WINNING AGAINST PARAPLEGIA STEP BY STEP

IRP SCHELLENBERG RESEARCH PRIZE

International Foundation for Research in Paraplegia
Fondation internationale pour la recherche en paraplégie
Internationale Stiftung für Forschung in Paraplegie

WINNING AGAINST PARAPLEGIA STEP BY STEP

IRP GENEVA
Rue François-Perréard 14
CH-1225 Chêne-Bourg - Geneva
Tel. +41 (0)22 349 03 03
Fax. +41 (0)22 349 44 05
info@irp.ch

IRP ZÜRICH
Rämistrasse 5
CH-8001 Zürich
Tel. +41 (0)43 268 00 90
Fax. +41 (0)43 268 09 80
research@irp.ch

BANKING DETAILS
Banque Piaget & Cie SA
Account number T-566191.001
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IRP Schellenberg Research Prize

Editorial Andreas Steck

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Since 1995, the IRP - International Foundation for Research in Paraplegia - has undertaken fundraising activities for financing the best basic and clinical research projects worldwide in the field of paraplegia, selected by the IRP Scientific Committee of international experts.

**IRP has helped to fund more than 150 research projects in Switzerland and abroad since it was founded, contributing over CHF 25,000,000 over 20 years.**

IRP has developed a partnership with FSP – Swiss Foundation for Paraplegics – until 2020 to finance clinical projects for CHF 500,000.- yearly.

**IRP funds:**

- IRP Research Grant (up to 150,000.– over 2 years)
- IRP Post-doctoral Fellowship (up to 80,000.– over 1 year)
- IRP Schellenberg Research Prize (up to 100,000.– every 2 years)
- IRP Professor Alain Rossier Chair at the University of Geneva
- IRP Spinal Cord Repair Chair at the EFPL (Swiss Federal Institute of Technology) in Lausanne.

There is one single objective driving our activities:

**WINNING AGAINST PARAPLEGIA STEP BY STEP**

Progress in the field of neuroscience research also benefits patients suffering from other disorders of the central nervous system, such as Parkinson’s disease, Alzheimer’s disease, multiple sclerosis and stroke.
The booklet that you have in your hands reflects the painstaking research, editing and graphic design work that was put together in just a few weeks by the General Secretariat of the IRP and Fritz Vischer, a former member of the IRP Foundation Board, who himself is paraplegic.

But above all, it reflects the outstanding nature of some of the research projects funded by IRP, driven by passionate researchers and which are gradually enabling a better understanding of the regeneration mechanisms of the spinal cord and improving living conditions for paraplegics.

A pursuit of excellence that leads me naturally to thank the members of the IRP Scientific Committee for their commitment. This Committee is made up of international experts in the field of neurosciences, who every year select the most promising projects for funding in a most rigorous process.

IRP, which is a private foundation, is proud to be able to share through this publication its firm belief that through the committed involvement of everyone, researchers and donors, paraplegia will one day no longer be an irreversible destiny.

Professor Theodor Landis
President of the IRP Foundation
The competition for the *IRP Schellenberg Research Prize* takes place every two years. It is awarded to researchers who, by the significance of their scientific contributions and their publications in scientific journals of renown, have furthered understanding of the development, lesion and regeneration processes relating to the spinal cord.

Set up in 2003, the *IRP Schellenberg Research Prize* perpetuates the memory of Ulrich Schellenberg, the founder of the IFP Foundation in Zürich and co-founder of the IRP Foundation in Geneva, who died in 2001.

The Prize, up to CHF 100,000, is aimed at rewarding a scientist’s outstanding work in the field of paraplegia. Priority is given to young but already established and successful scientists working experimentally in the above-mentioned fields. The funds awarded, by enabling the recruitment of new co-workers or personnel, and the purchase of equipment or supplies, should help investigate avenues that may, in due course, lead to progress in spinal cord regeneration and functional recovery.

IRP is proud to present in this brochure the

**IRP SCHELLENBERG RESEARCH PRIZE WINNERS**

Women and men who are IRP Ambassadors around the world and the symbol of our commitment to research in paraplegia.
Fifteen profiles, fifteen characters, fifteen scientific adventures: the following pages pay tribute to the 15 women and men researchers who have been recipients of the *IRP Schellenberg Research Prize* since it was founded in 2003.

Each one in their own chosen field has attracted the attention of the IRP Scientific Committee through the importance of their scientific contributions to paraplegia research, whether fundamental or clinical.

For a researcher, receiving an award such as the *IRP Schellenberg Research Prize* always comes with a special feeling because in addition to honouring tangible results achieved over several years, it also crowns a vision, approach and method that are unique to them as well as a team work.

As well as offering a financial package of 100,000 Swiss francs - one of the largest for a scientific prize, the *IRP Schellenberg Research Prize* also represents general recognition from one’s peers.

**Professor Andreas Steck**

President of the IRP Scientific Commitee
LAB DESCRIPTION

The Fawcett lab has three programmes.

**Reactivating plasticity**
Plasticity is the ability of the nervous system to bypass injuries. After childhood plasticity decreases to a low level, and recovery from brain and spinal injury is poor. The lab has developed an enzyme treatment, *chondroitinase*, that releases the brakes on plasticity. Combined with rehabilitation this reactivated plasticity allows much improved recovery from spinal cord injury.

**Stimulating nerve fibre regeneration**
After they mature, spinal cord nerve fibres lose their ability to grow, and when damaged they regenerate weakly. The lab has shown that this loss of growth ability is caused by the neuron directing growth molecules away from the nerve fibres. New treatments to transport growth molecules back into nerve fibres are being developed.

**Bladder control**
The lab is developing a new electronic method to control bladder emptying after spinal cord injury.

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**PUBLICATIONS – MILESTONES**

Exclusion of Integrins from CNS Axons Is Regulated by Arf6 Activation and the AIS.

Combination treatment with anti-Nogo-A and chondroitinase ABC is more effective than single treatments at enhancing functional recovery after spinal cord injury.

A microchannel neuroprosthesis for bladder control after spinal cord injury in rat.

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**IRP Schellenberg Research Prize 2003**

**Professor James W. Fawcett**
Great Britain

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**BIO EXPRESS**

Since 2000
Professor at the University of Cambridge;
Director of Studies King’s College;
Chairman Cambridge Centre for Brain Repair (BRC)

2003 First winner of the IRP Schellenberg Research Prize

1981 PhD in Medicine
1975 Medical Degree
LAB DESCRIPTION

Research in the Kiehn lab is directed to understand mechanisms by which neurons and neural networks operate to generate complex brain functions in particular movements in mammals.

Kiehn’s work has provided insights into the molecular and physiological organization of neuronal circuits in the spinal cord that generates locomotor movements. He discovered the identity of neuronal circuits in the spinal cord that control the ability to produce the alternating movements of the legs during locomotion and neurons that set the tempo in the rhythmically active networks. Current work has a focus on descending locomotor command systems, and to functionally integrate brainstem and spinal locomotor networks with higher brain functions.

Kiehn’s lab is also engaged in characterizing plasticity in spinal networks and motor neurons following lesions of the cord with an aim of devising targeted manipulation of these changes to alleviate dysfunctional motor symptoms following spinal cord injury.

PUBLICATIONS – MILESTONES


2003, Neuron: Butt SJB, Kiehn O Functional identification of interneurons responsible for left-right coordination of hind limbs in mammals.
LAB DESCRIPTION

Research in the Arber lab focuses on understanding the organization and function of neuronal circuits involved in the control of motor behaviour, and on how injury impacts on and leads to reorganization of these neuronal circuits. Using modern technologies, Arber’s lab has recently unravelled the organization of the communication matrices between the brainstem and the spinal cord. They found that highly specific modules exist for pathways from the brainstem to the spinal cord, as well as in the opposite direction.

Arber’s work has for example identified a previously uncharacterized brainstem nucleus involved in the control of grasping through the control of spinal circuits. Furthermore, using a model of incomplete spinal cord injury, the Arber lab found that sensory feedback from muscle spindles is absolutely essential for functional recovery after injury and reorganization of descending neuronal circuits from the brainstem and within the spinal cord. Together, this work highlights the importance of identifying specific neuronal populations as entry point to understand motor function in health and upon injury.

PUBLICATIONS – MILESTONES


2014, Cell: Pivetta C, Esposito MS, Sigrist M, Arber S Motor-circuit communication matrix from spinal cord to brainstem neurons revealed by developmental origin.
LAB DESCRIPTION

Brigitte Schurch specialises in problems related to bladder control in conjunction with neurological illnesses. She has expert knowledge in the treatment of paraplegic patients. In the nineties, she discovered that by treating patients locally with Botulinumtoxin [Botox], the nervousness of the neurogenic bladder could be reduced to the extent that the patient overcame incontinence.

In her team at the Lausanne University Hospital (CHUV), Professor Schurch works alongside neurologists, physiologists, therapists and specialised care workers. Her range of treatment is comprehensive and encompasses neurological symptoms such as, cerebral haemorrhages, spinal cord injuries, and multiple sclerosis.

Her research work examines the supraspinal control of the bladder function, and the use of new substances in the treatment of functional disorders of the neurogenic bladder. Professor Schurch is also actively involved in the Neuroprosthetic Project of Professor Grégoire Courtine, who is also a winner of the IRP Schellenberg Research Prize.

PUBLICATIONS – MILESTONES


LAB DESCRIPTION

Lars Olson’s Work has mainly concerned development, growth factors, regeneration, aging, transplantation in the central nervous system, models for Parkinson’s disease and its treatment, models for spinal cord injury and treatment strategies, the roles of proteins that regulate gene activity in the brain, genetic risk factors for Parkinson’s disease, and proteins that inhibit nerve growth in the nervous system.

Research has been taken all the way from animal studies to clinical trials.

Current focus is aging, neurodegenerative diseases, spinal cord injury and the role of the Nogo system in brain plasticity focusing on the formation of lasting memories and memory disorders.

PUBLICATIONS – MILESTONES

2016, Cerebral Cortex: Karlsson et al. A tunable sensor regulating formation, synaptic and dendritic plasticity. How levels of NgR1, a receptor for the nerve growth inhibitory protein Nogo, regulates density of contacts between nerve fibers.


LAB DESCRIPTION

Research in the Bradbury Lab focuses on understanding why the injured spinal cord is unable to repair itself, with a particular interest in the injury scar which blocks nerve regeneration and prevents tissue repair.

Bradbury’s work led to the discovery that treating the spinal cord with an enzyme called chondroitinase could enable nerve fibres to regenerate through scar tissue, form new connections with target cells and restore some function to paralysed limbs in experimental models. This work has had a major impact and chondroitinase is now a leading candidate for translating to the clinic.

Bradbury is a member of the international CHASE-IT Consortium (chondroitinase for injury therapy) who are developing and testing a chondroitinase gene therapy which is safe for human use. Current research is focused on combining chondroitinase gene therapy (to encourage nerve fibre growth or «neuroplasticity») with a neurorehabilitation programme to improve hand function.

PUBLICATIONS – MILESTONES

2015, Experimental Neurology: James ND, Shea J, Schneider BL, Muir EM, Bradbury EJ
Chondroitinase gene therapy improves upper limb function following cervical contusion injury. The first demonstration that chondroitinase gene therapy can restore upper limb function after cervical contusion injury.


Chondroitinase ABC promotes functional recovery after spinal cord injury. The first demonstration that chondroitinase treatment could restore function after spinal cord injury.
LAB DESCRIPTION

Over the past 15 years, Prof Courtine and his team have developed an unconventional therapeutic strategy that re-established voluntary control of leg movements in rats with a spinal cord injury leading to complete and permanent paralysis. This strategy is shortly described as follows: when an injury occurs, the brain signals to the spinal cord are severely compromised.

The neurons that control the muscles become dormant. To reawaken these neurons, a combination of chemical and electrical stimulation is delivered to the spinal cord. During training, the rats are placed in a cutting-edge robotic interface that supports their weight against gravity in a safe environment. This robot encourages the rat to voluntarily move itself toward a food reward. This intervention promotes the growth of neuronal connections. Even after a severe injury, the rats regain the ability to walk.

Professor Courtine has implemented a research program and founded a start-up to develop all the technologies necessary to apply these therapeutic concepts in paraplegic people.

PUBLICATIONS – MILESTONES

2016, Neuron: Martin Moraud E. et al.
2015, Science: Minev. I et al.
2014, Cell: Takeoka A. et al.
2014, Neuron: Borton DA. et al.
Research in the Raineteau Lab aims at understanding the capacities of the injured CNS (central nervous system) tissue to undergo plasticity and regeneration after a lesion. He has participated to research demonstrating that significant spontaneous recovery occurs after spinal cord injury. His work showed that this spontaneous but incomplete reorganisation could be potentiated by neutralization of the neurite growth inhibitor Nogo-A. He also explored the mechanisms by which digestion of the extracellular matrix by chondroitinase promotes functional reorganisation of CNS circuits.

His most recent research aims at better understanding the capacities of neural stem cells (NSCs) to participate to CNS repair. His group currently studies the plastic potential of postnatal CNS stem cells, that is to say their capacity to change fate upon manipulation of intrinsic or extrinsic factors. By unravelling how environmental signals and transcriptional networks determine NSCs behaviours, his research brings key knowledge to design innovative approaches for their recruitment after lesion or in pathologies.

PUBLICATIONS – MILESTONES

Transcriptional Hallmarks of Heterogeneous Neural Stem Cell Niches of the Subventricular Zone.

Peri-synaptic chondroitin sulfate proteoglycans restrict structural plasticity in an integrin-dependent manner.

Adult generation of glutamatergic olfactory bulb interneurons.

The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats.
LAB DESCRIPTION

Research in the Fainzilber Lab is focused on understanding basic mechanisms of intracellular communication along nerve axons, in particular how the axons communicate information about an injury to the neuronal soma.

Fainzilber and colleagues identified a central role for nuclear import factors called importins in injury signalling from axon to soma, and showed that localized translation of an importin mRNA in axons is required to trigger this process.

The Fainzilber lab is currently trying to identify small molecule agonists of these mechanisms as potential drug leads for the acceleration of nerve regeneration.

PUBLICATIONS – MILESTONES

Subcellular knockout of importin beta1 perturbs axonal retrograde signaling. Definitive proof of the role of local translation in axons in triggering retrograde injury signalling.

Signaling to transcription networks in the neuronal retrograde injury response. Identification of importin-dependent “master regulators” of the injury response.

Axoplasmic importins enable retrograde injury signaling in lesioned nerve.
LAB DESCRIPTION

Research in the Bradke lab focuses on how nerve cells grow during development and how these processes can be reactivated to induce nerve regeneration in the injured spinal cord. His laboratory has a special interest in the skeleton of the cell, called the cytoskeleton.

Bradke and his coworkers showed that manipulation of the cytoskeleton with low doses of anticancer drugs leads to regrowth of nerves and reduction of scarring.

His lab also developed a novel imaging technique that enables visualization of nerves at microscopic resolution within whole tissue.

PUBLICATIONS – MILESTONES

Axonal regeneration. Systemic administration of epothilone B promotes axon regeneration after spinal cord injury.

ADF/cofilin mediated Actin Retrograde Flow Directs Neurite Formation in the Developing Brain.

3D imaging of the unsectioned adult spinal cord to assess axon regeneration and glial responses after injury.
LAB DESCRIPTION

The research laboratory of the Spinal Cord Injury Center at the Balgrist University Hospital, University of Zürich, is devoted to research in humans suffering from paraplegia.

The clinical center is focused on translational research from bench (basic science) to bed (i.e. true clinical applications) and is spearheading novel approaches for clinical trial design and treatments in acute and chronic human spinal cord injury (SCI). It is chairing the European Multicenter Study in SCI (www.EMSCI.org) that is prospectively collecting the most comprehensive and standardized data sets about the recovery from SCI based on generous and visionary funding by IRP since 2001.

The SCI Center Balgrist has been centrally involved in designing and performing interventional clinical trials in acute SCI (phase I study with first in man intrathecal application of antibodies against Nogo-A; phase II study of Nogo-A antibodies in incomplete SCI [NISCI]; first international study for the transplantation of human neural stem cells into the cord of patients with SCI).

PUBLICATIONS – MILESTONES

2015, Annals of Neurology: Grabher P, Curt A
Tracking sensory system atrophy and outcome prediction in spinal cord injury.

2014, The Lancet Neurology: Klamroth-Marganska V, Curt A
Three-dimensional, task-specific robot therapy of the arm: a multicenter randomized clinical trial in stroke patients.

2013, Neurology: Ulrich A, Curt A
Improved diagnosis of in spinal cord disorders with heat evoked potentials.

2012, Spinal Cord: Curt A
The translational dialogue in spinal cord injury research.

2011, The Lancet: van Middendorp JJ, Curt A
A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study.
LAB DESCRIPTION

Translational research - «from bench to bed»
- Creation and development of the European Multicenter Spinal Cord Injury (EM-SCI), a network of paraplegic centres acting as a data base for research projects.

Technology and neurorehabilitation
- In association with the Swiss Federal Institute of Technology (ETH), development of the first walking robot Lokomat, to aid gait training and the ability to walk.

Main research projects
- Neuroplasticity in the case of paraplegia and stroke: What makes a functional training effective?
- Evidence of the development of a neuronal dysfunction in the event of severe paralysis.
- Alteration in the function of the reflexes following paraplegia or stroke.
- Initial description of a neuronal coupling between cooperative hand movements and their dysfunction following stroke.

PUBLICATIONS – MILESTONES


LAB DESCRIPTION

Pizzorusso’s long-term interest is to understand the functional basis of formation and response to pathology of cortical circuits in normal conditions. To answer this question, models of environmental (visual deprivation), genetic [models of neurodevelopmental disorders], and vascular lesions are used. The approach is to combine electrophysiological and imaging techniques with molecular studies.

The lab has a longstanding expertise in such experiments on visual system function and plasticity in mice.

Current main research topics are

- Role of epigenetic mechanisms in experience-dependent development of the visual cortex.
- Role of perineuronal nets in controlling critical periods of brain development.
- Plasticity mechanisms after stroke in juvenile and adult animals.
- Circuit development defects in Rett syndrome, an incurable developmental condition that mostly affects young girls.

PUBLICATIONS – MILESTONES


2015, Cerebral cortex: Gherardini L, Gennaro M, Pizzorusso T. Perilesional Treatment with Chondroitinase ABC and Motor Training Promote Functional Recovery After Stroke in Rats.


LAB DESCRIPTION

The Verhaagen lab focusses on understanding the molecular and cellular processes that drive regeneration in the peripheral nervous system and that underline the failure of regeneration in the central nervous system, with a focus on the role of regeneration-associated transcription factors and chemorepulsive proteins.

Verhaagen’s work led to the discovery that the expression of the chemorepulsive guidance protein Semaphorin3A is induced in the neural scar. He recently showed that Semaphorin3A is present in perineuronal nets, specialized extracellular matrix structures around mature neurons with a key role in regulating neuroplasticity. His laboratory was among the first to use viral vector-mediated gene transfer as a strategy to express pro-regenerative proteins in the injured nervous system and he is currently involved in generating novel regulatable gene therapy vectors based on “Stealth” technology.

Verhaagen is a member of the CHASE-IT consortium, which is developing gene therapy for chondroitinase, an enzyme which enables axon regeneration through scar tissue, most likely by releasing inhibitory molecules, like Semaphorin3A, from the matrix.

PUBLICATIONS – MILESTONES

Overexpression of ATF3 or a combination of ATF3, c-Jun, STAT3 and Smad1 promotes regeneration of the central axon branch of sensory neurons but without synergistic effects.

Developing a potentially immunologically inert tetracycline-regulatable viral vector for gene therapy in the peripheral nerve.

The chemorepulsive axon guidance protein semaphorin 3A is a constituent of perineuronal nets in the adult rodent brain.
LAB DESCRIPTION

With his group in Zurich Martin Schwab discovered the existence of potent nerve fiber growth inhibitory factors which are present in the adult brain and spinal cord. This new concept was rapidly adopted by the neuroscience community and became the basis of many studies on regeneration and repair after spinal cord and brain injuries in many laboratories worldwide.

An important further breakthrough was the demonstration that antibody-mediated neutralization of one of the most potent neurite growth inhibitory factors, Nogo-A, lead to long distance regeneration of injured nerve fibers in the rat spinal cord and to greatly improved functional recovery. These results overthrew the dogma that the adult mammalian spinal cord and brain would be unable to regenerate.

Intense rehabilitation training was shown to further enhance the structural and functional repair processes.

Today, anti-Nogo-A immunotherapy is in clinical trials and is widely seen as one of the most advanced and promising new therapeutic approaches to improve patients’ lives for spinal cord injury, brain injury, stroke and also multiple sclerosis.

PUBLICATIONS – MILESTONES


Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke.


Nogo-A-specific antibody treatment enhances sprouting and functional recovery after cervical lesion in adult primates.


Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen form monoclonal antibody IN-1.


Axonal regeneration in the rat spinal cord produced by an antibody against myelin-associated neurite growth inhibitors.
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