Fundación del Hospital Nacional de Parapléjicos para la Investigación y la Integración

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The hospital of the future

José Ignacio Echániz

Minister of Health and Social Affairs

The National Hospital for Paraplegics (HNP) in Toledo serves as an institutional model for the successfull coordination between patients care, research and teaching. In addition to being the national reference center, this hospital stands out as a symbol of modernization and progress for its integrated approach to the treatment and rehabilitation of spinal cord injuries.

To ensure its cutting edge clinical program, while maintaining patients wellbeing, the hospital combines high quality care with the latest advances in scientific research. This innovative approach is the essential tool for improving patients care for it allows a faster transfer of the latest research advances into the clinic and more efficient use of the available resources.

The National Hospital for Paraplegics has almost 40 years of health care experience and one of its main objectives still remains the integration of people with disabilities. Recognition of this aim is essential for the normalization of patient´s disability and also for raising awareness of its complexity.

Our citizens deserve a modern, humanized and high quality health care system, which is why the Castilla-La Mancha regional government encourages the study of new techniques and treatments for the repair of spinal cord injuries. The hospital of the future is one that cares for its patients, strives to improve their lives through research and transmits the acquired knowledge to new generations.

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Our Mission:

To improve lives and facilitate functional recovery of people with spinal cord injuries by using multidisciplinary research and raising social awareness about the importance of this reality

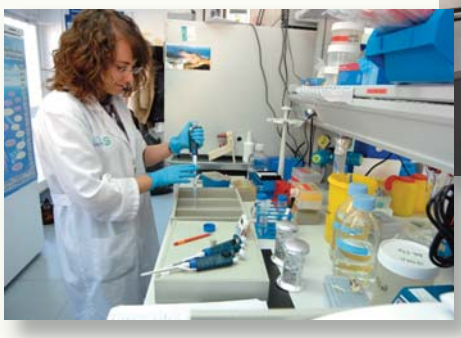
HNP we open new horizons in the fight against paralysis

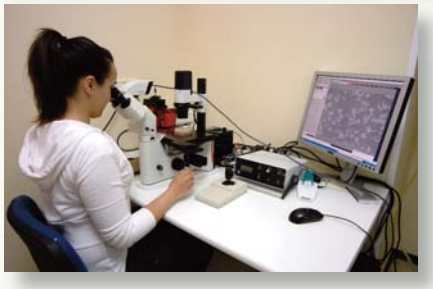
Multidisciplinary research for the repair of spinal cord injuries

Research at the National Hospital for Paraplegics

Experimental Neurology Unit of the HNP was founded in 2002 with only two laboratories and the objective of developing basic research in the field of spinal cord injury. Currently the unit includes more than a hundred researchers divided between eighteen research groups (basic and clinical) and the research support units (i.e. microscopy, flow cytometry, proteomics, MRI and animal facility). They work together to better understand the biology of spinal cord injury.

The Research Foundation of the HNP was created in 2004 to provide administrative support to researchers, to capture and manage financial resources, to inform the healthcare professionals and society about the latest advances in neuroscience research while ensuring legal and ethical principles in the research process. Furthermore, much of the Foundation´s effort is dedicated to the development of a financially sustainable system by attracting the national and international funds, sponsorships and volunteer work. This way we expect to realize the work of quality and relevance to people with spinal cord injury and also to the society as a whole.





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"Today we can identify galaxies light years away,
we can study particles smaller than the atom
but we still haven´t unlocked the mystery of
the three pounds of matter
that sits between our ears" -president Obama's remark on Brain-

Spinal cord injury in the world

Judging by the number and likely causes, the spinal cord injury presents a global problem. It is estimated that there are millions of spinal cord injured people worldwide with the yearly incidence varying from 40-55 persons, per million of habitants, in the US and Japan, 30 in Australia to 20-30 people in Europe. However, if we broaden the scope to include different central nervous system (CNS) diseases, also addressed in some of our basic research projects, these figures increase significantly. According to the World Health Organization (WHO) hundreds of millions of people around the world suffer from some form of neurological disorder, for example: 50 million people suffer from epilepsy, 62 million from cerebrovascular diseases, 326 million from migraine, whereas 24 million people have the Alzheimer's disease or some other type of dementia.

The common cause of SCI have changed over the years, mostly depending on the reality of each country and accompanying life style change. Recent clinical statistics at the National Hospital for Paraplegics indicate a general decline in the number of traumatic injuries caused by traffic accidents and an increase in the number of injuries caused by falls, as well as an increase in hospitalizations due to different spinal cord diseases.

Regardless of the cause that may produce it (i.e. trauma, infection, degenerative disorders, tumors, etc.), the enormous impact spinal cord injury exerts upon a patient, his immediate surroundings and the whole society makes it an area of great scientific interest.

Only half a century ago the life expectancy of a person with paraplegia would hardly reach a couple of years. Thanks to scientific and technological advances, current survival rate and life quality of these persons have undergone numerous positive changes. The knowledge and experience accumulated by professionals at the HNP, during almost forty years of its history, has contributed significantly to this trend.

Despite numerous advances in this field, clinicians at the center are faced daily with the same question posed by patients and their families: Is there a cure for spinal cord injury?

In the last five years, new tools and techniques for restoring damaged nervous system became available but most of them have only been approved for animal, especially rodent, use. Although, these new techniques are being gradually applied to some human spinal cord injuries, there is still a long way to go.

Fortunately, a growing body of data, more political willpower and the available financial and human resources are bringing us closer to crossing the final science frontier: the nervous system.

Two following examples speak in favor of this notion: under the platform "Horizon 2020" , the European Commission has decided to invest billions of euros in the "Human Brain" project, as well as in the project with graphene, a conductive material used as three-dimensional scaffold upon which long neuronal processes, called axons, can grow. The Commission indicates that the above projects will be the most advanced studies ever conducted in this field and will serve to develop personalized treatments for various neurological disorders. At least 15 EU member states, including Spain, are involved in these two studies.

The other example can be found on the other side of the Atlantic where, a Spanish scientist, Rafael Yuste coordinates the United States-led initiative of Obama Administration, known as BRAIN (Brain Research through Advancing Innovative Neurotechnologies) and aimed at mapping out all brain activities in the next 15 years. The idea, originally conceived by the Spanish scientist, currently involves hundreds of experts from around the world and provides yet another example of globalization.

What can we expect from the transfer of this knowledge?

Neurobiologists seem to agree that therapies aimed at the spinal cord regeneration have to incorporate several strategies at once. In line with that, scientists at the HNP are working on the most promising strategies that would allow patients to maximize their functional recovery.

Taking into account basic and clinical research advances in the field of spinal cord injury, one may ask the following questions: How do we translate these advances in terms of patients' hope? To which extent the available information is shared and coordinated between researchers working on neural regeneration worldwide?

Research doors wide open

Francisco Marí
Director of the National Hospital for Paraplegics

Brain activity generates electricity, which is why our thinking or the surge of brilliant ideas is symbolized by the picture of a light bulb hanging over our head. Following the metaphore, our communication partners have squeezed their "gray matter" up to wide open the door of our research and make it transparent to everyone.

In this issue we have done an important descriptive exercise on our scientific where-abouts, the important questions we need to answer and, of course, their possible solutions. All this unraveling in a complex, sometimes opaque and very competitive scientific environment.

Our research is translational, it ranges from basic to clinical and always strives to address patients´ problems.

It connects us with other institutions, groups and scientists from other countries. It produces results, articles, patents and biomedical advancements. It generates incentives, motivates and inspires clinicians and teachers alike.

It is in need of stable funding.

The material that follows is also included in our new web page and diffused through social networks. Let us see whether this new "visibility" will bring us better recognition in the form of new financial resources.

Basic research and clinical research

The fundamental goal of research in the field of healthcare is to produce knowledge on the molecular, biochemical, cellular, genetical, pathophysiological and epidemiological mechanisms underlying diseases and health problems, in our case the spinal cord injury and CNS diseases, and to develop strategies for their prevention and treatment. In the HNP are conducted two types of research: basic/preclinical and clinical.

Basic research seeks a better understanding of the molecular, biochemical and cellular mechanisms involved in the origin and outcomes of the disease, as well as to determine the involvement of epigenetic aspects in its genesis.

Clinical research, on the other hand, is centered on patients while realizing studies on the prevention, diagnosis and treatment of spinal cord injury. Clinical trials play an important role in this type of research as they serve to determine or verify clinical and/or pharmacological effects of a particular therapy, or an experimental compound, in order to address their safety and effectiveness.

Basic Research Groups

NEURAL PLASTICITY-CAJAL INSTITUTE
(CSIC, Dr. Manuel Nieto Sampedro)

NEUROINFLAMMATION
(Dr. Eduardo Molina Holgado)

NEURAL REPAIR AND BIOMATERIALS
(Dr. Jorge Collazos Castro)

SENSORY-MOTOR FUNCTION
(Dr. Julian Scott Taylor)

NEURONAL BIOENGINEERING
(Dr. Guglielmo Foffani)

EXPERIMENTAL NEUROPHYSIOLOGY
(Dr. Juan de los Reyes Aguilar Lepe)

MOLECULAR NEUROPROTECTION
(Dr. Rodrigo Maza y Dr. Manuel Nieto Díaz)

MOLECULAR NEUROLOGY
(Dr. Francisco Javier Rodríguez Muñoz)

DEVELOPMENTAL NEUROBIOLOGY
(Dr. Fernando de Castro)

MEMBRANE BIOLOGY AND REPAIR AXONAL
(Dr. José Abad Rodriguez)

VASCULAR PATHOPHYSIOLOGY
(Dr. María G. Barderas y Dr. Luis R. Padial)

NEURAL REGENERATION
(Dr. Jörg Mey)

Emergent Group: NEURO-REGENERATIVE CHEMISTRY
(Dr. Ernesto Doncel Pérez)

Clinical Research Groups

FUNCTIONAL EXPLORATION AND NEUROMODULATION OF THE CENTRAL NERVOUS SYSTEM
(GRUPO FENNSI, Dr. Antonio Oliviero)

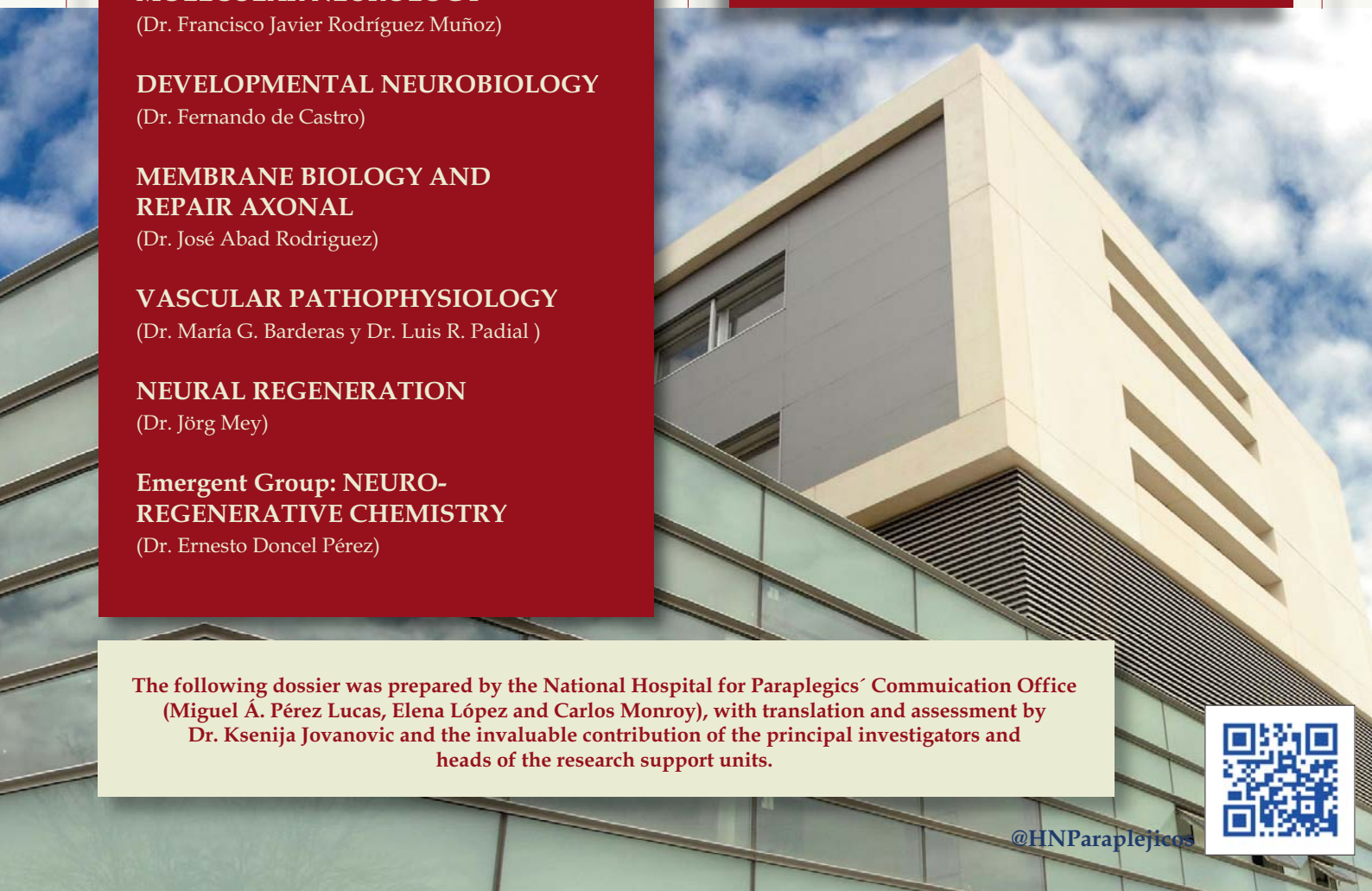
BIOMECHANICS AND TECHNICAL AID
(Dr. Angel Gil)

GAIT RE-EDUCATION AND FUNCTIONAL RECOVERY
(Dr. Ana Esclarín de Ruz)

ASSISTED REPRODUCTION
(Dr. Antonio Sánchez Ramos)

SPINE PATHOLOGY
(Dr. Andrés Barriga Martín)

UROLOGY
(Dr. Manuel Esteban)



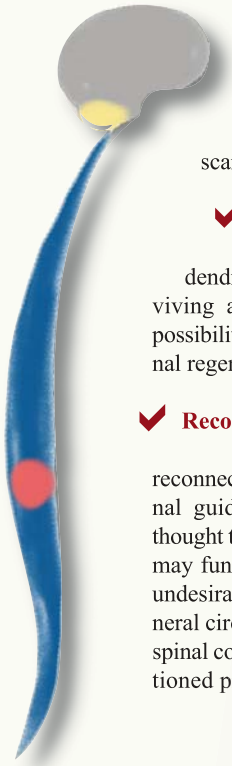
The following dossier was prepared by the National Hospital for Paraplegics´ Commuication Office (Miguel Á. Pérez Lucas, Elena López and Carlos Monroy), with translation and assessment by Dr. Ksenija Jovanovic and the invaluable contribution of the principal investigators and heads of the research support units.

This is the challenge

by **Manuel Nieto Diaz**, Research scientist at the HNP

To repair a spinal injury means to restore, albeit partially, functions damaged by the injury by restoring, to some extent, the structure and circuitry that existed prior to it.

This entails solving several problems:



✔ Reducing the death of neurons and oligodendrocytes or replacing them

The death of a large number of these cells during the acute phase and during, so called, secondary cell death is responsible for much of the functional loss. Following their death, our body is not capable of replacing them as both cell types are not produced during adulthood and the amount that is generated from stem cells or precursors is very limited.

✔ Promoting axonal regeneration

In other words, to make axons severed by the injury grow again and cross the injured area in order to restore interrupted spinal circuits. In principle, spinal axons have the ability to grow but do so very slowly and once they reach the injured area they encounter an inhibitory environment that impedes their growth. The culprits for this situation are myelin proteins such as MAG (myelin associated glycoprotein), Nogo, MOGP (myelin associated oligodendrocytic glycoprotein) or Tenascin, released in the injured area following oligodendrocyte cell death. Other molecules from the glycosaminoglycan family, present in glial scar-forming reactive astrocytes, also cause the inhibition.

✔ Promoting axon remyelination

The loss of myelin, resulting from the death of oligodendrocytes, leads to a poor nerve signals conduction in surviving axons. Therefore, remyelination of axons raises the possibility of improving their function even in the absence of axonal regeneration.

✔ Reconnecting damaged circuits

This approach involves processes that allow axons to reconnect with their targets. Certain molecules, important in axonal guidance during our development and growth, are also thought to be important in this process. Badly reconnected circuits may function even worse than the injured ones, thus producing undesirable consequences as neuropathic pain, spasticity and general circuit malfunctioning This is the least explored area in the spinal cord repair, mainly because it requires that the above mentioned problems are solved first.

The complexity and large number of processes triggered by the spinal cord injury have led to an equivalent number of research lines addressing its repair in very different, but largely complementary, ways. Some of these therapeutic approaches focus on only one aspect of the injury, while a great number of them attempts to solve several problems at once.

Basic approaches can be classified into:

❖ **Transplantation:** involves insertion of some tissue or material in the injured area to help repair the damage. The most common transplantation candidates include fetal spinal cord tissue, peripheral nerve grafts, different types of cells (neural or not) and even biomaterials.

❖ **Molecular strategies:** assume introduction of specific molecules that promote axonal regeneration directly or by inactivating molecules that inhibit axonal growth. This type of strategy also includes molecular neuroprotection with substances that promote the survival of neurons and oligodendrocytes.

❖ **Promotion of alternative circuits:** the nervous system has the capacity to change and adapt and is able to employ alternative circuits to perform some of the functions lost after spinal cord injury.

Other types of strategies may be based, for example, on biophysical factors as electrical activity that is capable of promoting the growth of axons and guiding them towards proper targets.

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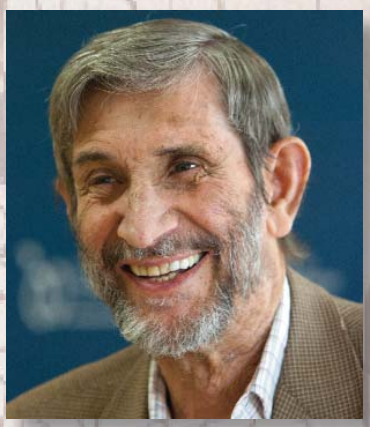
Neural Plasticity-Cajal Institute

"We investigate how to modulate the glial scar formation, a major obstacle to the adult CNS regeneration"



The group video

Main investigator

Manuel Nieto Sampedro

The problem

Lesions in the central nervous system (CNS) of adult mammals, being mechanical or degenerative, are not spontaneously repaired. One of the main obstacles is the formation of a fibrogliotic scar at the injury site. Although important in organism survival, the scar hinders growth of regenerating fibers towards their physiological targets and causes atrophy (i.e. collapse) of their growth cones.

The Research

For the last 35 years, the principal investigator has been studying the molecular bases of neural plasticity and their possible use in functional repair of the CNS injuries.

The present work topics of the group are:

Cell culture models of reactive glia.

Cellular and molecular mechanisms involved in glial scar formation.

Inhibition of glial scar formation by natural and synthetic compounds.

Progress

Manuel Nieto-Sampedro has devoted 46 years of his professional life to clinically oriented basic research. The first eight years of his career were dedicated to the action mode of antibiotics, while in the remaining years he studied neural plasticity.

His main accomplishments are the following:

First description of the mode of action of antibiotics that inhibit the synthesis of bacterial cell wall proteoglycans (penicillins, cephalosporins, vancomycin, ristocetin).

Structure and conformation of energy transducing ATPase.

First description of the synapse specific antigen PSD-95.

First description of injury-induced CNS neurotrophic activity and of glia as its main cellular source.

First description of the correlation of injury-induced neurotrophic activity and enhanced survival and integration of delayed transplants in the CNS wound cavity.

First description of the relationship between the nervous and immune system (first description of the presence of cytokines IL-1 and IL-2 in the brain).

First description of the regeneration, spinal cord re-entry and functional recovery of axons after dorsal rhizotomy.

First description and chemical purification of normal and injured CNS proteoglycans that negatively regulate axonal growth.

First description, chemical purification and structure determination of a glycolipid (neurostatin) that negatively regulates proliferation of cells of astroglial lineage.

Production of synthetic and semi-synthetic analogues of the glial division inhibitor, neurostatin.

Production of synthetic and semi-synthetic inhibitors of brain and spinal cord tumors (glioblastoma).

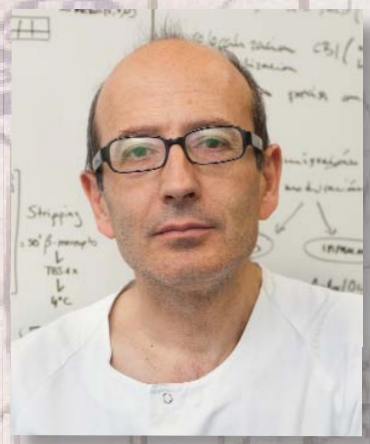
First studies on cytokine IL-15, as the initiator of glial reactivity and neuropathic pain following spinal cord lesions.

Collaborations

During the past decades the principal investigator has maintained numerous and friendly scientific collaborations, some of which are still active while others could be activated if required.

Some of his distinguished collaborators are: Dr. Håkan Aldkogius (Biomedical Center, University of Uppsala, Sweden). Dr. John P. Fraher (Department of Anatomy, University of Cork, Irland). Dr. Stephen B. Mc Mahon (St Thomas Hospital, London, UK). Dr. John V. Priestley (Division of Physiology, St Mary's Hospital, London, UK).

Photo: **Carlos Monroy**
(Left to right) **Manuel Nieto Sampedro, Natalia Yanguas Casás, Asunción de la Barreda Manso, Estela Dámaso Riquelme and Lorenzo Romero Ramírez.**



Neuroinflammation

"We have revealed an endogenous defense mechanism in the endocannabinoid system that must be potentiated to counteract spinal cord injury"

Main investigator

Eduardo Molina

The group video

The problem

Spinal cord injury is a complex reality, so to improve it and/or counteract it we must address numerous pathological processes. Our laboratory is focused on the study and therapeutic modulation of three events that occur after the injury:

The death of nerve cells (neurons and glia) that ultimately leads to the loss of neural function.

The inflammatory response, which in the acute phase (days following the injury) helps the spread of spinal damage and in the chronic phase (months to years later) may be among possible causes that prevent nerve regeneration.

Axonal dysfunction following the loss of the myelin sheet.

The Research

Our laboratory has over 15 years of experience in studying the endocannabinoid system. Endocannabinoids are the compounds our bodies naturally produce from cell membrane lipids and named after active ingredients of marijuana plant that also exert their effects by acting through the receptors of this system. Our results demonstrate that endocannabinoids may be an important therapeutic target, if not for solving, then at least for substantially reducing the above listed problems.

Progress

We have shown that the endocannabinoid system is activated after spinal cord injury and that exogenous administration of main endocannabinoid, 2-arachidonoylglycerol, reduces the injury-induced damage. In contrast, blocking the system´s endogenous activation changes the inflammatory profile of spinal cord, increases neurological damage and causes more functional loss. The spinal injury research has advanced tremendously in determining which pathological mechanisms should be contained to prevent the damage from further spreading. However, what we have found is the opposite: an endogenous defense mechanism that must be potentiated to counteract the injury.

Furthermore, we have observed that the endocannabinoid system promotes proliferation and preservation of neural stem cells, thus suggesting that its modulation may be useful in replacing the neural cell loss. Since there is a great interest in the therapeutic potential of spinal stem cells, we are studying and comparing the regions containing these cells, between experimental animals and in humans. Unexpectedly, our findings demonstrate numerous differences between humans and animals (rats, mice and various species of primates), the fact that will have important implications when it comes to transferring these results to the clinic.

Finally, we have also shown that the endocannabinoid system favors the migration and maturation of oligodendrocyte precursors (cells that produce the myelin sheet) and that treatment of rats and mice with substances acting upon cannabinoid receptors leads to an increase in myelination during their development, as well as in experimental models of multiple sclerosis.

Photo: **Carlos Monroy**
(Left to right) **Ángel Arévalo, Eduardo Molina, Daniel Gacía, Concepción Sánchez-Caro, Beatriz Paniagua y Alejandra Sánchez.**

Collaborations

Our grup colaborates with Dr. Florencia Labombarda (Laboratory for Neuroendocrine Biochemistry at the Institute of Biology and experimental Medicine "CONICET"; Department of Human Biochemistry, Faculty of Medicine, University of Buenos Aires, Argentina) and with Dr. Francisco Molina Holgado (Neural Stem Cell Laboratory at the University of Roehampton, Whitelands College, London, UK).

Neural Repair and Biomaterials

"Fabricating electroconducting microfibres to promote axonal growth and neural cell migration after spinal cord injury"

The group video

Main investigator

Jorge Collazos

The problem

Human spinal cord injuries are characterised by gross disruption of the neural architecture, formation of scars and tissue gaps with the size in centimetres. These changes provide a mechanical barrier to axonal regrowth and oriented cell migration and interfere with spatial cues that otherwise could aid repair. Implantable, three-dimensional scaffolds made of biomaterials are required to provide permissive substrates for neural cell migration and to stimulate and guide axonal growth across the lesion. Additionally, it is necessary to activate the intrinsic regenerative response of neurons and to develop animal models of spinal cord injury relevant to the human pathology, in order to investigate the pathophysiology of functional loss and the effects of therapeutic interventions promoting tissue repair and functional recovery.

The Research

With the aim of promoting reparative processes following spinal cord injury, our laboratory opts for an integrative approach based on three mainstays:

Development of implantable devices that incorporate electroconducting microfibres functionalised to provide stimulus, guidance and a physical support to the growing axons and migrating neural cells within the lesion area.

Pharmacological and genetical activation of intrinsic neuronal mechanisms leading to axonal regeneration.

Dynamic control of cellular responses by means of electrostimulation.

At the same time, we investigate the loss, compensation and recovery of neurological function after spinal cord injury using a combination of high resolution kinetics and kinematics and animal models of the lesion types and locations most frequently observed in patients. In addition to comprehensive analyses of the residual motor capability, we employ anterograde and retrograde neural tracers to visualise the disruption of neural circuits.

Progress

We have developed bioelectrochemical methods to control neural cell growth on conducting polymers and molecular complexes to functionalise the material surface and to selectively stimulate axonal growth or glial cell precursors proliferation and migration. Likewise, we synthesised new polymers and fabricated electroconducting microfibres that are very effective in promoting axonal growth and neural cell migration for long distances (eight millimetres in ten days). Additionally, we have described the biomechanics of locomotor disorders and neural circuits damaged by cervical, thoracic and lumbar spinal cord injuries, thus obtaining an excellent correlation between anatomy and function that allowed us a reliable evaluation of the effects produced by different therapeutic approaches. Finally, we have studied the mechanisms that animals use to compensate for lost motor functions, information that results critical for optimising the functional rehabilitation protocols.

Collaborations

Teamwork is necessary to advance in this complex research topic. We have maintained collaborations with the University of Castilla La Mancha and the CSIC in Spain, as well as with research institutions in the United Kingdom, Greece and Portugal. Presently, our efforts are directed at developing cooperations with industrial partners in pharmaceutics, micro- and nanotechnology. More specifically, we are establishing an R&D consortium with enterprises from the Basque Country and Germany, specialised in those fields, with the aim of fabricating implantable electrobiological devices to repair the injured spinal cord.

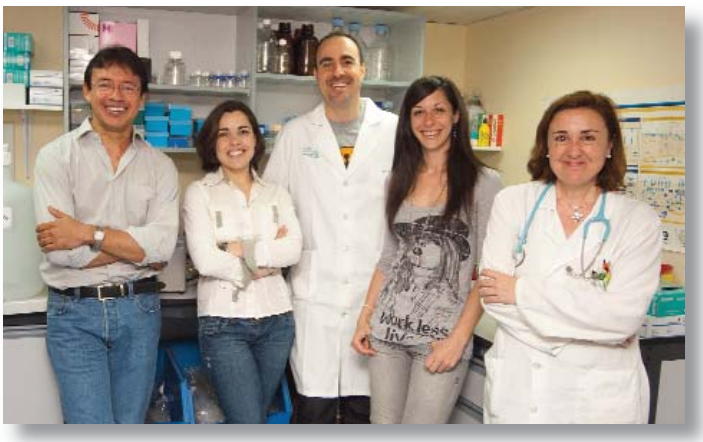


Photo: **Carlos Monroy**
(Left to right) **Jorge Collazos, Alejandra Alves, Hugo Vara, Concepción García-Rama and Elisa Dolado.**

Sensori-motor Function

"Addressing the chronic complications of spinal cord injury: neuropathic pain and spasticity"

Main investigator

Julian Taylor

The group video

The problem

Spinal cord injury produces different degrees of sensation and movement loss. However, the development of pain and spasticity, as the major chronic complications, are often perceived as more debilitating and contribute significantly to loss of quality of life. Failure to diagnose and adequately treat these additional symptoms during the recovery period requires the development of new tests and treatment strategies. Latest evidence points to the possibility that these symptoms are related to the type of injury, including bleeding within the injury area. These physical factors and clinical symptoms negatively impact on the small amount of functional recovery driven by neurorehabilitation programs, and may even block new ways to treat spinal cord injury.

The Research

The research group, organized between the basic and clinical labs, works to improve the diagnosis of spasticity and neuropathic pain by measuring the changes in sensation and movement that occur after spinal cord injury. In parallel, we work on developing new ways to treat or prevent these debilitating complications so that the subject can recover as much as possible.

To achieve these objectives we combine various experimental techniques to measure "pain" and "spasticity" in animal models and use standard neurological and new diagnostic tests that can spot the most damaging signs of these symptoms. In the basic lab, we employ a new screening platform that helps us identify new treatments that could help control different types of spasticity and neuropathic pain. In the clinical lab, we perform investigator and industry lead clinical trials to improve the diagnosis of these symptoms in the course of their rehabilitation in the hospital and at home. This allows us to test standard and new treatment strategies in collaboration with our specialized medical staff.

Progress

Our group has developed two new drugs based on natural fatty acids that control several damaging symptoms of spasticity and pain. Importantly, these drugs also allow better movement recovery after injury by making some surviving nerves grow more. A patented drug has already been registered as an orphan drug in Europe, while the others are being developed by industrial partners thanks to the new screening platform in our basic research lab.

At the clinical level, we are working on ways to give both the patient and clinician, early warnings about the development of the most debilitating symptoms of pain and spasticity. The clinical trials in progress, that include testing pharmacological, neuromodulation and training techniques, will help to control some of these complications.

Collaborations

Our group collaborates with respected national and international experts at both the basic and clinical level including Dr. Martin Marsala (San Diego, USA), Dr. Nanna Finnerup, (Arrhus, Denmark), Dr. Jose Luis Pons (Madrid, Spain), Dr. Volker Dietz (Balgrist, Switzerland), Dr. Miguel Ruiz (Madrid, Spain), Dr. Vivian Mushahwar (Edmonton, Canada) and the Guttmann Institute (Badalona, Spain). Other strategic links include University of Liverpool, University of Glasgow, as well as Stoke Mandeville and the London Hospital. We work with industrial partners interested in related viable clinical solutions, especially Lipopharma S.L. (Palma de Mallorca, Spain). Our group is the responsible Toledo arm of the European Medical Spinal Cord Injury and EuroDolmed network. Finally, we believe that good solutions emerge when we collaborate with clinicians dedicated to the same problems produced by spinal cord injury.

Photo: **Carlos Monroy**
(Left to right) **Juan Avendaño, Cristina Simón, Elisabeth Bravo, Julio Gómez, Águeda Ferrer, Iriana Galán, Gerardo Ávila y Julian S. Taylor.**

Neuronal Bioengineering

"Developing methodologies for neural signal recording and analysis to extract pathophysiological information from neuronal activity"

The group video

Main investigator

Guglielmo Foffani

The problem

Neuronal activity represents the basis for information transmission in the nervous system. When the nervous system is damaged, for example due to a spinal cord injury or a neurodegenerative disease, neuronal activity becomes altered, leading to pathological consequences such as neuropathic pain in spinal cord injury or tremor in Parkinson's disease. In our group we address neurological problems from the perspective of the alteration in neuronal activity.

The Research

Modern neurophysiological techniques allow scientists to record neuronal activities of increasing complexity (e.g. populations of single neurons, local field potentials, multichannel EEG recordings, functional imaging, etc) but their very complexity often impedes the correct pathophysiological interpretation of the recorded activity. Therefore, the overall research theme of our group includes the development and application of methodologies for recording and analyzing neural signals to extract pathophysiological information from complex neuronal activities. Specifically, our main research lines are the following: brain reorganization after spinal cord injury; neuronal oscillations in neurodegenerative disorders; neural coding in the somatosensory system; development and application of neuromodulation techniques to treat neurological disorders.

Progress

We have developed methods to exactly quantify the information that neuronal populations can transmit by means of the quantity or the temporal precision of their activity in physiological and pathological conditions. One of the most fascinating consequences of the temporal precision of neuronal activity is that large networks of interacting neurons tend to oscillate. Thus, we have generated a solid knowledge base about the role of cerebral oscillations in spinal cord injury and in neurodegenerative diseases such as Parkinson's disease and epilepsy. Regarding the spinal cord injury problem, our results have immediate practical consequences on the control of anesthesia in patients, as well as far-reaching implications in the mechanisms that lead to brain reorganization after spinal cord injury and a consequent emergence of neuropathic pain. In line with that, we are presently developing novel techniques for brain stimulation to prevent/treat neuropathic pain after spinal cord injury. So far, these techniques show very promising potential in treating neurological disorders with high social impact, such as epilepsy and migraine. To maximize the social impact of our research, we have created a spin-off company at the Fundación del Hospital Nacional de Parapléjicos: Neurek S.L. (*www.neurek.com*).

Collaborations

The closest collaborators of the group are Dr. Juan de los Reyes Aguilar and Dr. Antonio Oliviero at our institution (also co-funders of Neurek S.L.), Dr. Liset Menéndez de la Prida at the Cajal Intitute in Madrid, Dr. Alberto Priori at the University of Milan in Italy and Dr. Karen A. Moxon at Drexel University in the USA. Furthermore, every time we send a paper to a scientific journal for possible publishing, that paper is sent to, at least two, other scientists who act (for free) as anonymous reviewers, offering their opinions, suggestions and critique to improve the work or to reject it. We do the same with articles from other scientists. This means that any scientist who publishes and actively participates in the process of peer reviewing is continuously collaborating, in a very active way, with the international scientific community.

Experimental Neurophysiology

"We investigate physiological changes that happen in the brain after a spinal cord injury"

Main investigator

Juan de los Reyes

The group video

The problem

The somatosensory system receives peripheral signals in order to process all the information related to touch, proprioception, pain and temperature. The system is composed of different pathways that carry these signals through structures located at the level of the spinal cord, brainstem, thalamus and cortex. A spinal cord lesion interrupts the sensory pathways, which carry peripheral signals from the body regions below the lesion level to the cerebral structures of the somatosensory system. Furthermore, it creates an imbalance in these structures because each of them receives inputs from the intact body areas but fails to receive inputs from the areas below the lesion.

It is well known that after a spinal cord injury the somatosensory cerebral cortex undergoes reorganization; a phenomenon in which the deafferented cortical area starts to respond to stimulation of intact body areas (i.e. above the lesion level). This phenomenon develops in a broad time window (i.e. from months to years) and could be the origin of pathologies such as neuropathic pain and phantom limb. Therefore, it is very important to understand neurological effects that a spinal cord injury triggers in cerebral structures that fail to receive signals from the periphery, because an aberrant activity may be the origin of various pathologies.

The Research

In our lab we use electrophysiological recordings from cerebral cortex and thalamus in animals under control conditions and after a spinal cord injury. More specifically we record the neural activity from thalamic and cortical regions corresponding to the forepaw and hindpaw, which allow us to compare neuronal activity between the intact and deafferented regions at cortical and thalamic levels after a spinal cord injury. Consequently, these data are helping us attain better understanding of the change that happens in the brain after a spinal cord injury.

Progress

Our results show that spinal cord injury produces an immediate change in the functional state of the somatosensory cortex (switching it from delta activity to slow-wave activity). At the same time, this change of spontaneous activity modulates evoked responses in the intact cortex (the region that receives signals from above the lesion level). Moreover, our results demonstrate that both the intact and deafferented cortex undergo two processes related to immediate functional changes: the first one is state-dependent, as triggered by the state change, while the second one leads to state-independent increased responses in both cortical regions. Taken together, our results provide a close up view of the very first moments following a spinal cord injury, thus allowing us to better understand the initiation of cortical reorganization, a process which ultimately may trigger different pathologies.

Molecular Neuroprotection

"We study cell death produced by spinal cord trauma and seek the therapy to reduce its effects"

The group video

Mains investigators

Rodrigo M. Maza
Manuel Nieto Díaz

The problem

Functional losses associated with the spinal cord injury (SCI) are not exclusively due to the damage directly inflicted by the trauma. Following the initial trauma, the injury also triggers a cascade of noxious stimuli causing a wave of cell death within undamaged spinal cord tissue. Most of these cells die through a form of programmed cell suicide, known as programmed cell death, whitch greatly increases the spinal cord damage and is responsible for a significant part of the resulting functional deficits.

Photo: **Carlos Monroy**
(Left to right) **Mª Ángeles del Águila, Teresa Muñoz, Rodrigo Maza, David Reigada, Rosa Navarro y Manuel Nieto**

The Research

Our group studies the cell death role in the pathophysiology of spinal cord injury and evaluates the effect of novel cytoprotective therapies in functional recovery after SCI. There are several different cell death programs including apoptosis, necroptosis and autophagic death. While the role of apoptosis in SCI is rather well known, the contributions of necroptosis and autophagy remain almost unexplored. Thus, we aim to evaluate the importance of all these processes, as well as the effect of their regulation. In parallel, we are also studying the change that SCI produces in several regulators of cell death and other important processes (i.e. reactive gliosis, inflammation, regeneration). More specifically, our studies deal with changes in the abundance of microRNAs (the purinergic system components and global regulators of RNA expression) or different bioactive lipids (e.g. sphingosine-1-phosphate), as well as with the consequences these changes exert upon cell death processes.

Furthermore, we have also developed studies on axonal growth processes that take place during annual regeneration of deer antlers, a spontaneous regeneration model unique among mammals. We aim to identify the mechanisms underlying deer antler regeneration and to evaluate their therapeutic potential for treating SCIs.

Progress

So far, our research has provided several very interesting results. On one hand, we have established that SCI causes a general decrease in the expression of microRNAs (i.e. regulators of gene expression), which in turn, further facilitates the injury triggered processes such as cell death, inflammation and/or neural regeneration. On the other hand, our in vitro studies established important, cytoprotective properties of compounds pertaining to the diadenosine polyphosphates family, which ultimately translate into a significant, post-injury improvement of motor functions in rodent models of spinal cord injury. Promising results were also obtained from the study on bioactive sphingolipids where a reduction in the S1P degrading enzyme had been shown to cause an increased tissular preservation and better motor outcomes. These results, together with our ongoing work, point out to novel therapeutic targets and experimental tools for treating spinal cord injury.

In parallel, our deer antler studies have revealed that the growing antler provides a specific biological environment (including soluble promoters, substrate guidance molecules and mechanical tension processes) highly conducive to the nerve fibers growth.

Collaborations

Our work is based on collaboration with other national and international researchers: Drs. Casas and Fabrias at the Institute of Advanced Chemistry of Catalonia (CSIC; Barcelona, Spain); Prof. Dr. Paul P. Van Veldhoven at the Department of Cell and Molecular Biology, "LIPIT" (Leuven, Belgium); Prof. Dr. Dan Lindholm at the Minerva Institute for Medical Research "Biomedicum" (Helsinki, Finland) and Dr. Chunyi Li at the University of Otago (New Zealand).

Molecular Neurology

"Combined treatments for the repair of injured nervous system based on drugs, cell transplants, gene therapy and biomaterials"

Main investigator

F. Javier Rodríguez

The group video

The problem

Spinal Cord Injury (SCI) is a major cause of functional disability yet without a standard, clinically accepted treatment. Functional impairments following SCI are produced by multi-factorial processes as a result of primary mechanical damage, secondary cell death and a low capacity of the CNS to regenerate damaged axons and replace lost cells.

The Research

The Molecular Neurology Group was created in 2005 with the objective of screening for new therapeutic targets and developing combined therapies for neuroprotection and promotion of axonal regeneration and cell replacement. This broad experimental approach allows us to address the challenge of neural repair through multidisciplinary research ranging from its very molecular aspects to the correlation in motor and sensory functional outcomes, electrophysiology and histology in clinically relevant rodent models of CNS and PNS damage.

Progress

Major research findings include the description of a wide expression of the Wnt family of proteins in the adult spinal cord, with a key role after an injury, as well as the presence of a novel source or autologous stem cells located in the leptomeninges of the adult spinal cord, with the potential to generate new neurons and oligodendrocytes. Our current research interests aim to unravel the role of Wnts and Leptomeningeal Stem Cells (LeSCs) in the pathophysiology of spinal cord injury, to develop novel, drug-based therapies (e.g. leptin- and ibuprofen-based) and adult, autologous cell transplants (such as adipose mesenchymal cells) currently used in clinics and proven, by our own research, as highly neuroprotective and promoters of functional recovery. The final goal is to elucidate the molecular and cellular mechanisms underlying neural damage and develop novel, clinically feasible repair therapies.

Collaborations

Drs. Xavier Navarro and Rubén López-Valés (Group for Neuroplasticity and Regeneration, Department of Cell Biology, Physiology and Immunology, Autonomous University of Barcelona; Spain). Dr. Ernest Arenas (Molecular Neurobiology Unit, Medical Biochemistry and Biophysics Department, Karolinska Institute; Sweden). Drs. Guido Fumagalli, Ilaria Decimo and Franceso Bifari (Department of Clinical and Experimental Medicine and Department of Medicine and Public Health, University of Verona; Italy). Dr. Javier Díez (HISTOCELL, Biotech Company specialized in Tissue Engineering and Cell Therapies; Spain). Consorcio NEURIMP: IK4-Tekniker e HISTOCELL (Basque country). ContiPro Pharma (Czech Republic).Vornia (Irland). University of Sheffield and University of Westminster (UK).

Photo: **Carlos Monroy**
(Left to right) **Carlos González, F. Javier Rodríguez, Virginia Pérez, Alfredo Maqueda, Sandra Vázquez, Pau González y Marta Fernández.**

Developmental Neurobiology (GNDe)

"We seek better diagnostics and therapeutic targets for multiple sclerosis repair"

The group video

Main investigator

Fernando de Castro

The problem

Our main research line focuses on the study of oligodendrocytes, the cells that form the myelin sheath around nerve fibers and facilitate the nerve impulse transmission. These cells die in multiple sclerosis (MS) and other demyelinating diseases.

We study the basis of myelination and demyelination to identify potential biomarkers that better diagnose multiple sclerosis (the second leading cause of paraplegia after different traumas) and to advance the neural repair therapy of the disease. We are especially interested in oligodendrocyte precursors (OPCs) in the adult central nervous system (CNS), comprising 3-8% of total cells thereof.

The Research

Our experimental work, employing samples from patients with MS and animal models of the disease, addresses different molecular interactions underlying the development of oligodendrocytes and myelination, as well as *in vitro* studies of OPCs and other relevant cell types.

The oligodendrogliogenesis and myelination are still poorly understood processes despite their direct implications in congenital demyelinating diseases and indirect implications in other pathologies of this kind. Certain factors, as extracelular matrix associated glycoprotein anosmin-1, are important players in the oligodendrogliogenesis and also in MS. The OPCs generated in different regions of the neural tube do not behave equally, hence the importance of knowing their normal physiology, studying their behavior under a pathological condition and seeking a cure for it.

The latter presents the ultimate goal of our research with the OPCs found in the adult brain. Contrary to an earlier notion, that these OPCs are similar to those populating the CNS during embryonic and postnatal development, a growing body of evidence demonstrates their differences in both biological characteristics and potential.

We study demyelinating pathology in mice, by inducing experimental autoimmune encephalomyelitis (EAE), and in patients´ samples, where we can confirm how the pathology actually unfolds in human brain. Additionally, we analyze the cerebrospinal fluid of patients in order to detect components that may help us diagnose earlier the disease and differentiate between groups of patients so as to to predict its outcomes and determine possible treatments.

Progress

We have developed a protocol for efficient separation of OPCs from adult animal brains that is also applicable to neurosurgical samples from patients and, thanks to which, we can now identify different molecules with the functions characteristic of OPCs (i.e. survival, proliferation, differentiation into myelinating oligodendrocytes). Using samples´from patients, we have also established that some of these molecules (e.g. anosmin-1) are specific to lesions in which there is no spontaneous remyelination, while other molecules (e.g. FGF-2) are specific to lesions in which spontataneous remyelination does occurr. Concordantly, this knowledge will help improve the disease diagnostic by identifying patient subtypes and specific targets for potential reparative therapies.

We have also shown that myeloid suppressor cells (MDSCs) enter from the blood stream to the nervous parenchyma in response to inflammatory demyelinating damage. Unlike in other pathologies (e.g. cancer, infections), the MDSCs in MS limit the inflammation, thus limitting the damage, which ultimately converts them into a potential therapeutic target.

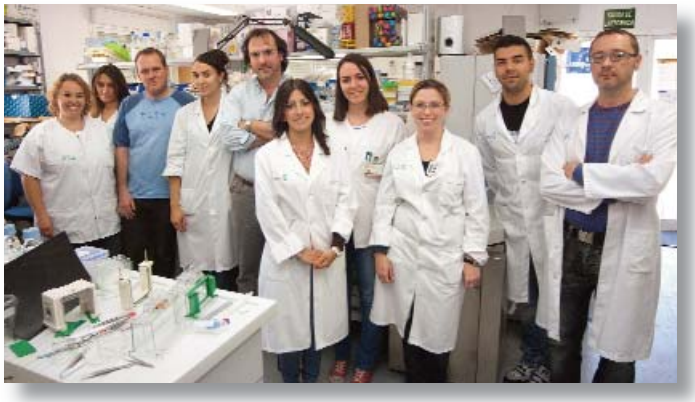


Photo: **Carlos Monroy**
(Left to right) **Isabel Machin, Eva Medina, Diego Clemente, Iris Sanchez, Fernando de Castro, Carolina Melero, Cristina Ortega, Ana Bribián, Rafael Lebrón, Pedro Esteban**

Collaborations

Besides different Spanish groups and networks, we collaborate with Roland Martin and Mireia Sospedra (University Hospital Zürich, Switzerland), Ferdinando Rossi (University of Torino, Italy), Benedikt Böerninger (University of Mainz, Germany) and Bernard and Catherine Lubetzki (AFTA, Institut du Cerveau et de la Moelle, Paris, France).

Membrane Biology and Axonal Repair

"We investigate the cell membrane role in axon formation, growth, and regeneration"

Main investigator

José Abad

The group video

The problem

After certain injuries and/or diseases affecting the central nervous system axons, i.e. long neuronal processes, are not capable of regenerating, which impairs the recovery of neuronal function. The cell membrane is at the core of this problem. Firstly, because the broken membrane allows the entry of external factors into the neuron, wich may even kill the cell. Secondly, even if the axon actually seals its damaged membrane, it still has to overcome the injured nervous tissue that inhibits its growth and the formation of new synaptic contacts.

The Research

Our laboratory investigates the role cell membrane plays in axon formation, growth, and regeneration. The membrane is heterogeneous structure composed of micro-domains that can be imagined as "little islands", where specific proteins and lipids are found together. These "islands", known as "membrane rafts", function as biosensors that communicate changes in the external milieu to the cell interior, hence modulating its responses.

We aim to understand how this membrane organization is altered after an injury and to develop strategies for reverting the injury effects, hence stimulating axonal regeneration.

To accomplish our objectives we study lipid (i.e. gangliosides) and protein components of membrane rafts. Considering that most of these components are associated with different sugar chains we also study the function of carbohydrates in the axon membrane using specific carbohydrate-binding proteins (galectins).

Progress

Besides other relevant results, our group has established that the plasma membrane ganglioside–specific sialidase (PMGS/Neu3) modulates axonal growth and that its over expression promotes the CNS axon regeneration in vitro. Moreover we have demonstrated that the phosphorylated form of galectin-3 regulates axonal branching, while galectin-4 regulates axonal growth. These and other galectins appear to be potentially useful tools for CNS regeneration.

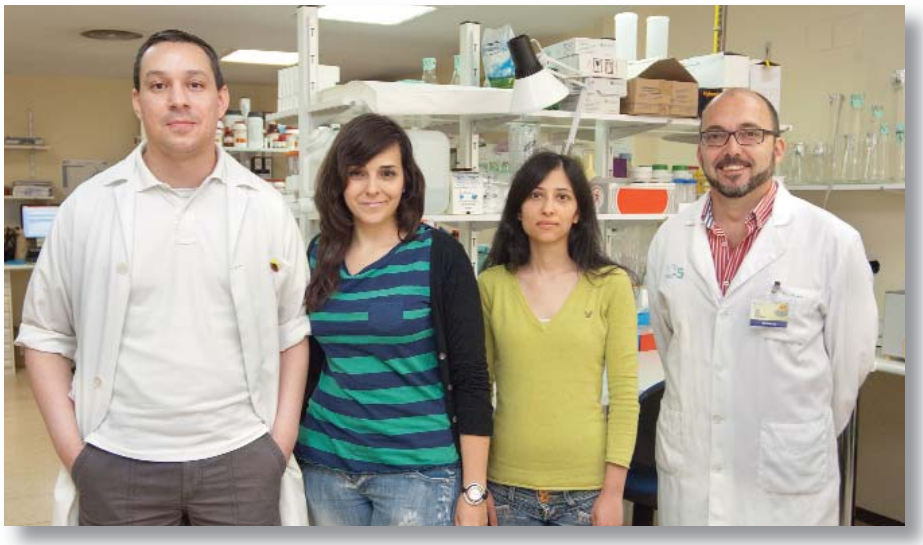


Photo: **Carlos Monroy**
(Left to right) **Alonso Higuero, Natalia Díaz, María Peña y José Abad.**

Collaborations

We have established important international collaborations which have been essential for our research. Some relevant examples are: Dr. Taeko Miyagi (Miyagi Prefectural Cancer Center, Miyagi, Japan), Dr. James Fawcett (Brain Repair Center, Cambrigde Univ, UK), Prof. Dr. Hans-Joachim Gabius (Munich Univ., Germany), and Dr. Carlos Dotti (VIB-Leuven Catholic Univ, Belgium).

Vascular Pathophysiology

"We aim to better understand the pathophysiology of different vascular diseases to improve their early detection and prevention"

The group video

Main investigators

María G. Barderas
Luis R. Padial

The problem

Since most acute cardiovascular diseases (i.e. acute coronary syndrome, stroke, coronary heart disease, congenital heart effects, etc.) bear a high mortality rate and severe complications, there has been a steady development of new treatments aimed to decrease their incidence. However, a precise and rapid diagnosis, crucial for selecting the most appropriate therapy in each clinical setting, is still missing. There are many approaches that help to establish, or rule out, the correct diagnosis and those based on novel biomarkers present a potentially powerful tool.

The Research

In this context, Proteomics and/or metabolomics arise as potent strategies that involve instrumentation and techniques capable of solving problems implicated in different research areas that are in continuous evolution. Joint use of biomarkers and proteomics/metabolomics, notably amplifies the information obtained from the analysis of traditional risk factors (e.g. hypertension, diabetes, hyperlipidemia and smoking), thus revealing novel disease mechanisms. Furthermore, it has been demonstrated that the combination of biomarkers from different pathological pathways adds substantial information regarding the death risk from cardiovascular causes. With all this in mind, we could associate a disease phenotype with individual protein/metabolite or proteins/metabolites profiles through the simultaneous analysis of a set of proteins/metabolites that are present at a certain time point in a particular cellular compartment, cell, tissue or biological fluid. As a result, novel biomarkers of the disease can be identified.

Progress

Our group has been centered on cardiovascular proteomics and metabolomics research for several years now and plays a leading role in this field both nationally and internationally. We have approached the study of circulating monocytes of acute coronary syndromes (ACS) as an alternative source of biomarkers and we have described, for the first time, that such cells express a characteristic profile associated with ACS. A characteristic of this protein profile is the absence of 15 proteins in monocytes of patients with ACS, the situation (i.e. absence of proteins) that has been repeated in several proteomic studies searching for biomarkers in different pathologies.

We have also contributed to a study regarding the vascular biological aspect of degenerative aortic stenosis by describing a characteristic protein profile and consequently published different articles and patented a new prognostic and diagnostic marker of this disease.

Moreover, we have studied other vascular disease such as acute coronary syndrom, stroke and hypertension and we are presently applying our knowledge to pathologies related to the spinal cord injury.

Finally, we are included in the Human Proteome Project.

Collaborations

Our collaborations with other scientists and/or research institutions include:

The Human Proteome Project, with participating laboratories distributed around the world (e.g. Korea, Russia, Iran, Japan, Canada, USA, China, etc.). Dr. Pedro Moreno (Mount Sinai Hospital, New York City, USA), Dr. Ruilope (Hospital 12 de Octubre, Madrid), Dr. Fernando Vivanco (IIS-Fundación Jimenez Díaz, Madrid), Dr. Miguel Rivera (Hospital la Fe, Valencia), Dr. Juan Antonio Lopez (CNIC, Madrid), Dr. Juan Pablo Albar (ProteoRed), Dr. Pedro Luis Sánche (Hospital Gregorio Marañón, Madrid), Dr. Angel Garcia (Universidad de Santiago de Compostela), Drs. Jose Moreu and Carlos Marsal (Complejo Hospitalario de Toledo) y Dr. Antonio Oliviero (National Hospital for Paraplegics, Toledo.

Photo: **Carlos Monroy**
(Left to right) **Montse Baldán, Tamara Sastre, Rafael Moreno, Laura Mouriño, Luis R. Padial, Maria Eugenia González y Fernando de la Cuesta.**

Nerve Regeneration

"In the future, we want to substitute nerve transplants with artificial scaffolds"

Main investigator

Jörg Mey

The group video

The problem

Basically, we are interested in regeneration after spinal cord injury and in neurodegenerative diseases. To solve the regeneration problem it is necessary to prevent cell death and, subsequently, to promote axonal growth and synaptic plasticity. In order to develop therapeutic strategies for spinal cord injury we need to understand the endogenous mechanisms of compensation and repair as best as we can. In the peripheral nervous system, regeneration is already possible because peripheral nerves from the same individual can be transplanted. However, since this approach has several disadvantages, including sensory deficits at the donor site, the challenge consists in developing alternatives to replace the autologous nerve transplants.

The Research

We focus on two lines of research:

The first one is based on the following hypothesis: Transcription factors of the NR/RXR type, which include the receptors of lipid soluble vitamins, play an important role in regenerative processes of the nervous system. Their functions include the control of neuroinflammation, of lipid metabolism and of neuronal plasticity. We are investigating the mechanisms by which NR/RXR transcription factors act after spinal cord injury, during peripheral nerve regeneration and in neurodegenerative diseases. The second line of research has the objective to construct a cell-free, artificial implant to serve as a bridge for the repair of peripheral nerves. Our guidance structures for cell migration and axonal growth are based on synthetic polymers that are functionalized with proteins and peptides from the extracellular matrix.

Progress

We discovered that retinoic acid, the biologically active derivative of vitamin A which activates nuclear receptors RAR/RXR, is involved in physiological repair mechanisms after lesions of peripheral nerves and of the spinal cord. At the cellular and molecular level, we have characterized the anti-inflammatory activity of RAR/RXR agonists. With the goal of developing artificial implants for nerve regeneration, we were the first to use the technique of electrospinning to produce orientated polymer fibers as guidance structures for axonal growth. We have improved methods to give the substrates biological functions and the first generation of implants is being presently tested in the rat sciatic nerve.

Collaborations

The principal investigator is the organizer of the European Master of Translational Neuroscience program, which integrates academic teaching and research between the neuroscience departments of eight universities in the Netherlands (Maastricht), Germany (Aachen, Köln, Homburg), Belgium (Liège, Bruxelles, Hasselt) and France (Lille). The group has contributed to various international research consortia funded by the European Union (FP6, FP7 and Erasmus Mundus). Present cooperations include groups in the UK (Peter McCaffery, Aberdeen), Germany (Gary Brook, Markus Kipp, Katrin Goebbels, Aix-la-Chapelle) and the Netherlands (Pilar Martínez, Maastricht). Jörg Mey is Professor at RWTH Aachen University, where the group also maintains a laboratory.

Neuroregenerative Chemistry

"We work on design, synthesis and evaluation of chemical compounds in order to repair the CNS injury and disease"

Main investigator

Ernesto Doncel

The group video

The problem

Damage to the adult central nervous system (CNS) often leads to persistent deficits due to the inability of mature axons to regenerate after injury. Experimental and clinical evidence suggest that the glial environment of the adult CNS, including inhibitory molecules as the CNS myelin components and astroglial scar, may present a major obstacle to successful axon regeneration. We study the molecular basis of these inhibitory influences and how to overcome the limitations of axonal growth, re-myelination, neural repair, as well as other types of structural plasticity. Greater insight into the glial inhibition is crucial for developing therapies that promote functional recovery after neural injury.

The Research

Our main research interest is directed toward regeneration and repair of the lesioned CNS. Within this broad field we particularly focus on control of the glial scar formation and promotion of neu-

Photo: **Carlos Monroy**

(Left to right) **Isabel García Álvarez, Sandra Moreno Lillo, María Sanchez-Sierra Revenga y Ernesto Doncel Pérez**

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ral/axonal growth in the lesioned area. To accomplish these objectives we opt for a chemical approach that includes new drugs development, their de novo chemical synthesis and a biological evaluation of their effectiveness. In addition, we study bio-compatible and bio-degradable polymers and their potential as vehicles for drug delivery and/or possible substrates for cellular transplants. Important part of our effort is also dedicated to design, synthesis and evaluation of compounds that allow for controlled proliferation and differentiation of mammalian neural precursors.

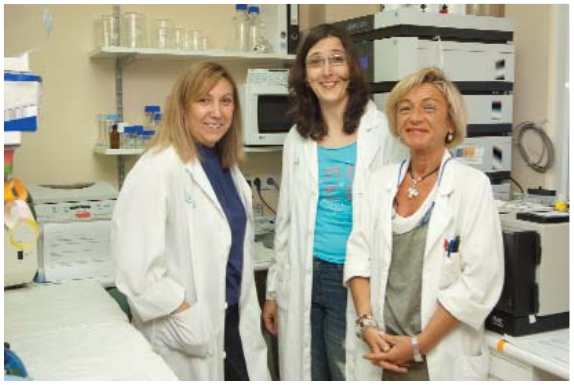
Progress

So far we have created several novel compounds that can be used as promoters of neuronal regeneration and/or inhibitors of the glial scar formation or glial tumors. The subsequent evaluation of these new molecules in neural cell cultures (i.e. neurons, astrocytes and oligodendrocytes) and in the rat spinal contusion model have shown a considerable functional recovery after spinal cord injury. .

Collaborations

The new drugs development line has been realized in collaboration with Prof. Fernández-Mayoralas at the Institute of Organic Chemistry, in Madrid. The manufacturing of polymers is being conducted in collaboration with Prof. Leoncio Garrido at the Institute of Polymers Science and Technology in Madrid and at a local biotechnological company (ProBioVet, Ciudad Real). The analysis of gene expression has been realized in collaboration with Prof. José de la Fuente at the Department of Veterinary Biopathology (Center for Veterinary Health Sciences, Oklahoma State University, USA).

Proteomics core facility



Gemma Barroso
Verónica Moral

The facility is focused on searching for new and better experimental designs, protocol optimization and implementation of the latest knowledge and technology in the field of proteomics. It offers support not only to the hospital´s researchers but also to external users from other regional institutions. Proteomics techniques provide a highly valuable data source for basic and clinical research alike.

The facility routinely performs protein identification and characterization by MALDI TOF/TOF; protein separation and differentiation by 2-dimensional gel electrophoresis 2D-DIGE and screening for possible biomarkers by MRM.

Animal housing facility

Enrique Páramo Rosel

The facility is dedicated to high standards breeding, housing and management of laboratory animals. Our installations include several animal housing rooms, with the total capacity for 2000 rodents, surgical rooms, as well as especially equipped rooms for behavioral and kinematics studies.

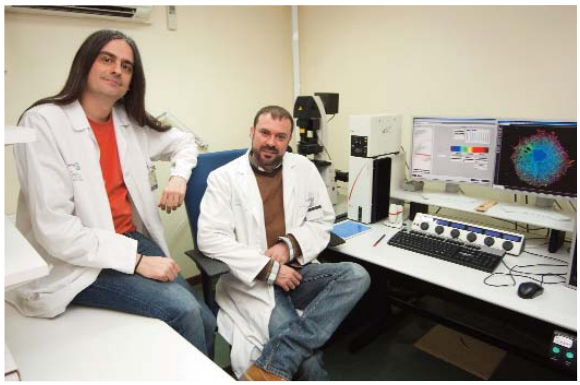
The facility also provides teaching and training courses on animal care and surgery for the research personnel, while ensuring fundamental principles of bioethics, offering alternatives to animal experimentation, as well as refinement and optimization of experimental protocols.

The hospital also counts with state-of-the art MRI facility (led by Jose Florensa) shared by the research and clinics and an impending cell culture facility, led by Monica Carballo. The latter will provide professional assistance to the research part of the hospital and allow for the development of new cell culture protocols and cellular experimentation adjusted to meet specific needs of individual projects.

The personnel is also committed to training and formation of research- and healthcare professionals, as well as collaborating with the local community on various educational activities.

The National Hospital for Paraplegics also counts with several facilities that provide technical support to the basic research unit. They were founded with the objective of providing professional technical assistance and information sharing for the researchers and to assure the maximum efficiency of the available equipment. Each facility counts with the latest equipment, installations and highly qualified personnel that provide support not only to in-home research groups, but also to other public and private companies in the area.

Microscopy and image analysis



José Ángel Rodríguez
Javier Mazarío

The facility counts with the ultimate generation of equipment for traditional and fluorescence microscopy, multicolor immunofluorescence imaging and for a variety of live cell and in-tissue studies. Available equipment includes: microscopes for capturing videos of live cells, laser capture microdissector, two confocal microscopes (one equipped for work with live tissue samples and the other one with automatic capture of images and their analysis i.e. High Content Screening), as well as computer programs for preparation and analysis typical of neuroscience research (e.g. NewCAST, Neurolucida, ImageJ). We also count with one laser scanning electron microscope that allows for more advanced and detailed structural studies.

The facility routinely acquires high magnification images of micro- and macro structures (macroimages of tissue sections) that require image tilting and stitching, performs studies of cell migration and co-localization, stereological studies, micro-dissection of tissue regions for RNA and protein analysis, processing and analysis of digital images and other microscopy related techniques.

Cytometry

Virginia Vila del Sol

Flow cytometry presents a special form of laser-based multicolor microscopy in which prelabeled cells, suspended in a stream of fluid, are passed by an electronic detection device whereby simultaneous multiparametric measurements are taken for later quantification of biochemical, phenotypical and/or molecular properties of individual cells. The analysis is performed at the speed of up to thousands of cells per second, which in turn provides the data of high statistical reliability.

Available equipment includes one benchtop cell analyzer, FACS Canto II, which allows for multiparametric analysis of complex cellular populations and one benchtop cell sorter FACS Aria (BD Bioscience) that provides high velocity physical separation of specific cellular populations for their later use in biochemical and molecular assays, cellular differentiation or as transplants in animal models.

The facility offers services such as sample preparation and separation, data acquisition and analysis, as well as professional assistance in experimental design, protocol optimization and up-to-date information about the use of new techniques and reagents.

The group video

FENNSI Group

"We seek therapies to improve motor functions and use non-invasive brain stimulation to fight pain in patients with spinal cord injury"

Main investigator

Antonio Oliviero

The problem

Spinal cord disorders frequently result in some incurable impairment. In general, patients with complete spinal cord injuries(SCI) recover very little of lost functions while patients with incomplete injuries achieve more functional recovery. Some patients that are initially assessed as having complete injury may be later reclassified as having incomplete injury.

The main problems we aim to solve are: improving evaluation of spinal cord injured patients in the early and chronic stages of the injury; and addressing the lack of available treatments (more so than rehabilitation procedures) useful for improving motor functions in spinal cord injury patients.

The central nervous system (CNS) is a very complex system where different parts perform distinct functions. Majority of drugs commonly used for treating CNS disorders, including spinal cord disorders, have neuroactive properties and even though we would prefer them to act only in a very restricted area of the CNS, that is not the case. Namely, once a drug has entered the CNS it usually exerts beneficial effects in a restricted part of the CNS but at the same time produces various unwanted effects in most of the remaining brain and spinal cord.

The application of electric currents or magnetic fields over or deep inside the brain can be used to selectively target a specific area, thus producing desired therapeutic effect. These techniques are known as brain stimulation or brain neuromodulation techniques. When electric currents or magnetic fields are applied transcranially the technique is referred to as non-invasive. In line with this, our main goals are: to find better non-invasive neuromodulation strategies and to improve the clinical application of non-invasive neuromodulation techniques in treatment of CNS disorders and spinal cord injury.

The Research

SCI clinical trials (GH, CB1 Antagonists). The SCI has no cure. Rehabilitation improves only some clinical signs related to affected motor functions. Thus, we are testing different drugs to improve these functions, as an add-on therapy to neurorehabilitation. Human growth hormone and CB1 antagonists/inverse agonists are the molecules we think may be useful for improving motor functions in incomplete spinal cord injury patients.

Treatment of pain in SCI using non invasive brain stimulation (NIBS) approach. Neuropathic pain is referred to as the most important symptom in about 10% of SCI patients. Although drug treatments have improved significantly in the last decade, they are often not well tolerated (or effective) in a great number of patients. NIBS offers a simple, inexpensive and safe treatment option.

Psychoneurophysiology and neuroradiology of SCI.

Hand Functions and Cognitive functions in SCI.

Transcranial static magnetic field stimulation as a new non-invasive neuromodulation strategy.

Optimization of tDCS using NIRS. This approach will allow us to determine an individualized treatment and a follow-up of the biological effects of tDCS.

Improvement of brain computer inteface (BCI) strategy using NIBS (tDCS). The main goal is to speed-up the learning process in the BCI users by improving the "informative" signals detection and decoding.

Collaborations

UCL, London, UK; EPFL, Lausanne, Switzerland; Drexel University, Philadelphia, US; Centro de Tecnología Biomédica, Madrid, Spain; Universidad A Coruña, A Coruña, Spain.

Photo: **Carlos Monroy**
(Left to right) **Carmen Carrasco, Antonio Oliviero, Michela Campolo sitting, Lucía Contini**

Biomechanics and Technical Aids

"We investigate the role of Biomechanics in improving the quality of life of people with spinal cord injury"

Main investigator

Ángel Gil-Agudo

The group video

The problem

Spinal Cord Injury (SCI) causes serious movement disorders that, in many cases, require technical aids to compensate for altered motor function. As a multidisciplinary field of knowledge, Biomechanics offers expert support to clinicians in making therapeutic decisions, provides useful tools for gathering movement-related quantitative data and for facilitating the appearance of new technologies for motor deficits compensation and/or rehabilitation following SCI.

The Research

Based on Biomechanics principles, our laboratory works to find specific solutions to compensate or rehabilitate motor deficits in SCI patients. Accordingly, our research activity follows two main lines: movement analysis and technical aids evaluation for SCI patients. We offer our services to clinical staff by providing quantitative assessments and proposing solutions for gait disorders, as well as offering pressure mapping at the user-cushion interface in wheelchair cushion prescriptions.

This group has acquired great experience in managing high level technology for biomechanical analysis of human movement, modeling biomechanical design and data extraction. Consequently, our activity encompasses a variety of movement-related studies such as gait analysis in incomplete syndromes, manual wheelchair propulsion, functional evaluations and upper limbs movements in activities of daily living. As of recently, the movement analysis is being applied to robotics (i.e. design of neuro-robotics and neuro-prosthetics to compensate for- or to restore movement disorders) and in developing virtual reality systems for upper limb motor rehabilitation. Furthermore, our technical aids evaluation services (e.g. pressure mapping at the user-cushion interface, physiological assessment of tissue at high risk of developing pressure sore, functional wheelchair evaluation with specific circuits, elbow crutches with load cell) are also offered to manufacturers, distributors and enterprises related to technical aids market.

Photo: **Carlos Monroy**
(Upper left to right) **Marta Solís, Beatriz Crespo, Ángel Gil, Soraya Pérez e Iris Dimbwadyo.**
(Left to right) **Fernando Trincado, Enrique Pérez, Antonio del Ama y Vicente Lozano.**

Progress

Our group has defined gait patterns in specific, incomplete SCI syndromes such as Central cord and Brown-Sequard syndromes. We have developed our own upper limb model and implemented the technology required to analyze manual wheelchair propulsion ergonomics. Thus, we created a system for obtaining relevant biomechanical data on how patients with different levels of SCI perform manual wheelchair propulsion. Furthermore, we have defined the hybrid control strategy (actuators and functional electrical stimulation) to be implemented in lower limb portable robots. Finally, our laboratory has contributed to the development of a virtual reality system for the upper limb motor rehabilitation (Toyra project). This device includes latest version of Kinect software (Microsoft) as a motion capture system to be applied in Tele-Rehabilitation platforms.

Collaborations

Given our dependence on high level and fast advancing technology, we could not improve our research without strategic interactions with other scientists and research institutions in the field. Some relevant examples are: Prof. Rory A. Cooper (Human Engineering Research Laboratory, University of Pittsburgh, USA), Prof. Meten Akay (University of Houston, USA), Prof. José Luis Pons (Bioengineering Group, CSIC, Spain) and Indra Systems (Spain).

The group video

Gait Re-education and Functional recovery

"We investigate to achieve greater independence and functional capacity of people with spinal cord injury"

Main investigator

Ana Esclarín

The problem

Spinal cord injury is a pathology that affects different areas of patient's life such as the mobility, sensation, bowel and bladder function as well as his sexual ability.

Depending on its severity, the injury may affect pelvic organs, lower extremities, trunk, abdomen and upper extremities. Furthermore, secondary complications such as spasticity and pain, that usually accompany the injury, may significantly delay, as well as interfere with the rehabilitation process.

The Research

The group includes physicians specialized in rehabilitation medicine and physiotherapists specialized in robotic gait-training system (Locomat). Our daily alternation between the work with patients and clinical research has opened several research lines:

The study of different treatments for optimization of gait recovery in persons with neurological disorders, with two research projects completed and a new one pending.

Defining protocols for a better evaluation of treatments applied in daily clinical practice.

New treatments that are incorporated daily at the clinic are in need of detailed assessments, hence it is important to develop new systems that will allow for a precise evaluation of their outcomes.

The study of medical complications in people with spinal cord injury such as phonation (or lack of it), pain, spasticity and vesico-uretheral dysfunction.

In the future we plan to incorporate new types of treatments acting directly on the brain and to follow their effects on patients' functional recovery. Moreover, we will also incorporate the Isokinetics unit in order to improve the accuracy of analytical measurements and increase benefits of presently used muscle treatments.

Progress

Through the research we learned that incomplete spinal cord injury patients develop more stamina and fatigue resistance during gait when trained with the Lokomat robotic system

In other lines of research, as the one regarding the vesico-urethral dysfunction, we have learned that applying prophylactic antibiotics prior to the change of indwelling urinary catheter and initial bladder retraining decreases significantly urinary tract infections.

Collaborations

The group collaborates with the European Multicenter Study on Spinal Cord Injury with the goal of creating a European database of traumatic spinal cord injuries. It also collaborates in a randomized, triple-blind, clinical trial on the efficacy and safety of growth hormone (GH) use in patients with spinal cord injury, which is currently being conducted at the HNP

Together with the Biomechanics Unit of the HNP, the group participates in projects featuring comparative analysis of clinical and biomechanical parameters of the gait in patients with spinal cord hemisection and Central cord syndrome. Our group is also participates in a multicenter project called "Advanced Systems EEF and UMI for developing soft-robots in the field of rehabilitation robotics: REHABOT II project.", coordinated by the Institute of Industrial Automation and the Institute of Biomechanics from Valencia, Finally, the group collaborates on a project called REHABILITA-Disruptive technologies for the rehabilitation of the future within the national strategic program for technical research consortia (CENIT-e) of the Ministry of Science and Innovation.

Photo: **Carlos Monroy**
(Left to right) **Silvia Ceruelo, Francisco Talavera, Rosa Casado, Ramiro Palazón, Mónica Alcobendas, Ana Esclarín y Guillermo Pérez.**

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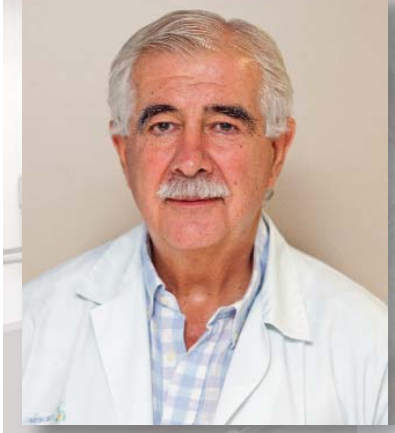


Assisted reproduction

"We seek solutions for sexual health and fertility changes produced by spinal cord injury"

Main investigator

Antonio Sánchez Ramos

The group video

The problem

Among other problems, persons with spinal cord injury also experience changes in their sexual response and fertility. These changes are partially due to immediate organic changes caused by the injury but also due to the psychological component that patients develop after being confronted with the new situation.

Our research unit studies the alterations in sexual responses that both men and women develop after spinal cord injury.

In male patients we study erectile dysfunction and its possible treatments (e.g. oral treatments, intracavernous, intraurethral, etc), as well as the potential of these treatments for improving fertility, which is normally decreased in these patients. Similarly, in female patients we study problems that develop after spinal cord injury to help them maintain satisfactory sexual relations and to provide them with the pregnancy and childbirth recommendations.

The Research

Our research firstly aims to evaluate patients´ responses to different erectile dysfunction treatments, including the inhibitors of PDE (sildenafil, vardenafil, tadalafil), intracavernous (prostaglandin E1, papaverine) or intraurethral drugs, by applying the satisfaction rating scale to their sexual activity. Secondly, we study fertility, its change in men with spinal cord injury and possible application of various techniques for achieving the semen production (i.e. vibro-stimulation, electro ejaculation etc) either alone or in combination with available pharmacological treatments (i.e. Physostigmine or Midodrine). Finally, we study different techniques for assisted reproduction to ensure an adequate treatment for every person and their type of spinal cord injury.

Photo: **Carlos Monroy**
(Left to right) **Ana Galán, Eduardo Vargas, Antonio Sánchez Ramos y Rosi Arriero.**

Progress

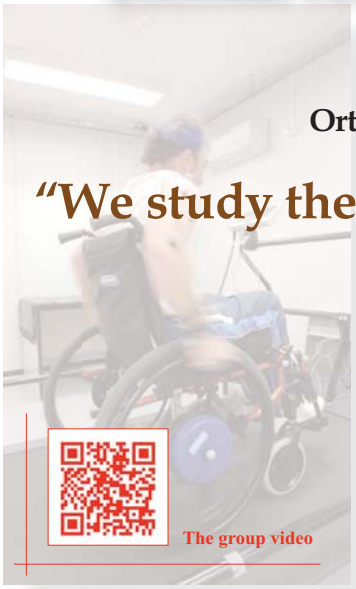
By using testicular biopsies from men with complete spinal cord injury (ASIA A), we studied the change in spermatogenesis during acute phase of the injury characteristic of the injury level (the latter being established by electro-physiological and clinical studies).

We have assessed different treatments for erectile dysfunction by using objective measuring methods (RigiScan plus) and evaluation scales for achieved erectile responses.

Furthermore, we evaluated the degree of satisfaction with their sexual activity in men with erectile disfunction that received pharmacological treatment, by applying satisfaction rating scales to their own and their partner´s activity, whereby we managed to improve the planning of steps to be taken in the course of pregnancy and childbirth in women with spinal cord injury.

Collaborations

Our projects have been conducted in collaboration with different Spanish and foreign centers and universities. We maintain close professional ties with Prof. Manuel Mas (Department of Physiology; University of La Laguna, Canary Islands. CESEX Group); Dr. Martin de Francisco (Hospital Virgen de la Salud, Toledo) and Dr. Antonio Oliviero (FENSII group, the National Hospital for Paraplegics, Toledo), as well as with with Prof. Giuliano (Raymond Poincare Hospital, Garches, France).



Orthopedic Surgery and Traumatology department

"We study the relationship between angular kyphosis and pain in patients with vertebral fractures"

The group video

Main investigator

Andrés Barriga

The problem

Kyphosis presents a forward rounding of the spine and usually refers to an exaggerated rounding of the upper back (i.e. thoracic vertebrae). The principal problem that our group is trying to resolve is the relationship between the degree of kyphotic angular deformity (i.e. kyphotic angle), consequent spinal lesion and the presence of mechanical pain in patients who suffered vertebral fractures.

The Research

To achieve this objective our group has undertaken a clinical study in which we examined radiographs of 700 patients treated at the National Hospital for Paraplegics and analyzed a series of pain- and disability-related inquiries they were asked to complete.

Photo: **Carlos Monroy**
(Left to right) **Jesús de Juan and Andrés Barriga**

Progress

Our study still remains to be completed but, based on the data collected so far and contrary to the prevailing field notion, we believe that the degree of kyphotic angular deformity (i.e. kyphotic angle) as an isolated value does not correlate with the presence (or absence) of pain in these patients.

Collaborations

Our group collaborates with the Spanish Network of Researchers in the Back Ailments and with the AOSpine Europe, the international community of spine care professionals with the headquarters located in Duebendorf, Switzerland.

Functional Urology and Urodynamics

"We design personalized treatments for vesico-urethral reflux caused by spinal cord injury"

Main investigator

Manuel Esteban

The group video

The problem

Clinical research in the field of functional Urology faces numerous challenges when it comes to patients with spinal cord injuries, one of them being vesico-urethral reflux that frequently causes renal failure and impacts on life expectancy of the lesioned. Fortunately, there are new and reliable diagnostic tools, such as Ambulatory Urodynamics and Computerized Videourodynamics, as well as therapeutic approaches for the identification of this pathology.

The Research

We investigate the difference between the conventional and Ambulatory Urodynamics with the objective of compiling data, classifying and documenting differences in the behavior of bladder sphincters. Additionally, we combine Teleurodynamics (i.e. a highly reliable long distance diagnostics) and Videourodynamics that allow us to conduct an individualized study of lower urinary tract in each case of vesico-urethral reflux. Therefore, our research efforts and a specific, personalized treatment for each patient translate directly into a significant increase in patients´ life expectancy.

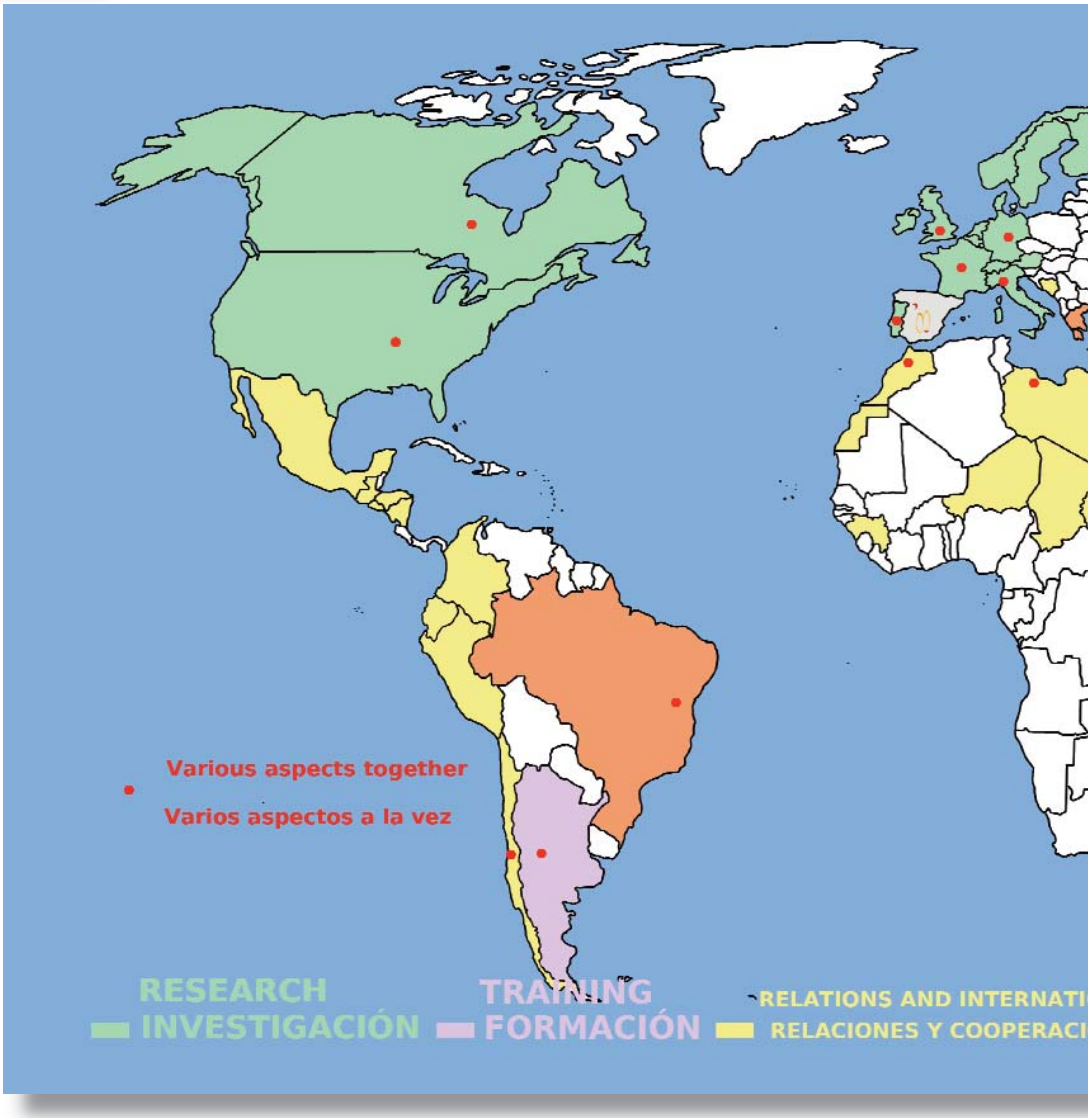
Progress

Our group has documented the existence of various, unexpected signs in the behavior of lower urinary tract that depend on the lesion level. This discovery helped us create specific treatment protocols for each, individual vesico-urethral reflux characteristic of the lesion level, documenting in total six distinct behavioral patterns.

Photo: **Carlos Monroy**
(Left to right) **Manuel de la Marta, Isabel del Cerro, Vicente Gandía, Manuel Esteban, Miguel Vírseda, Mª Eugenia del Castillo, Antonio Miguel López, Pilar Nombela y Ana Sánchez.**

Collaborations

We have established important collaborations with other scientists and institutions in the field. Our group has been awarded numerous stipends and subventions from the national public (Spanish Urology Association and FIS) and private institutions as well as from the International Continence Society, through which we lead the International Group of Videourodynamics.



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Spirit of solidarity and sport at the HNP

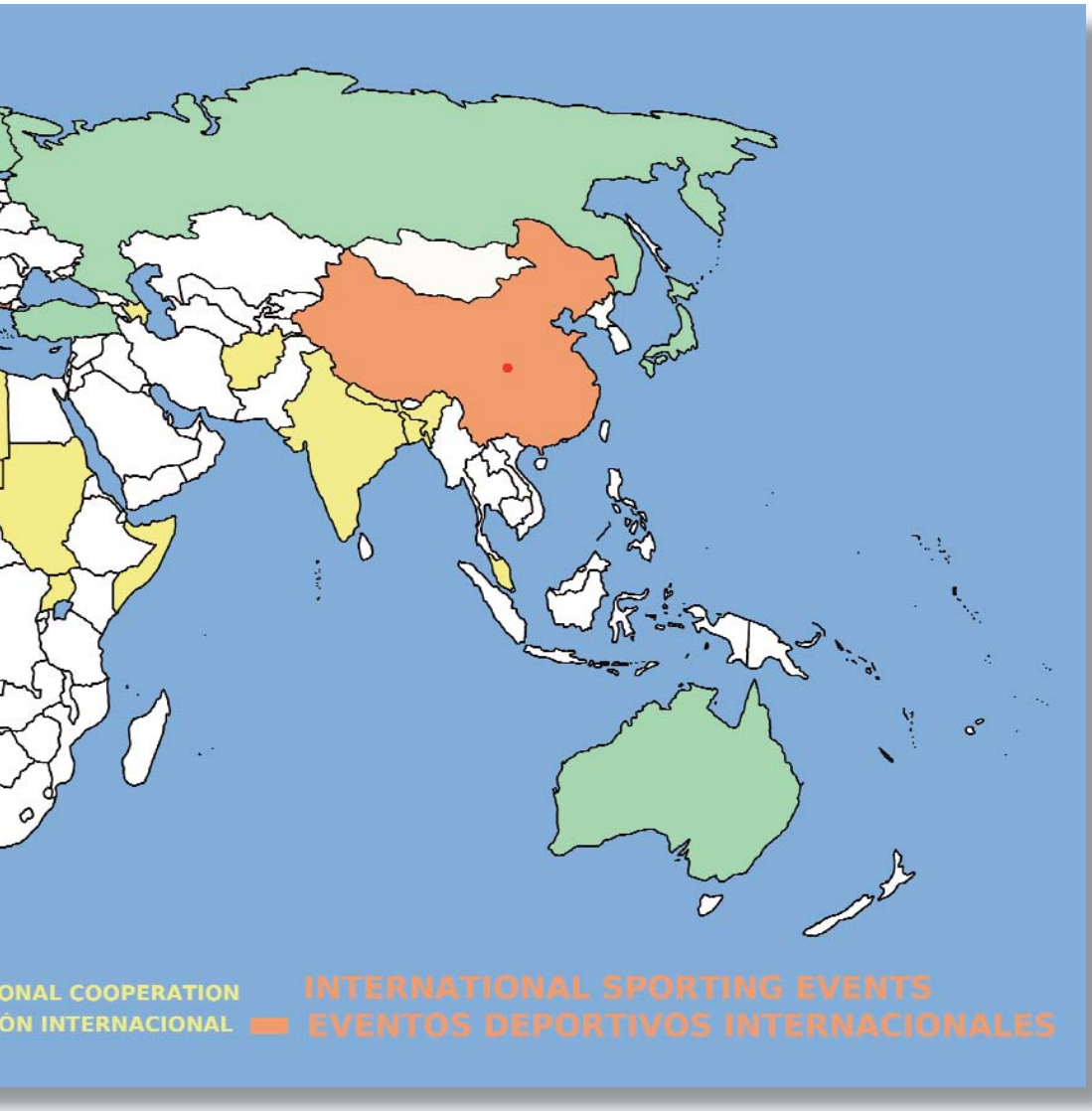
Contrary to the world of globalized science, where information and funding flow freely, there is still a long way to go to achieve globalization of human dignity for the most disadvantaged groups. One of these groups is particularly close to our line of work and includes persons with disabilities.

With the above concept in mind, many of our professionals have participated in executing and/or developing different international cooperation projects, some of which will be highlighted here:

The collection and delivery of wheelchairs and prosthetic equipment to war zones, as Afghanistan (Herat) and Bosnia, in collaboration with the Spanish Army; The treatment of spinal cord injuries in victims of gunshot wounds from Libya; ´´Surgical brigade´´, formed by our urologists, providing medical care for disadvantaged populations of Honduras (Tegucigalpa) and other Central American countries; Professional cooperation program (including donations, volunteering and counseling) with the Spinal Injury Rehabilitation Center in Nepal; Collaboration with the Foundation "Maestros de la supervivencia" in Colombia; Professional training in Rehabilitation medicine for a physician Sorab Hussein from a Hospital in Bangladesh;

Financial aid and counseling program for the Association HANAN of Morocco; Collaboration with the Foundation Vicente Ferrer on the project ''Fisios Mundi'' in India, or various humanitarian initiatives in countries as Senegal, Ethiopia and Angola are only some of the examples depicted in the map.

Following the motto ''Open to the World'', starting with the '92 Olympic games in Barcelona to 2008 in Beijing, to 2012 in London and with great expectations for the upcoming games in Brazil, the HNP has served as a breeding ground for some of the best international athletes in Paralympic sports. Some of their stories are captured in the book ''Beyond Sport''.



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