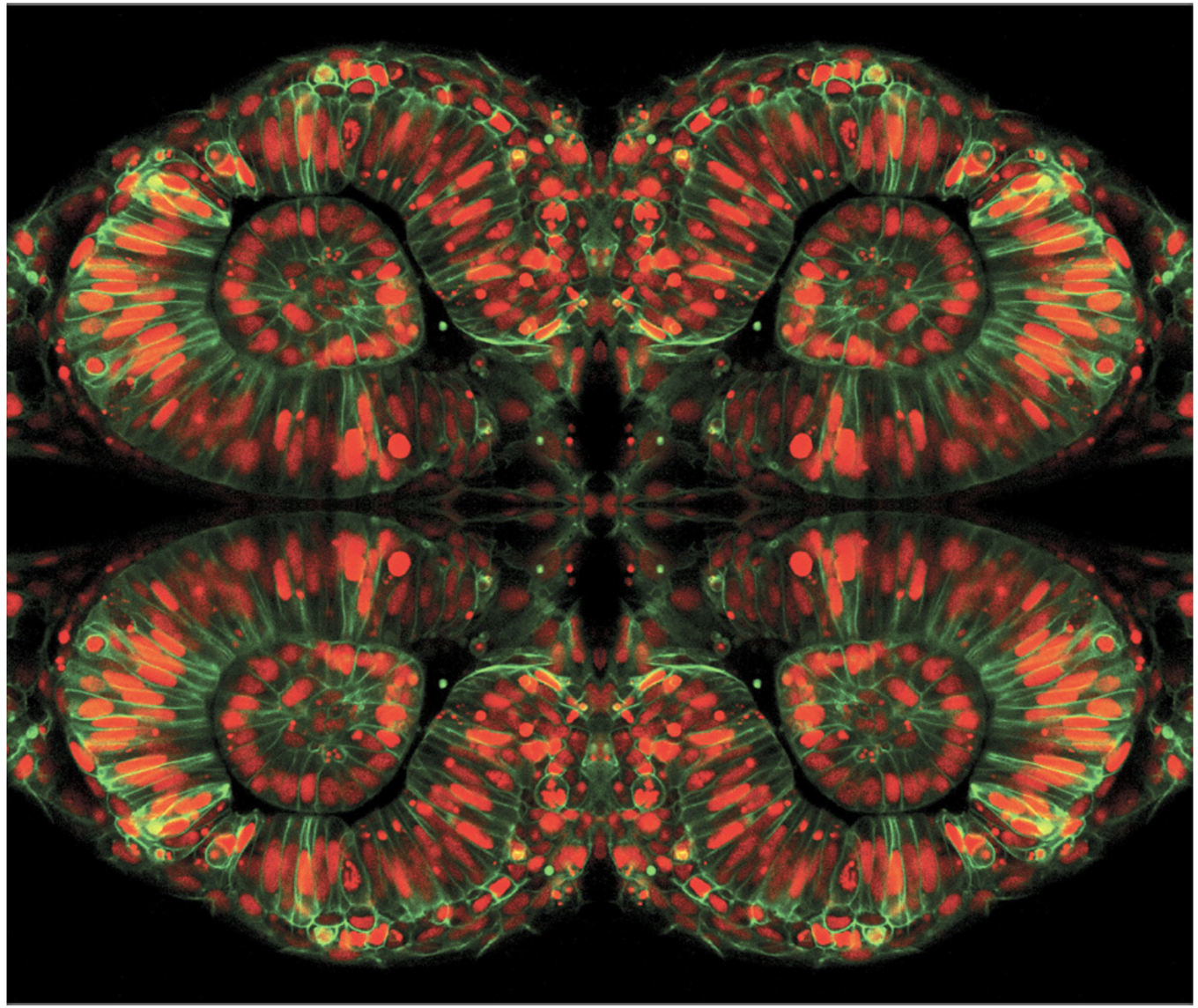
Rodriguez-Aznar, E. and Nieto, M.A (2010). Repression of Puma by Scrtach2 is required for neuronal survival during embryonic development. **Cell Death Diff.** In press

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 a tandem duplication in the last common ancestor of the Diploblasts and Bilateria (2009). We have also characterized the nuclear import pathways that regulate the activity of Snail proteins as representatives of C2H2 zinc finger transcription factors (2009). These studies will favour the analyses of ancestral and acquired functions. We have found that Scrtach is not involved in the

27 Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications
Personnel



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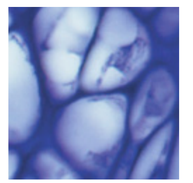

27 Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications
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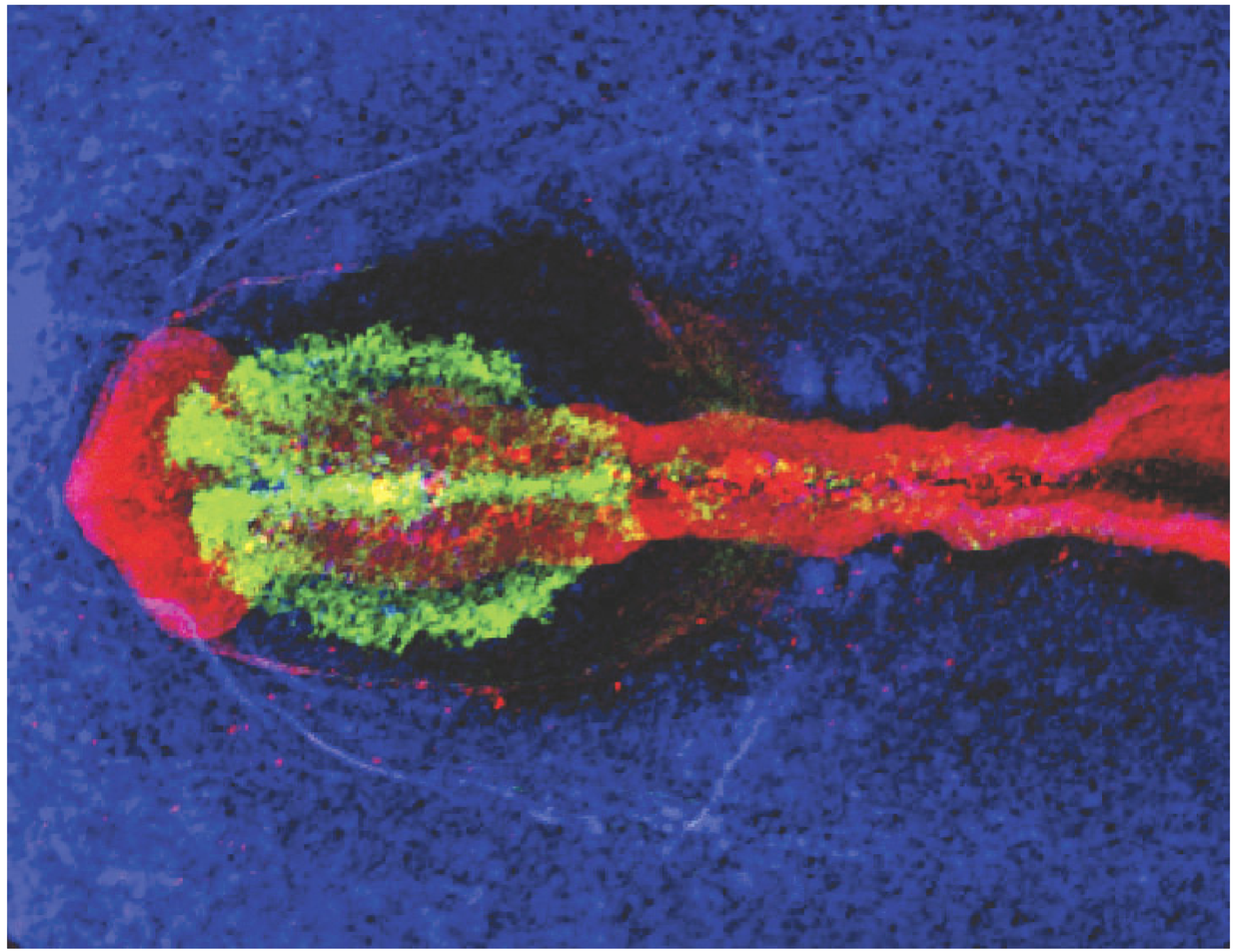

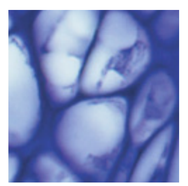

27 Cell movements in development and disease

M. Angela Nieto CSIC

Selected Publications
Personnel

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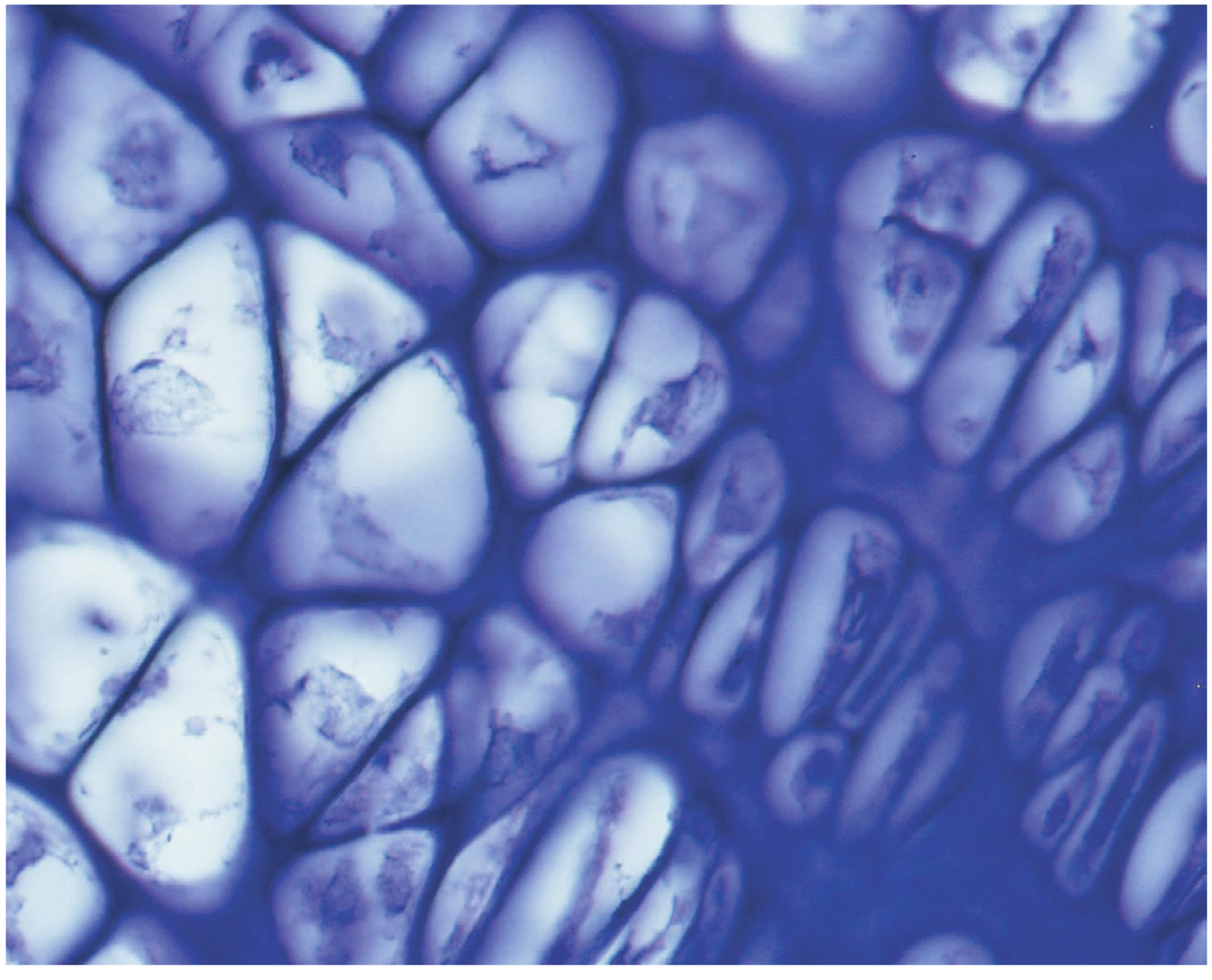
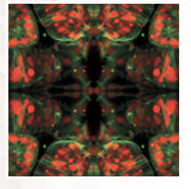
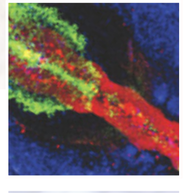






28 Neural circuit formation and remodeling

Beatriz Rico CSIC

Principal Investigator
Beatriz Rico

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

PhD Student
Mariola R. Chacón
Ana Navarro
Carlos Sánchez

Technical Staff
Diana Baeza

BR

AN

DB

CGF

28 Neural circuit formation and remodeling

Beatriz Rico CSIC

Rico, B., Xu, B., Reichardt, LF. (2002). TrkB receptor signaling is required for the establishment of GABAergic synapses in the cerebellum. **Nature Neuroscience**, 5(3): 225-233.

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).

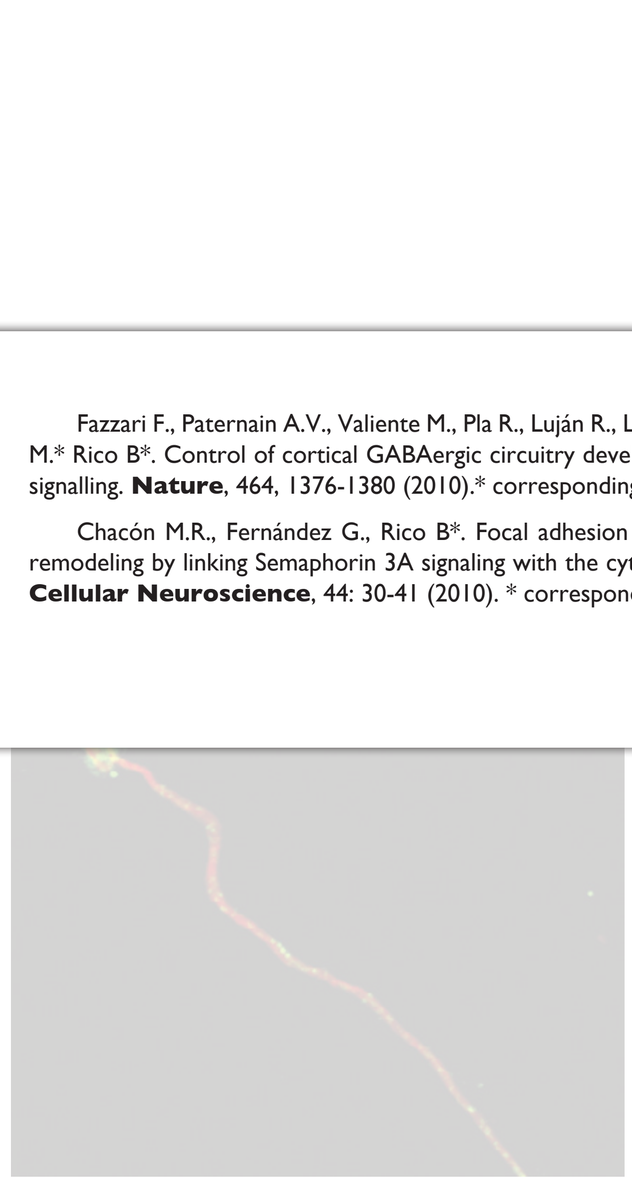
Sánchez-Huertas and Rico B*. BDNF/TrkB signaling controls the maturation of the GABAergic synapses via transcriptional regulation of GAD65. **Cerebral Cortex**. on line, August 25, doi:10-1093 (2010). * corresponding author.

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.

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 arborization. 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 which might be involved in the assembly of neural circuits.

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



29 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
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Maria Letizia Campanari

Technical Staff
Carol Serra Basante

JS

29 Altered molecular mechanism in Alzheimer's disease and dementia

Javier Sáez Valero UMH

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).

García-Ayllón MS, Riba-Llena I, Serra-Basante C, Alom J, Boopathy R, Sáez-Valero J. Altered levels of acetylcholinesterase in Alzheimer plasma. **PLoS One** 5:e8701 (2010).

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)

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

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)

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.

We also collaborate actively with clinicians and basic research in the study of liver cirrhosis and its most common neurological complication, hepatic encephalopathy.

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.

30 Biophysics and pharmacology of ionic channels

Francisco Sala UMH
Salvador Sala UMH

Selected Publications
Personnel

Principal Investigator
Francisco Sala
Salvador Sala

PhD Student
Jose A. Bernal
Philip Wikman

Technical Staff
José Mulet

JM

SS

FS

30 Biophysics and pharmacology of ionic channels

Francisco Sala UMH
Salvador Sala UMH

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

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.

31 Molecular neurogenetics

Francisco Tejedor CSIC

Selected Publications
Personnel

Principal Investigator
Francisco Tejedor

PhD Student
Guillermo Jofre
Edgar Ulin Avila
Roberto Narducci

Technical Staff
Rodrigo Barriuso Porras
Esther Llorens
Jitka Hájková

EUA EL

FT

31 Molecular neurogenetics

Francisco Tejedor CSIC

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.

B. Hammerle, C. Elizalde, J. Galceran, W. Becker, and F.J. Tejedor (2003) The MNB/DYRK1A protein kinase: Neurobiological functions and Down Syndrome implications. In "Advances in Down Syndrome Research" **J. Neural Trans, Suppl.** 67: 129–137

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.

JA. Troca-Marín, A Alves-Sampaio, FJ. Tejedor, and ML Montesinos (2010) Local translation of dendritic RhoA revealed by an improved preparation of mouse forebrain synaptoneurosomes. **Mol. Cel. Neurosci.** 43(3):308-14.

F.J. Tejedor and B. Hämmerle (2010) MNB/DYRK1A as a multiple regulator of neuronal development **FEBSJ** 277

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.

32 Cell signalling during neuronal migration

Miguel Valdeolmillos UMH
Fernando Moya UMH

Selected Publications
Personnel

Principal Investigator
Miguel Valdeolmillos
Fernando Moya

PhD Student
Francisco Martini
Sarah Mertens

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32 Cell signalling during neuronal migration

Miguel Valdeolmillos UMH
Fernando Moya UMH

Selected Publications
Personnel

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.