CSIC
Consejo Superior de Investigaciones Científicas

UNIVERSITAS Miguel Hernández

INSTITUTO DE NEUROCIENCIAS

MEMORIA 2008-2009

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JUAN LERMA

Since the last progress report (2006-2007), the Instituto de Neurociencias (IN) has established itself as the most important neuroscience centre in Spain. As in previous years, the IN has increased the size of its staff, reaching a relatively stable population in these last two years. More important, examination of its scientific productivity reveals a rather significant increase, reaching quality values remarkably above the national average and above comparable European centres.

During these two years, some of our tenure-track researchers have left the IN to follow their careers in other centres or activities (Alejandro Barrallo, Albert Compte, Minerva Giménez-Ribotta, Juan Luque, José A Ortiz). We are very happy, however, with the new additions to the IN staff. These indicate a degree of turnover, always desirable and necessary in Science. Victor Borrell, Ana Carmena, Ana Gomis, Guillermina López-Bendito, Miguel Maravall and Javier Sáez were promoted from the Ramon y Cajal tenure track programme, and recently Santiago Canals took up the tenure position of Assistant Professor or equivalent. In further good news, Carmen de Felipe, Oscar Marín and Luis Miguel Gutierrez were promoted to Full Professors. Félix Viana, Francisco Tejedor y Angel Barco were also promoted to the category of CSIC Investigator. On the other hand, Mavi Sanchez-Vives moved on to a senior position at IDIBAPS to continue her research in Barcelona.

Concerning personnel demographics, we are proud of our 60% female / 40% male gender distribution, and 20% of our personnel comes from abroad.

Scientifically speaking, these two years have been excellent for the IN in both financial support and scientific productivity, evaluated relative to previously outlined plans. Remarkably, more than three fourths of the personnel are supported by contracts from competitive grants. This determines that the IN's scientific productivity and international impact keep growing, indicating the high dedication of its personnel to their duties. These two years have brought plenty of relevant milestones, fulfilling the IN's mission of contributing to fundamental knowledge about the brain. A list of selected milestones can be found elsewhere in this report. The evolution of our scientific impact can be appreciated by comparing the 2000-03 and 2006-09 four-year periods. While we have increased the number of papers by 60%, the number of citations to the periods' papers has more than doubled.

We are equally proud to announce that during these last two years, a number of IN members have received significant recognition by different institutions. Carlos Belmonte was awarded the National Prize in Medicine "Gregorio Marañon"; Maria Dominguez received the Cobos Foundation 2008 Research Prize; Oscar Marin was the awardee of the III Banco Sabadell Prize for Biomedical Research. Moreover, in 2009, Angela Nieto was the recipient of the Rey Jaime I Award for Basic Research and appointed as a member of the Academia Europea; Salvador Martínez was appointed as "Importante" and "Ilicitano en la Onda" by the newspaper Información and the broadcast station Onda Cero, respectively; I was voted President-elect of the Spanish Society for Neuroscience, which Presidency was just left by another member of the IN, Roberto Gallego. Further, Oscar Marin was elected as a member of the European Molecular Biology Organization (EMBO), adding to our IN community of 4 EMBO members. Last but not least, Guillermina López-Bendito obtained one of the prestigious ERC starting Grants, which will allow her to continue her studies on the plasticity of the thalamocortical pathway. This rewards

SALUTATION

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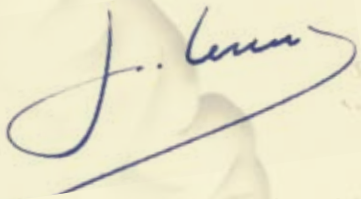
the IN's commitment to supporting young researchers and ratifies our belief in their future.

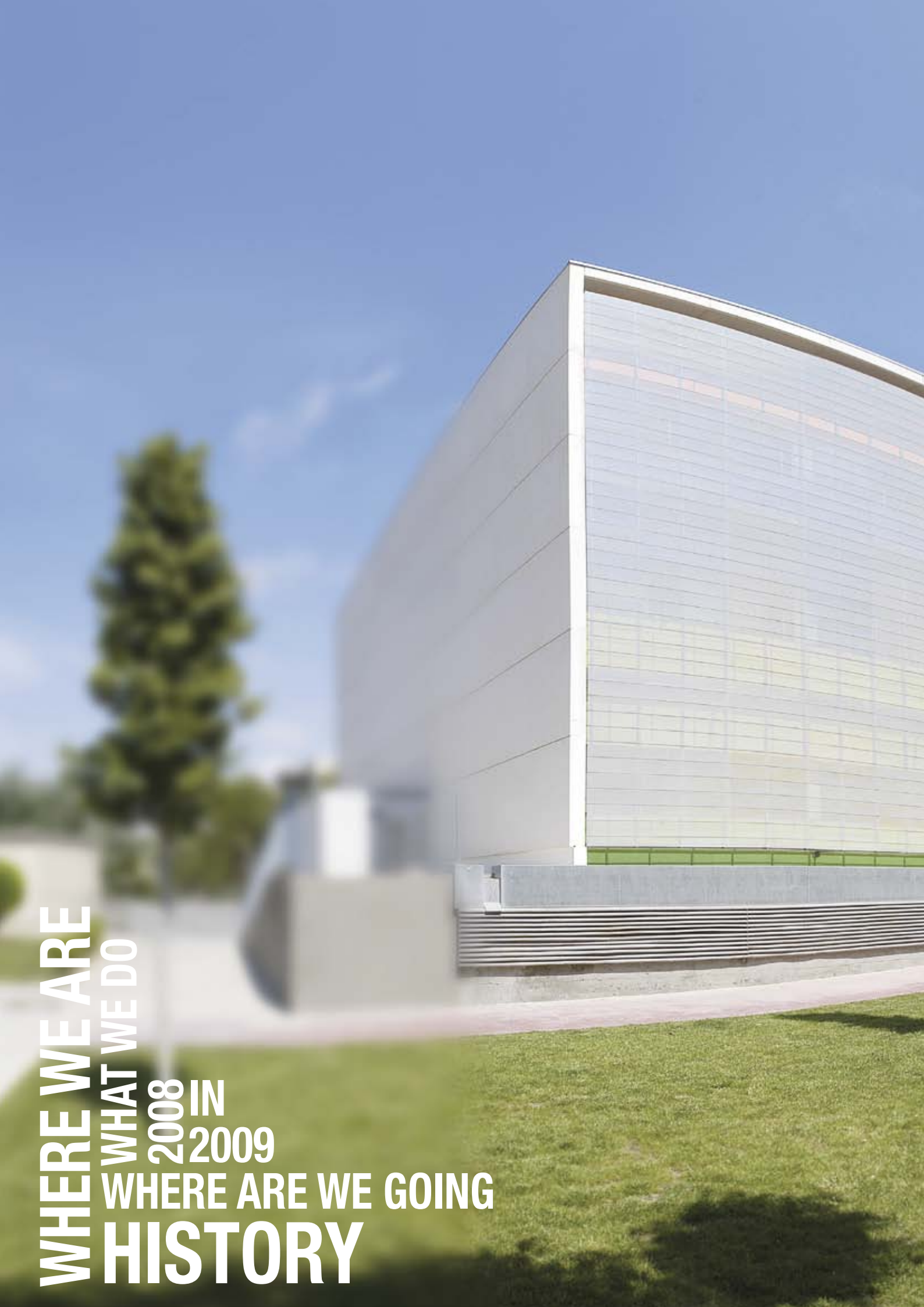
In 2009, we prepared and defended our action plan for 2010-2013. This was evaluated by an international panel of experts and scored very highly. We defined what we want to be, what we have, what we need and our strategy to fulfill our objectives. Along these lines, we strongly look forward to incorporating new cutting-edge technology to our Centre, in order to allow IN researchers to perform frontier brain research under similar conditions to our European and American colleagues. Indeed, the IN is in the process of incorporating latest-generation techniques such as high-field functional nuclear magnetic resonance imaging (fMRI) and fluorescence assisted cell sorting (FACS). This amounts to a 2.2 million € investment in 2010, obtained thanks to the support of the MICINN, Valencian Community Government, CSIC and UMH. These new technologies will allow us to obtain high-resolution images from working brains as well as to isolate cells according to their specific markers, which will be crucial for the search of new molecules involved in tumorogenesis, brain disease and helping development of cell therapy.

A key development during this biennium has been launching an International PhD programme starting in the 2008-2009 academic year. Thirty one students have been admitted to this programme, 10 of them being supported by our 5-year CONSOLIDER programme.

Science and especially Neuroscience is going to change future social thinking and behavior; it is going to introduce radical changes in human attitudes and customs. I thank everyone at the IN, in one or another position, for their effort along these two years of contribution to the IN's 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.



Juan Lerma
Director



INSTITUTO DE NEUROCIENCIAS

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

The IN houses over fifty 60-70 m^2 laboratories for independent

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

WHAT WE DO

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

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

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

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

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

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 recognised international prestige. The IN currently has 40 tenured researchers (21 from the UMH and 19 from the CSIC), 8 non-tenure scientists, 142 doctoral and postdoctoral researchers and 92 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 successful competition for funding and awards. The number and quality of publications generated not only for the preceding period, but during 2008-2009 place the IN as one of the highest-ranking research centres in Spain with a competitive level in Europe (See graphic Impact Factors and Budget growth).

WHERE WE ARE GOING

In 2009, the IN completed its I Strategic Plan, which was requested by the CSIC in 2005, and prepared its II Strategic Plan for 2010-2013. In the former, the projects of the IN over the 2005-2009 period were outlined; in the latter, we delineate the strategies to follow for consolidation and for becoming a centre of excellence in the European Research Area. This Plan reaffirmed the IN's pursuit of excellence and the purpose of strengthening its lines of research dedicated to studying the brain at a systems level as well as to the study of brain pathology. To this end, we plan to stimulate transdisciplinarity and systems neurobiology and reinforce the study of integrative mechanisms that underlie human nervous system diseases. We will incorporate cutting-edge technology and will encourage collaboration with hospitals and health care centres. Development of state of the art facilities in imaging technology to study and explore the brain is in progress. The Institute is committed to incorporating outstanding international scientists and fully collaborating with other research centres, particularly those of European origin.

SELECTION OF THE MOST RELEVANT MILESTONES OF THE IN

1. A molecular characterization of thermal responses was undertaken in somatic and visceral sensory neurons. It has been determined in visceral neurons that the transducer of cold is the ionic channel TRPA1 (Fajardo et al., J. Neuroscience 2008). Moreover, this ion channel was identified as a new molecular target of 1,4 dihydropyridines, a large family of drugs extensively used in the treatment of hypertension and other cardiac diseases (Fajardo et al., Channels 2008). Similarly, the ionic channel TRPC5 was identified as a transducer of osmo-mechanical stimuli (Gomis et al., J. Physiology 2008) and that threshold to cold is determined by a balance in the expression of ionic channels TRPM8 and Kv1 in somatic neurons (Madrid et al. J. Neuroscience, 2009).

2. The involvement of direct transcriptional mechanisms in the control of neuronal migration shown for the first time. This work, which got the cover of Neuron, identified a new postmitotic function for a transcriptional factor typically involved in the specification of neuronal progenitors (Nobrega-Pereira et al., Neuron 2008).

3. The function of the chemokine CXCL12 and its receptor CXCR4 in the integration and regional distribution of interneurons in the cerebral cortex (López-Bendito et al., J. Neurosci. 2008) has been revealed.

4. Discovered a novel function for the PDZ domain-containing protein Canoe/AF-6 as a key regulator of asymmetric cell division, a universal and fundamental mechanism to generate cell diversity (Speicher et al., Current Biology 2008).

5. In the visual pathway, the axon guidance molecules involved in determining laterality at the midline during the formation of the optic chiasm have been previously unveiled. However the transcripcional mechanisms controlling this process remained unknown. We have identified the genetic program — the transcription factor Zic2 and its main effector molecule EphB1—that regulates the retinal axon decision of not-crossing the midline at the optic chiasm (García-Frigola et al., Development 2008).

6. We reached two important milestones on the characterization of tactile responses in the brain. First, we found that neurons in the somatosensory region of the cerebral cortex are intrinsically able to adjust their sensitivity to compensate exactly for variations in the overall magnitude of ongoing sensory stimuli, a behavior that recapitulates previous observations in vivo (Díaz-Quesada and Maravall, J. Neurosci. 2008). Second, we determined the nature of the tactile information represented by neurons of the main thalamic relay nucleus that sends information to the cortex. While different neurons all participate in encoding a stimulus, each transmits a different kind of information – a different message, representing a particular aspect of the stimulus (Petersen et al., Neuron 2008).

7. A direct interaction between two key proteins, presenilin 1, an enzyme involved in the generation of the β-amyloid peptide, and acetylcholinesterase, implicated in the pathogenesis of Alzheimer's disease has been found (Silveyra et al., Mol Cell Biol 2008). This interrelationship may be relevant to the design of therapeutic strategies, because both molecules are targets in Alzheimer's therapy.

8. The first direct evidence of a cholinergic imbalance in the brain as a consequence of liver failure has been found. This fact has been observed in the brain from both cirrhotic patients and rats subjected to bile duct ligation. Therapies based on the use of cholinesterase inhibitors for treating neurological manifestations associated with liver diseases thus deserve further consideration (García-Ayllón et al., Brain 2008).

9. We found that the metabotropic glutamate receptor mGlu1 regulates synaptic efficacy of hippocampal pyramidal neurons in alert mice during associative learning. Genetically or pharmacologically induced mGlu1 receptor insufficiency leads to impaired learning and diminished synaptic plasticity in neuronal circuits of the hippocampus (Gil-Sanz et al., Cerebral Cortex 18:1653-1663, 2008).

DURING 2008-2009.

10. A pioneering study has shown the extraordinary capacity that the brain has to re-establish fundamental axonal connections, such as the thalamocortical projection. Using a mutant mouse for Semaphorin 6A, this work shows how visual thalamocortical axons finally arrive to their target cortical area following alternative routes throughout the postnatal brain (Little et al., Plos Biol 2009).

11. A new study has unveiled a fundamental factor in the control of adult bone homeostasis, providing insight into the aetiology of pathological demineralization processes. This study shows that the activity of the Snail1 gene regulates osteoblast differentiation in such a way that while it is crucial for the initial steps of osteoblast differentiation, it needs to be downregulated for final differentiation to occur. As such, aberrant Snail1 activation leads to the generation of an immature osteoblast population unable to mineralize the bone, leading to osteomalacia (De Frutos et al., EMBO J., 2009).

12. The dual function of CREB in the modulation of synaptic and intrinsic plasticity has been uncovered in transgenic mice with altered levels of CREB activity. Also its role in memory and the deleterious consequences of its malfunction (Viosca et al., Learning and Memory 2009a; 2009b; Jançic et al. Cerebral Cortex 2009).

13. In collaboration with scientists at the Katholieke Universiteit Leuven (Belgium), it was explained the irritant effects of nicotine in patients using nicotine dermal patches during smoke cessation therapies. The discovery reveals that nicotine is a powerful activator of the ion channel TRPA1 in nociceptive sensory terminals (Talavera et al., Nat Neurosci 2009).

14. Finding that SNAP25, a protein of the SNARE complex, interacts with synaptic glutamate receptors and plays a fundamental role in regulating the strength of neuronal communication in a long lasting manner. This process is regulated by synaptic activity (Selak et al. Neuron 2009).

15. A new method to resolve the fine structure of the neural circuits of the cerebral cortex has been developed. This is based on the concept of potential synapse, a location in neuropil where an axon and a dendrite come within a certain distance so that a synapse can be formed by growing a spine or a bouton (Stepanyants et al., Cerebral Cortex, 2008). And allows to infer synaptic connectivity of a visual cortical column through the quantitative, statistical analysis of neuron morphology (Stepanyants et al., PNAS, 2009).

16. It has been established that a specific splicing form of neuregulin 1 gene controls Schwann cell proliferation in peripheral nerves, and that alterations in this signalling system is probably involved in the development of tumours of the peripheral nervous system like neurofibroma and Schwannoma (Gomez-Sanchez et al. J Neurosci. 2009)

17. Demonstration that mild hypothyroxinemia in gestating mothers induces a delay in neurocognitive development in children and that this delay is prevented by supplementing gestating mothers with potassium iodide from beginning of gestation (Berbel et al., Thyroid, 2009).

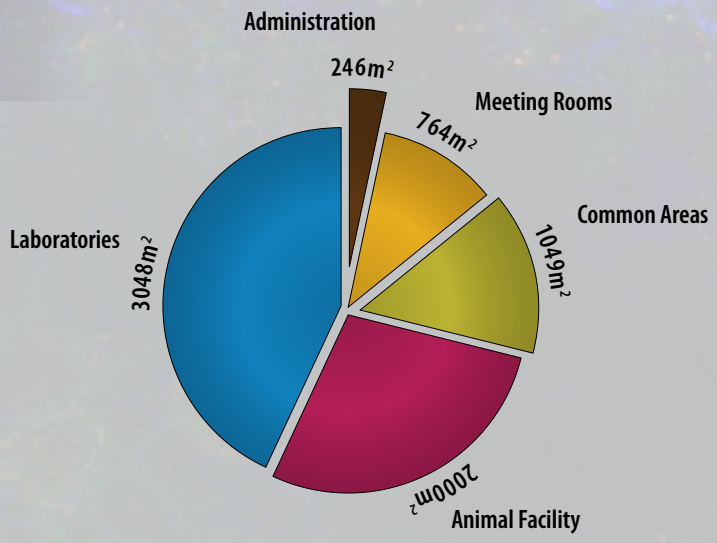
18. Demonstration of a specific function for the epigenetic modulation of transcription at a reduced number of biologically relevant loci on non-homeostatic, long-lasting, drug-induced behavioral plasticity (Sanchis-Segura et al. Neuropshychopharmacology, 2009).

19. Proposal of a new model of chemotaxis during neuronal migration and axon guidance, based on the fact that responses to chemoattractant signals take place by generating new leading process branches that are better aligned with the source of the gradient, and not by reorienting previously existing branches propose that directional sensing relies on growth cone dynamics (Martini et al. Development 2009).

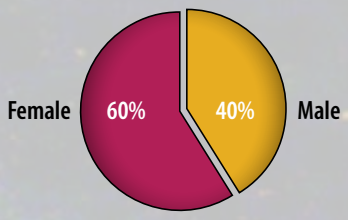
20. Description of new process of organizer formation and function, such that the morphogenetic organizer is a regulatory node integrating growth control by multiple oncogene and tumour suppressor pathways (Gutierrez et al. EMBO Reports, 2009).

THE INSTITUTE IN NUMBERS

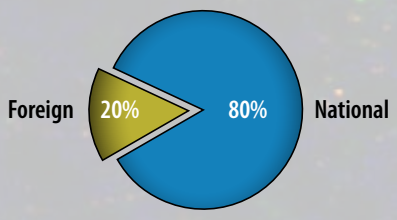
SURFACE DISTRIBUTION



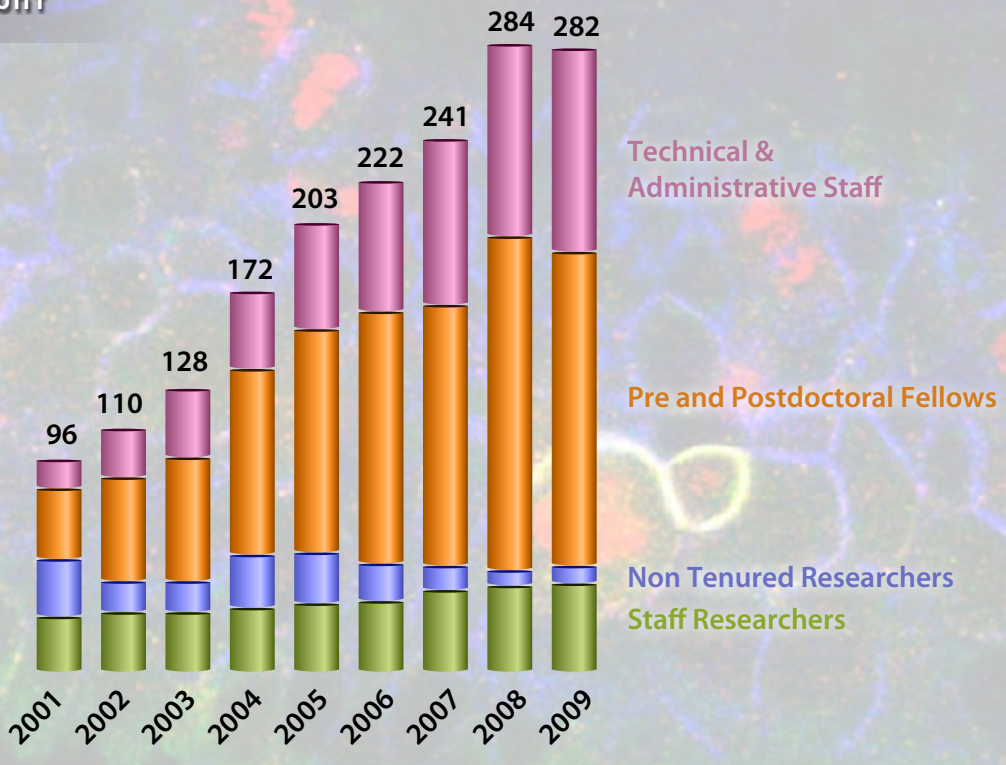
PERSONNEL BY GENDER



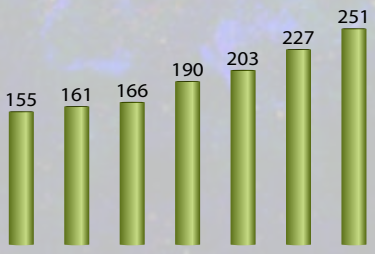
PERSONNEL BY ORIGIN



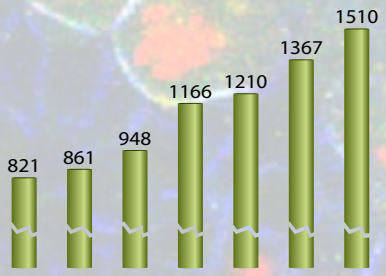
PERSONNEL BY CATEGORY



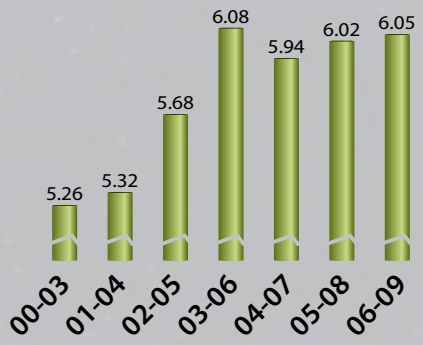
Number of Published Articles



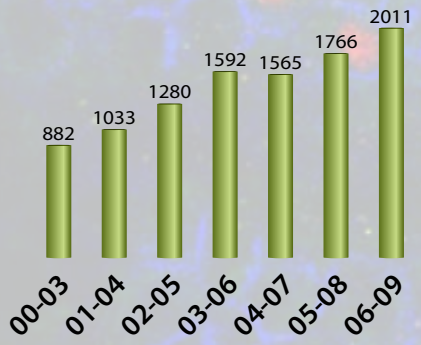
Cumulated Impact Factor



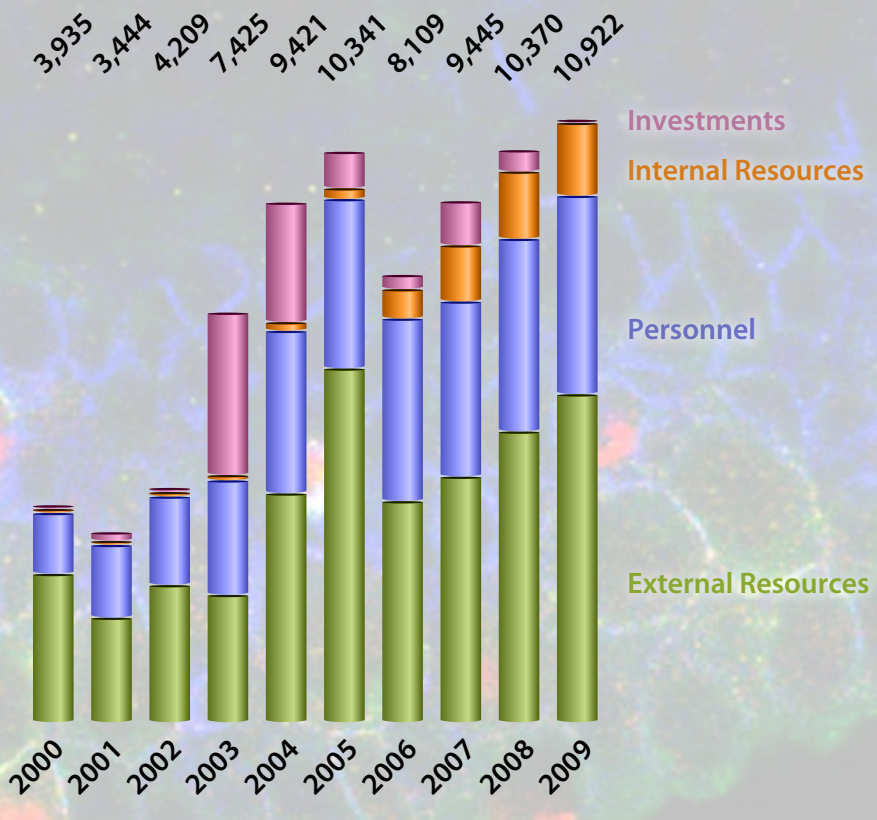
Average Impact Factor



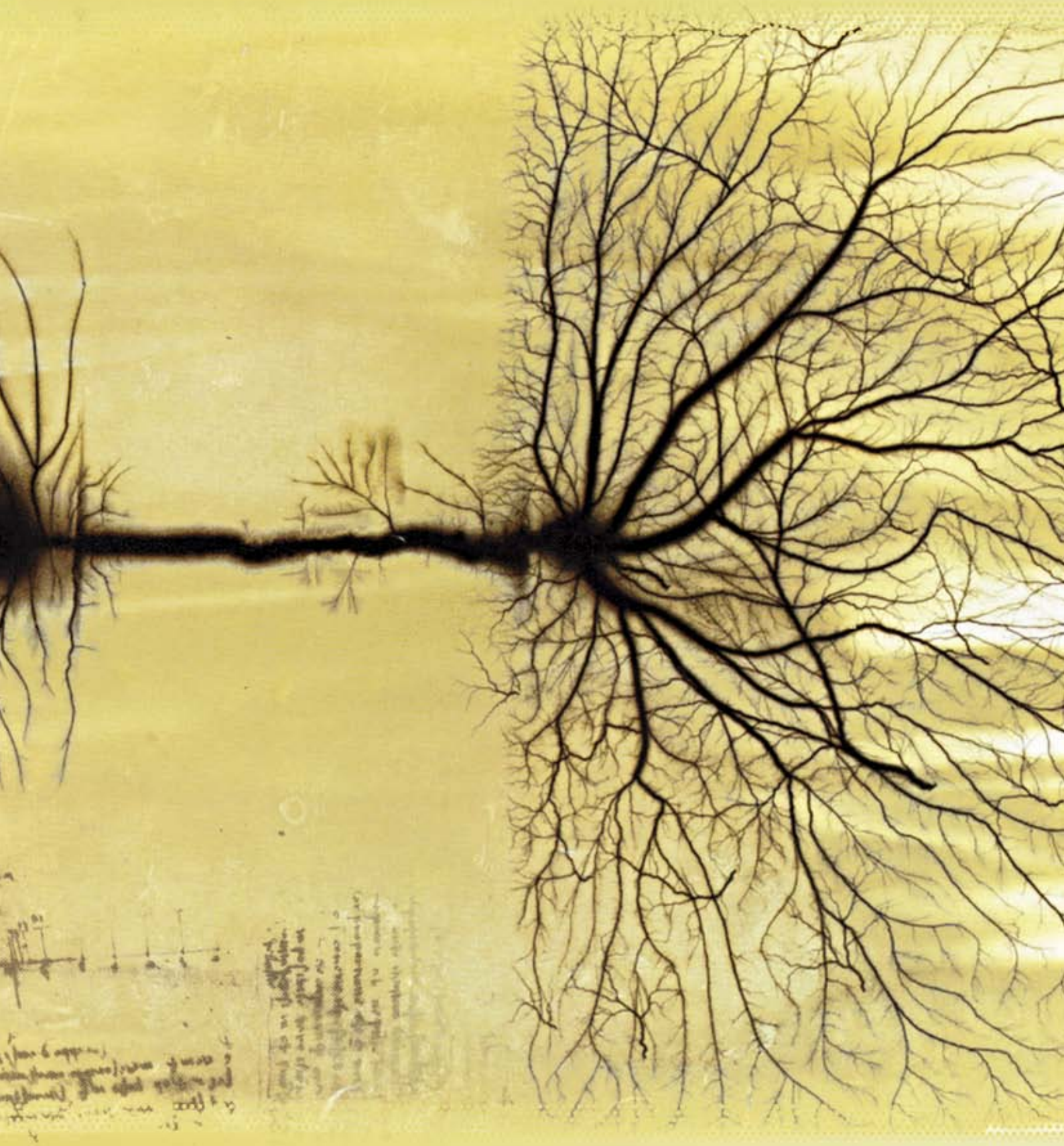
Citations



BUDGET GROWTH IN THOUSANDS OF EUROS



RESEARCH UNITS



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: Manuel Criado

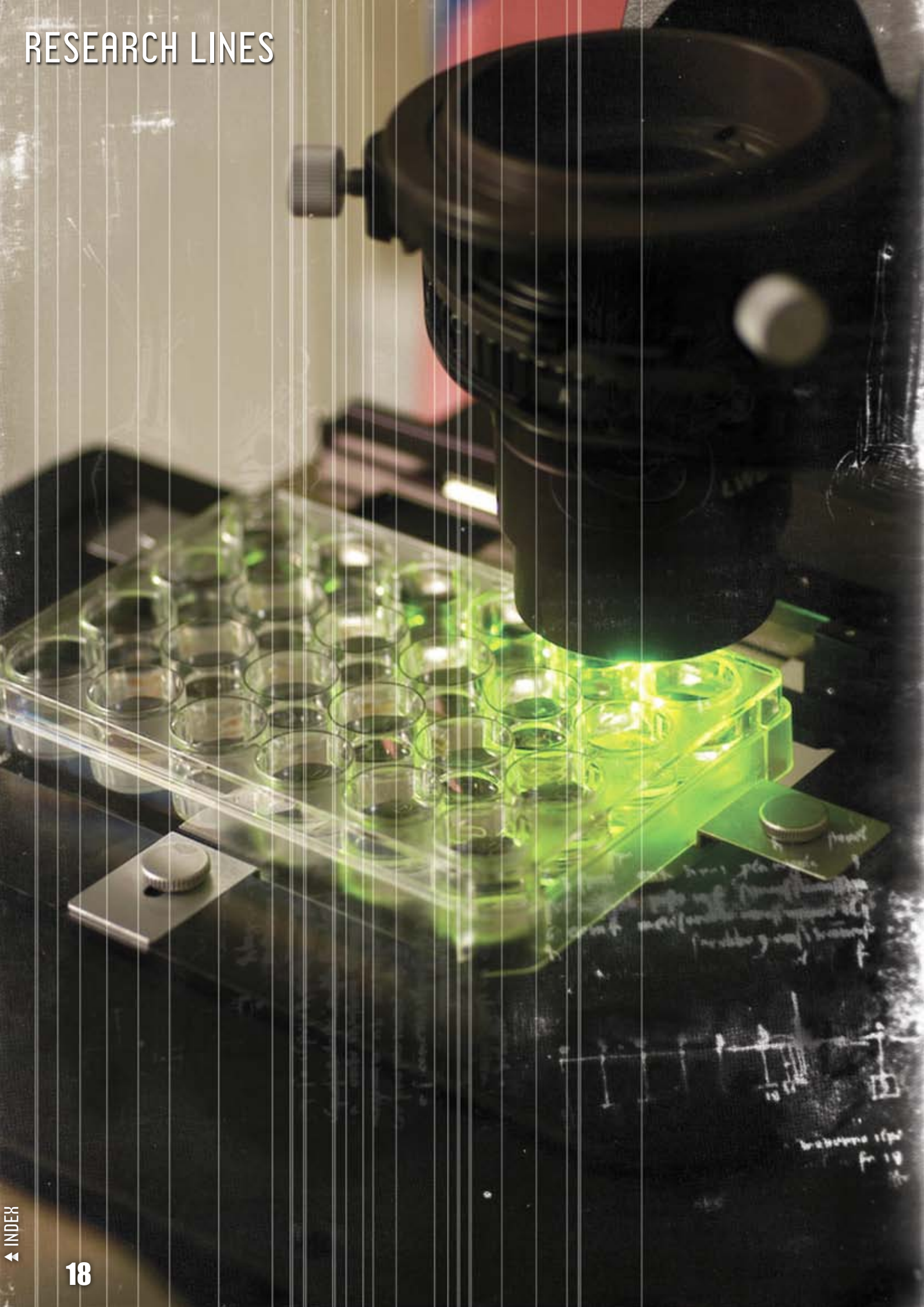
The Molecular Neurobiology Unit carries out research aimed to understand essential functions of the nervous system using a molecular approach. Towards this end, we use biochemistry, biophysics, pharmacology and molecular genetics and biology techniques (frequently combined with non molecular techniques 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.

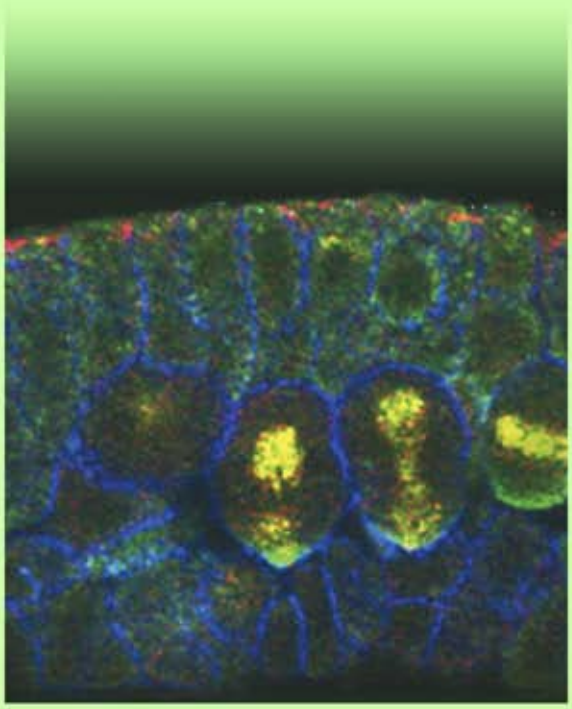
CELLULAR AND SYSTEMS NEUROBIOLOGY

Director: Roberto Gallego

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.

RESEARCH LINES





The nervous system is composed by a great diversity of cellular types interconnected within complex neural circuits. This neuronal activity allows the individual to respond and to adapt itself to its environment. The broad functional and cellular diversity of the nervous system is established mostly during the embryonic development, with the exception of some cells that are generated during the postnatal and adult period.

The groups included in the "Neurogenesis" line of research have as a common aim to characterize the cellular and molecular mechanisms that underlie the generation of neural cell diversity.

Using Drosophila as a model organism, some groups are studying the genetic bases that regulate the proliferation of neural precursors or the functional signaling networks that modulate the generation of neuronal identities during processes such as asymmetric cell division and neuronal morphogenesis. Other groups use the chick and the mouse as model organisms to study how proliferation and differentiation of neural precursors is regulated. Experimental embryology, cellular biology, biochemistry and molecular biology techniques are widely used by all groups of this research line to comprehend the mechanisms that generate the different cellular types that build the nervous system.

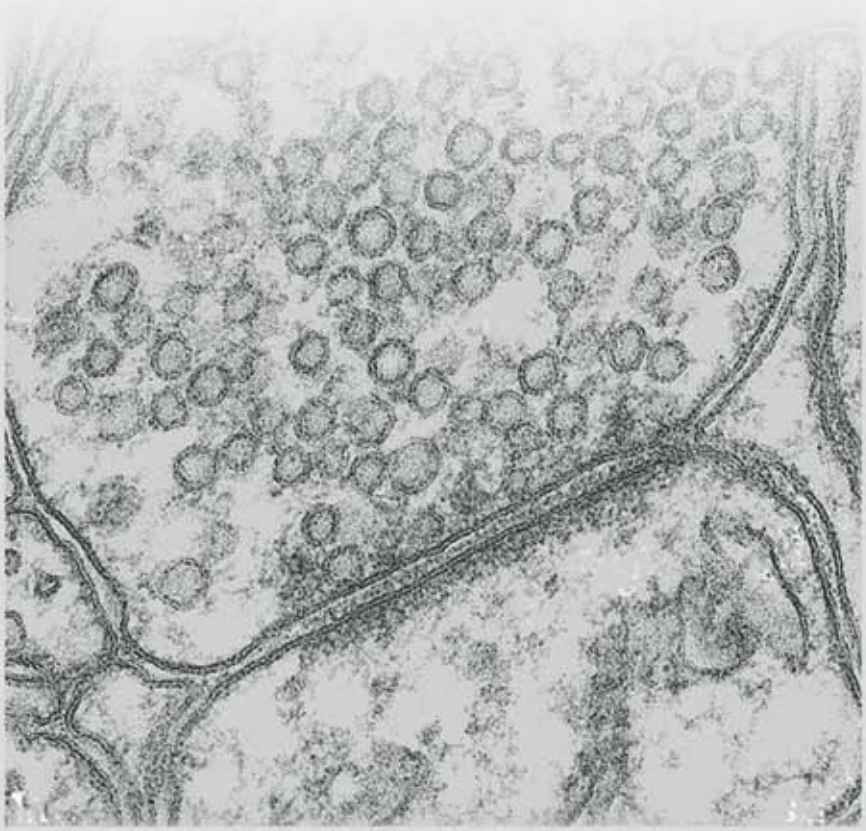
The functioning of the nervous system is determined by a system made up of billions of specific connections between neurons, as well as connections between neuronal and non-neuronal cells. The question of how this complex architecture of interactions is generated is one of the central problems in neuroscience.

During development precursor cells and neurons must often migrate from their point of origin to their final position. The neurons must then extend their axons and dendrites to establish connections, frequently in areas located far away from their cell bodies. The process of migration, as well as axon guidance, is controlled by an intricate network of chemical signals that guide precursors, neurons and axons via dynamic regulation of the cytoskeleton. What signalling systems control the formation of these thousands of millions of connections? How does cell identity control the guidance process? How is the exquisite reproducibility between individuals of this gigantic system of thousands of millions of connections attained during development?. These are fundamental questions tackled at IN with a multidisciplinary approach in which the genetic, cellular and molecular approaches in different organisms and model systems are implemented, with the use of modern imaging, biochemistry and electrophysiology techniques.

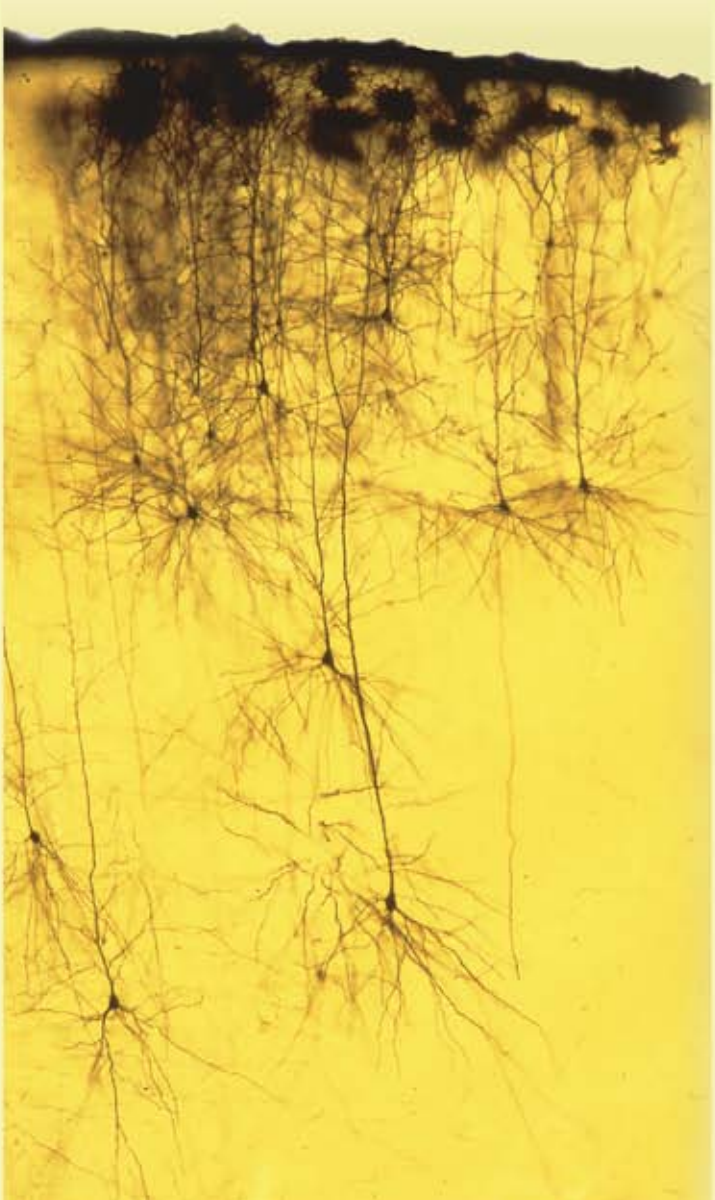
The term "morphogenesis" refers to the origin and development of the distinct parts that make up an organism and in the particular case of the nervous system to the formation of the distinct areas that compose the adult brain. During the process of morphogenesis it is necessary for precursor cells to 'make the correct decisions' regarding proliferation, differentiation, migration and survival. The coordination of these processes is frequently linked to the formation, in both vertebrates and invertebrates, of localized signalling centres called "organizers".

The investigations underway at IN aim to decipher the mechanisms used by these organizers to instruct neuronal precursors to divide or adopt different roles. In particular, we study the organizers associated with different signalling molecules and the connection between disruption of these pathways and several pathologies, including mental diseases and cancer. In this respect, other studies involve the functional analysis of the Snail family of transcription factors, which has important implications for both morphogenesis and tumor progression. Other investigators are contributing to the knowledge of cellular and molecular bases that specifically govern the morphogenesis of the telencephalon.

This line of research makes use of multidisciplinary approaches in terms of models and experimental strategies. These groups use the fruitfly Drosophila melanogaster, mouse, chick and zebrafish embryos as models in which Cell and Molecular Biology techniques together with imaging and Experimental Embryology are combined with high throughput screenings and molecular analysis at the genome level.



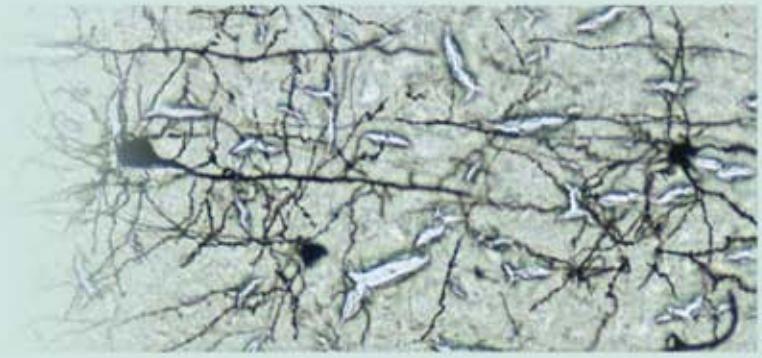
The study of cellular and molecular mechanisms that control processes of transmission and synaptic plasticity is essential to further understanding the functioning of the nervous system. The objectives of this line of research are centered on the understanding of the synapse and the role of synaptic plasticity processes in complex cerebral functions such as learning, memory, and addiction. Changes in synaptic activity are now considered as physical substrates for the formation of memories. In addition, alterations in these mechanisms underlay important pathologies of the nervous system. The subjects of investigation tackled by these groups range from detailed study of the mechanisms regulating processes of exocitosis and neurotransmission, to the study of regulation of synaptic plasticity during development and refinement of neuronal circuits that represent the anatomical substrate for the formation of memories, and their posterior modulation by the environment and experiences of the adult animal. The highly multidisciplinary approach takes advantage of diverse techniques: biochemistry and structural studies of a variety of receptors and channels, morphological studies based on advanced confocal and multiphoton microscopy techniques, diverse electrophysiological recording techniques in tissue and cell culture, as well as genetic expression studies and behavioural studies in genetically modified animals.

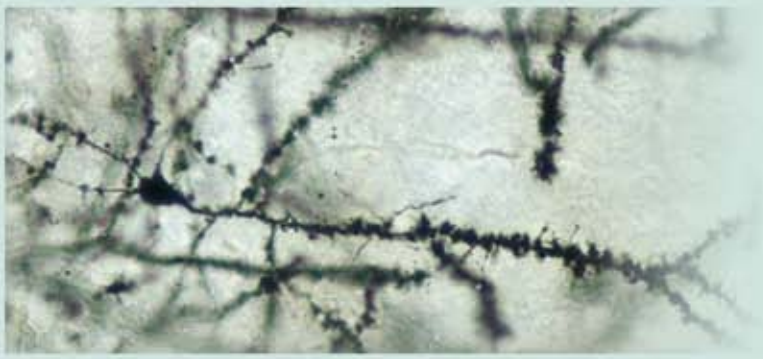


This research line concerns the study of how neuronal circuits are constituted and interact to perform the brain's characteristic functions. Most of our work is carried out in the cerebral cortex, studying developmental as well as adult stages. Our studies involve characterization of the anatomical properties, electrophysiology, biophysics and structure of neuronal networks, with the general aim of identifying relationships between these properties and the cerebral functions they give rise to. This area brings together researchers from various disciplines (medicine, biology, physics, and psychology) who study the brain at different levels ranging from synaptic and cellular biophysics and morphology to intact neuronal systems.

These studies are performed using diverse techniques: electrophysiological recording of neuronal and synaptic activity in brain slices and in the whole animal (anesthetized or awake with chronically implanted recording electrodes), immunohistochemistry, pathway tracing, imaging (including conventional, electron and fluorescence microscopy), genetically modified animals, computational models and virtual reality. All these methods are combined within intramural and extramural collaborations. These cover issues ranging from the epidemiology of hypothyroxinemia and its effects on cortical development during human gestation to the formulation of computer models that describe how activity in cortical neuronal networks emerges and propagates during complex tasks, or the measurement of electrical activity in the human cortex in the presence of virtual stimuli.

Our organism is constantly bombarded with signals from the outside world that the different sensory systems (sight, hearing, smell, taste, touch, nociception) must detect and translate into a common language that permits transmission from the periphery to the central nervous system. The final result of detection of these diverse signals is the generation of distinctsensations. Furthermore, another group of specialized sensors is in charge of monitoring the state of our internal environment in order to perform, normally unconsciously, the necessary corporal adjustments in the face of a changing external environment. The common language for all the sensory receptors consists in the generation of coded messages in the form of bursts of electric activity that contain information about the localization, intensity and duration of the different stimuli. The studies performed by groups in this line of investigation are directed to give us a better understanding of the cellular and molecular bases of transduction of somatosensory stimuli to electrical signals, with particular emphasis on those that produce painful sensations. These emotionally disagreeable sensations can be initiated by mechanical, thermal or chemical stimuli, which are generally of high intensity. Other investigations aim to decipher functioning of chemoreceptors of the carotid body. These sensory receptors detect changes in partial pressures of O_2 and CO_2, and in pH of the blood, as well as participating in control of respiration. This line of work is sustained by distinct groups at IN with diverse approaches such as psychophysical studies in humans, electrophysiological recording from neurons, receptors and sensory nerves, imaging studies, pharmacological studies, and molecular and biochemical analyses of distinct transduction proteins.





Due to its high complexity, the nervous system may develop many disabling pathologies. A diversity of researchers from the Instituto de Neurociencias is trying to understand (using molecular, genetic, electrophysiological and pharmacological approaches) the pathophysiology of the main human nervous system diseases, like Parkinson disease, Alzheimer's disease, Down syndrome, pain, demyelnating diseases, spinal cord injury and drug abuse.

With a focus on basic science, but also a strong interest in translational research, these groups collaborate with other hospital researchers and clinical departments within the country and abroad. Their aim is not only to unveil the genetic, molecular and cellular bases of neurological diseases but also to develop novel therapeutic approaches, to understand the mechanisms of action of the drugs currently used in clinics and to identify new molecular markers to improve the diagnosis and prognosis of nervous system diseases.

RESEARCH GROUPS

PHYSIOLOGY OF THE PREFRONTAL CORTEX
PHYSIOLOGY OF THE CAROTID BODY

Principal Investigators
Laura Almaraz
Emilio Geijo

PhD Students
Víctor Rovira

Scientist Collaborators
Carlos Pastore
Ofelia González

Our group is interested in the physiology of the nervous system. We are developing three 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 fibres 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). This work is carried out in collaboration with Dr. Salvador Martínez (Institute of Neurosciences).

- The physiology of the carotid body type I cells; these cells are quimioreceptors sensitive to the blood pH and partial pressure of O2 and CO2. We use membrane voltage and current recordings from dissociated carotid body cells kept in primary cultures. The specific objectives of this line of work are the study of: i) the calcium voltage dependent currents present in these cells and their role in the secretion of catecholamines. ii) the effects of natural stimuli and of metabolic venoms on the electrophysiological responses of carotid body cells.

- In addition to the above lines of work, and in collaboration with members 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

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MECHANISMS AND RECEPTORS INVOLVED IN ANALGESIA AND ADDICTION

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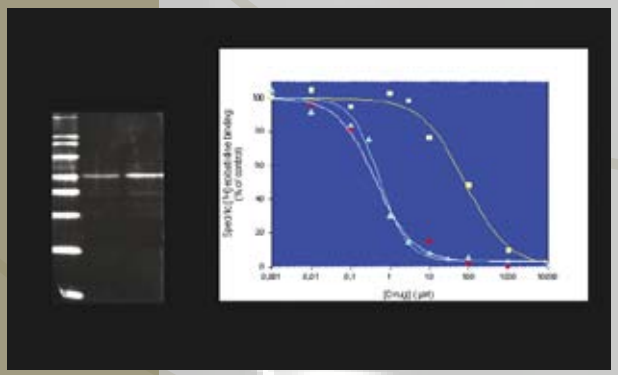
Nowadays, the most potent clinically used analgesics are the opioids. However, their clinical use is limited by their problems, such as tolerance, dependence and addiction. Neuronal nicotinic receptors are also involved in antinociceptive mechanisms, being some nicotinic agonists more potent analgesics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



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TRANSCRIPTIONAL REGULATION OF NEURAL PLASTICITY

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Marusa Arencibia

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.

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María Pertusa
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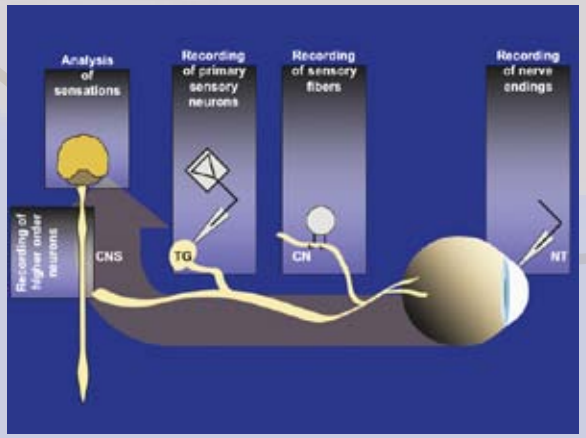

SENSORY TRANSDUCTION AND NOCICEPTION

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.

THYROID HORMONES AND ORGANIZATION OF THE CEREBRAL CORTEX

Principal Investigator
Pere Berbel

PhD Investigators
Jose Víctor G. Velasco
Thomas Starke

PhD Students
Daniela Navarro

Technical Staff
Eva Ausó

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.

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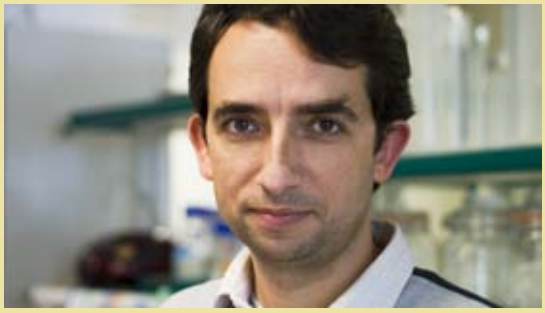
NEUROGENESIS AND CORTICAL EXPANSION



Principal Investigator
Víctor Borrell

PhD Investigators
Camino de Juan

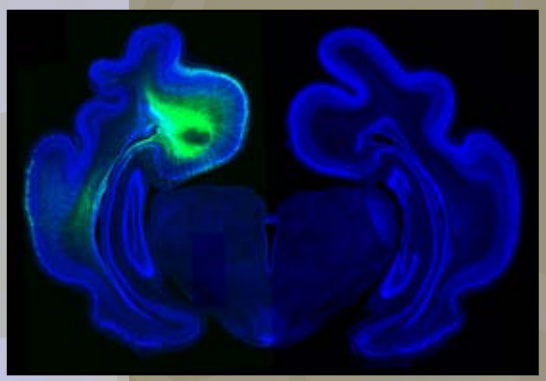
PhD Students
Isabel Reillo
Jesús Gomis

Technical Staff
Maria Dolores Luna

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.



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Borrell V, Yoshimura Y, Callaway EM (2005) "Targeted gene delivery to cortical interneurons by directional in utero electroporation". **Journal of Neuroscience** Methods 143:151-158.

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MOLECULAR CONTROL OF AXONAL MYELINATION

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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 cells 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 10% 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 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 gefinitib 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.

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PLASTICITY OF BRAIN NETWORKS

Principal Investigator

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PhD Students

Efrén Álvarez Salvado

A fast response to changes in environmental conditions increases the fitness and reproductive success of organiThe 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.

Selected Publications

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PDZ PROTEINS AND SIGNALING NETWORKS DURING THE SPECIFICATION OF NEURONAL IDENTITIES

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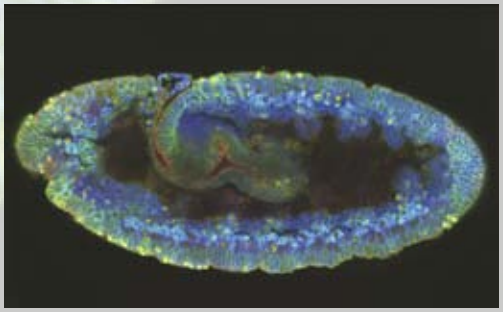
During the development of the nervous system a great diversity of neuronal types is generated. Indeed, the human brain has more than 100.000 millions of neurons, most of them specified during the embryonic development. Unraveling the molecular mechanisms that underlie the acquisition of neuronal identities 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.



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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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MOLECULAR NEUROBIOLOGY OF NEURONAL NICOTINIC RECEPTORS

Principal Investigator
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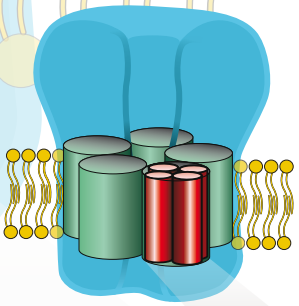
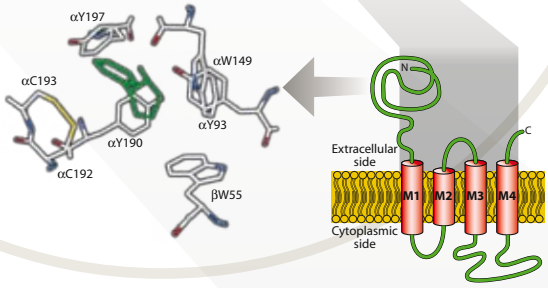
The nicotinic acetylcholine receptor is widely distributed in the central and peripheral nervous systems. Important functions and pathologies specific to the nervous system, such as memory, anxiety, analgesia, cerebral circulation, nicotine adiction and Alzheimer disease, could be better understood and/or 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.



• Search for 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.

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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.

In November 1998 derivation of the first human embryonic stem (ES) lines was reported, representing a major step forward for basic research and a potential clinical use in humans. ES cell cultivation in vitro and isolation of specific cell types should lead to their use as renewable source of cells for tissue transplantation, cell replacement and gene therapies. Clinical targets for these cell therapies would include neurodegenerative disorders, diabetes, spinal cord injury, hematopoietic repopulation and myocite grafting. We use a mouse model to test the usefulness of ES cell therapy in the treatment of Alzheimer and Parkinson diseases. The aim of this project is to drive neuronal differentiation of mouse ES cells towards cholinergic and dopaminergic phenotypes, that will be transplanted in the brain of the Alzheimer and Parkinson diseases mouse models. These cell therapies should lead to the functional recovery of the brain damage and impaired spatial memory.

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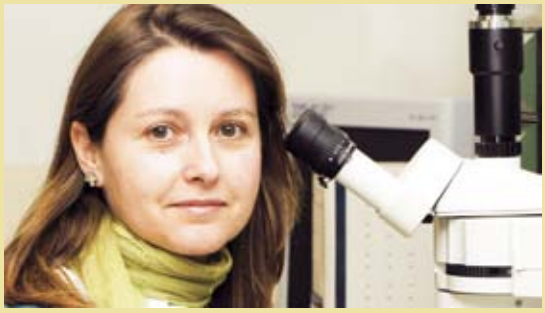

MECHANISMS OF GROWTH CONTROL AND CANCER IN DROSOPHILA

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Alisson Marques Gontijo
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Miguel Yus Najera
Dolors Ferres-Marco
Veronica Miguela Fernández
Zeus Andrea Antonello Biasotti

Technical Staff
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Esther Ballesta
Irene Oliveira Avalos

Selected Publications

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).

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

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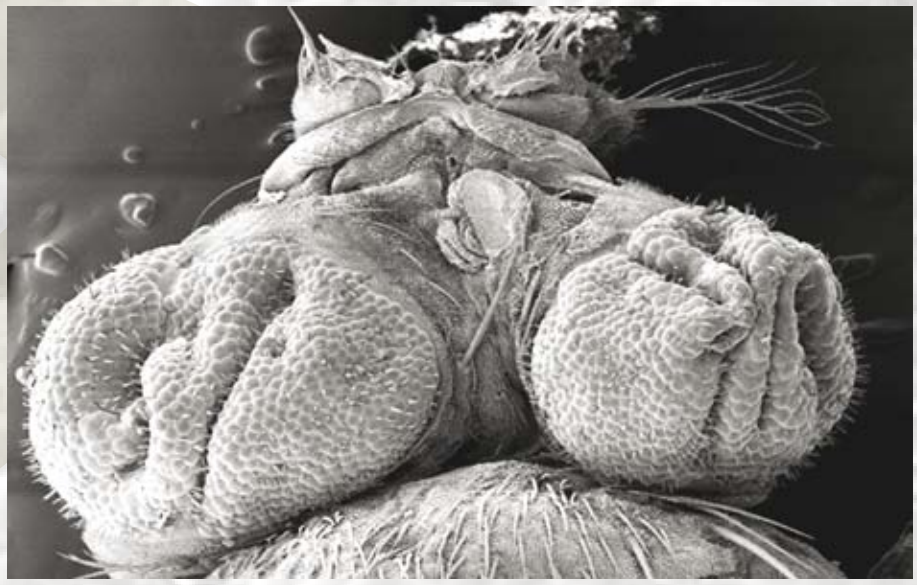

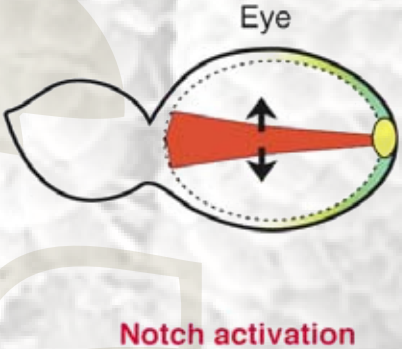

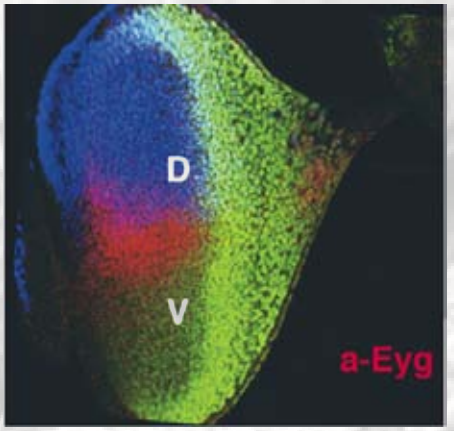

Our studies are focused on four research projects:

• 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.

CORTICAL DEVELOPMENT

Principal Investigator
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Visiting Investigator
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Associate Investigator
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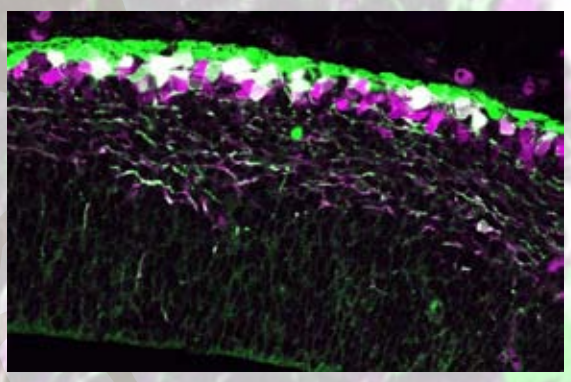
PhD Students
Martín Cortés Pardo
Lilian Enríquez Barreto
Ana Espinosa Martínez
Cristina Gil Sanz
Cecilia Palazzetti
Nuria Ruiz Roig

Technical Staff
Belén Andrés Bayón

Cortical function depends on the ordered integration of the cortical cells into neuronal microcircuits. Developmental studies are of supreme importance to understand the cortex in normal and pathological states. We are interested in knowing how alterations in the development of the diverse populations of neurons and axonal systems induce changes in the fine anatomy and in the physiology of the adult cerebral cortex and hippocampus, and how this influences behavior. This is a systems neurobiology approach to cortical development.

In the past few years, our group has characterized different early-born neuronal populations in the cortical primordium, some of them transient. One of these populations is formed by a class of neurons that project early corticofugal axons to the subpallium, which we named pioneer neurons accordingly. We are studying the places of origin and the migration paths of these neurons, and their relationships with other early-generated neurons of the cortical primordium. We attempt to ascertain the possible roles these and other early neurons play in the development of the cerebral cortex and the hippocampus. To this end, we use genetically modified mouse lines that affect diverse properties of these early-born neurons. We have shown that perlecan, a proteoglycan expressed in the basement membranes of the neuroepithelium, intervenes in the regulation of neurogenesis in the the subpallial and pallial generative zones. We are analyzing in knockout mice the role of neurotransmitter receptors in corticogenesis, in particular that of the metabotropic glutamate receptor mGlu1.

Our work will contribute to the understanding of clinical conditions such as migration disorders that cause intractable epilepsy in children, and schizophrenia.



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NEUROBIOLOGY AND NEUROMODULATION OF THE OPIOID ACTIONS

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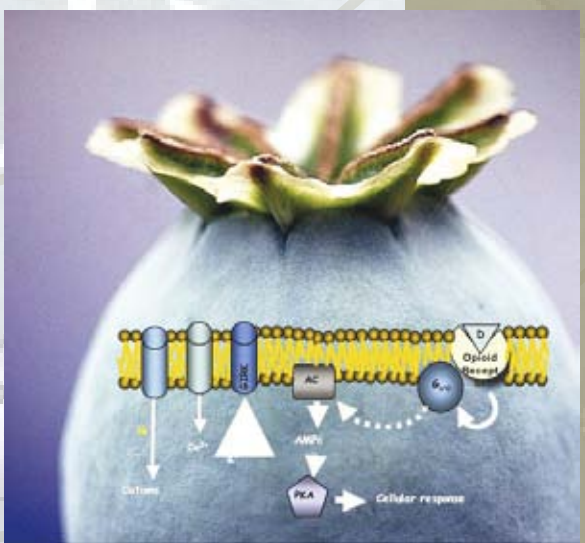
The improvement in the benefit–risk ratio for analgesic therapies is a relevant issue. Opioids are still the most potent and prescribed analgesic drugs. However, their clinical and non-clinical uses still have serious problems such as variability in the analgesic response, tolerance, dependence, addiction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



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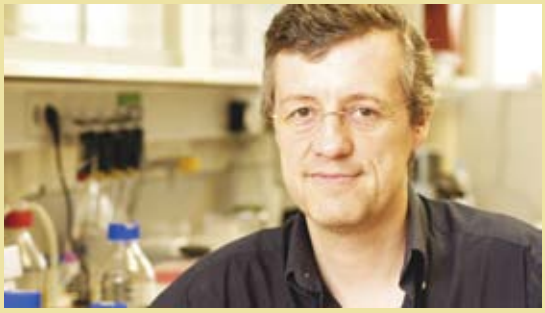

TRANSCRIPTIONAL REGULATION DURING NEUROGENESIS

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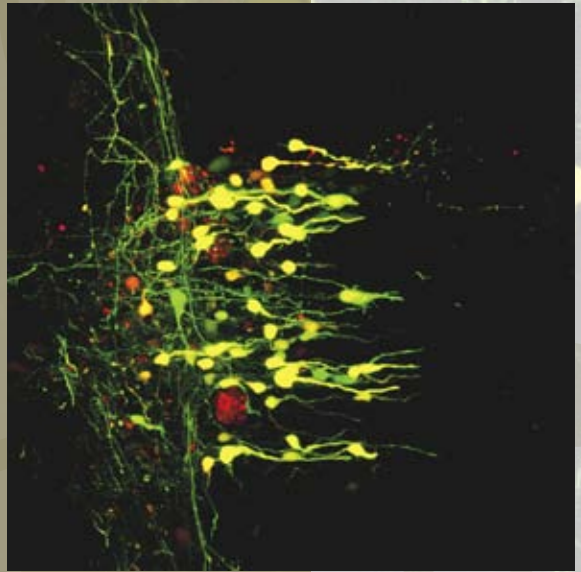
The functionality of the nervous system depends on the correct interplay between a large variety of cell types that are generated during embryogenesis. The identity and number of each one of these cell types is exquisitely regulated during development in such a way that the cells are placed at the proper place and time but also its number is the adequate.

The processes that control the number and identity of the components of the nervous system have been described and studied. However, the mollecular mechanisms that control the number, specification and differentiation of these cells remains partially unknown.

Our main goal is the identification of the signaling mechanisms that control the generation of the cellular diversity in the nervous system. As working model we study the dual specificity protein kinase MNB / DYRK1A gene. This gene is expressed transiently during development at the onset of neurogenesis and its expression ceases when these cells become neurons. It is of special interest to describe the mechanisms that regulate this gene since they will provide invaluable information that will contribute to understand the whole process of neurogenesis.

This gene is of special interest since it has been described that its gene product is able to modulate several signaling pathways. The fact that this protein kinase is able to increase or decrease the signal transduced through other pathways could provide essential information on the processes of signal integration during development to generate a complex nervous system.

We have been able to identify the regulatory elements of the chick, murine and human promoters and we are characterizing the mechanisms of signal integration by studying the effect that its presence causes on several signaling pathways.



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OCULAR NEUROBIOLOGY

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Technical Staff
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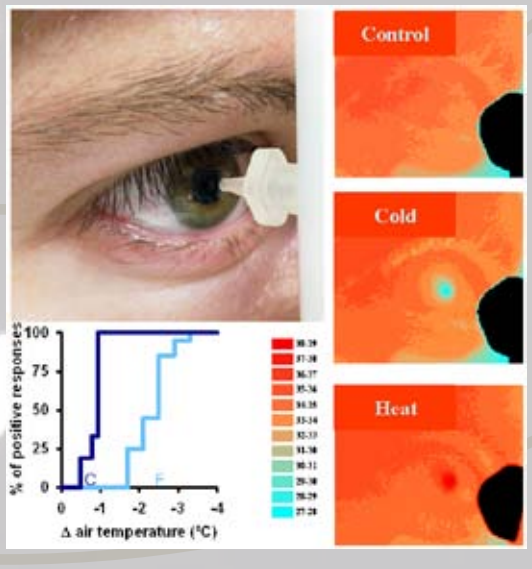
PhD Investigators
Illés Kovács

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 of ocular structures. 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 tear reflexes.

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.



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DEVELOPMENTAL NEUROGENETICS

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PhD Students
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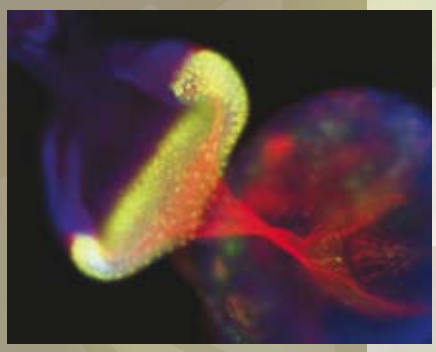
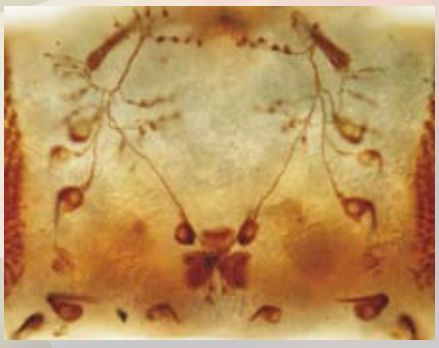
Technical Staff
Sigrid Baars

Nervous System function is determined by its network architecture, between neurons and between neurons and other target cells. During embryonic development, billions of neural connections are formed with exquisite precission and fidelity. This process is established in three consecutive steps: neurogenesis in a species specific pattern, stereotyped guidance of each axon and dendrite, and synaptogenesis with the specific target cells for each axon and dendrite. Every one of these steps is critically controlled by cell communication mechanisms. Our lab is interested in the mechanisms that determine neural connectivity, its specificity and its fidelity. We aproach the study of these mechanisms using Drosophila melanogaster as animal model.

Our work focuses on the study of functional 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 in certain axon tracts. Both, L1- and NCAM-type proteins function in cell communication mechanisms as positive modulators of FGF and EGF receptors. Our more recent work reveals that the specificity of both L1- and NCAM-type proteins as modulators of FGF and EGFR receptor function has been conserved along evolution. The co-expression of these molecules in different organisms is likely to reflect a requirement for functional overlap as a means to ensure fidelity in the axon guidance process.





The evolutionary conservation of cellular and molecular specificity in L1- and NCAM-type proteins opens the possibility for characterizing functional alterations of human L1 pathogenic proteins (causing MASA syndrom) in a transgenic model in Drosophila.

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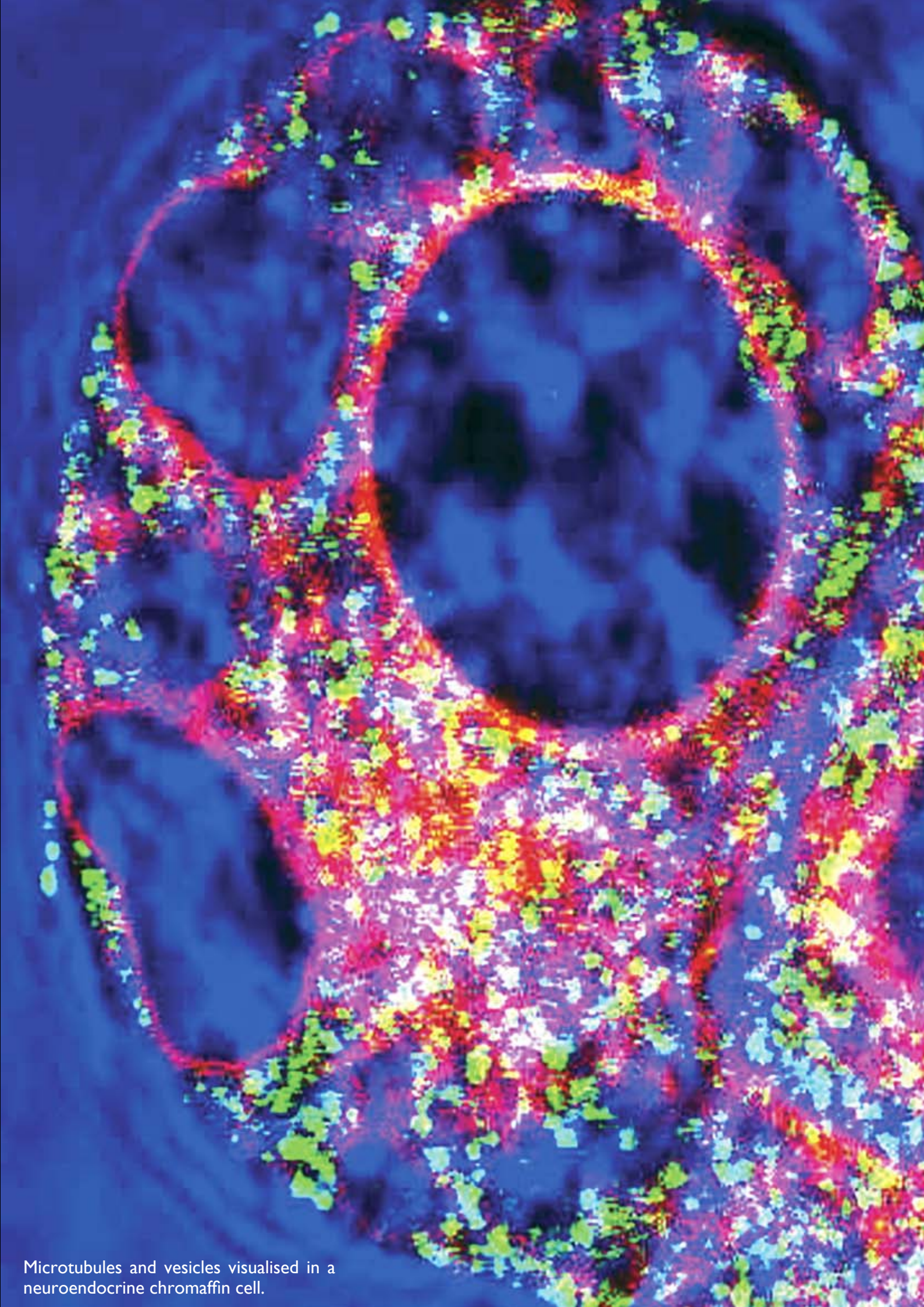

Microtubules and vesicles visualised in a neuroendocrine chromaffin cell.

MECHANOTRANSDUCTION IN MAMMALS

Principal Investigator
Ana Gomis

PhD Investigators
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PhD Students
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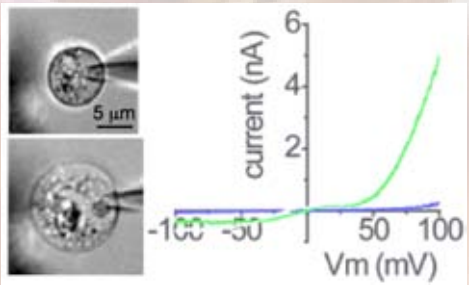
Technical Staff
Ana Miralles

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 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.



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MOLECULAR MECHANISMS OF NEUROSECRETION

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PhD Investigators
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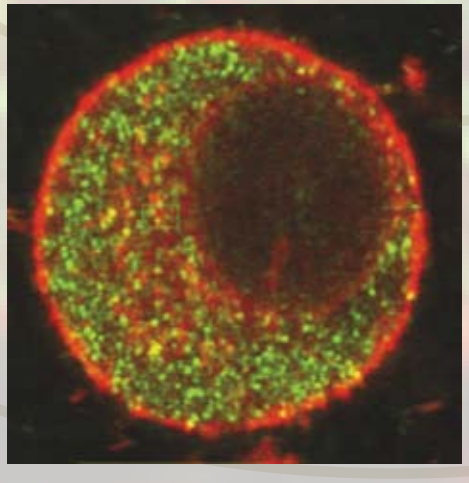
Inmaculada López

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.



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DEVELOPMENT AND ASSEMBLY OF BILATERAL NEURAL CIRCUITS IN MAMMALS

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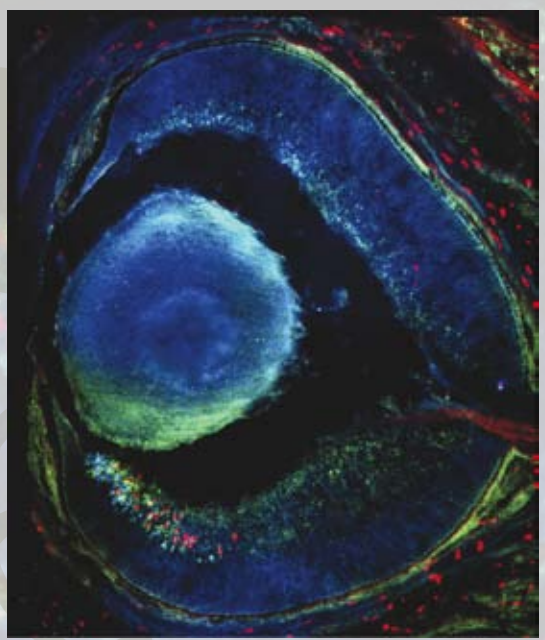
Technical Staff
Celia Vegar

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 to cross the midline during development, or in the assembly or function of these 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 during development as well as the assembly of bilateral circuits at the target tissues. We then investigate whether these newly identified molecules and mechanisms play similar functions in other bilateral pathways of the CNS such as the spinal cord.



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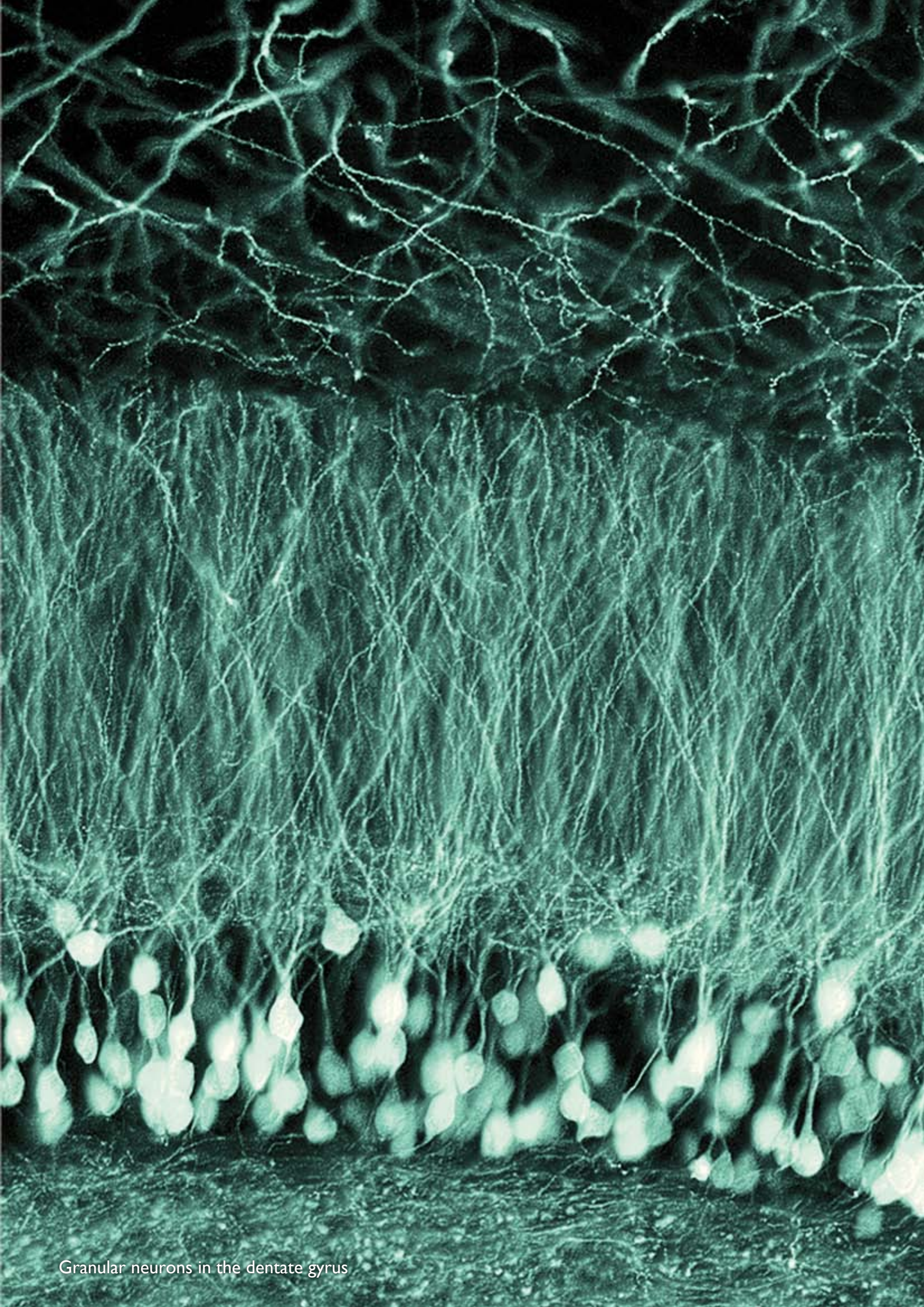

Granular neurons in the dentate gyrus

SYNAPTIC PHYSIOLOGY

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Selected Publications

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

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

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

Christensen, JK, Paternain, AV, Selak, S, Ahring PK and Lerma, J. (2004) A mosaic of functional kainate receptors in hippocampal interneurons. **J. Neuroscience** 24: 8986-93.

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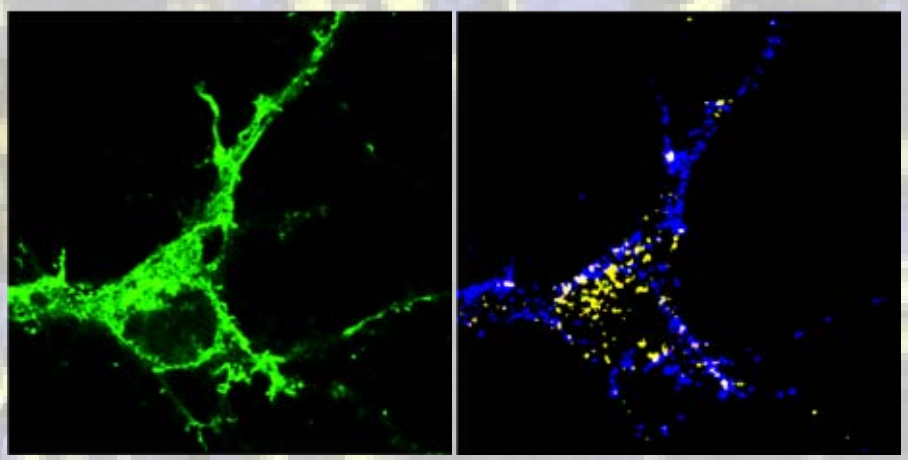
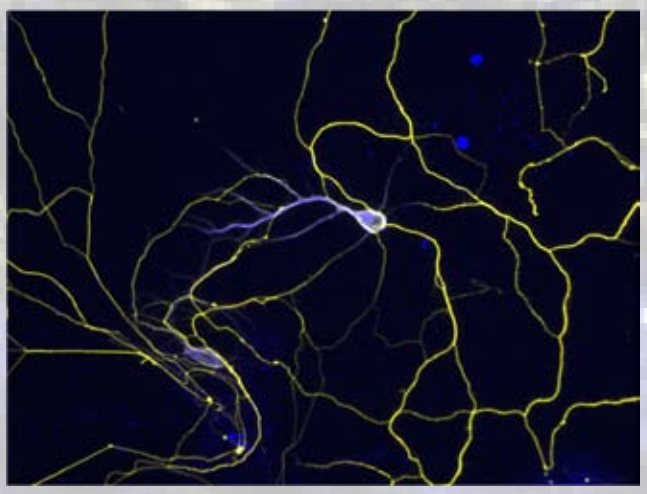
Rozas, J.L., Paternain A.V. and Lerma J. (2003) Non-canonical signaling by ionotropic kainate receptors. **Neuron** 39: 543–553.

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

Regalado, M. P., Villarroel, A. and Lerma, J. (2001) Inter-subunit cooperativity in the NMDA receptor. **Neuron**. 32, 1085-1096.





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.

CELLULAR & MOLECULAR MECHANISMS OF BRAIN WIRING

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PhD Students
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Paula Marcos Mondéjar
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Technical Staff
Noelia García Lillo

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.

Selected Publications

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.

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

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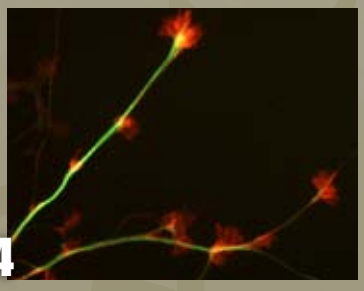
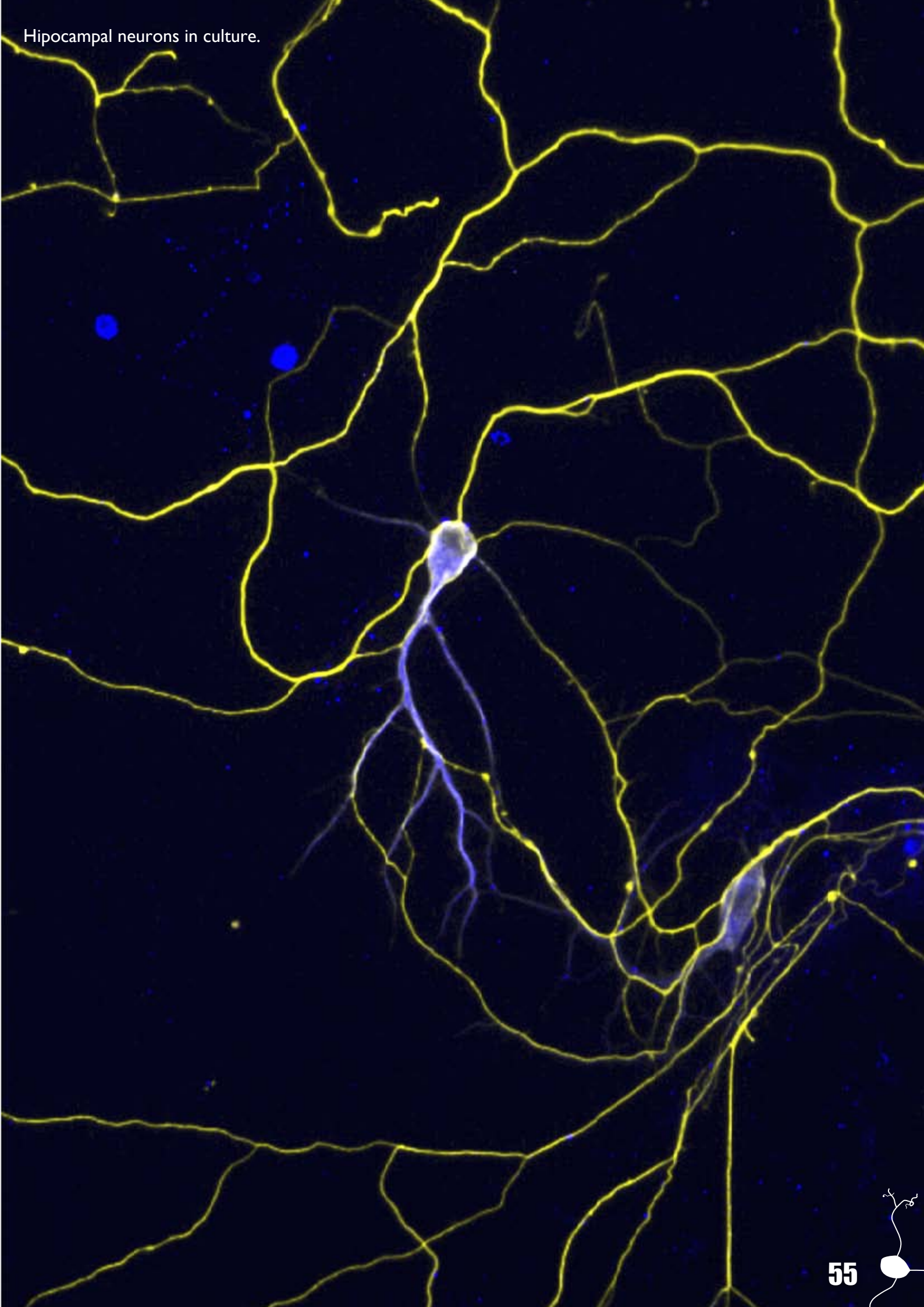
Jones L,* López-Bendito G*, Gruss P, Stoykova A, Molnár Z (2002) Pax6 is required for the normal development of the forebrain axonal connections. **Development** 129:5041-5052.





Hipocampal neurons in culture.

TRANSLATIONAL NEUROPSYCHOPHARMACOLOGY OF NEUROLOGICAL AND PSYCHIATRIC DISEASES

Principal Investigator
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Students
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Technical Staff
Patricia Rodríguez García
Analía Rico Rodríguez

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.

Selected Publications

Rubio, G., Ponce, G., Manzanares, J. Naltrexone for alcohol dependence. (Letter) **The New England Journal of Medicine** 346 April 25(17): 1329-1331(2002).

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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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Ildiko Racz, Xavier Nadal, Judith Alferink, Josep-Eladi Baños, Jennifer Rehnelt, Miquel Martin, Belén Pintado, Alfonso Gutierrez-Adan, Elena Sanguino, Jorge Manzanares, Anne Zimmer, and Rafael Maldonado"Crucial role of CB2 cannabinoid receptor in the regulation of central immune responses during neuropathic pain. **Journal of Neuroscience** 28(46): 12125-12136 (2008).

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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DYNAMICS AND PLASTICITY OF CORTICAL SENSORY RESPONSES

Principal Investigator
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José Miguel Sorando

PhD Investigators
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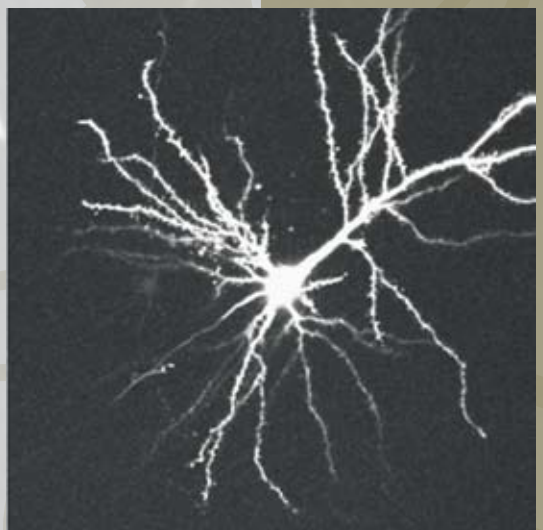
Andrea Alenda

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.



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

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

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Maravall, M; Koh, IYY; Lindquist, WB; Svoboda, K. (2004). Experience-dependent changes in basal dendritic branching of layer 2/3 pyramidal neurons during a critical period for developmental plasticity in rat barrel cortex. **Cereb. Cortex**, 14: 655-664.

NEURONAL SPECIFICATION AND MIGRATION

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Technical Staff
Trinidad Gil
María Pérez
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Administration
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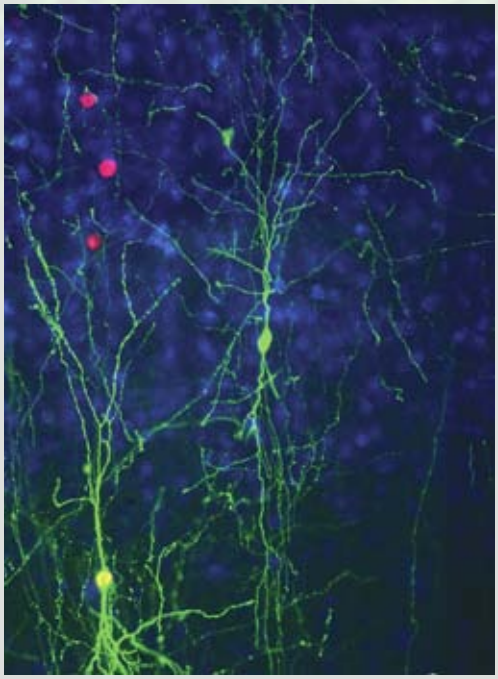

Selected Publications

Marín, O; Rubenstein, JL. (2003). Cell Migration in the Forebrain. **Annual Review of Neuroscience**, 26: 441-86.

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.

Pla, R; Borrell, V; Flames, N; Marín, O. (2006). Layer acquisition by cortical GABAergic interneurons is independent of Reelin signaling. **Journal of Neuroscience**, 26: 6924-34.

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

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

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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.

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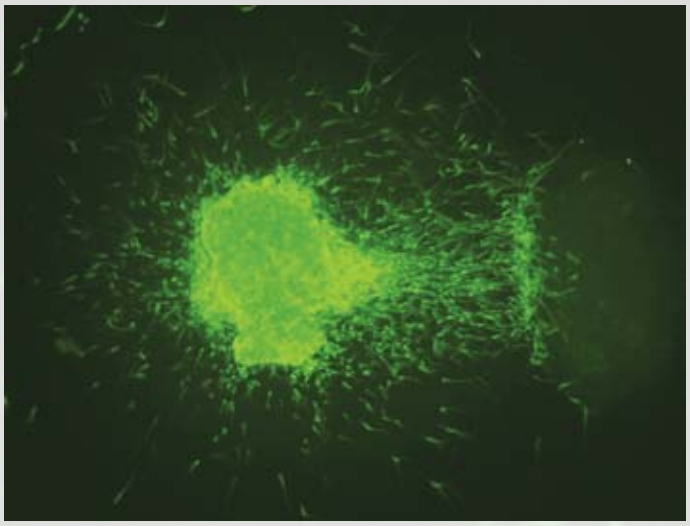
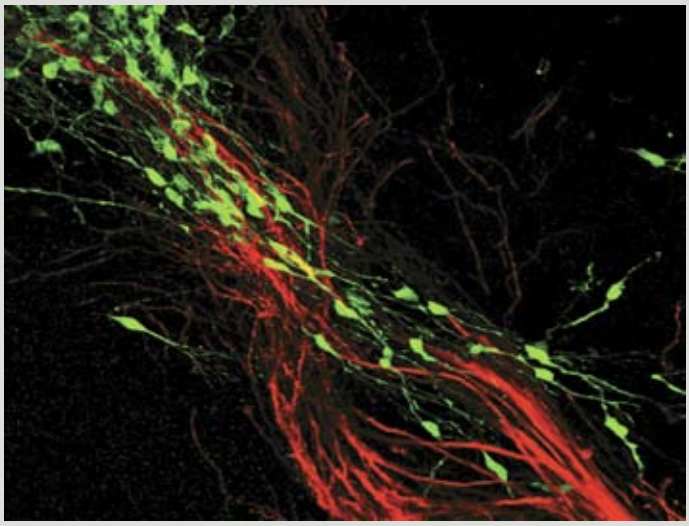


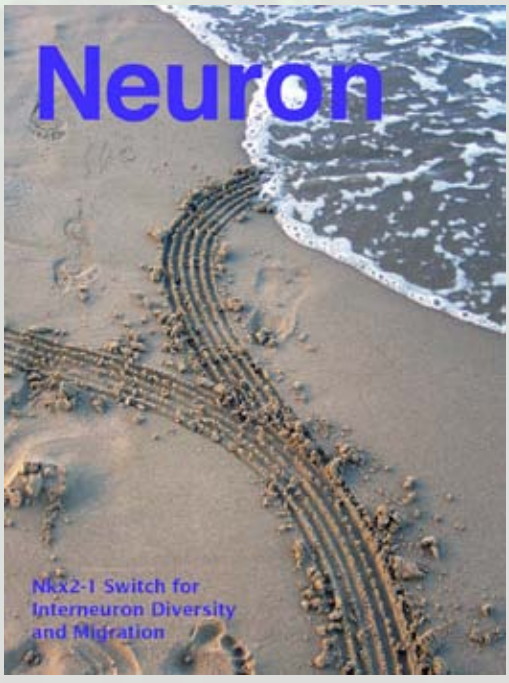


The main aim of our laboratory is to understand the molecular and cellular mechanisms controlling the development of the most anterior region of the brain, the telencephalon. The telencephalon contains key structures for the function of the mammalian brain, such as the basal ganglia and the cerebral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



VISUAL NEUROSCIENCE LABORATORY

Principal Investigator
Luis M. Martínez.

PhD Students
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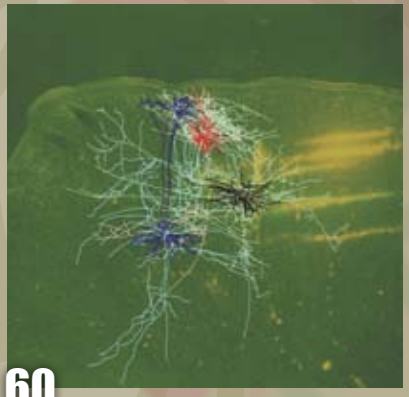
Isabel Benjumeda Wijnhoven
Manuel Molano Mazón

Technical Staff
Joaquín Márquez Bugella

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.



Selected Publications

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

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

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

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

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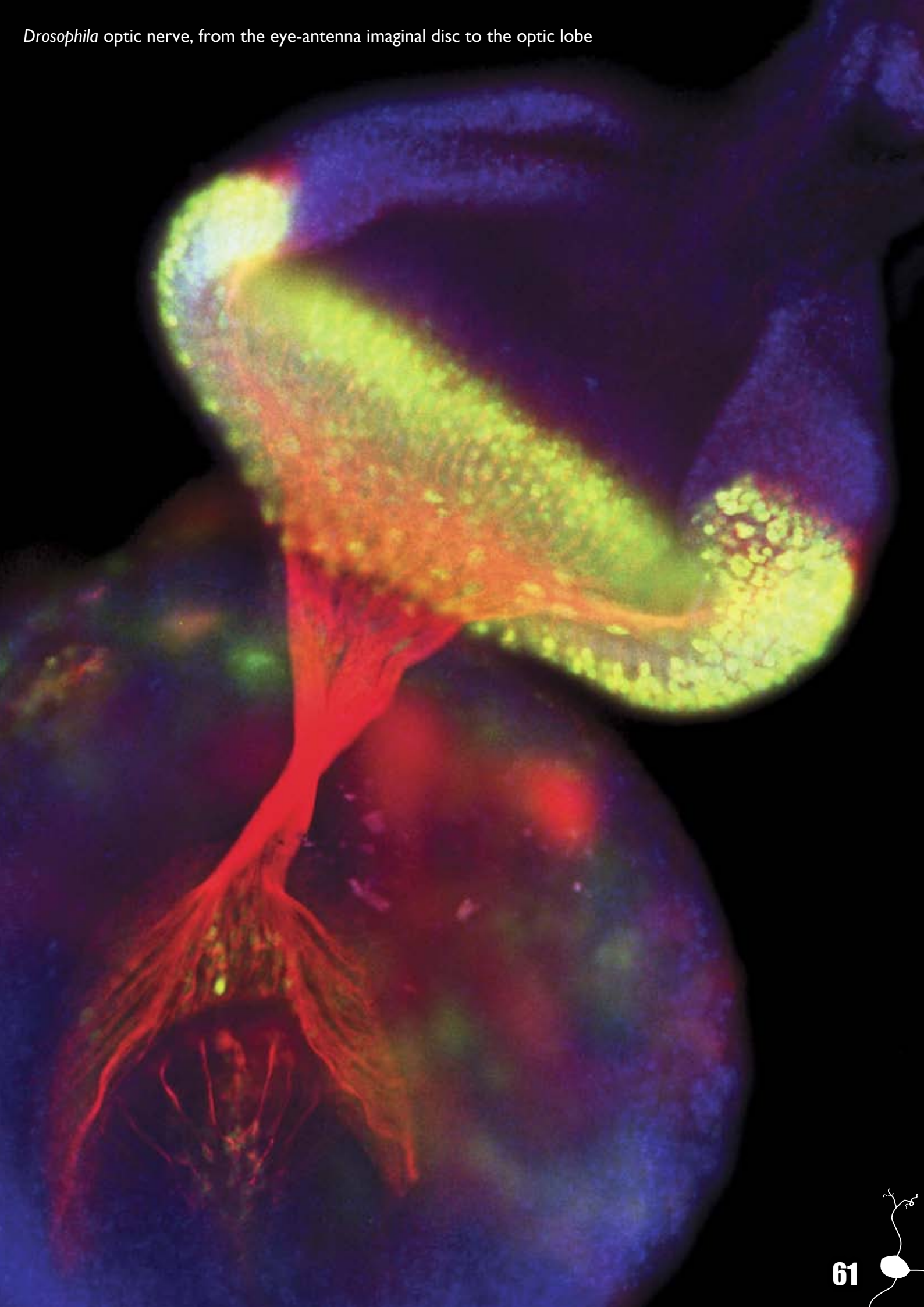
Martinez LM (2006) "The generation of visual cortical receptive fields." Progress in Brain Research. 154:73-92.

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

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

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

Drosophila optic nerve, from the eye-antenna imaginal disc to the optic lobe



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Dusart I, Guenet JL, Sotelo C. (2006) Purkinje cell death: differences between developmental cell death and neurodegenerative death in mutant mice. **Cerebellum**. 5(2):163-73. Review.

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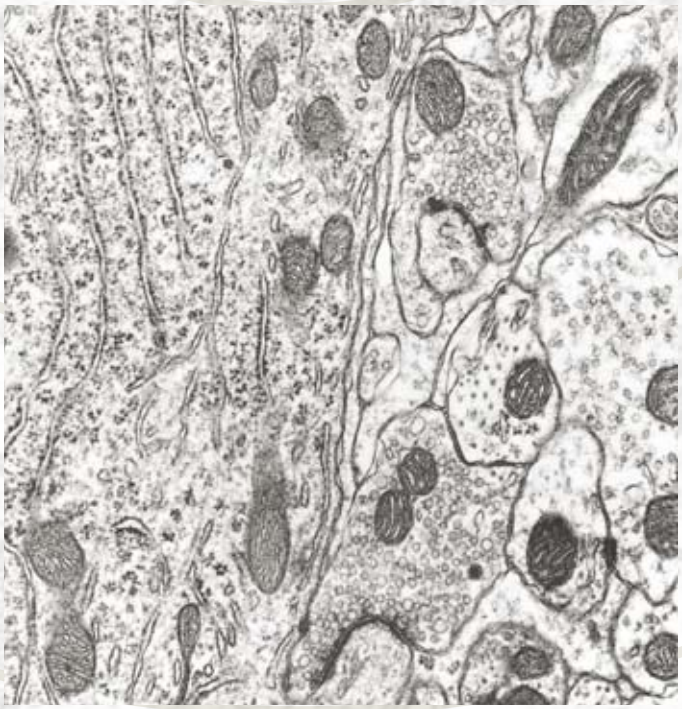

Our studies are focused on four research projects:

Experimental Embryology: manipulations in mouse and chick embryos allow us to study cellular and molecular factors that control the regionalization, segmentation, proliferation, differentiation and cellular migration processes of the Central Nervous System. We concentrate our research work in the understanding of the molecular factors that control the development and morphogenetic activity of the secondary organizers of the anterior neural tube of vertebrates. Our work explores particularly the molecular action of 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 underlying the development of inhibitory cerebellar circuits.

Stem Cell Research: we are developing experimental models that permit to demonstrate the neural 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.

CELL MOVEMENTS IN DEVELOPMENT AND DISEASE

Principal Investigator
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Sonia Martin

Selected Publications

Vega, S., Morales, A.V., Ocaña, O., Valdés, F., Fabregat, I. and Nieto, M.A. (2004). Snail blocks the cell cycle and confers resistance to cell death. **Genes Dev.** 118, 1131-1143.

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.

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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.

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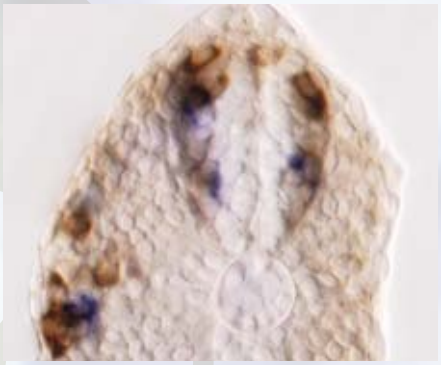
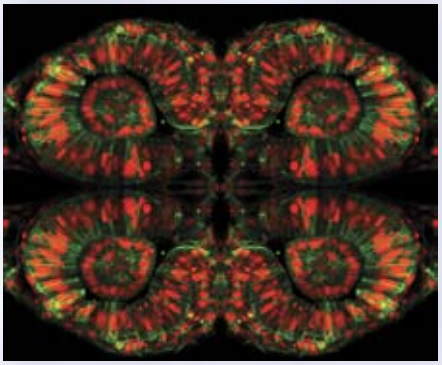
Acloque, H., Adams, M., Fishwick, K., Bronner-Fraser, M. and Nieto, M.A. (2009). Epithelial-mesenchymal transitions: The importance of changing cells' state in development and disease **J. Clin. Invest.** 119, 1438-1449.

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.



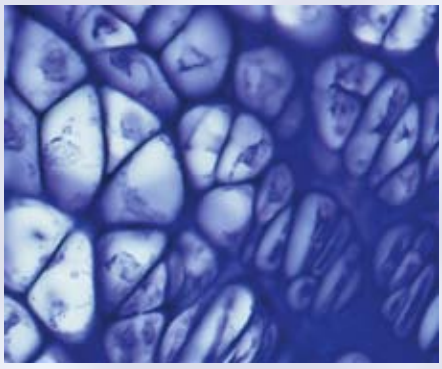


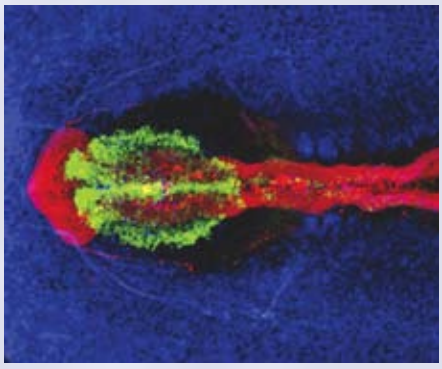
We have been interested in the analysis of cell behavior in development and disease for more than 15 years. We have been working on the functional analysis of the Snail gene family, and have shown its implication in different processes during embryonic development in vertebrates, including the formation 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). Snail endows cells with migratory properties, attenuates proliferation and confers resistance to cell death (2004). These three functions have a big impact on both embryonic and tumour cells. 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.

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 and of the competence of the different cell contexts to respond to Snail and/or Scratch, important for the understanding of the reactivation of developmental programmes in adult pathologies and that of their activity by the control of their subcellular localization.

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





NEURAL PLASTICITY AND SYNAPTOGENESIS

Principal Investigator
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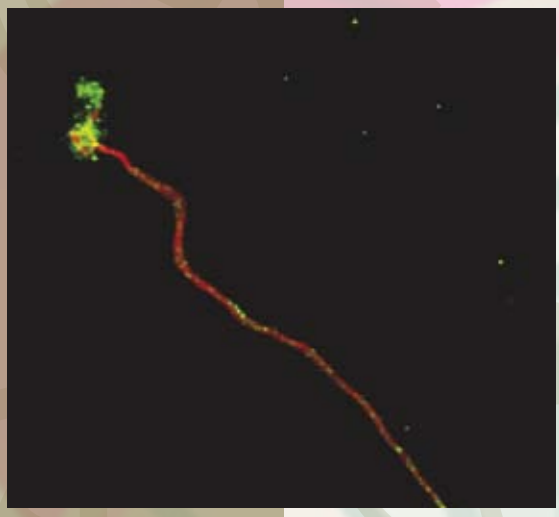
Our research focuses on the study of the cellular and molecular mechanisms controlling the development of neural networks. Brain wiring is a tightly regulated process involving a number of consecutive steps. Once immature neurons have reached their final destination, they extend axons to different regions. 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.



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Bamji, SX., Rico, B., Kimes, N., Reichardt, LF. (2006). BDNF mobilizes synaptic vesicles and enhances synapse formation by disrupting cadherin-beta-catenin interactions. **Journal of Cell Biology**, 174: 289-299.

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ALTERED MOLECULAR MECHANISM IN ALZHEIMER'S DISEASE AND DEMENTIA

Principal Investigator
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PhD Students
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María Ximena Silveyra
Iolanda Riba Llena

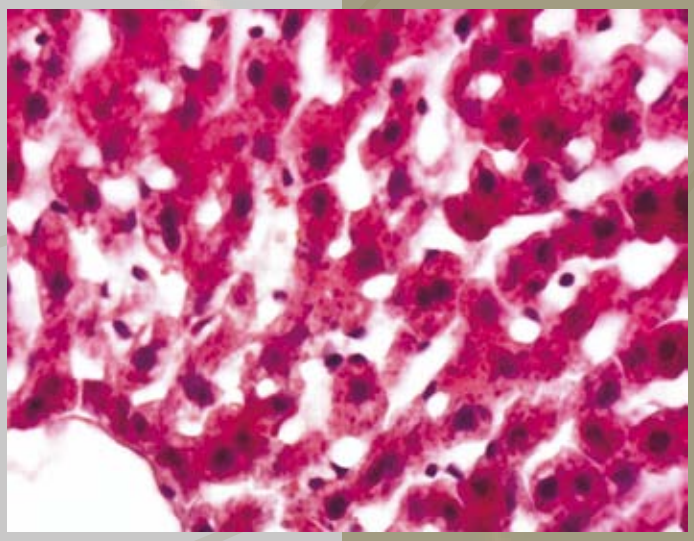
Our aim in the IN was to introduce a line of research into Alzheimer's disease (AD) and dementia that originated from a basic point of view but that was relevant to the development of clinical-diagnostic applications.

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.



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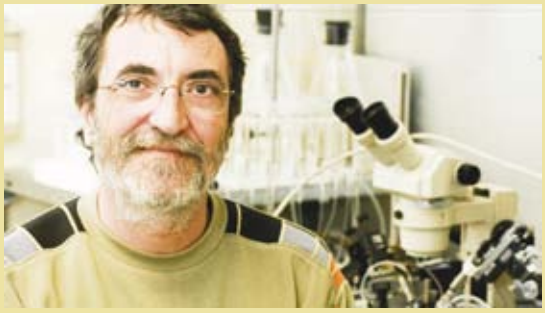

BIOPHYSICS AND PHARMACOLOGY OF IONIC CHANNELS

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Salvador Sala

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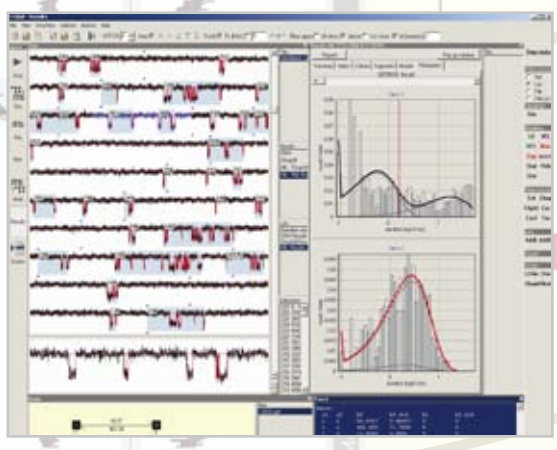
Philip Wikman

Technical Staff
José Mulet

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.



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Sala, F., Mulet, J., Valor, LM., Criado, M., Sala, S. (2002). Effects of benzothiazepines on human neuronal nicotinic receptors expressed in xenopus oocytes. **British Journal of Pharmacology**, 136(2): 183-192.

Sala, F., Mulet, J., Choi, S., Jung, S., Nah, S., Rhim, H., Valor, LM., Criado, M., Sala, S. (2002).Effects of gingenoside Rg2 on human neuronal nicotinic acetylcholine receptors. **Journal of Pharmacology and Experimental Therapeutics**, 301: 1052-1059.

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

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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** (in press)

MOLECULAR NEUROGENETICS

Technical Staff
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Principal Investigator
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PhD Investigators
Bárbara Hämmerle

PhD Students
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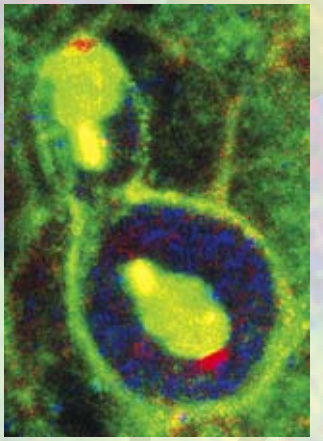
David Fenosa
Guillermo Jofre
Edgar Ulin Avila

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.



Selected Publications

W. Becker, Y. Weber, K. Wetzel, K. Eirmbter, F.J. Tejedor, and H-G. Joost (1998) Sequence characteristics, subcellular localization, and substrate specificity of DYRK-related kinases, a novel family of dual specificity kinases. **J. Biol. Chem.** 273, 25893-902

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

Ceron J. Tejedor F.J. Moya F. (2006) A primary cell culture of Drosophila postembryonic larval neuroblasts tostudy cell cycle and asymmetric division. **Eur J. Cell Biol.** 85(6):567-75

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

CELL SIGNALLING DURING NEURONAL MIGRATION

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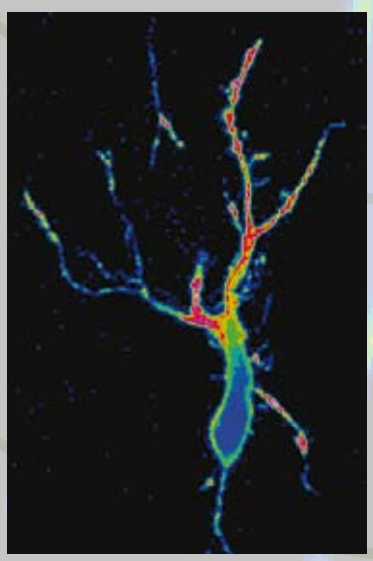
Fernando Moya

PhD Students
Francisco Martini
Sarah Mertens

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 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.



Selected Publications

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

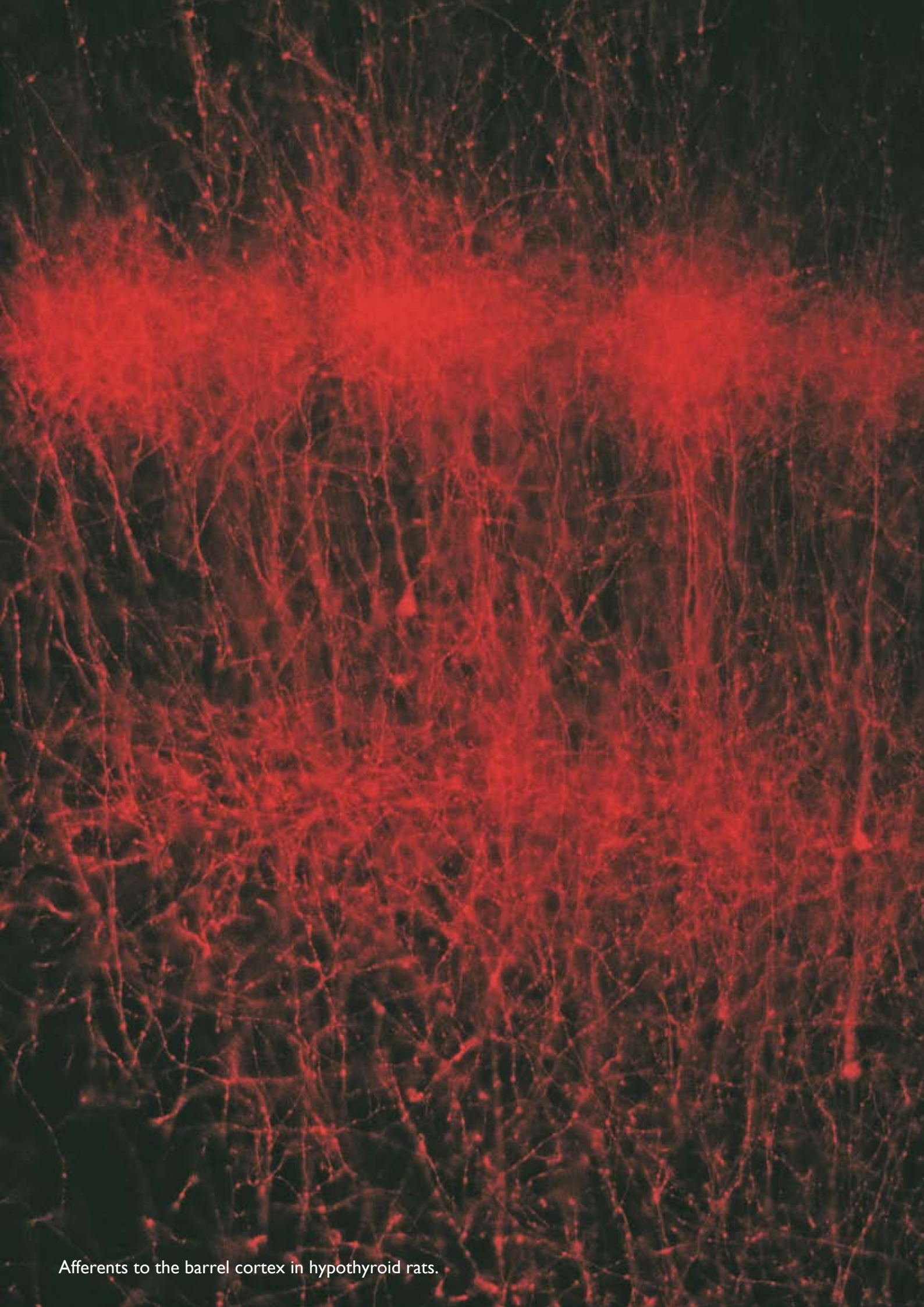
López-Bendito G., Sánchez-Alcañiz J. A., Pla R., Borrell V., Picó E., Valdeolmillos M.& Marín O. (2008). Chemokine signaling controls intracortical migration and final distribution of GABAergic interneurons. **The Journal of Neuroscience** 28:1613–1624.

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

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

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

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



Afferents to the barrel cortex in hypothyroid rats.

PhD PROGRAM

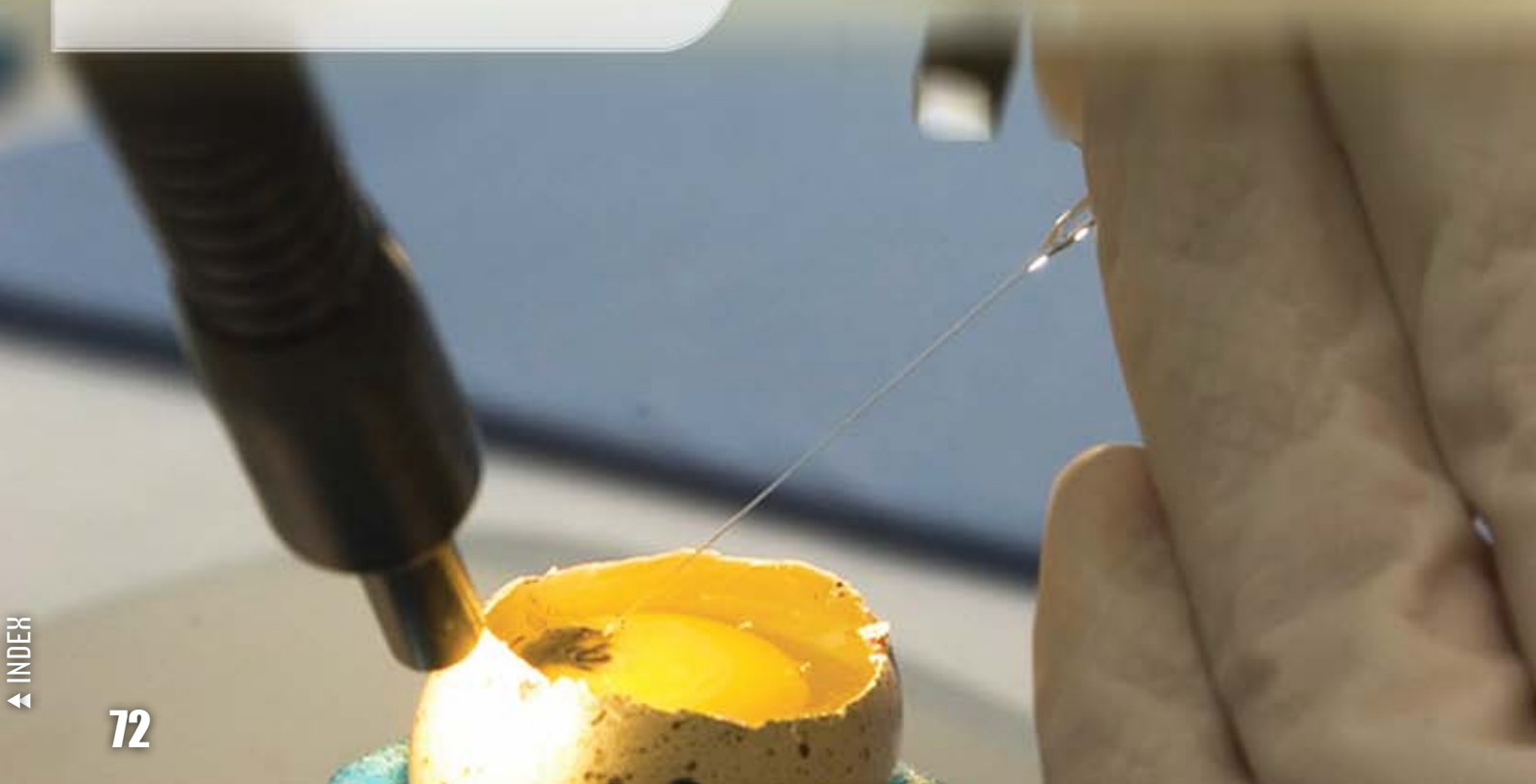
The PhD Program has been an ongoing activity at the Institute since its foundation, and it has played an important role in the professional formation of scientists in the field. A high percentage of students completing the program have subsequently been incorporated into national research teams or have taken up overseas postdoctoral positions. The program is intended for graduate students to complete a PhD thesis based on experimental work in neuroscience. The Program offers the official title of PhD in Neurosciences as established by the Real Decreto 1393/2007 and has received the "Quality Mention" of the Spanish Ministry of Education.

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 Neuroscience (24ECTS)

Coordinated by Fernando Moya

MODULE 1 EMBRYOLOGY (Nov 2-10)

- Introduction. Angela Nieto
- Early Development: Gastrulation and Neural Induction - Herve Acloque
- Embryonic axis - Alejandro Barrallo
- Nervous System Morphogenesis - Salvador Martínez/Eduardo de Puelles
- Early brain development - Diego Echevarría/Eduardo de Puelles
- The Neural Crest - Alejandro Barrallo

- Practicum.

Chick embryo development - Herve Acloque/Diego Echevarría/ Eduardo de Puelles.

Zebrafish embryo development - Alejandro Barrallo

Transposable elements and their artificial derivatives: powerful tools in molecular genetics -Ana Carmena

The nematode Caenorhabditis elegans as a model organism in developmental genetics -Alisson Gontijo

Mouse genetics: Transgenesis, Gene Targeting, Genetic Mosaics, loxP-Cre and FRT-FLP -Beatriz Rico

Tools for Bioinformatic analysis of gene expression and evolution - Juan Galcerán

Discussions on research papers

MODULE 2: GENETIC ANALYSIS (November 11- 18)

- Fundamental concepts in Developmental Genetics (L. García Alonso)
- Evolutive conservation of the genetic basis of nervous system development (F. Tejedor)
- Methods and Logic in High throughput Genetic Screens (María Domínguez)
- Experimental techniques in Drosophila. Transposable elements and their artificial derivatives: powerful tools in molecular genetics (A. Carmena)
- The nematode Caenorhabditis elegans as a model organism in developmental genetics (A. Gontijo)
- Mouse genetics: Transgenesis, Gene Targeting, Genetic Mosaics, loxP-Cre and FRT-FLP (Beatriz Rico)
- Zebrafish as a model for genetic analysis in vertebrates (A. Barrallo)
- Tools for Bioinformatic analysis of gene expression and evolution (Juan Galcerán)
- Practicum: Molecular genetic and evolutive analysis of a gene (Juan Galcerán)
- Discussions on research papers.

MODULE 3 NEUROANATOMY (Nov 19 -30)

- Introduction - Salvador Martínez
- Spinal Cord - Salvador Martínez
- Medulla Oblongata - Diego Echevarría
- Cerebellum - Diego Echevarría
- Mesencephalon - Eduardo De Puelles
- Diencephalon - Eduardo De Puelles
- Cerebral Cortex - Alfonso Fairén
- Basal ganglia - Alfonso Fairén
- The Amigdala - Alfonso Fairén

Practicum 1: Identification of brain structures - Alfonso Fairén

Practicum 2: Identification neural tube Landmarks - Eduardo De Puelles

MODULE 4 CELLULAR COMPONENTS OF THE NERVOUS SYSTEM (Dec 1-9)

- Types of neural cells. Morphological and functional types of neurons. Structure of dendrites and axons - Beatriz Rico
- Axonal transport - Fernando Moya
- Glial cells. Oligodendrocytes and Schwann cells. Function of astrocytes and microglia. Neuron-glia interactions. Structure of peripheral nerves. Myelinated axons - Hugo Cabedo
- Intercellular contacts. Types of synapses. Structure of neuromuscular junction - Constantino Sotelo

MODULE 5 INTRACELLULAR SIGNALLING (Dec 10-16)

- General principles of cell signalling. Second messenger pathways - José Manuel Mingot
- Role of calcium in neuronal signalling - Miguel Valdeolmillos
- Nitric Oxide as a signalling molecule in the nervous system - Fernando Moya
- Protein kinases and phosphatases modulation of neural function - Hugo Cabedo
- Control of nuclear-cytoplasmic protein transport - José Manuel Mingot
- Regulation of gene expression and protein synthesis - Ángel Barco

MODULE 6 ELECTRICAL SIGNALLING IN THE NERVOUS SYSTEM (Dec 17-18 - Jan 7-16)

- Introduction to the Course - Félix Viana
- Ionic Currents and the Action Potential - Félix Viana
- Electrical potentials across nerve cell membranes - Salvador Sala
- Voltage-dependent membrane permeability I - Miguel Valdeolmillos
- Voltage-dependent membrane permeability II - Miguel Valdeolmillos
- Electrical signaling I - Elvira de la Peña
- Electrical signaling II - Elvira de la Peña
- Ionic channels and transporters - Salvador Sala

MODULE 7 SYNAPTIC TRANSMISSION (Jan 18-23)

- Neural communication and synaptic transmission. Electrical synapses and gap junctions - Miguel Valdeolmillos
- Chemical synapses I: Presynaptic mechanisms. Quantal release of neurotransmitter and the role of calcium in transmitter release - Francisco Sala
- Chemical synapses II: Molecular mechanisms of transmitter secretion - Luis Miguel Gutiérrez
- Chemical synapses III: Postsynaptic mechanisms and synaptic integration - Salvador Sala
- Neurotransmitters and receptors I: Glutamate receptors - Juan Lerma
- Neurotransmitters and receptors II: ACh, GABA and others - Manuel Criado
- Synaptic plasticity - Emilio Geijo

MODULE 8 NEURAL SYSTEMS (Jan 25 -30)

- Organization of sensory systems. Visual system - Luis Miguel Martínez
- Auditory and Somatosensory Systems - Miguel Maravall
- Common Themes in sensory pathways - Miguel Maravall
- Plasticity. Superior Cognitive Functions - Santiago Canals
- Systems Neurophysiology Lab. - S. Canals, M. Maravall & LM Martínez

Course B. Lab Rotations and IN Seminars (20 ECTS)
Coordinated by José Manuel Mingot

MODULE 1 LAB ROTATIONS
Each student will rotate during 8-12 weeks distributed in 2 or 3 different labs, distributed between February and June

MODULE 2 RESEARCH SEMINARS
Aprox. 30 IN Research Seminars from October to July

Course C. Molecular and Cellular Mechanisms of Neural Function (16 ECTS)
Coordinated by Guillermina López-Bendito and José Manuel Mingot

MODULE 1: DEVELOPMENTAL NEUROBIOLOGY: FROM NEUROGENESIS TO NEURAL CIRCUITS FORMATION (Feb 1-5)
Responsible: Beatriz Rico
Teachers/Labs: A. Carmena, M. Domínguez, J. Galcerán, L. García Alonso, F. Tejedor, O. Marín, F. Moya, M. Valdeolmillos, A. Fairén, A. Nieto, B. Rico, E. Herrera, G. López-Bendito, V. Borrell, S. Martínez.

Contents:
•Neurogenesis, Migration and Neuronal Differentiation.
•Axon Guidance.
•Synaptogenesis and Corticogenesis.

MODULE 2: SYNAPTIC FUNCTION (Feb 8-12)
Responsible: Francisco Sala
Teachers/Labs: F. Sala, S. Sala, M. Criado, L. M. Gutiérrez, S. Viniegra, J. Lerma, E. Geijo, A. Barco, A. Gomis, C. Belmonte, F. Viana, M. C. Acosta, C. Morenilla, K. Talavera

Contents:
•Molecular and cellular basis of synaptic transmission
•Molecular and cellular basis of sensory transduction
•Synaptic plasticity

MODULE 3: INFORMATION PROCESSING IN THALAMOCORTICAL AND CORTICOCORTICAL CIRCUITS (Feb 15-19)
Responsible: Luis M. Martínez.
Teachers/Labs: S. Canals, M. Maravall, L. M. Martinez

Contents:
•Visual information processing in the cerebral cortex and visual perception.
•Somatosensory information processing
•Plasticity of brain networks

MODULE 4: NEUROPATHOLOGY (Feb 22-26)
Responsible: Jorge Manzanares
Teachers/Labs: J. Manzanares, S. Martínez, J. Sáez, H. Cabedo, F. Tejedor, C. Faura, C. De Felipe, J. J. Ballesta

Contents:
•Neuropsychopharmacology of neurological and psychiatric diseases.
•Cell therapy in the treatment of neurodegenerative disorders.
•Therapeutic targets in Alzheimer´s disease.
•Axonal myelination and neurological disorders.
•Genetic,cellular, and molecular basis of mental retardation.
•Neurochemical mechanisms involved in pain and analgesia.
•Neuroplastic changes associated to drug addiction.
•Role of molecular pharmacology in the study of cognitive disturbances.

COLLABORATIONS AND AGREEMENTS

The IN has established collaborations with public and private institutions suchs 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 Cancer

Consolider
Nervous SystemDevelopment and Plasticity
Programa Consolider-Ingenio 2007-2011

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CONSELLERIA DE SANITAT
Unidad Asociada del Hospital de Sant Joan

enet
European Network of Neuroscience Institutes

Network of European Neuroscience Institutes

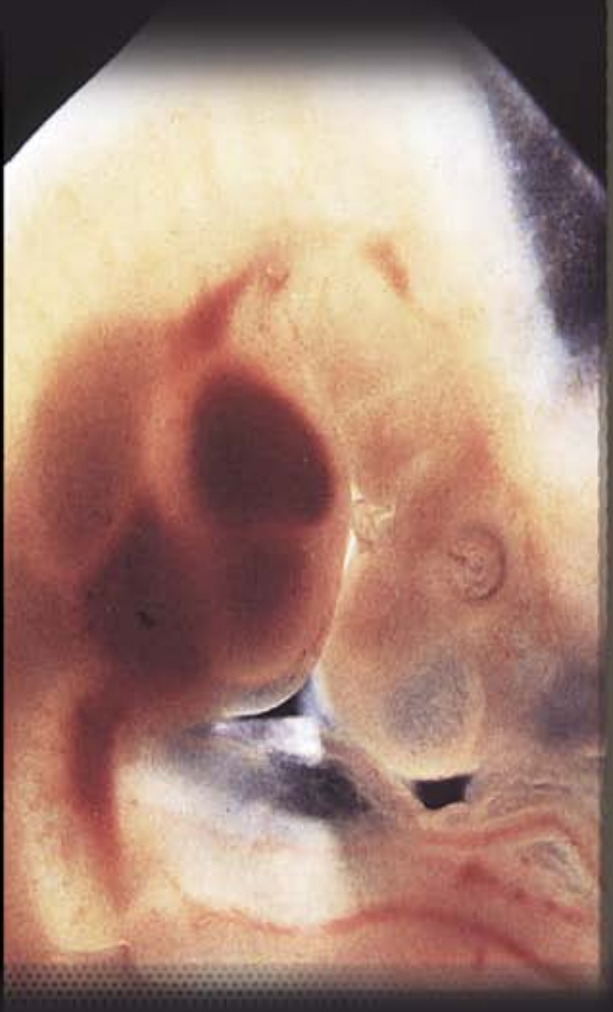
European Research, particularly on Neuroscience, depends heavily on the creative contributions of young investigators. In recognition of this important need, fourteen major European Neuroscience Institutes have formed a network, dedicated to the promotion of the independent work of young investigators. 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"

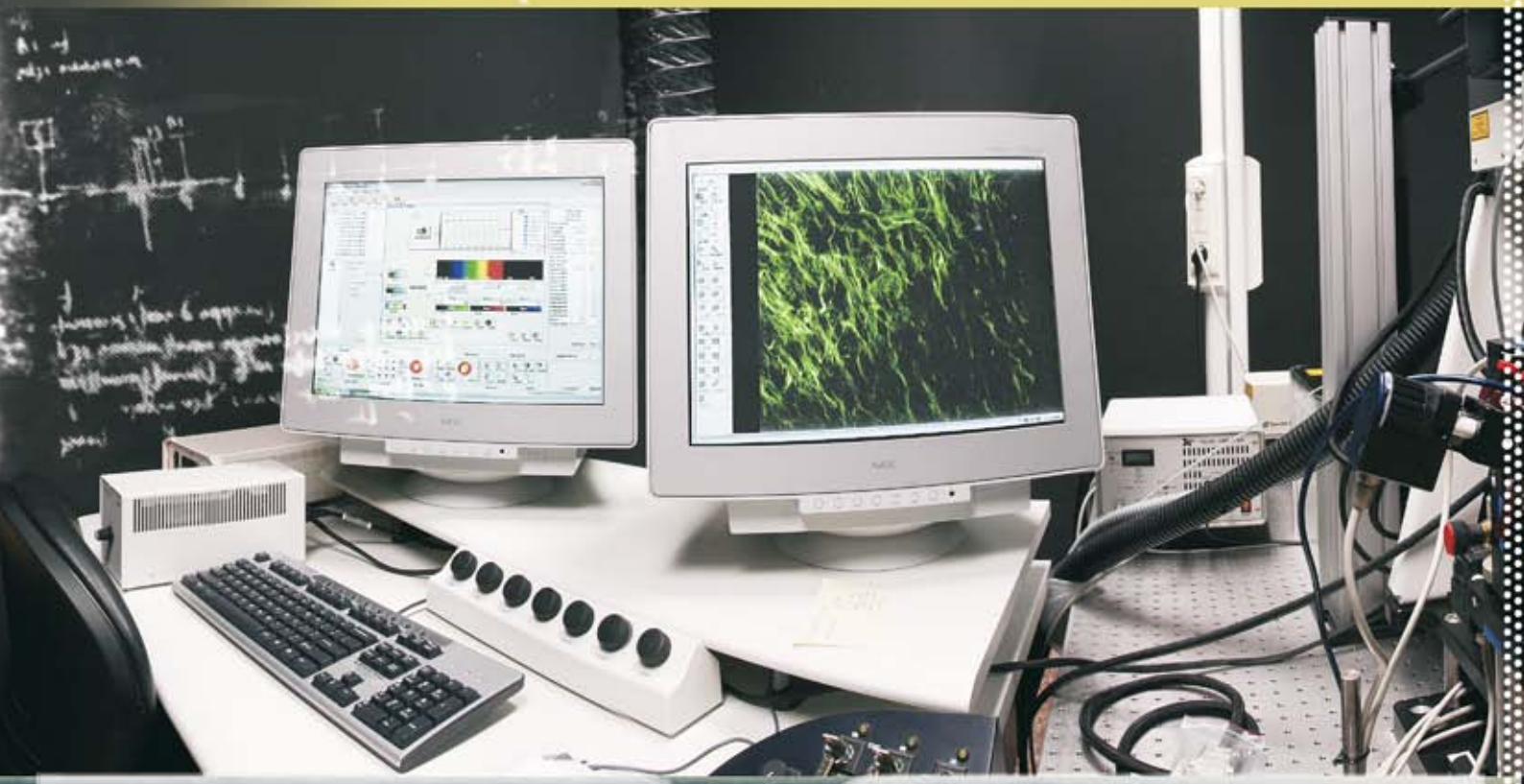
PROFESORA REMEDIOS CARO ALMELA

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).



SERVICES AND FACILITIES



ZEBRAFISH FACILITY

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

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

LIVE CELL IMAGING PLATFORM

In order to take advantage of the latest live cell imaging techniques, the IN has an imaging platform composed of:

- Conventional confocal microscope, which allows image acquisition of fixed material at several wavelengths.

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

- Multiphoton microscope, equipped with two work stations. 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.

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 anestesia machine, medical oxygen, a small anaesthesia chamber and a homeothermic blanket. There is an anesthesic gas elimination system installed. The protocols used at the Unit are approved by the Institute's Ethical Comittee for Animal Experimentation.

CELL CULTURE FACILITY

The facilities are distributed in several areas of common use:

- Cell lines culture room: equipped with hoods, CO2 incubators, centrifuges, normal and fluorescence microscopes. This room is used exclusively for cell lines, which are routinely tested for mycoplasma.

- Primary culture rooms: with similar equipment, this facility is devoted to animal cell primary culture from several sources.

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

ELECTRONICS WORKSHOP

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

BEHAVIOURAL STUDIES AREA

(two units: one of them allocated a the genetically modified mice animal house; the other in the general animal house)

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

ILLUSTRATION AND PHOTOGRAPHY

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

PURCHASING AND STORES

This service manages all the institutional purchasing requirements, giving support and advice to research groups when acquiring material and equipment. The new service's space covers 200 m^2 with more than 900 lineal meters of shelves and specific cabins for flammables and reactive products. A stock of frequently used material for research groups and other services is maintained. The Service is coordinated with the Institute´s administration in order to effectively place orders, manage their payment and assign them to the different grants.

BRAIN IMAGING

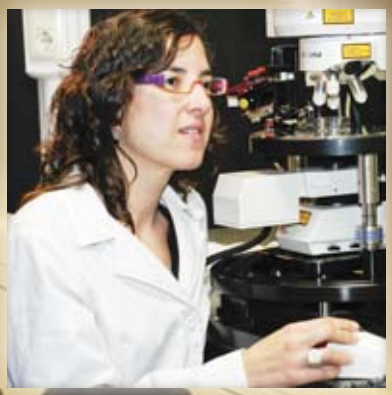
The Institute's brain Imaging service is equipped with a Bruker Biospec 70/30 Magnetic Resonance Imaging system with high performance (up to 675 mT/m) gradients and capacity for the application of modern techniques of multimodal and parallel Imaging in animal experimentation (rat, mouse, rabbit and cat)

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

FLUORESCENCE ASSISTED CELL SORTING

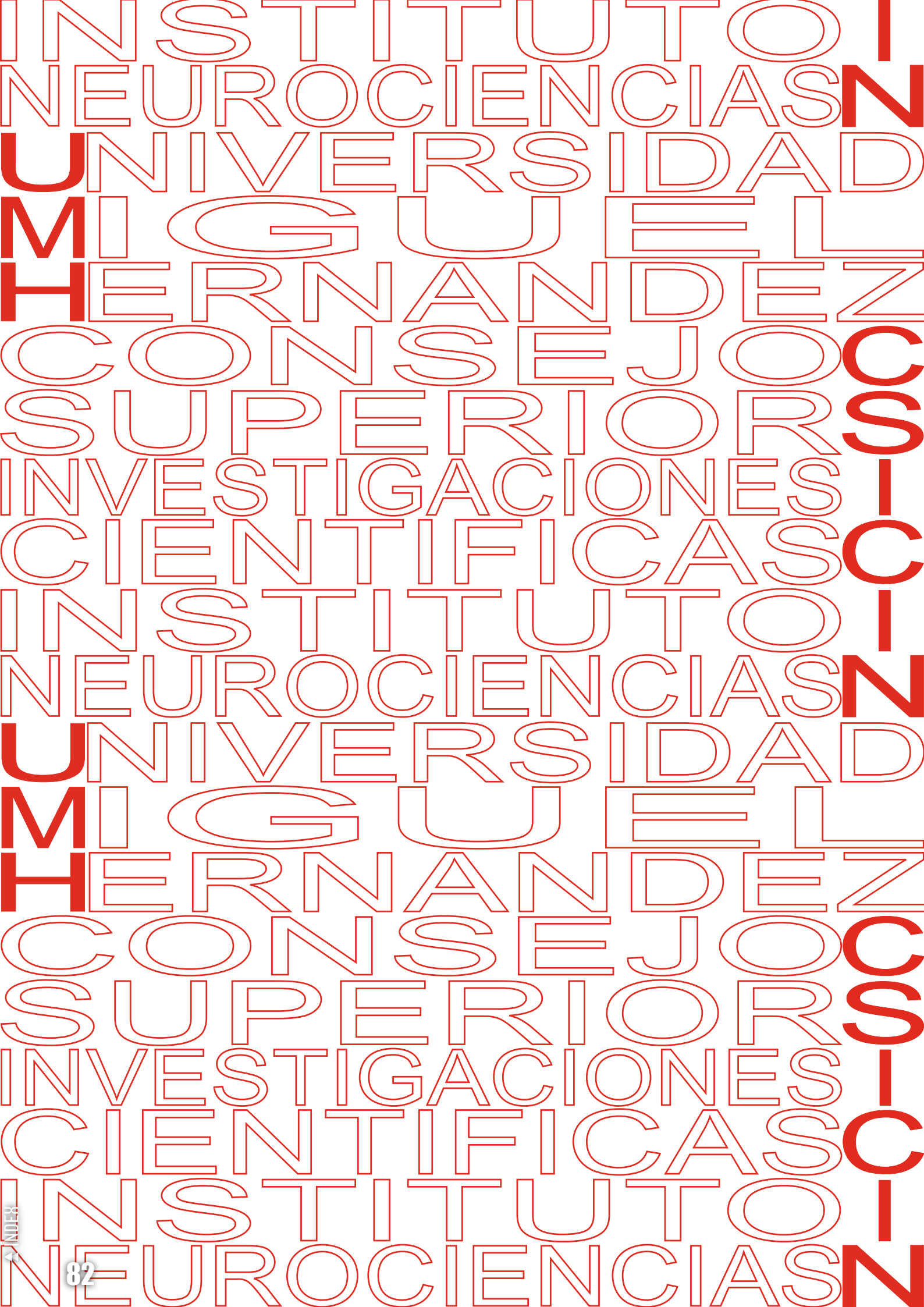
The Institute runs the latest generation "Fluorescence Activated Cell Sorting" (FACS) currently available. Our FACSAria is a digital analyzer/sorter of high precision and sensitivity for sorting and analysis of cell populations with differently tagged structures, used in studies such as: the search for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





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PUBLICATIONS: 2008–2009

PUBLICATIONS 2008

Acloque H., Thiery JP., Nieto MA. 2008 The Physiology and Pathology of the Epithelial to Mesenchymal Transition. **EMBO Rep.** 9:322-326 *7,10*

Acloque H., Wilkinson DG., Nieto MA. 2008 In situ hybridization analysis of chick embryos in whole-mount and tissue sections. **Method Cell Biol** 87:169-185 *1,60*

Aller MI., Wisden W. 2008 Changes in expression of some two-pore domain potassium channel genes (KCNK) in selected brain regions of developing mice. **Neuroscience** 151(4):1154-1172 *3,56*

Barco A., Lopez de Armentia M., Alarcon JM. 2008 Synapse-specific stabilization of plasticity processes: The synaptic tagging and capture hypothesis revisited ten years later. **Neurosci. Biobehav. Rev.** 32(4):831-851 *7,80*

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Botella-Lopez A., De Madaria E., Jover R., Bataller R., Sancho-Bru P., Gomis C., Compañ A., Perez-Mateo M., Martinez S., Saez-Valero J. 2008 Reelin is overexpressed in the liver and plasma of bile duct ligated rats and its levels and glycosylation are altered in plasma of human with cirrhosis. **Int. J. Biochem. Cell Biol.** 40:766-775 *4,18*

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Diaz-Quesada M., Maravall M. 2008 Intrinsic mechanisms for adaptive gain rescaling in barrel cortex. **J. Neurosci.** 28(3):696-710 *7,45*

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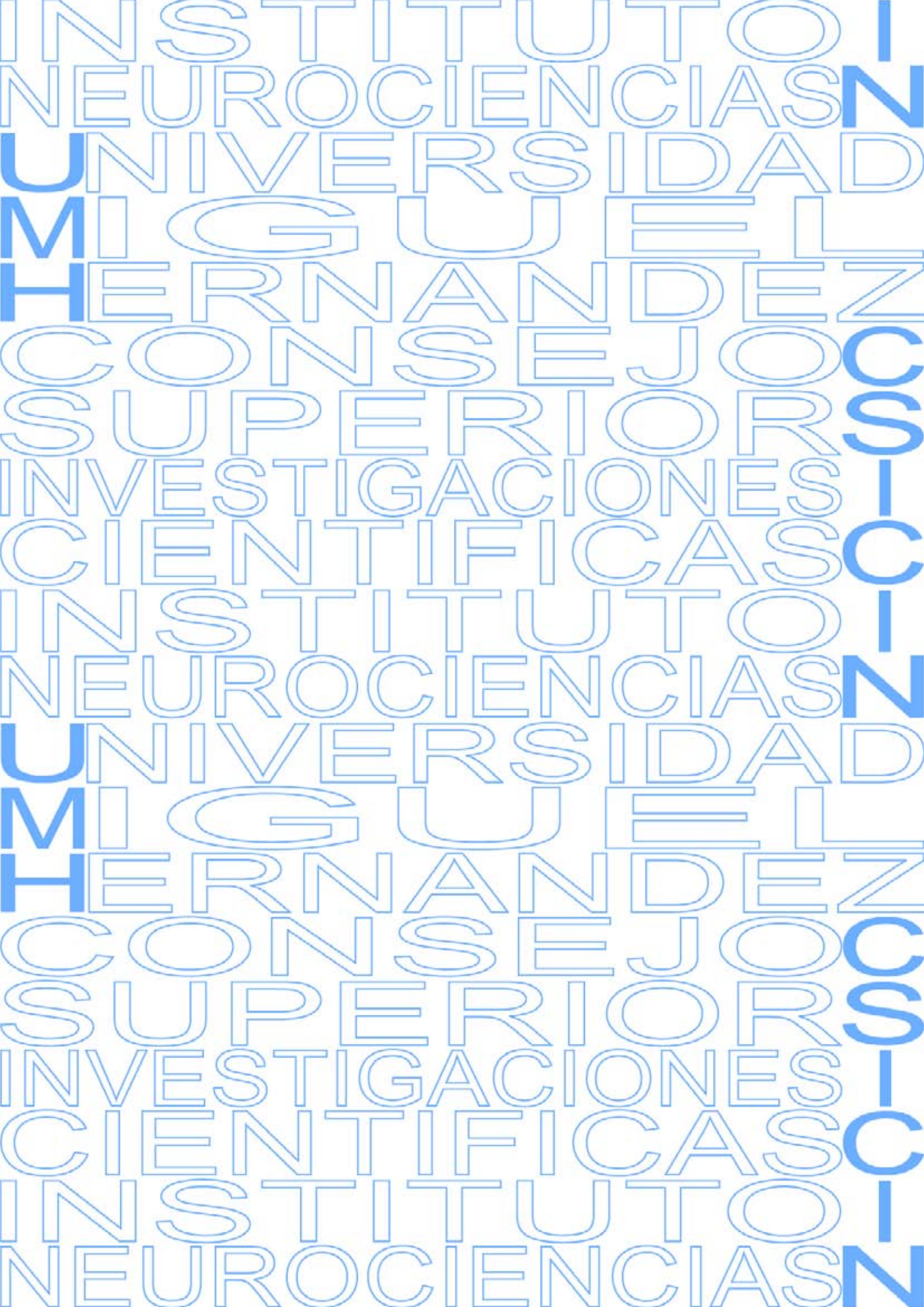
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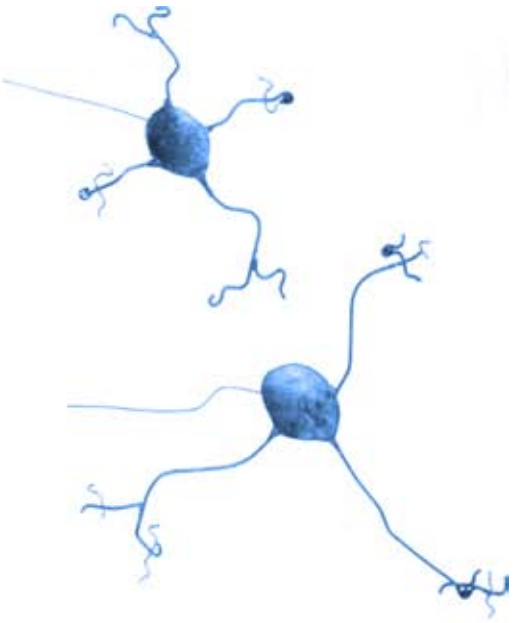

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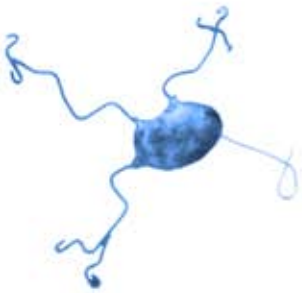
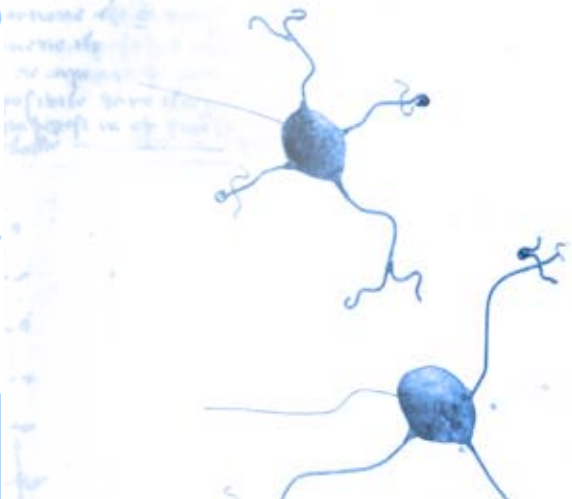




SEMINARS 2008

Signaling beneath the surface: Regulation of cortical neurogenesis by the meninges, **Samuel J. Pleasure,** Department of Neurology. University of California. USA, 07-01-08.

The pyramidal neuron in cognition, **Javier de Felipe,** Instituto Cajal, Madrid, España., 11-01-08.

Neurotransmitter receptor heteromers as targets for neurodegenerative diseases, **Rafael Franco,** Universidad de Barcelona, España, 18-01-08.

New asymmetries in stem cell development and malignant transformation in Drosophila, **Cayetano González,** Instituto de Investigación Biomédica de Barcelona, España, 25-01-08.

Novel roles for GABAergic interneurons in human and rat cortical network, **Gabor Tamas,** University of Szeged, Hungary, 01-02-08.

A molecular dissection of neural induction, **Claudio Stern,** University College London, UK, 08-02-08.

About ataxin_1 and the expanded polyglutamine: novel insights into the molecular mechanisms triggering ataxia and cerebellar neurodegeneration, **Antoni Matilla,** Research Institute Germans Trias i Pujol (IGTP), Barcelona, 12-02-08.

Tripartite signalling between T-type Ca2+ channels, SK2 channels, and SERCAs gates sleep-related oscillations in thalamic dendrites, **Anita Luthi,** Biozentrum, University of Basel, Switzerland , 15-02-08.

Regulation of differentiation in the vertebrate body axis, **Kate Storey,** University of Dundee, United Kingdom, 22-02-08.

Genetic analysis of dopaminergic systems development in zebrafish, **Wolfgang Driever,** University of Freiburg, Freiburg, Germany, 29-02-08.

Planarian enjoys continuous morphogenesis: functional description of signaling pathways that control axial polarity, **Emili Salo,** Universitat de Barcelona, 06-03-08.

AMPA receptors and regulation of dendritic spines, **Maria Passafaro,** Telethon, Roma, Italy, 07-03-08.

ApoER2 and VLDL receptor: key players in brain and oocyte development, **Johannes Nimpf,** University of Vienna, 14-03-08.

Assembling motor circuits for function, **Silvia Arber,** Biozentrum, University of Basel, 11-04-08.

Specification and integration of cerebellar neurons, **Ferdinando Rossi,** University of Turín, Italy, 18-04-08.

Functional MRI of synaptic plasticity, **Santiago Canals,** MPI for Biological Cybernetics. Tuebingen, Germany, 21-04-08.

Life-long neurogenesis and olfaction., **Pierre Marie Lledo,** Institut Pasteur, Paris, France, 25-04-08.

Life imaging of GABA(B) receptors, **Emilio Casanova,** Ludwig Boltzmann Institute for Cancer Research (LBI-CR). Medical University of Vienna, 09-05-08.

Kainate receptor interacting proteins ; role in traffic and physiolog, **Françoise Coussen,** UMR-CNRS. Institut F. Magendie. Bourdeaux, France, 16-05-08.

Regulation of the expression and function of the Iroquois complex genes of Drosophila melanogaster, **Sonsoles Campuzano,** Centro de Biologia Molecular Severo Ochoa, Madrid, España, 23-05-08.

Graded Sonic Hedgehog Signaling and the Control of Neural Cell Identity, **James Briscoe,** National Institute for Medical Research, London, 30-05-08.

Spiking Research: From cortical circuit dynamics to a virtual body. Research at the INA 2000-2008, **Maria Victoria Sánchez-Vives,** Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 06-06-08.

New morphogenetic mechanisms in restricting epithelial-to-mesenchyme transition in the gastrulating embryo, **Joaquim Egea,** Max-Planck Institute of Neurobiology, Munich, Germany, 12-06-08.

Cellular basis of the electroencephalogram: at last!, **Oscar Herreras,** Instituto Cajal, Madrid, 13-06-08.

Addressing Brain Complexity, **Nathaniel Heintz,** The Rockefeller University, New York, 18-06-08.

Grandmother cells in the human brain?, **Rodrigo Quiroga,** University of Leicester, United Kingdom., 20-06-08.

Cuartas Jornadas Científicas del INA, **Investigadores del INA,** Instituto de Neurociencias , 26-06-08.

Cuartas jornadas cientificas del INA, **Investigadores del INA,** Instituto de Neurociencias, 27-06-08.

Conserved regulatory logic of dopaminergic terminal differentiation, **Nuria Flames,** Columbia University, Department of Biochemistry and Molecular Biophysics. New York, USA., 04-07-08.

Entrega del premio "Remedios Caro Almela". Caro Almela Lecture, **François Guillemot,** National Institute for Medical Research, Division of Molecular Neurobiology, London, UK., 17-10-08.

Decoding a decision process, **Carlos Acuña,** Laboratorios Neurociencia, Facultad de Medicina de Santiago de Compostela, España., 24-10-08.

Coordination between cell cycle and neurogenesis in the vertebrate nervous system , **José María Frade,** Instituto Ramón y Cajal CSIC, Madrid, España, 31-10-08.

Atypical Celsr cadherins, planar polarity and brain development., **Andre M. Goffinet,** Center for Neurosciences, Developmental Neurobiology Unit, University of Louvain, Brussels, Belgium., 07-11-08.

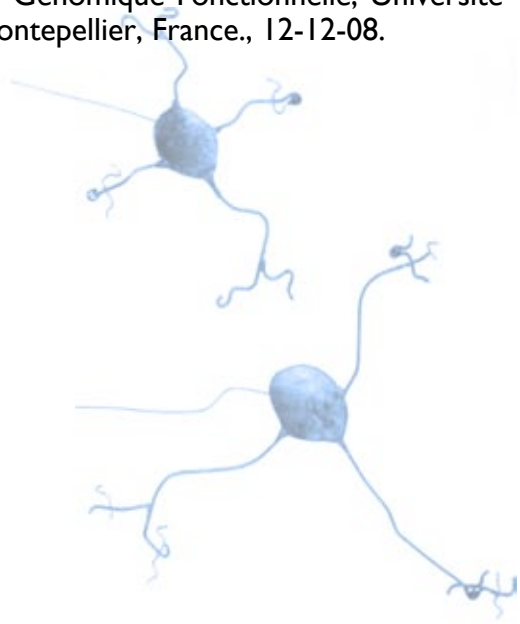
The control of nerve development, damage and repair by c-Jun and Notch in Schwann cells, **Kristjan R. Jessen,** Depeartment of Anatomy and Developmental Biology, UCL, London, United Kingdom., 14-11-08.

Modeling cancer in mice, **Mariano Barbacid,** Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, España., 21-11-08.

Genetic mechanisms that determine dorso ventral pattern in the vertebrate , **Elisa Martí,** Instituto de Biología Molecular CSIC, Barcelona, España., 28-11-08.

Regulation of neuronal differentiation in the embryonic midbrain, **Juha Partanen,** Institute of Biotechnology, University of Helsinki, Finland., 05-12-08.

Metabotropic glutamate receptors: allosteric machines for new drugs , **Jean Philippe Pin,** Institute Génomique Fonctionnelle, Université I et II Montepellier, France., 12-12-08.



SEMINARS 2009

Specification of neuronal subtypes by the sequential integration of positional, temporal and local cues, **Stefan Thor,** Department of Clinical and Experimental Medicine, Linksping University, Sweden., 16-01-09.

Emergence of synaptic specificity in the mouse cerebellum , **Peter Scheiffele,** Neurobiology Neurozentrum, University of Basel, Switzerland., 23-01-09.

Modulation of dopaminergic signaling and associative learning in C. elegans, **Nektarios Tavernarakis,** Inst. Molecular Biology and Biotechnology Foundation for Research and Technology, Crete, Greece., 30-01-09.

Propagation, reverberation and complexity: visual cortex near the edge of chaos?, **Yves Fregnac,** Unité de Neurosciences Intégratives et Computationnelles. Gif-sur-Yvette, France. , 06-02-09.

Peripheral pain mechanisms, **John Wood,** Department of Biology, University College London, United Kingdom., 13-02-09.

Vitamin D, Wnt, Snail1 and colon cancer , **Alberto Muñoz,** Instituto de Investigaciones Biomédicas, Madrid, 20-02-09.

Imaging the spatial and temporal dynamics of synaptic proteins in cultured neurons: mechanisms and function , **Paul De Koninck,** Département de Biochimie et Microbiologie. Centre de Recherche Université Laval Robert-Giffard. Québec, Canada., 27-02-09.

The temporal dimension of spatial maps in the rat somatosensory system , **Guglielmo Foffani,** Hospital Nacional de Parapléjicos: Toledo, España & Drexel Biomed: Philadelphia, USA. , 06-03-09.

Tissue-type plasminogen activator (tPA): a two faces neuromodulator, **Denis Vivien,** GIP Cyceron, Université de Caen, France., 13-03-09.

De rerum natura in morbo Parkinson , **Justo García de Yébenes,** Servicio de Neurología. Hpistal Ramón y Cajal, Madrid., 23-03-09.

Fate specification and molecular development of corticospinal motor neurons, **Paola Arlotta,** Harvard Stem Cell Institute, Hardvard University, USA., 27-03-09.

Interpreting spikes in the whisker system , **Miguel Maravall Rodríguez,** Instituto de Neurociencias CSIC - UMH, Alicante, 03-04-09.

To Cross or not to Cross: Mechanisms Regulating Midline Axon Guidance in Drosophila, **Greg J. Bashaw,** Dept of Neuroscience: Develop. Stem Cell & Regenerative Biology Program. University of Pennsylvania, Philadelphia, USA, 17-04-09.

Activity dependent gene expression in the brain: From c-Fos to synaptic plasticity via extracellular proteolysis, **Leszek Kaczmarek,** Nencki Institute, Warsaw, Poland., 08-05-09.

Membrane changes and dynamics during neuronal aging: survival at the expense of performance?, **Carlos Dotti,** Neuronal Differentiation Unit. KULeuven, Center for Human Genetics. Leuven, Belgium, 14-05-09.

The multiple tricks of serotonin during development, **Patricia Gaspar,** INSERM, Hôpital Salpêtrière, Paris, France., 15-05-09.

Wnt signalling controls directional migration of neural crest cells, **Roberto Mayor,** Department of Anatomy and Developmental Biology: University College London, UK , 22-05-09.

Control of cortical inhibition and excitation by endocannabinoids: Novel insights into anxiety and epilepsy., **Tamas F. Freund,** Institute of Experimental Medicine: Hungarian Academy of Sciences. Budapest, Hungary., 27-05-09.

Consolidation of Prosthetic Motor Skill in Primates, **José M. Carmena,** Dept. of Electrical Engineering & Computer Sciences. Hellen Wills Neuroscience Institute, Univ. of California, USA, 02-06-09.

Chemotaxis in Drosophila: from odorant receptors to behavior, **Matthieu Louis,** Center for Genomic Regulation, Barcelona, 05-06-09.

Mapping behaviour to the brain by circuit genetics in Drosophila , **Martin Heisenberg,** Biozentrum of the University of Würzburg, Germany., 12-06-09.

Ras-GRF1 as signalling integrator in striatum-dependent plasticity and diseases, **Riccardo Brambilla,** Institute of Experimental Neurology and Dep. of Neuroscience: San Raffaele Foundation. Milano, Italy., 19-06-09.

The role of the Neural Crest in the Development and Evolution of Vertebrates, **Nicole Le Douarin,** Collège de France. Académie des Sciences: Paris, France, 03-07-09.

Tuning of synaptic responses in a cognitive circuit, **Matt Nolan,** Centre for Cognitive and Neural Systems. University of Edinburgh, Scotland., 11-09-09.

Amygdala-enriched genes in learned fear and social behavior, **Gleb Shumyatsky,** Rutgers University, Department of Genetics. Piscataway, New Jersey, USA, 21-09-09.

Deconstructing synapses with Wnt Antagonists, **Patricia Salinas,** Department of Anatomy and Developmental Biology. University College London, United Kingdom., 23-10-09.

The Role of PDZ Domain Proteins in the Sorting of Glutamate Receptor in Neurons, **Bill Green,** Department of Neurobiology. University of Chicago, USA, 06-11-09.

TRP channels V1 and A1 mediate drug side effects and inflammatory disease, **Peter Reeh,** Institute of Physiology and Pathophysiology. University of Erlangen-Nuremberg. Erlangen, Germany, 13-11-09.

Molecular control of myotopic organisation of spinal motor neurons, **Artur Kania,** Department of Biology. McGill University, Montreal, Quebec. Canada, 18-11-09.

GABAergic circuitries in the hippocampus, **Thomas Klausberger,** MRC Anatomical. Neuropharmacology Unit. Oxford, UK, 20-11-09.

Regimes of operation in visual cortex, **Matteo Carandini,** Institute of Ophthalmology. London, UK, 27-11-09.

Endoplasmic reticulum stress impedes differentiation and translational homeostasis in hereditary demyelinating neuropathy, **Lawrence Wrabetz,** San Raffaele Scientific Institute, DIBI. Milano, Italy, 04-12-09.

A genetic painting approach for mapping circuitry and cellular interactions in the nervous system, **Jean Livet,** INSERM Institut de la Vision. Paris, France, 11-12-09.

Análisis funcional de SCRATCH2 en la médula espinal del pez cebra, **Eva Rodríguez Aznar,** Instituto de Neurociencias CSIC-UMH, 15-12-09.

The role of feedback in awareness and attention , **Stephen Macknik ,** Laboratory of Behavioral Neurophysiology. Barrow Neurological Institute. Phoenix, USA., 21-12-09.

Effects of fixational eye movements on physiology, perception and cognition, **Susana Martínez-Conde,** Laboratory of Visual Neuroscience. Barrow Neurological Institute. Phoenix. USA., 22-12-09.

Intracellular proteins implicated in the migration of cortical neurons, **Manuel Valiente Cortés,** Instituto de Neurociencias CSIC-UMH, 22-12-09

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