

ERA-NET Neuron NEWSLETTER 26



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News From NEURON Cofund

The first JTC of ERA-NET NEURON Cofund on “External Insults to the Nervous system”, was organized by 22 funding agencies in 18 countries

93 Pre-proposals were submitted. 19 Project were selected to be funded, with 92 participants and a total budget of ~17.9 m€

From the desk of the coordinator | March 2017




Marlies Dorlöchter

The year 2016 saw a number of important NEURON events: With the kick-off of ERA-NET NEURON Cofund in January 2016 and the launch of the Joint Transnational Call (JTC) on “European Research Projects on External Insults to the Nervous System” NEURON started under a propitious star.

Due to the joint national efforts of NEURON partners and EC contribution we succeeded in achieving our as yet highest funding rate. NEURON will fund 19 excellent projects with a total of 17.9 m€ as of mid 2017. In total, 92 research groups from 16 countries across Europe, Canada, Israel and Norway collaborate in these projects. The topics addressed by the consortia range from basic research of axonal regrowth after spinal cord injury to rehabilitation after traumatic brain injury using cutting-edge brain-computer-interfaces. We expect and are looking forward to the most interesting results with high impact for the affected patients. The projects are listed on the NEURON website (<http://neuron-eranet.eu/en/700.php>) and described on the following pages.



More information can be found on our website
<http://www.neuron-eranet.eu/index.php>
 era-net neuron

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An intense exchange of viewpoints from various angles between the research community and the funding organizations in NEURON took place at several occasions, e.g. at the [symposium](#) on “Interactions between scientists, clinicians and the society in neurosciences” in January, 2016 in Berlin), or the [workshop](#) on “Neuroethics” in May 2016 in Milan, or the symposium on “Neuroinflammation” of the NEURON-funded projects in September 2016 in Madrid (for details see Newsletters no. 24 and 25, and this Newsletter, page 3).

At the FENS Forum in Copenhagen NEURON sponsored a [Plenary Lecture](#) held by Hannah Monyer from Germany. Another highlight in Copenhagen was the ceremony of the “Excellent Paper in Neuroscience Award”. The awardee, Julien Courtin from Basel, Switzerland, presented his work to a numerous audience. A likewise highlight was the well-attended [networking event](#) for early career scientists, which NEURON had organized in collaboration with the FENS Committee of Higher Education and Training (CHET) and the Human Mind Research Program of the Academy of Finland. More than 300 young neuroscientists participated in the event interested in networking and developing their career perspectives in the field of human mind, or basic, translational and clinical neuroscience.


2017 promises to be equally exciting with the following measures and events:

Two joint calls for proposals were launched in January. One addresses research projects on “Synaptic Dysfunction in Disorders of the Central Nervous System” (<http://neuron-eranet.eu/en/698.php>). The deadline for proposal submission was on March 14, 2017. The other one aims for research projects on “Ethical, Legal, and Social Aspects (ELSA) of Neuroscience” (<http://neuron-eranet.eu/en/711.php>). The deadline for proposal submission is on May 3, 2017.

NEURON is fully committed to the highest possible standard of quality assurance, including working to nationally and internationally recognized best practices. NEURON partners therefore discussed with renowned scientists measures of quality assurance and reproducibility of results in a [special workshop](#) within the regular meeting in January 2017 in Oslo. We are now working on measures to be implemented in our joint calls for proposals.

“Emerging fields in mental health” are of highest societal importance and will therefore be addressed with a symposium in May 2017 in Amsterdam. More intense involvement of patient organizations in our work, and the aim to create deeper links between psychiatry and neurology will be important agenda items of this meeting.

The September highlight will be a joint symposium for the NEURON-funded projects of JTC’s 2015 ‘Neurodevelopmental Disorder’ and ‘ELSA of Neuroscience’ to present their progress. Embedded in the program are the activities for the Early Career Scientists: the annual award ceremony and key note lecture of the winner of the Excellent Paper in Neuroscience Award, as well as a poster session and poster prize of the JTCs 2015.



I would like to thank our NEURON partners for the successful and high-spirit work year 2016 and wish us all the same enthusiasm for 2017. A special thank you goes to our Scientific Advisory Board and all our guests who follow our invitations and support our work with invaluable advice.

Yours sincerely,



Marlies Dorlöchter.

Midterm symposium on “Neuroinflammation” Madrid, September 2016

To get some insight into the progress of research of the funded NEURON projects, and to increase the networking among the funded consortia, the researchers funded in JTC 2014 ‘Neuroinflammation’ were invited to a Midterm symposium.

The meeting, held in Madrid, provided not only an excellent occasion for scientific exchange between funded principal investigators within and between the consortia, but also included early career scientist. Graduate students and postdocs from the funded projects received NEURON travel grants to attend the meeting and present their research in a dedicated poster session. It was a pleasure to watch how vividly they discussed their results and networked with their peers and seniors. It was a special pleasure for Erkki Raulo, the leader from AKA, Helsinki, to award the best poster. The poster prize went to a joint poster titled “CnsAflame: Neuroinflammatory mechanisms following traumatic brain injury” by three early career researchers C. Albert-Weissenberger (Germany), S. L. Zaltsman (Israel), and B. Rodriguez-Grande (France), who illustrated the international, collaborative spirit of NEURON.

Poster Prize Winners:
Erkki Raulo (Young Scientist
Programme leader), Beatriz
Rodriguez-Grande, Sigal Lir
Zaltsman, with Marlies Dorlöchter
(NEURON Coordinator)



Poster session in
Madrid, September
2016




The first collaborative results of the JTC 2014 'Neuroinflammation' were presented by the coordinators of the ten funded consortia in September 2016 (all funded projects summaries can be found at <http://neuron-eranet.eu/en/549.php>).

Understanding neuroinflammatory processes will contribute to the development of future therapeutic strategies for a number of brain diseases. At the symposium, Etienne Audinat reported of the progress within the consortium BrIE – “Brain Inflammation, Glia and Epilepsy” where new biomarkers and putative therapeutic targets for epilepsy are to be identified. Analogous, Nikolaus Plesnila and the CnsAflame consortium work on “Neuroinflammatory mechanisms of chronic neurodegeneration and cognitive decline following traumatic brain injury”. As Plesnila pointed out, ‘Acute TBI triggers a chronic neuroinflammatory response which lasts for month and years and causes, among others, progressive post-traumatic neurodegeneration resulting in cognitive decline and dementia’.

On the topic of chronic pain, the consortium IM-PAIN – “Identification and study of different immune cell populations and their role in chronic pain” led by Stephen McMahon studies immune cells as important pain mediators.

Two other projects focus their efforts to combat neurodevelopmental impairments in children, caused by neuroinflammation. An investigation of a childhood-onset brain disease, Aicardi-Goutières Syndrome (AGS), is coordinated by Yanick Crow in the Neuro-IFN consortium – “Investigation of the neuroinflammatory basis of human type I interferonopathies” using a translational genetic approach. MICRO-MET is a consortium established to research the “Role of microglial metabolism in perinatal neuroinflammation”, led by Pierre Gressens. Their findings may help unravel the complex functions of microglia to tackle perinatal brain injury.

A number of consortia explore neuroinflammation from a cellular and pre-clinical angle. In MELTRA-BBB – “Mechanisms of Lymphocytes Transmigration Across the Blood Brain Barrier” Ari Waisman and colleagues investigate how cells of the immune system can infiltrate the brain via the blood-brain-barrier. TraInflam, a consortium coordinated by Michael Heneka, studies the “Transition from acute to chronic neuroinflammation” in preclinical models of e.g. Alzheimer’s disease.



Pre-clinical work is revealing what molecules are involved in the crosstalk between the gut microbiome and the host organism. Findings in animal models shall ultimately be transferred to the human condition. 'What are the molecules involved in the crosstalk between the gut microbiome and the human host' is one of the questions addressed by the consortium μ NeuroINF – “The role of the Gut Microbiome on Neuroinflammation and Neurodevelopmental Disorders”: Marc-Emmanuel Dumas and his international consortium investigate mouse models of Down syndrome, Fragile X syndrome and Autism Spectrum Disorders, to verify molecular pro-inflammatory factors in vitro and in vivo. Another consortium, MS_NANOMED – “Advancing an antigen-specific nanomedicine for the treatment of central nervous system autoimmunity” coordinated by Pere Santamaria is promoting the advance of nanomedicine for the treatment of central nervous system neuroinflammation in Multiple Sklerosis towards clinical trials. Last but not least, Martin Rottenberg of the NEUINF consortium – “Master regulators of neuroinflammation in parasitic brain infections” presented first insight into neuroinflammation processes caused by parasitic infections of the brain like malaria or toxoplasmosis.

The coordinators received feedback on their consortia progress by one of the original reviewers, who chaired the symposium. He was impressed by the achievements and the enthusiasm in the projects. The presentations and discussions provided inspiration and motivation for the common JTC efforts within NEURON.



European Research Projects on 'External Insults to the Nervous System' Joint Transnational Call 2016

93 pre-proposals were initially submitted by 359 participants, requesting a total budget of ~72.5 m€s. 43 consortiums of the 93 were asked to write a full proposal. Finally, the 19 best projects with 92 participants were selected for funding. Consequently, twice as many researchers are funded under JTC2016 in comparison to previous NEURON call.

A total of 98 female and 261 male applicants submitted propositions to the preproposal phase, 51 and 141 respectively to the full proposal phase, and finally 30 female and 62 male scientist were financed. Nonetheless, the proportion of female partners and female coordinators increased respectively from 27 to 32 percent and from 36 to 42 percent between the preproposal and the final selection of projects. [The next pages are dedicated to the JTC 2016 funded projects. We wish them much success, and are intrigued to learn their results.](#)

Altered Chloride Homeostasis in Reactive Plasticity upon Brain Trauma (ACRoBAT)

Project Coordinator: Claudio Rivera, Institut de Neurobiologie de la Méditerranée
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Liset Menendez de la Prida, Instituto Cajal CSIC, Madrid, Spain



Claudio Rivera



Traumatic brain injuries are the main injury-related causes of permanent disability, and are the third leading cause of mortality in Europe. Worldwide, more than 10 million people are affected every year. Post-traumatic epilepsy is the most common cause of new-onset epilepsy in young adults; following penetrating brain wounds, the likelihood of developing epilepsy is more than 50%. 30 to 40% of patients with post-traumatic epilepsy have seizures that are incompletely controlled with currently available medication. Moreover, unnecessary treatment with currently available antiepileptic drugs may then impair neurorehabilitation after brain trauma. It is evident that this field desperately needs new therapeutically relevant targets. In order to find them, we need to understand in detail the mechanisms engaged upon brain trauma. Our project aims to disclose the mechanisms and impact of trauma-induced changes in inhibitory neurotransmission in the cortex.

Our preliminary results allow us to propose a working hypothesis in which a major component of altered inhibitory neurotransmission upon brain trauma is the malfunction of proteins involved in chloride transport in neurons. Subsequent abnormalities in neuronal chloride regulation not only perturb inhibitory signals, but also appear to be crucial for post-traumatic neuronal survival and proliferation, leading to altered activity of neuronal networks.

We will address these questions using a combination of state-of-the-art transgenic tools for both temporal and cell-specific control and monitoring of intracellular chloride as well as chloride regulatory proteins after TBI. ACRoBAT incorporates several innovative dimensions aimed to design novel tools, biomarkers and intervention strategies. Ultimately, we will test the therapeutic relevance of novel compounds modulating chloride homeostasis and GABAergic transmission in TBI experimental models. Thus, the multifaceted impact of chloride transport malfunction in neurons makes it a particularly promising target with strong potential for innovative therapeutic strategies to improve rehabilitation of brain trauma patients in the future.

Spinal cord repair: releasing the neuron-intrinsic brake on axon regeneration (AxonRepair)

Project coordinator: Joost Verhaagen, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

Project partners:

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Lawrence Moon, King's College, London, United Kingdom

Alyson Fournier, McGill University, Montreal, Canada

Frank Bradke, German Center for Neurodegenerative disease, Bonn, Germany

Dasa Cizkova, Slovak Academy of Sciences, Bratislava, Slovakia



Joost
Verhaagen



Spinal cord injury (SCI) leads to permanent disability and is a significant clinical problem with 130,000 new cases/year worldwide. Following SCI long axon tracts fail to regenerate. This is the primary reason for the sustained loss of bodily functions.

AxonRepair aims to develop a strategy to promote long-distance axon regeneration and functional recovery after SCI by reprogramming neurons into a regenerative state and by overcoming the axon transport block that is a barrier to axon regeneration. In AxonRepair we bring together world-class experts on the transcriptional control of axon regeneration, axon transport and therapeutic gene delivery.

We already have identified factors that promote CNS axon regeneration and modest sensorimotor recovery in animal models of SCI. We now seek to combine these factors to deliver greater axon regeneration and clinically significant functional recovery. We will use clinically translatable adeno-associated vector-based gene delivery, novel techniques to quantify axon trajectories in cleared spinal tissue and innovative, automated methods for assessing dexterity in rats. Work package (WP) 1 aims to reprogram neurons into a regenerative state by testing the effect of combinatorial delivery of key transcription factors identified in our collective's discovery pipelines. WP 2 aims to restore axonal transport of growth-related receptors (integrins) to injured spinal axons. WP 3 aims to provide novel mechanistic insight into how interventions at the transcriptional and axon transport level work and whether these interventions act synergistically in rat models of SCI.

At completion of the project we expect to have developed a method to release the brake on axon regeneration. The participation of the world-leading gene therapy company uniQure ensures that newly generated know-how will be exploited rapidly by entering into a co-development agreement and/or intellectual property strategy.

Developing and validating blood and imaging BIOmarkers of AXonal injury following Traumatic Brain Injury (BIO-AX-TBI)



David Sharp

Project coordinator: David Sharp, Centre for Restorative Neurosciences
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Project partners:

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Guido Bertolini, IRCCS Mario Negri Institute for Pharmacological Research, Milan, Italy

Sandra Magnoni, Department of Intensive Care, IRCCS, Milan, Italy



Traumatic brain injury (TBI) occurs when the brain is physically damaged, for example after a car crash. It is common and survivors often have major on-going problems. It is very difficult to predict how patients will do after TBI. One reason for this is that we are unable to measure all the effects of TBI. An important factor is that the connections between nerve cells are damaged by the impact on the brain of an injury (axonal injury). This damage has been difficult to measure in the past, but new ways to scan the brain and more sensitive ways of picking up the effects of this injury in the blood could change this. In other parts of medicine tests of this type have had a dramatic effect on how we treat patients. For example, the products of heart muscle damage that have leaked into the blood can be used identify a heart attack and guide treatment. We need similar tests to be available in TBI. This should be possible as the products of axonal injury also leak into the blood and we have a sensitive way to pick this up. An accurate test for axonal injury would guide treatment choices and allow us to predict how patients will recover. We have brought together an international team who have been working on different aspects of this problem for many years. Together we will conduct a large study to identify the best measures of axonal injury. We will carefully test whether these measures help us predict outcomes and will study where the blood markers come from using a safe method to measure the effects of axonal injury directly from the brain. The work links into some large projects that have already started and will use a standard way to assess patients after their injury. This is important because it will allow us to share results across studies. We hope the work will allow us to identify a blood marker for TBI that could be widely used to quickly identify the presence of axonal injury. We will also show what brain imaging measure is best at picking up axonal injury and how best to combine the measures to best predict how patients recover. This will allow doctors to diagnose problems after TBI more accurately, choose the right treatments and give patients and their families accurate advice about what will happen after discharge from hospital.



Non-invasive electrical stimulation of the cervical spinal cord to facilitate arm and hand functional recovery in incomplete traumatic cervical spinal cord injured patients (CERMOD)



Guillermo
García-Alías



Project coordinator: Guillermo García-Alías, Dept. Cell Biology, Physiology and Immunology, and Institute of Neuroscience, Universitat Autònoma de Barcelona, Spain

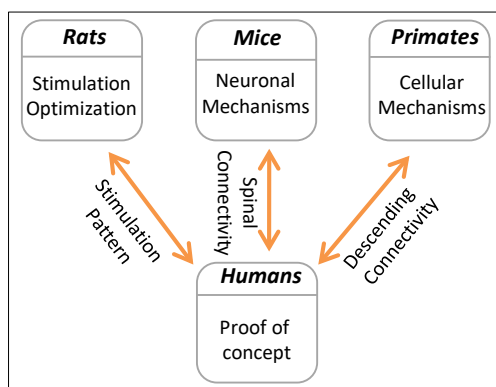
Project partners:

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Andrew Jackson, Institute of Neuroscience, Newcastle University, United Kingdom

Joel Glover, Department of Molecular Medicine. Institute of Basic Medical Science, University of Oslo, Norway

Injury to the spinal cord is irreparable. There are no current treatments that promote the reconnection between the brain and the spinal cord neurons below the injury. Over the last years several strategies have focused on promoting the regeneration of the damaged spinal axons across the injury. Although several treatments have shown promising results in experimental animal models, none of them are yet available for treating human patients. A novel approach, which has opened great expectations, is the development of bioengineering technologies. The development of bio-electronic devices is intended to modulate the preserved connections between the brain and the spinal cord or to further resituate the damaged nervous tissue in more severe neurological conditions. Along this line, experiments in which electrical current has been delivered to the spinal cord through implantable electrodes have facilitated hind limb function in both animal models and human patients. However, it is unknown whether or not the same technology can be applied to the cervical spinal cord to facilitate recovery of arm and hand function. In the present proposal, we have designed a set of experiments both in animal models and in human patients to obtain a proof of principle of the utility of non-invasive transcutaneous electrical stimulation to facilitate arm and hand recovery.



Emergence of a spinal micturition reflex after SCI: abolition by silencing of hyper-excited C-fiber bladder afferents by gene therapy to restore continence and micturition (ELPIS)



François Giuliano



Project coordinator: François Giuliano, R. Poincaré Hospital, Université de Versailles Saint Quentin/INSERM, France

Project partners: Francesco Montorsi, Urological Research Institute, Ospedale San Raffaele, Milano, Italy

Francisco Wandosell, Spanish Research Council Centro de Biología Molecular Severo Ochoa, Madrid, Spain

Our project aims to develop a gene therapy to treat neurogenic detrusor overactivity (NDO) and ultimately to restore urinary continence and voluntary micturition, which remains an unmet medical need in spinal cord injured patients who are currently emptying their bladder by intermittent catheterization. NDO is a severe disabling disorder caused by spinal cord injury (SCI) and characterized by involuntary bladder contractions, resulting in urinary incontinence, recurrent urinary infections and, if untreated, renal failure, which can be fatal. Bladder function is controlled by a reflex organized as a neural loop, constituted of nerves from the bladder to the spinal cord (bladder afferents) and back from the spinal cord to the bladder (bladder efferents) and the urethral sphincter, with the spinal cord being under the control of the brain. After SCI, bladder afferents send aberrant information to the spinal cord resulting in chaotic bladder contractions. There is also a loss of brain control on the spinal cord responsible for a lack of voluntary control on micturition. Current NDO treatments comprise oral antimuscarinics or botulinum toxin (BoNT) injections into the bladder, both of which inhibit bladder contractions by blocking bladder afferents, consequently paralyzing the bladder. Intermittent bladder catheterization (5-6 times a day) is therefore mandatory for bladder emptying, which is responsible for recurrent urinary infections and for a significant decrease in quality of life by increasing disability.

We aim to design an original gene therapy to inhibit the transmission of aberrant information from the bladder to the spinal cord via bladder afferents to treat NDO without bladder paralysis. We will design herpes simplex virus-based vectors to be injected into the bladder to silence bladder afferents neurons. By infecting bladder afferents, these vectors will blunt their intracellular machinery for neurotransmission by expressing relevant intracellular transgenes. Vectors will be tested and selected in a variety of assays, including SCI rats with NDO to assess their therapeutic effect and safety. The neural command of micturition will thus remain available for on-demand electrical stimulation by an implantable stimulator (already available in humans) to elicit micturition without bladder catheterization. Ultimately, this should revolutionize the management of NDO in SCI patients.



Understanding the mechanisms of atrophy associated with spinal cord injury: the application of MRI-based in vivo histology and ex vivo histology (hMRIofSCI)



Armin Curt



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Nikolaus Weiskopf, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Pawel Tabakov, Department of Neurosurgery, Wroclaw Medical University, Poland

Spinal cord injuries (SCI) are mainly caused by traumatic events, such as traffic and sports accidents and violence. Paraplegia (paralyzed legs) and tetraplegia (both legs and arms are paralyzed) permanently, severely and dramatically reduce the quality of life of the affected person as well as his/her ability to remain a member of the workforce. These negative consequences arise because functional recovery following SCI remains limited and the majority of patients are left with severe impairments in the longer term. While rehabilitative training can improve clinical outcome following SCI, which is a major benefit to the patients' quality of life, the degenerative processes as well as the mechanisms underpinning any neurological and functional recovery are not well understood. Recent advances in the field of magnetic resonance imaging (MRI) have vastly improved how we can visualize and interrogate the structural organization and functioning of the central nervous system. Notable among these advances is the emerging ability to investigate "microscopic" changes in the human central nervous system. This includes distinguishing white and grey matter – two fundamental divisions of structure in the spinal cord, brainstem, and brain. Using microscopic MRI protocols we have shown that structural changes occur over time following a specific spatial and temporal pattern. In fact these changes occur early after the injury and happen both in the cord and in the brain. However so far, the range of biological changes that may underlie the observed changes cannot be disentangled. By means of in vivo histology using MRI (hMRI) – an emerging field in MRI – we aim to establish the missing link between measured MRI signals and changes in the underlying tissue microstructure, which will help us to explain and better understand the disease processes associated with spinal cord injury.



David K Menon



International Collaboration On Neuroinflammation in Traumatic Brain Injury (ICON-TBI)

Project coordinator: David K Menon, University of Cambridge, United Kingdom

Project partners:

Karen Barlow, Cummings School of Medicine, University of Calgary, Canada

Vincent Degos, Hopital Pitié Salpêtrière, Université Pierre et Marie Curie, Paris, France

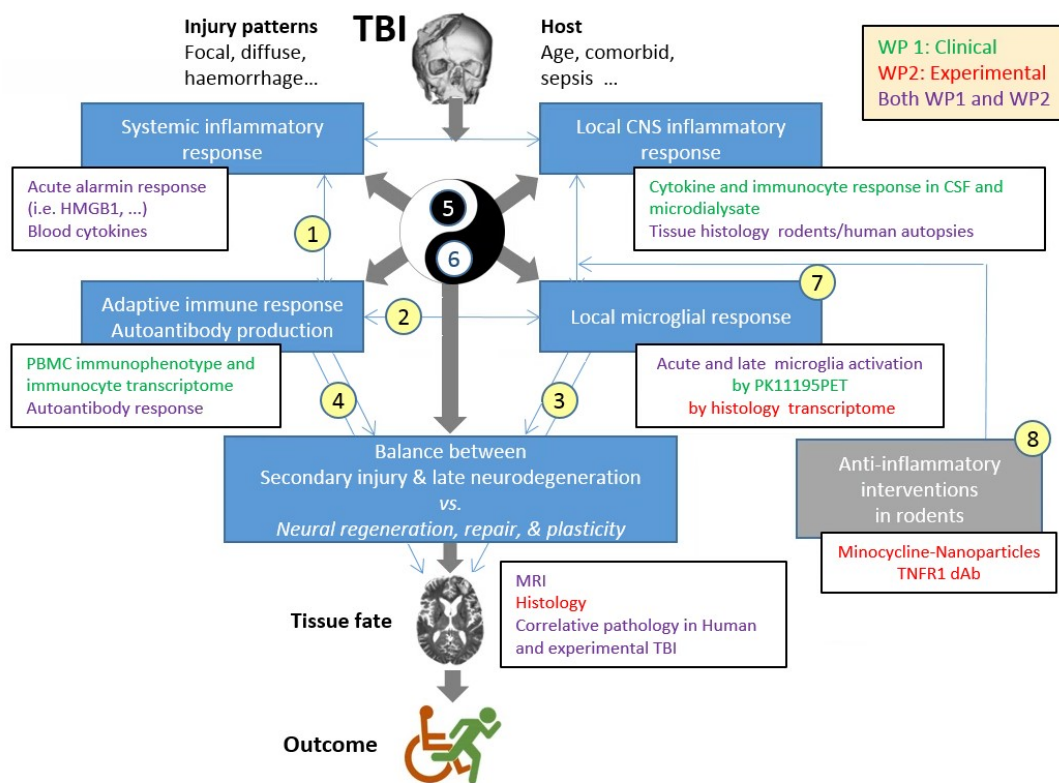
Elisa Zanier, Istituto Ricerche Farmacologiche "Mario Negri", Milan, Italy

There is a growing acceptance that traumatic brain injury (TBI) represents an acutely initiated event which results in long-lasting physical, psychiatric and psychological disability. In a sizeable minority, TBI may also be a progressive disease, resulting in worsening neuroimaging findings and neurology over months and years, and/or increase the risk of late dementia. The mechanisms underpinning this progressive/late risk of neurological deterioration/neurodegeneration are uncertain, but are thought to critically involve neuroinflammation.

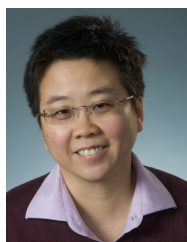
There is strong support for a role for neuroinflammation in the acute stage of more severe TBI, where it includes a systemic and intracranial humoral and cellular innate inflammatory response, including microglial activation. However, evidence is accumulating that neuroinflammation may also occur in mild TBI, and may result in activation of an adaptive immune response with autoantibody production and chronic microglial activation. However, there is limited data in this area in the context of clinical TBI. The ICON-TBI consortium will address this deficiency through complementary clinical and experimental research, involving 175 patients with a range of TBI severity. We will bank serial blood, CSF and brain microdialysis samples, and obtain serial MRI to characterise tissue fate, and undertake serial imaging of microglial activation in a subgroup of patients with moderate-severe TBI. Peripheral and CNS immunocytes will be characterised using immunophenotyping and expression profiling, and we will measure the development of autoantibody responses. We will characterise the role of the acute alarmin response, immunocyte profile, and CD8 T cell exhaustion in promoting such autoantibody production; and investigate whether such adaptive immune responses are detrimental (by causing ongoing tissue injury) or beneficial (through "protective autoimmunity").

These clinical studies will be underpinned by studies in experimental models of diffuse and focal TBI of different severities, which will investigate the role of age and gender in modulating the neuroinflammatory response, and explore novel immunomodulatory therapies.

Our research outputs could lead to a better understanding of how an initial acute biomechanical injury is converted into chronic and/or progressive pathology, and provide a knowledge base for precision medicine approaches to dealing with this transition following TBI.



Paediatric Brain Monitoring with Information Technology (KidsBrainIT): Using Information Technology (IT) Innovations to Improve Childhood Traumatic Brain Injury Intensive Care Management, Outcome, and Patient Safety (KidBrainIT)



Tsz-Yan Milly Lo



Project coordinator: Tsz-Yan Milly Lo, Child Life and Health, University of Edinburgh, United Kingdom

Project partners: Ian Piper, Clinical Physics at Southern General Hospital, University of Glasgow, United Kingdom

Bart Depreitere, University Hospitals Leuven, Leuven, Belgium

Juan Sahuquillo, Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain

Stefan Mircea Lencean, Neurosurgery Department, GrT Popa University of Medicine and Pharmacy, Lasi, Romania

PROJECT AIM: We aim to test two hypotheses: After sustaining traumatic brain injury (TBI), paediatric patients with a longer period of measured cerebral perfusion pressure (CPP) maintained within the calculated optimal CPP (CPP_{opt}) ranges have (1) an improved outcome, and (2) better tolerance against raised intracranial pressure (ICP).

WORK PLAN: We set up a new multi-centre, multi-disciplinary and multinational clinical and research collaborative called KidsBrainIT. In a 2-year prospective observational study, 10 centres contribute paediatric TBI patients' anonymised clinical, high-resolution physiological, and outcome data to a central repository (KidsBrainIT Data-bank). Using the same methodology as our pilot (optimal CPP calculation and ICP dose-response plots), the main data-set is used to test our hypotheses. A sub-set of data is used to test novel technology and data models. Calculated validated indices is used as metrics of clinical management quality assurance for feedback to contributing units to improve treatment.

EXPLOITATION OF RESULTS: By bringing senior clinicians, engineers, and scientists from different centres and countries to the group, KidsBrainIT facilitates testing of clinically relevant therapeutic thresholds and validating new monitoring technologies which are then readily translated back into clinical practice through contributing units. It will also address inequality and variations in TBI management between adult and paediatric practices.

New therapeutic strategies in the treatment of traumatic brain injury by targeting the LECTIN Activation Pathway of complement (LEAP)



Maria Grazia De Simoni

Project coordinator: Maria Grazia De Simoni, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy

Project partners:

Anna M Planas, Institut d'Investigacions Biomèdiques de Barcelona (IIBB), Consejo Superior de Investigaciones Científicas (CSIC), Barcelona, Spain

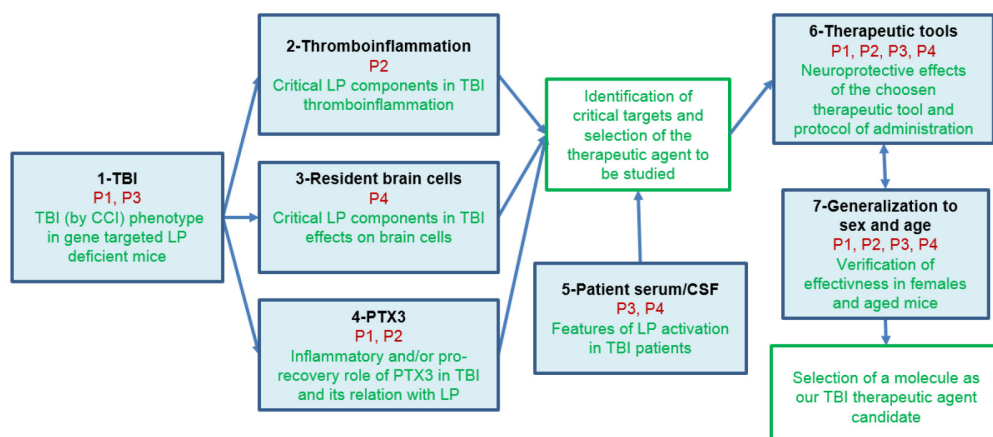
Wilhelm Schwaeble, Department of Infection, Immunity and Inflammation, University of Leicester, United Kingdom

Eberhard Weihe, Philipps-University Marburg, Germany

Joanna Mika, Institute of Pharmacology Polish Academy of Sciences, Krakow, Poland



The Lectin Pathway (LP) of complement activation has emerged as one of the key players in the mediation of post-traumatic inflammatory pathology of various organs. The LEAP project is based on the hypothesis that LP drives a disease promoting phenotype within the pathophysiology of traumatic brain injury (TBI) and that modulating LP dependent inflammation and tissue loss can markedly improve the clinical outcome. LEAP will apply basic-science and clinical approaches to characterize the events that trigger LP activation in TBI and to assess the therapeutic utility of clinically tested inhibitors or modulators of LP functional activity. Specific objectives of the project will include: i) identification of the key molecules and the pathogenic cascades by which the LP determines to the outcome of TBI injury in a clinically relevant mouse model; ii) assessment of the features of LP activation and their association with clinical parameters in TBI patients; iii) identification of appropriate therapeutic target/s and pharmacological tool/s; iv) definition of appropriate protocols and therapeutic opportunities to facilitate the introduction of a significantly improved clinical treatment of TBI pathology. The unique combination of a clinically relevant mouse model, the availability of highly specific molecules that have already been clinically tested and approved, or that are in development for other indications, highlight the translational promise of LEAP programme



Cortical microcircuitry after traumatic brain injury: molecules to networks (Micronet)



Aya Takeoka



Project coordinator: Aya Takeoka, Neuro-Electronics Research Flanders, University of Leuven, Belgium

Project partners:

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Magdalena Goetz, Institute of Stem Cell Research, Helmholtz Zentrum München, Neuherberg, Germany

Daniel Wójcik, Nencki Institute for Experimental Biology, Warsaw, Poland

Acute disconnection and degeneration of neuronal circuits after traumatic brain injury (TBI) leads to onset of severe motor, sensory and cognitive dysfunctions. Although remarkable anatomical and functional recovery takes place after the injury, its extent remains limited. Both the acute deficits and the recovery depend on changes in neuronal connectivity, but little is known about the identity of these connections and how they are broken and re-established.

We will combine advanced rabies-based monosynaptic tracing approaches, unbiased three dimensional kinematic analysis, cutting edge light sheet volumetric imaging and innovative neuroinformatic tools to provide a new, systems neuroscience-based conceptual framework for TBI.

Specifically, we will map how specific patterns of input connectivity to primary somatosensory cortex are linked to the onset and recovery of sensorimotor deficits, with a focus on Parvalbumin interneuron networks. We will use two sets of unbiased, comprehensive technologies, mass spectrometry and single-cell signaling analysis, to identify new prognostic markers for successful rewiring and new targets for protecting existing connectivity and enhancing the formation of functional new circuit networks. We will then validate new potential candidates for therapeutic intervention using quantitative behavioral measures, with a particular emphasis on drug-repurposing strategy.

This will pave the way in providing viable therapeutic options for a class of disorders in which lack of pathophysiological understanding has prevented effective interventional options in the field.

Spinal cord repair from endogenous stem cells in the spinal niche (NEURONICHE)



Catherina
G.Becker



Project coordinator: Catherina G.Becker, Centre for Neuroregeneration, The University of Edinburgh, United Kingdom

Project partners:

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Michell M.Reimer, DFG-Center for Regenerative Therapies Dresden Cluster of Excellence, TU Dresden, Germany

Matthias Kirsch, Dept. of Neurosurgery, Carl Gustav Carus Universitätsklinikum Dresden, TU Dresden, Germany

Serge Muyldermans, Cellular and Molecular Immunology, Vrije Universiteit Brussel, Belgium

Slawinska Urszula, Nencki Institute of Experimental Biology, Department of Neurophysiology, Polish Academy of Science, Warsaw, Poland

Spinal cord injury in humans leads to permanent loss of function. This is despite the presence of stem cell like cells in the spinal cord. In contrast, zebrafish regain full swimming capacity after a lesion, and their spinal stem cells make new neurons that contribute to the repair.

We hypothesize that small differences in the environment of zebrafish and mammals spinal stem/progenitor cells determine regenerative success or failure. We need to characterize and compare the cellular diversity and differential properties of adult spinal cord stem cell niches in zebrafish, rodents and human. We will elucidate the molecular mechanisms controlling niche dormancy vs activation and stem cell fate after spinal cord injury, exploring why mammals spinal cord stem cell do not generate neurons after SCI. We will explore the human spinal cord stem cell niche and generate human spinal cord stem cell lines for further investigation of human niche cell properties. We aim to enhance functional repair after mammalian spinal cord injury by defining innovative tools (nanobodies) and identifying molecules to manipulate the activity and fate of spinal cord neural stem and progenitor cells after injury. Furthermore, we will adapt a new microscopy technique to monitor repair in live fish and rats as it happens.

This project will identify repair factors that could then be taken into clinical trials. Our team comprises colleagues from the UK, Germany, Belgium, France and Poland, among them basic neuroscientists and neurosurgeons.

Repurposing Acute Therapies for Enhanced Recovery after Spinal Cord Injury (RATER SCI)



John Kramer

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Project partners:

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Soler Dolors, Institut Guttmann, Badalona, Spain



Profound sensorimotor deficits are the hallmark of damage in the central nervous system (CNS). Among the more difficult to manage are muscle paralysis and neuropathic pain. The combination of these deficits is particularly cruel: burning or dysesthesia in areas of the body that are otherwise numb and incapable of volitional movement. The economic burden to the individual, caregivers, and European and Canadian societies are enormous.

The proposed research project will evaluate the effectiveness of pharmacological and rehabilitation interventions to increase motor function and/or relieve neuropathic pain. Our aims are to determine: 1) if existing treatment options already used to manage neuropathic pain can be repurposed to improve motor function and 2) whether an existing rehabilitation intervention to improve locomotion can be repurposed to relieve neuropathic pain.

Projects will be carried out in Canada, Switzerland, Germany, and Spain, and involve research in humans and animal models of spinal cord injury. An investigation into pain medications will be primarily focused on the use of anticonvulsants. These are a particular class of drug that is commonly administered for neuropathic pain after spinal cord injury. Two rehabilitation therapies will be investigated for their potential to resolve neuropathic pain and increase muscle strength. In Spain, a research project will incorporate the use of electrical stimulation applied to the brain as a strategy to improve hand function. Parallel studies in Canada will investigate if gait training reduces pain whilst improving how people walk. At the end of the proposed research project, our goal is to understand the relationship between pain and the recovery of muscle strength, and develop new strategies to enhance neurological recovery in humans with SCI.

Induction of Reactive Neural Stem Cells by Traumatic Brain Injury in the Adult Hippocampus (REACT NSCs)



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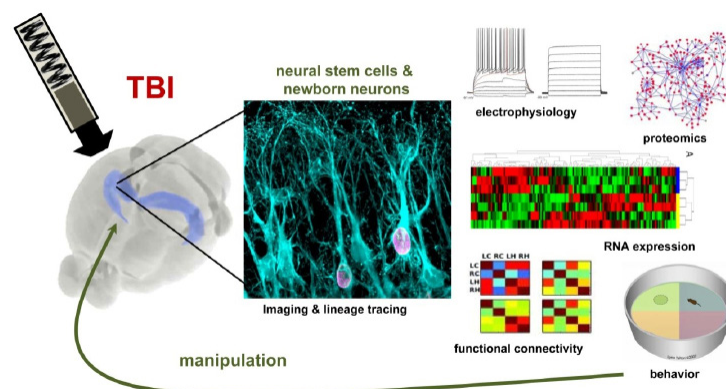
Carlos P Fitzsimons, Swammerdam Institute for Life Sciences, Universiteit von Amsterdam, The Netherlands



Traumatic brain injury (TBI) is becoming a “silent epidemic” worldwide. In Europe, almost 8 million people have significant disabilities due to TBI and the economic cost has been estimated in EUR 100 billion. TBI survivors often develop long lasting neurological symptoms such as decision-making and memory deficits, depression or aggressive behavior, negatively impacting on their quality of life. Several of the important brain functions affected by TBI depend on the hippocampus, which is highly vulnerable to injury. Even when not directly mechanically affected, the hippocampus undergoes atrophy and synaptic alterations. In addition, postnatal and adult hippocampal neurogenesis, the process of generating new neurons from neural stem cells (NSCs) located in the dentate gyrus is affected by TBI. We hypothesize that TBI induces long-term changes in NSCs and newborn neurons, drastically altering the process of neurogenesis and thereby negatively affecting hippocampal circuitry and function. We propose NSCs and hippocampal neurogenesis should be considered a novel target for developing innovative strategic therapies against brain damage. Hippocampal neurogenesis is highly sensitive to changes in turn, neuronal activity and impairment or alterations of hippocampal neurogenesis may account for some of the symptoms associated with TBI, such as memory, learning, and anxiety deficits, as these are hippocampal functions in which neurogenesis participates.

We have shown that NSCs modify their behavior readily in response to neuronal damage and changes in neuronal activity. Depending on the intensity of the stimulus they: 1) Boost transiently neurons generation (neurogenesis) and afterwards become depleted; or 2) Switch to a reactive phenotype (reactive NSCs) entering symmetric division and generating reactive astrocytes (reactive astrogliogenesis) at the expense of abandoning almost completely the generation of new neurons.

In both cases, the generation of ectopically newborn neurons with altered morphology and connectivity ("aberrant neurogenesis") takes place, potentially affecting the processing of neuronal input into the hippocampus. In this research we aim to investigate both the changes induced in NSCs and in newborn neurons in a multilevel and integrative manner using imaging, lineage tracing, proteomics, micro RNA expression, electrophysiology, functional connectivity and behavior. Our project will demonstrate the utility of hippocampal neurogenesis as a potential novel therapeutic target for TBI.



Inga Katharina Koerte

Repetitive Subconcussive Head Impacts – Brain Alterations and Clinical Consequences (ReImpact)

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Roald Bahr, Norwegian School of Sport Sciences, Oslo, Norway

Peter Filipcik, Slovak Academy of Science, Bratislava, Slovakia

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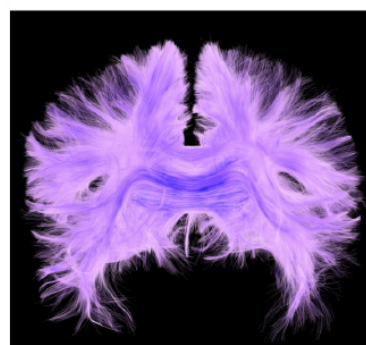
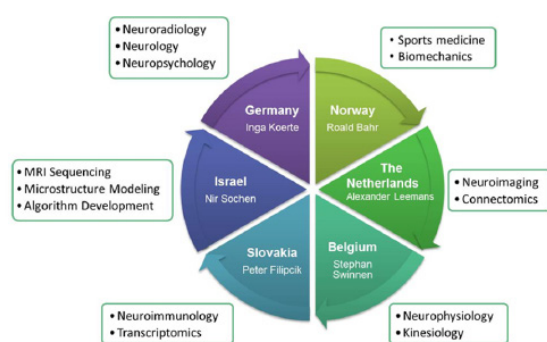


Concussions are especially prevalent in athletes who participate in contact-sports. Recent evidence suggests that, similar to concussions, subconcussive head impacts, especially multiple impacts in close proximity in time, may lead to brain alterations and clinical impairment. Despite the large prevalence, and although evidence indicates cumulative effects, no studies have determined whether or not exposure to repetitive head impact in childhood and adolescence leads to impaired brain development. There is an urgent need to determine the effects of repetitive head



impacts on the brain, potentially putting millions at high risk for brain alterations and clinical consequences. Soccer provides an accessible model for understanding the effects of repetitive subconcussive head impacts, and for determining risk factors that lead to brain alterations and clinical consequences. Our central hypothesis is that exposure to repetitive head impacts – even in the absence of concussion – will result in alterations of the brain’s structure, function, and connectivity, and that these alterations will be accompanied by clinical consequences. We perform a longitudinal study of professionally trained youth soccer players exposed to repetitive head impacts, compared with a control group of athletes involved in non-contact sports. We will form a multidisciplinary, multinational consortium of experts to perform 1) fundamental research to understand the basic mechanisms of repetitive external insults to the central nervous system on a biological and functional level using a comprehensive battery of innovative MRI techniques, high density EEG, and blood and saliva sample arrays; and 2) clinical research to develop new strategies for diagnosis, prediction, and prevention of brain alterations after repetitive external insults, where we will apply established behavioural tests and novel quantitative measures of exposure to head impacts. Our research will also yield technological advances such as innovative image analysis algorithms implemented in shared resources, and easily applicable saliva tests for the improvement of early diagnosis.

In summary, our multidisciplinary, longitudinal approach will substantially improve our understanding of the basic pathomechanisms of repetitive head impacts during a critical phase of adolescent development. This important scientific effort will pave the way for new strategies for diagnosis, prediction, and prevention of brain alterations after repetitive head impacts and thus may have far-reaching impact on the health of millions in Europe and worldwide.



Consortium ReplImpact. Left: Complementary expertise based in six different nations. Right: Whole-brain tractography.

Identification of novel bioactive mediators of tissue scarring, inflammation and extracellular matrix remodeling after spinal cord injury (SCI-NET)



Elizabeth Bradbury

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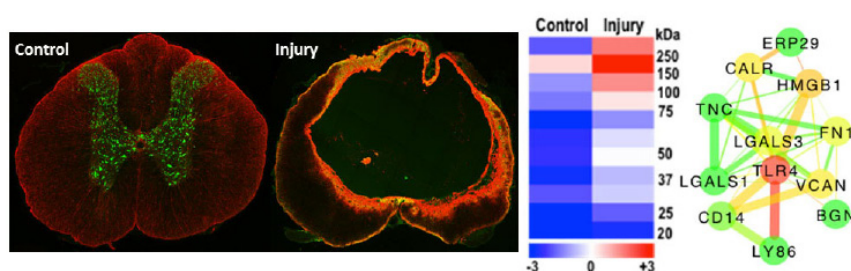
Jan Schwab, Charité Universitätsmedizin, Berlin, Germany

Ralph Schlapbach, Swiss Federal Institute of Technology, Zurich, Switzerland



Spinal cord injury (SCI) can result in severe and lifelong disability, with profound social, health and economic consequences. With an estimated 4 million people worldwide living with SCI, healthcare costs among the highest of any medical condition, and no regenerative or disease-modifying therapies available to SCI patients, there is an urgent need for innovative approaches to understand the molecular and cellular processes that underlie the chronic tissue pathology that is intractable to repair. Chronic dysregulated inflammation, tissue scarring and maladaptive changes in the extracellular matrix are central pathological processes responsible for the failure of tissue repair and functional recovery following traumatic SCI. Yet these processes are still poorly understood. In this translational project we will utilise multidisciplinary and complementary expertise to study how distinct inflammatory mechanisms affect extracellular matrix synthesis and fibrotic tissue remodelling after SCI.

The SCI-NET Consortium will examine the role of inflammatory activation on tissue remodelling and scarring in clinically relevant rat (Bradbury group) and mouse (David group) models of SCI, while the presence of endogenous alarmins will be assessed for the first time in human SCI plasma and cerebrospinal fluid (Schwab group). Advanced proteomics analysis (Schlapbach group) will characterize changes in the extracellular proteome related to alarmin signalling in rodent SCI tissues and human SCI cerebrospinal fluid. The high-throughput discovery approach utilised in this study will provide a valuable dataset resource for the field, new mechanistic insight into inflammatory tissue remodelling, and will identify novel targets and bioactive mediators with diagnostic and therapeutic potential for human SCI. This work should lead to the development of novel therapeutics to target post-injury tissue remodelling and improve pathological and functional outcome for SCI patients.



Spinal Cord Injury-induced Systemic Maladaptive Immune Response and Autoimmunity to Central Nervous System Antigens - European Network Approach (SILENCE)



Jan M. Schwab

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Traumatic spinal cord injury (SCI) represents a lifelong disease, for which there is neither a pharmaceutical, neurobiological nor immunomodulatory therapy available for the restoration of lost neurological function. The variability of the limited spontaneous recovery after SCI is insufficiently explained. A maladaptive systemic immune response (MSIR) occurs early after SCI and is characterized by at least two hallmarks: an emerging immune reaction against central nervous system-neo-antigens and the spinal cord injury-induced immune deficiency syndrome (SCI-IDS). By means of well-characterized SCI specimen banks from international prospective multicenter trials, tissue repositories, and experimental models we target the objectives: i) deciphering time-dependent spreading of humoral autoimmunity profiles, ii) evaluation of functionally relevant auto-antigens in a bed to bench-side approach, iii) linking autoimmunity to clinical outcomes, iv) and validation across CNS-injury pathologies.

An interdisciplinary, translational consortium comprising expertise in immunology, proteomics, neuropathology, neurology, rehabilitative medicine, epidemiology, and paraplegiology will decipher distinct signatures of autoimmunity in experimental as well as clinical studies linking those to long-term neurological and functional recovery. Based on data from pilot studies, we will challenge the hypothesis whether patients with poor response to rehabilitative treatment differ from normal rehabilitation responders in terms of distinct autoimmunity patterns. To characterize SCI patients by the occurrence and severity of the MSIR enables the definition of patient subgroups as a basis for the development of new individualized treatment concepts after SCI.

A New Traumatic Axonal Injury Classification Scheme based on Clinical and Improved MR Imaging Biomarkers (TAI-MRI)



Anne Vik



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David Menon, Department of Medicine, Division of Anaesthesia, University of Cambridge, United Kingdom

Traumatic Axonal Injury (TAI) is now considered to be a frequent and important injury in all severities of traumatic brain injury (TBI). The global aim of TAI-MRI is to develop a novel classification for TAI using data from multimodal MRI and to determine its clinical value for the characterization of injury severity and prediction of outcome.

This project will use MRI datasets obtained early after injury (including clinical and advanced MRI) from two local studies (The Trondheim and Cambridge TBI studies) and the EU-funded multicenter CENTER-TBI study. TAI-MRI will thus be the largest MRI study worldwide (~1300 patients). These datasets comprise a comprehensive collection of acute phase variables reflecting the severity of injury with the possibility to adjust for confounding variables. Outcome measures are obtained at multiple time points during the first year. Several training sets will be used for model selection. Automated methods involving deep learning techniques will be developed and used for lesion mapping in combination with manual assessments. Methods for computer aided diagnosis (CAD) will be refined and validated, and analyses will determine which aspects of CAD based evaluation could replace expert clinical evaluation by radiologists. Finally, this novel MRI classification system will be validated in the large CENTER-TBI dataset.

An improved MRI-based classification system of TAI will provide both a better assessment of injury severity in the acute phase and better outcome prediction. Recent advances in CAD provide a unique opportunity to develop a classification with great clinical applicability. Hence, we will provide a timely new tool for neuroradiologists, clinicians and researchers to facilitate TBI diagnosis, thus improving the treatment and rehabilitation of TBI patients. Finally, TAI-MRI will bring the field forward by increasing our understanding of the pathophysiology of TBI, and how reduced consciousness can be linked to injury type and location and outcome.

Seeing-Moving-Playing: Early Rehabilitation utilizing visual and vestibular technology following traumatic brain injury (SiMPLyReha)



Isabelle Gagnon

Project coordinator: Isabelle Gagnon, School of Physical and Occupational Therapy, Research Institute of the McGill University Health Center, Canada

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Michal Katz-Leurer, Tel Aviv University, Israel



Traumatic brain injuries (TBI) are among the most commonly occurring injuries internationally. Dizziness and visual problems commonly occur following TBI and in many cases symptoms and functional limitations persist and require treatment. The current literature evaluating injury to the visual and vestibular systems is limited. There is emerging evidence suggesting that rehabilitative strategies that include ocular and vestibular rehabilitation may be of benefit following TBI. Thus, the aim of this translational research program is to bring together an international group of clinician scientists with expertise in TBI across the spectrum of severity and age to: 1) Evaluate ocular, vestibulo-ocular and visual perception deficits that occur following TBI; and 2) Evaluate the efficacy of rehabilitative strategies for individuals where impairments in oculomotor, vestibuloocular and visual perception persist for greater than 10 days.

This study will include 465 youth and young adults (aged 6-30 years) who sustain a TBI of any severity (as per the InTBIR recommended definition). An initial evaluative phase utilizing the best available technology to evaluate oculomotor, vestibulo-ocular and dynamic visual attention in conjunction with standard clinical tests will be performed. If symptoms and functional alterations persist 10 days following injury, participants will be randomly allocated to a treatment group (including oculomotor and vestibulo-ocular exercises (as per our pilot studies) or a control group (standard of care). The primary outcomes of interest are return to sport (mild TBI), goal attainment (moderate and severe TBI) and quality of life (PedsQL). It is expected that this program will inform clinical practice and future research leading to a multifaceted intervention program in TBI across the spectrum. Ultimately, this program will lead to optimization of health care delivery and minimization of the public health burden from this commonly occurring injury.

Time dependent Remote Alteration after Injury to the Nervous System (TRAINS)



Jerome Badaut

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Michal Schwartz, Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Pierre Gressens, Paris Diderot University, Robert Debré Hospital, INSERM, France

Krzysztof Selmaj, Department of Neurology, Medical University of Lodz, Poland

Maija Dambrova, Latvian Institute of Organic Syntheses, Riga, Latvia



Injury to the brain and/or the spinal cord results in long-lasting cognitive, sensory and motor deficits in patients. Traditionally it was believed that these impairments are solely caused by the initial local brain/spinal cord damage. However, an increasing body of evidence now indicates that in addition to the acute local changes also distant areas of the central nervous system (remote brain injury) connected to the primarily injured area are also critically involved in this process. The six teams of our TRAINS consortium will join their effort in an integrative approach to unravel the mechanisms resulting in the remote changes after CNS injury, and to explore novel therapeutic strategies aimed to prevent longterm functional deficits following traumatic brain and spinal cord injuries.

TRAINS consortium is composed of internationally recognized experts in the field of brain and spinal cord injuries : Drs Barrière and Badaut from Bordeaux (France), Pr. Selmaj from Lodz (Poland), Drs Dambrova & Zvejniece from Riga (Latvia), Drs Plesnila and Hellal from Munich (Germany), Dr Schwartz from Rehovot (Israel) and Dr Gressens from Paris (France). They will be using newly developed in vivo and ex vivo CNS imaging technologies together with state-of-the-art treatment and drug development approaches to tackle this clinically relevant question.