

ERA-NET Neuron

NEWSLETTER 21



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News From NEURON II

A unique "Widening activity", aimed at integrating research into the funding circle groups from countries less represented in funded proposals, was first implemented in ERA-NET NEURON. This activity, mediated by NEURON, led to the incorporation of research groups from Latvia and Slovakia into two research consortia funded in the frame of the JTC 2014 on Neuroinflammation.

This 'widening activity' is a promising approach to further shape the European Research Area.

From the desk of the coordinator | February 2015



Priv.-Doz. Dr.
Marlies Dörlichter

The ERA-NET NEURON II has one more year to go, and at the start of the year 2015 I would like to summarize our work and achievements of the past months and give an outlook on our plans.

In January 2014, we enjoyed the final symposium summarizing the projects funded under the Transnational joint call for proposals (JTC) launched in 2010 on 'Mental Disorders'. Coordinators of the 11 multi-disciplinary transnational consortia presented the important results of the three years funding period of their projects on mental disorders including depression and bipolar disorders, schizophrenia and psychotic disorders, phobia and anxiety disorders, substance use disorders, autism and mental retardation. <http://www.neuron-eranet.eu/en/525.php>

In May 2014, the ERA-NET NEURON organized an international conference on 'Synaptopathies' in Bonn, Germany in which the amazing complexity of the human brain was exposed: 100 billion neurons, wired with axons and dendrites are connected by more



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

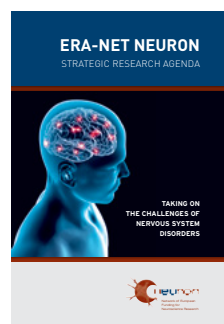
Produced by CSO-MOH, IL



Audience to a presentation during the international conference on 'Synaptopathies' in Bonn, Germany, May 2014

than 100 trillion synapses. Understanding the normal and pathological synapse activities is, therefore an immense challenge. Currently, researchers thrive to estimate how many synaptic types there are in the brain. Another question is the role of synaptic proteins in disease and pathological conditions. For that we need the most advanced knowledge on the synapse. The conference comprised high level contributions from renowned scientists. A summary of the presentations is available via <http://www.neuron-eranet.eu/index.php>.

May 2014 was also the beginning of composing the Strategic Research Agenda (SRA) for NEURON by our Scientific Advisory Board (SAB) and additional experts from various fields of basic neuroscience, neurology, and psychiatry. The full text - delineating the current needs and future development in the NEURON area for the next years – is also available on <http://www.neuron-eranet.eu/index.php>.



Cover page of the Strategic Research Agenda (SRA) for NEURON's scientific activities.

The July 2014 highlight was the 6th EPNA ("Excellent Paper in Neuroscience Award") ceremony, organized by ERA-NET NEURON at the FENS Forum meeting in Milan. Last year's winner, Dr. Kaouane (IMP, Vienna, Austria) described the impressive neuroscientific findings on how Glucocorticoids can induce PTSD-like memory impairments in mice (published in Science, 335, 1510, 2012) (<http://www.neuron-eranet.eu/en/534.php>). Next to the ceremony, a small networking event for early-career scientists covered issues of mobility and grant opportunities.

Also in July 2014, as a part of the 'Neuroscience to Society' efforts, NEURON launched a new video clip on schizophrenia in which psychiatrists described the disease and the approaches for treatments and patients talked about their lives and challenges with the disease. The educational video clips have become quite an asset in our outreach activities.

In September 2014, NEURON organized in Malaga, Spain, a midterm symposium of the funded projects from 11 projects of the JTC launched in 2012 on 'Novel Methods and Approaches towards the Understanding of Brain Diseases'. Project leaders presented fascinating findings, such as how to immobilize tadpoles or make them swim by illuminating proteins in their brains.



The participants of the midterm symposium on "Novel Methods and Approaches towards the Understanding of Brain Diseases", Malaga, Spain, September 2014.

In December 2014, an impact report was published on the outcome of the first NEURON's JTC launched in 2008 on the topic of 'Neurodegeneration' <http://www.neuron-eranet.eu/index.php>. Research projects of the 12 successful consortia were funded for three years. Monitoring the results of the projects and evaluating their outcome provides information on the success or shortcomings of this joint NEURON funding programme. The evaluation indicated that the call 2008 was a very successful funding measure. The collaboration among the researchers was high and fruitful as indicated by the impressive publication record reported. The funding organizations were very glad to see that taxpayers' money was well invested.

In January 2015, our Vienna meeting witnessed the EPNA ceremony and the prize for 2014 was given to Anai Gonzalez Cordero (University College London, UK) who impressed the audience by her research findings "Photoreceptor Precursors Derived from Three-Dimensional Embryonic Stem Cell Cultures Integrate and Mature within Adult Degenerate Retina" published in Nature Biotechnology.



Presentation of the EPNA prize to Dr. Anai Gonzalez Cordero.

As major highlights also in January 2015, two calls for proposals were launched. The first one, in which 16 partners participate, is on 'Neurodevelopmental Disorders' <http://www.neuron-eranet.eu/en/553.php> focusing on questions relating to the neurodevelopmental nature of neurological and psychiatric disorders. In parallel to this NEURON call, six partners teamed up to another joint activity, a call for proposals in the area of 'Ethical, legal, and social aspects (ELSA) of Neuroscience' <http://www.neuron-eranet.eu/en/555.php>.

We are looking forward to hearing about the first results from the work of the 10 successful consortia from the joint call 2014 on 'Neuroinflammation'. They are negotiating their contracts with the funding organizations and will start their research projects in spring and summer 2015.

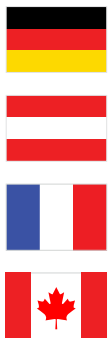
Sincerely yours,
Marlies Dorlöchter

In response to the 7th Joint Translational Call (JTC) on Neuroinflammation, 136 pre-proposals were submitted to the Joint Call Secretariat, this time - MINECO, Spain. The pre-proposals involved 556 researchers requesting a total of €128.5 million. An international team of relevant experts reviewed the pre-proposals and qualified 43 of them (31.6% success) for the next stage of submitting full applications. These were evaluated by a peer review panel who, following an extensive and thorough evaluation process, recommended the funding of the 10 (30.8% success) most pertinent projects. The funding organizations are expected to provide € 10.1 million to support these projects, backing a total of 43 researchers from the respective partner countries.

The abstracts of the 10 funded research projects are presented below:



Ari Waisman



Mechanisms of Lymphocytes Transmigration Across the Blood Brain Barrier (MELTRA-BBB)

Project Coordinator: Ari Waisman, Institute for Molecular Medicine, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Project Partners: Alexander Flügel, Institute for Multiple Sclerosis Research, Georg-August-Universität Göttingen, Göttingen, Germany

Hans Lassmann, Center for Brain Research, University of Vienna, Vienna, Austria

Roland Liblau, Unit 1043, INSERM, Toulouse Cedex 3, France

Alexandre Prat, CRCHUM, Université de Montréal, Montreal, Canada

Many central nervous system (CNS) diseases are affected by strong involvement of the immune system, and are therefore considered inflammatory diseases of the CNS. Multiple sclerosis (MS), Alzheimer's disease (AD) and even stroke are among these diseases. The focus of the MELTRA-BBB consortia is to investigate how cells of the immune system infiltrate the CNS, focusing on a specific structure referred to as the blood-brain barrier (BBB). The BBB is composed of endothelial cells, which together with cells of the CNS form a structure that prohibits the free movement of cells from the blood into the CNS. We will use state-of-the-art microscopy to track how various immune cells enter the CNS in real time. We will use new mouse strains, which will allow us to manipulate important molecules expressed by BBB cells, to understand the role these molecules play in promoting or preventing immune cell CNS infiltration. In addition, we will employ our extensive collection of samples from human CNS inflammatory disease patients to validate our findings in a human setting and to identify new targets for the animal systems. A better understanding of the nature of the mechanisms that lead to the migration of immune cells into the CNS will allow us to more adeptly manipulate this process and provide more effective therapies for inflammatory diseases of the CNS in the future.



Etienne Audinat



Brain Inflammation, Glia and Epilepsy (BrIE)

Project Coordinator: Etienne Audinat, Inserm U1128; Paris Descartes University, Institut National de la Santé et de la Recherche Médicale, Paris, France

Project Partners: Marco de Curtis, Unit of Epilepsy and Experimental Neurophysiology, Fondazione Istituto Neurologico Carlo Besta, Milano, Italy

Frank Kirchhoff, Institute of Physiology, University of Saarland, Homburg, Germany

Christian Steinhäuser, Institute of Cellular Neuroscience, University of Bonn, Bonn, Germany

Kjell Heuser, Department of Neurology, Oslo University Hospital, Oslo, Norway

Epilepsies comprise a family of neurological disorders affecting about 1% of the population worldwide. Six million European citizens currently suffer from active epilepsy and approximately 30% of these present with seizures that are not treatable by currently

available medication. This compromises the quality of life of patients who have to cope with the disease their entire life and generates an enormous economic burden on individuals and public health systems. Several forms of epilepsy are associated with an inflammatory reaction of the cerebral tissue. Recent observations suggest that this phenomenon is involved in the pathogenesis of epilepsy. BrIE will evaluate the role of brain inflammation in the progression and aggravation of epilepsy. The main focus will be on the role of a cellular component of the brain (glial cells) and that of the biological barrier that separates the brain from the blood stream (the blood-brain barrier). Both of these components are functionally altered during epileptic seizures and throughout the progression of the disease. The study will be conducted by a team of clinicians firmly rooted in epilepsy research and a group of neuroscientists involved in a long-term collaboration focused on the study of glia and epilepsy. Understanding how brain inflammation contributes to the process that aggravates epilepsy will aid in the development of future therapeutic strategies.



Marc-
Emmanuel
Dumas



The Role of the Gut Microbiome on Neuroinflammation and Neurodevelopmental Disorders (mNeuroINF)

Project Coordinator: Marc-Emmanuel Dumas, Division of Computational and Systems Medicine, Dept of Surgery and Cancer, Imperial College of Science Technology and Medicine, London, UK

Project Partners: Xavier Altafaj, Institute of Neuropathology, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain

Laetitia Davidovic, Institut de Pharmacologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique, Valbonne, France

Boris Macek, Proteome Center Tuebingen /Interfaculty Institute for Cell Biology Eberhard Karls Universitaet Tuebingen, Tuebingen, Germany

Neurodevelopment results from a precise sequence of events, which, when disrupted by genetic defects or environmental insults, such as infections, provokes irreversible developmental alterations. Inflammation in the brain (neuroinflammation) is one of the hallmarks shared by various neurodevelopmental disorders, such as Down syndrome, Fragile X syndrome and Autism Spectrum Disorders.

Recent studies point to the existence of a gut-brain axis through which the intestinal microbiota is able to modulate inflammation and influence brain function and behaviour. The μ NeuroINF project will explore the hypothesis that gut bacteria can trigger neuroinflammation, which in turn, affects metabolism and behaviour, and ultimately contributes to the progression of neurodevelopmental diseases. Using mouse models of Down syndrome, Fragile X syndrome and Autism Spectrum Disorders, we will study the

gut bacteria, their genes, proteins and metabolites to identify which microbial metabolites shared by these diseases are absorbed in the gut and diffused into the bloodstream to reach the brain.

The possible pro-inflammatory role of these metabolites will be investigated in vitro by screening their pharmacological targets in the host, and in vivo in the animal models of the disease.

Insights obtained from μ NeuroINF will ultimately lead to novel therapeutic strategies for the treatment of neurodevelopmental diseases driven by gut microbiome. The project will not only demonstrate one of the most fundamental mechanisms by which gut bacteria affects behaviour, but it will also identify the microbial metabolites ("biomarkers") that can be used to better monitor brain inflammation or to lead to new drugs ("lead compounds") for the treatment of neuroinflammation.



Michael
Heneka



Transition from acute to chronic neuroinflammation (TraInflam)

Project Coordinator: Michael Heneka, Department of Neurology, University Hospital Bonn, Bonn, Germany

Project Partners: Joseph Bertrand, Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

S  verine Boill  e, Institut du Cerveau et de la Moelle   pini  re (ICM), Paris, France

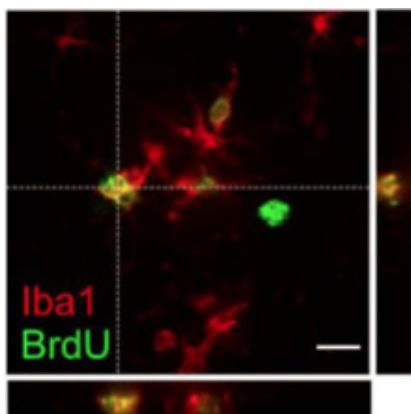
Eran Segal, Dept. of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot, Israel

Marie-  ve Tremblay, Dept. of Molecular Medicine, Universit   Laval, Quebec, Canada.

Neuroinflammation is how the brain's immune system fights disease. As a natural defense mechanism, this reaction may harbor beneficial effects, but under circumstances not yet well understood, it may also have detrimental consequences for the brain and even contribute to the progression of the disease that initially stimulated the immune reaction.

TraInflam will study the mechanisms by which neuroinflammation can transition from a beneficial to a detrimental outcome in preclinical models of Alzheimer's disease (the most prevalent form of dementia), amyotrophic lateral sclerosis (the most common motor neuron disease), and septic encephalopathy (the leading cause of mortality in intensive care units), three diseases sharing a prominent inflammatory component. In addition, it aims to identify genetic factors marking the key steps of this transition, both in preclinical models and in samples of patients

suffering from the respective diseases, in order to identify points of intervention for early diagnosis and the development of better targeted and more efficient therapeutic strategies.



BrdU incorporation indicative of proliferation in an Iba-1 immunopositive microglial cell at the site of focal activation in an 8-month old APP/PS1 transgenic mouse.



Nikolaus
Plesnila



Neuroinflammatory mechanisms of chronic neurodegeneration and cognitive decline following traumatic brain injury (CnsAflame)

Project Coordinator: Nikolaus Plesnila and Ali Ertürk, Institute for Stroke and Dementia Research (ISD), Ludwig-Maximilians University, Munich, Germany

Project Partners: Jerome Badaut, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, University of Bordeaux, Bordeaux, France

Niklas Marklund, Department of Neuroscience & Neurosurgery, Uppsala University Hospital, Uppsala, Sweden

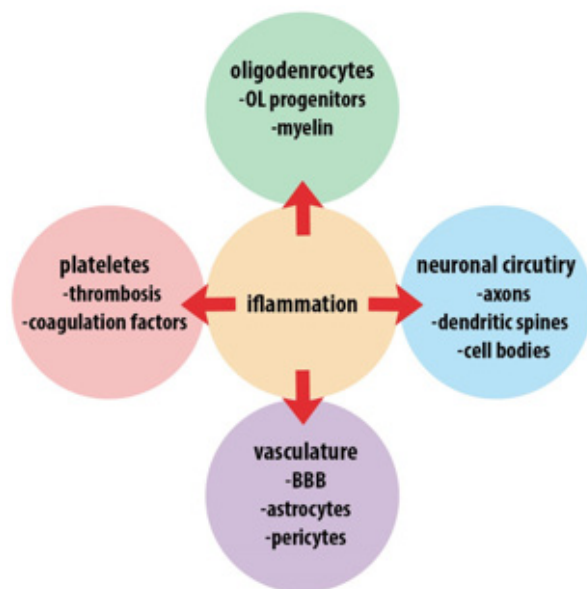
Esther Shohami, Institute for Drug Research, The Hebrew University, Jerusalem, Israel

Anna-Leena Siren, Department of Neurosurgery, University Hospital Würzburg, Würzburg, Germany

Each year approximately 1.5 million people in the EU are affected by traumatic brain injury (TBI), a disorder caused by external force to the head typically during a traffic or sport accident or a fall. On average 70,000 of these patients, mostly children and young adults, die and 100,000 become disabled. While many lives have been saved in recent years due to improved emergency and hospital care, it has become evident that surviving patients often suffer from various chronic brain disorders, such as epilepsy, depression and progressive dementia for the rest of their lives. Treatments that could tackle these chronic TBI-induced complications (chronic TBI) are currently lacking.

The CnsAflame consortium aims to bring together experienced European TBI researchers to investigate whether, following an initial injury, the brain stays inflamed for the long

term; and, if so, whether this chronic inflammation is involved in the above-mentioned chronic complications. The ultimate aim of the project is to determine the underlying causes of chronic TBI to facilitate the development of an effective cure. We will use experimental models of TBI and examine TBI patients with innovative state-of-the-art histological and imaging technologies. We will first monitor the inflammation and degeneration of the brain over months in animal models. We will then investigate how chronic inflammation affects essential brain components in the human brain. Finally, we will block the chronic inflammation of the brain with small molecules and antibody-based drugs in experimental TBI models in order to develop novel treatments for chronic TBI.



Pere
Santamaria



Advancing an antigen-specific nanomedicine for the treatment of central nervous system autoimmunity (MS_NANOMED)

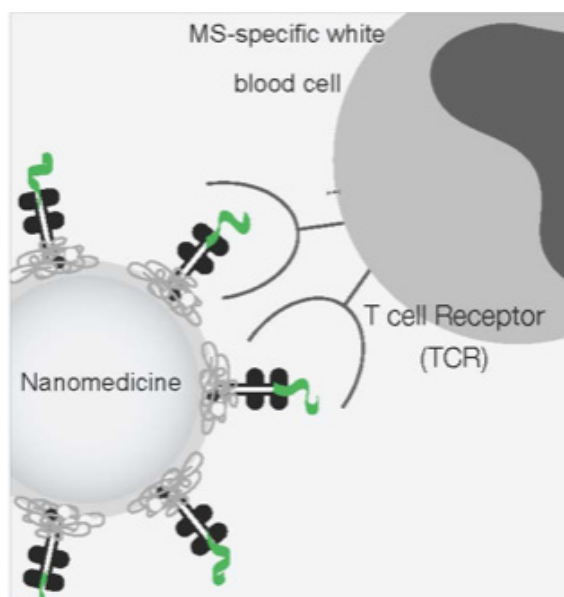
Project Coordinator: Pere Santamaria, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

Project Partners: Manuela Battaglia, San Raffaele Diabetes Research Institute, Ospedale San Raffaele, Milano, Italy
Pau Serra, Consorci Institut D'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

MS_NANOMED is founded on the discovery of a new, potentially groundbreaking, paradigm in the treatment of autoimmune disease. Traditionally, vaccines have been used to expand the number of white blood cells capable of protecting against viruses, bacteria or cancer, or to eradicate white blood cells capable of causing autoimmune diseases, such as multiple

sclerosis (MS) and diabetes. We have developed a nanoparticle-based medicine that can blunt anti-self immune responses by selectively expanding what we call 'autoregulatory' white blood cells (T-lymphocytes). These constitute a new type of 'autoreactive' white blood cell, whose function is to thwart disease-causing autoimmune attacks. Our nanomedicines are capable of expanding this population of white blood cells, enhancing their disease-countering capabilities, while blunting autoimmune responses, without causing a general suppression of the immune system.

This project is an effort to advance a nanomedicine developed for the treatment of central nervous system inflammation in MS patients towards clinical trials. Current MS therapies rely on systemic immunosuppression and are not curative. Our research will focus on relapsing-remitting MS patient samples and will test eight different nanomedicines with high population coverage in a novel assay system using mice transplanted with peripheral blood lymphocytes drawn from patients. We will demonstrate that treatment with disease-specific nanomedicines leads to the expansion of the same type of disease-suppressing white blood cells, which resolve neuroinflammation in mouse models of MS. Our work seeks to identify MS-specific nanomedicines which are likely to work in early-stage clinical trials, hence reducing drug development risk and facilitating clinical translation.



A nanoparticle displaying a "bait" for disease-causing white blood cells



Pierre
Gressens



Role of microglial metabolism in perinatal neuroinflammation (MICRO-MET)

Project Coordinator: Pierre Gressens, Robert Debre Hospital, Institut National de la Santé et de la Recherche Médicale, Paris, France

Project Partners: Peter Carmeliet, Vesalius Research Center (VIB) KU Leuven, Leuven, Belgium

Henrik Hagberg, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

Claudia Verderio, Istituto Clinico Humanitas (IRCCS), Humanitas Mirasole SpA, Milan, Italy

Infants born preterm are at a markedly increased risk of perinatal brain damage. Birth at less than 28 weeks gestation bears an 80-fold increased risk of developing brain injury and cerebral palsy (CP) the most common cause of severe disability in children.

A leading cause of brain damage in preterm infants is exposure to systemic inflammation, a maternal/foetal infection normally contracted during their hospital stay, which induces inflammation in the brain (neuroinflammation).

Neuroinflammation impairs the development of oligodendrocytes, the cells responsible for enabling high-speed transfer of information between neurons. Microglia (MG), the brain's immune cells orchestrate the inflammatory response. These cells can promote both beneficial and detrimental functions in developing brains; however, the cellular mechanisms governing these contrasting functions are poorly understood. Novel insights are needed to prevent the deleterious functions regulated by MG and alter them into neurosupportive functions. The metabolic features of MG have yet to be investigated, although it is increasingly clear that in several cell types metabolic activity has a key impact on cellular function.

The objectives of MICRO-MET are to understand the links between MG metabolism and MG function and to identify the genes responsible for these mechanisms. We will selectively block key metabolic pathways and assess the consequences on MG function and will manipulate key metabolic MG pathways in a mouse model relevant to perinatal brain damage. Our research will help unravel the complex MG functions to combat perinatal brain injury.



Stephen
McMahon



Identification and study of different immune cell populations and their role in chronic pain (IM-PAIN)

Project Coordinator: Stephen McMahon, Kings College London, Wolfson CARD, London, UK

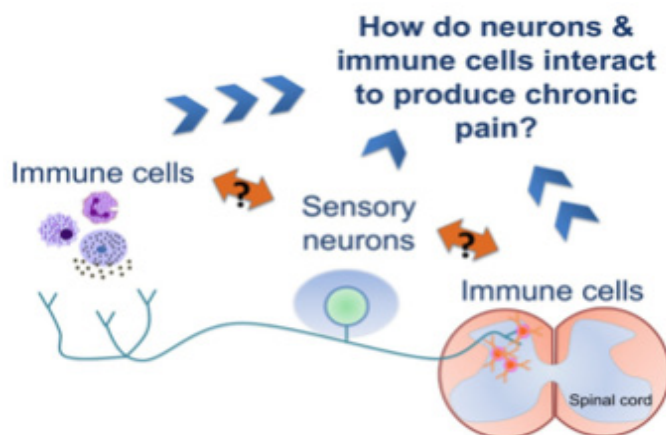
Project Partners: Ralf Baron, Dept. of Neurology, Christian-Albrechts-Universität Kiel (CAU-Kiel), Kiel, Germany

Camilla Svensson, Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden

Approximately one in five individuals is likely to suffer from chronic pain in their lifetime. Many diseases and conditions can cause intractable pain, such as rheumatoid arthritis or nerve damage caused by an injury or viral infection. The pain from these conditions frequently has devastating consequences. While scientists have yet to identify broadly efficacious treatments, they have made some important advances in understanding what goes wrong in the body of a chronic pain sufferer.

We now know that the way our immune system responds to injury or infection can have an important impact on chronic pain. What is less clear is exactly which cell types are involved and what it is about their response that is so damaging to the surrounding neurons. Could the nature of the immune response predispose people towards developing chronic pain?

In this project we will investigate these questions using new experimental methods to isolate immune cells and study their molecular responses. We will also study patients suffering from acute pain in order to identify whether their immune response makes them more or less likely to develop persistent pain. Our research can potentially identify risk factors for chronic pain as well as novel avenues for treatment.





Yanick Crow



Investigation of the neuroinflammatory basis of human type I interferonopathies (Neuro-IFN)

Project Coordinator: Yanick Crow, Genetic Medicine, University of Manchester, Manchester, UK

Project Partners: Jose Luis García-Pérez, Fundacion Publica Andaluza Progreso y Salud, Centro de Genómica e Investigacion Oncologica, Granada, Spain
Thomas Michiels, de Duve Institute VIRO, Université catholique de Louvain, Brussels, Belgium

Brigitte Onteniente, Genopole Entreprises, Phenocell SAS, Evry cedex, France

Marco Prinz, Institute of Neuropathology, University of Freiburg, Freiburg, Germany

Aicardi-Goutières syndrome (AGS) is a childhood-onset brain disease. The associated neurological damage results from an inflammatory process involving the production of the major anti-viral cytokine, type I interferon. In normal circumstances interferon is produced following a viral infection. In AGS, however, a primary genetic defect leads to the accumulation of excess interferon, which causes brain dysfunction and possible permanent neurological damage. Given the severity of the condition there is an urgent need to develop new treatments for AGS. To do so, a better understanding of how the genetic changes responsible for AGS drive interferon production is essential.

Neuro-IFN will use the latest technologies to understand how brain cells are damaged by inflammation in AGS. We will study pathology samples from AGS patients, make use of state-of-the-art methods for creating 'brain cells' in a test-tube (derived from the cells of AGS patients), and analyse a mouse strain which has undergone changes in one of the AGS-related genes.

Although AGS is rare, the study of the genes and the proteins related to the disease has become highly important. The same molecules affecting AGS are also involved in the response to HIV-1 infection. There is also an overlap between AGS and so-called autoimmune diseases, a situation in which the body attacks itself. Our work, therefore, will not only be relevant to children and families directly affected by AGS, it may also have implications for a much wider set of human medical disorders.



Martin
Rottenberg



Master regulators of neuroinflammation in parasitic brain infections (NEUINF)

Project Coordinator: Martin Rottenberg, Karolinska Institutet, Dept Microbiology Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

Project Partners: Antonio Barragan, Stockholm University, Dept Molecular Biosciences, Wenner Gren Institute, Stockholm University, Stockholm, Sweden

Monique Lafon, Institut Pasteur, Virology Dept, Paris, France

Carlos Penha Gonçalves, Instituto Gulbenkian de Ciencia, Oeiras, Portugal

Dirk Schlüter, Institute of Medical Microbiology, Infection Control and Prevention, Otto-von-Guericke-University, Magdeburg, Germany

The primary role of neuroinflammation is to protect the central nervous system (CNS) from invasion by microbes. Such invasion is hindered by the immune system and by physical barriers between the blood and the CNS, which preserve equilibrium (homeostasis) in the brain. Inflammatory molecules, however, may also be detrimental to the integrity of these physical barriers and as a result, to brain function.

We will study the neuroinflammation processes caused by three parasitic infections of the brain: Malaria, Toxoplasmosis, and African trypanosomiasis, using mouse models which mimic many features of the human disease. We will study how these parasites are recognized by the immune system and identify the specific requirements for the immune responses generated by infection to mediate brain damage.

The rabies virus inhibits neuroinflammation to promote its own survival. We have discovered one molecule of rabies virus that has anti-inflammatory properties and will test its efficacy in the neuroinflammation-inducing models of Malaria, Toxoplasmosis and African trypanosomiasis. Specifically, our research will focus on the relevance of type I interferons (I IFN) and TRAF3 proteins in neuroinflammation induced by parasitic infections. It will also investigate the molecular characterization and properties of rabies virus-derived anti-inflammatory molecules, and their ability to regulate the neuroinflammation resulting from various parasitic infections.

