ERA-NET NEURON

# NEWSLETTER 37

Belgium | Canada | Croatia | Estonia | Finland | France | Germany | Greece | Hungary | Israel | Italy | Ireland | Latvia | Norway | Poland | Portugal | Romania | Slovakia | Spain | Switzerland | Taiwan | Turkey | United Kingdom

## ANNOUNCEMENTS FROM NEURON COFUND2

### DON'T MISS

**NEURON 2021 Call:**
**"Excellent Paper in Neuroscience" Award (EPNA) – thematic focus on Biomarkers**

If you a first author of an outstanding article on biomarkers in neuroscience published in 2020 - you may have a chance to win 3000€ and a special lecture in FENS2022

**Submission deadline: 30 Oct 2021, 19:00 CET**

Eligibility and Application

### COMING UP!

**Lay Audience Webinar**
**ERA-Net NEURON Lecture Series: Challenges and Opportunities in Stroke Care and Research**

Prof. Martin Dichgans

**October 29th, 2021, 17:00 CET**

On occasion of "World Stroke Day"

Register here

### STAY TUNED!

**NEURON's JTC2022**

coming up soon...

www.neuron-eranet.eu/

### CHECK OUT NEURON'S

**NEW**
**Website**
**&**
**LinkedIn group**

Funded by the European Commission

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

Produced by CSO-MOH, IL

# From the desk of the coordinator | October 2021


Marlies Dorlöchter

Dear All,

The summer holidays are well behind us and we, at NEURON cofund2, are keeping busy. The evaluation of the full proposals submitted under the co-funded JTC2021 on 'Neurodevelopmental Disorders' by the panel of experts has just taken place and final results should be announced soon.

In May, we held our traditional Foresight Symposium. On this occasion, the topic of the symposium was 'The Brain-Blood Barrier and Cerebrovascular diseases'. The symposium was organized virtually by NEURON partners Etienne Hirsch (INSERM) and Bernard Poulain (CNRS) and included presentations from renounced scientific experts and a discussion panel, led by NEURON's coordinator, Marlies Dorlöchter, in which scientists and representatives from patient organizations discussed the key issues that need to be addressed in research on this topic. More on the Foresight Symposium on page 3.

Lastly, but very importantly, we at NEURON are relentlessly working on improving our communication and dissemination channels, as well as providing opportunities for the formation of a **community** of stakeholders with interest in neuroscience research advancement. Accordingly, we have spent the past few months in planning, designing and launching a NEW and improved website for NEURON, which includes all of NEURON's calls, details about projects funded by NEURON, early career researchers engagement activities, success stories, newsletters, educational video-clips, resources for researchers, networking tools and more.
Furthermore, we have recently launched a brand new **NEURON LinkedIn Group** seeking to provide neuroscientists and clinicians with a trustworthy focused space to network, showcase new developments in brain research and raise awareness on new priorities, tools and methods.
Please feel welcome join our community here.

With this, we wish you good health and welcome you to keep up with our activities by following us on twitter @EraNeuron, as well, in order not to miss further information on our calls and events.

Sincerely yours

## Foresight Symposium on Blood-Brain Barrier and Cerebrovascular diseases

The virtual foresight symposium has been an insightful full-day discussion to identify the important questions that should be addressed in a future call-for-proposals. It gathered 10 experts of the field, including basic scientists, clinicians and people representing lay organizations, 6 members of NEURON's scientific advisory board and over 25 representatives from the NEURON partner organizations.

The topic of "Blood-Brain Barrier and Cerebrovascular diseases" was obtained from the merging of two subjects highlighted in the 2020 update of the NEURON Strategic Research Agenda (SRA). One of the issues that was highlighted in this update was the importance of conducting research not only on neuronal networks, but also on non-neuronal cells and their interactions with neurons. Indeed, impairments in the non-neuronal compartments have been linked with neuronal dysfunction and the development of neurological diseases. Recent advances have allowed for new approaches for studying these mechanisms, urging toward more multidisciplinarity in brain research. In addition, the SRA highlighted how cerebrovascular diseases are among the most life-threatening neurological events and are at high risk to cause severe long-term disabilities.

NEURON funding organizations, thus, agreed on the importance for the neuroscience research community to work towards uncovering the mechanisms of cerebrovascular diseases and to investigate novel therapeutic concepts. This symposium served as an important consultation step for the NEURON funding organizations to receive a scientific update on the topic and to develop the upcoming call text. We are grateful to the experts, whose insights greatly assist us in developing valuable activities for brain research.

Dr Steven Proulx

## General overview on the brain-blood interface


# Dr Steven Proulx

Theodor Kocher Institute, University of Bern, Switzerland


Several barriers ensure the separation of the brain and other compartments, including blood: the blood-brain barrier around arterioles and venules, the pia at the surface of the brain, the arachnoid barrier from the dura, and the brain-cerebrospinal fluid barrier in the choroid plexus. These barriers play an important role in neuronal function by ensuring ion and fluid homeostasis and waste removal. The blood-brain barrier, composed of different compartments (endothelial cells, perivascular space, and glia limitans), is especially important in this regard, due to its selectivity for molecules, proteins and cells entering and leaving the brain parenchyma. These barriers make the central nervous system an immune privileged organ, protecting the central nervous system not only from peripheral antigens and toxins, but also from damage by inflammatory responses. Because of these complex roles and regulation, understanding the mechanisms underlying these barriers and their role in regulating homeostasis and immune responses in the central nervous system is especially important in order to tackle cerebrovascular diseases.

Recent studies illustrated that immune cells can cross the barriers at the post-capillary venules or, presumably, at the choroid plexus, with T cells reaching the perivascular space by diapedesis and neutrophils being recruited by PAMP and DAMP. Yet, only in case of breach of the glia limitans can these cells reach the brain parenchyma, which only occurs in pathological conditions, such as accumulation of macrophages in the perivascular spaces and production of matrix metalloproteinases, which degrade the basement membrane of the parenchyma. Elucidating the mechanisms of drainage of the central nervous system is also fundamental, and tracer studies in mice provided interesting results regarding outflow routes of the cerebrospinal fluid. This allowed for a revision of an historical concept and had led to controversial theories in the last 6 years about the meningeal lymphatics in the dura mater. The glymphatic model, for example, suggests that cerebrospinal fluid flows in the perivascular spaces to reach the subarachnoid space and follow efflux routes along the cranial nerves toward the lymphatic system. These cerebrospinal fluid outflow routes have very strong implications for stroke and other cerebrovascular disorders, and it is thus critical to pursue more research in this direction to get a better understanding on the physiological and pathological mechanisms involved.

Prof Élisabeth Tournier-Lasserve

## General overview on small-vessels diseases

# Prof Élisabeth Tournier-Lasserve

Lariboisière Hospital, University of Paris, France

Cerebral Small-Vessel Diseases (CSVD) are abnormalities in the cerebral white and deep grey matter, supposedly caused by abnormalities of the cerebral blood vessels, and represent a huge health issue, accounting for 25% of stroke and 45% of dementia. Still, we have a very limited knowledge of the pathogenic mechanisms underlying these diseases. Interestingly, progress was made in unravelling the general mechanisms and neuropathological features not by investigating sporadic CSVD, but through intensive research on the less common inherited monogenic CSVD.

Investigations into the mechanisms of COL4A1 angiopathies for example, a very heterogeneous type of monogenic CSVD, have allowed to build valuable knowledge on the role of vascular smooth muscle cells modifications in intracerebral haemorrhages. Another type of disease and a more frequent one, CADASIL, is characterized by stereotyped mutations in the gene encoding for the transmembrane receptor Notch3 and has been the focus of intensive mechanistic work in the past 25 years. This allowed to get a better understanding of the underlying disease mechanisms and how the aggregation of mutated Notch3 protein causes the abnormal recruitment and dysregulation of various extracellular matrix proteins. These advances have been extremely important in the development of preclinical cellular and animal models to explore potential therapeutic strategies, such as immunotherapy and mutation exon skipping.

Still, an important challenge lies in the translation of these preclinical data into humans. In CADASIL, genotype data from large databases highlighted that the characteristic NOTCH3 mutations have a much higher frequency than expected in the general population, raising important questions in terms of risk factors for stroke and of potential protective variants that remain to be identified. In addition, gene identification is a major challenge for other genetic CSVD, and as much as 80% of familial CSVD patients who are referred to molecular screening, show no mutation in known genes. Because of the extreme heterogeneity of these diseases, we need to develop novel computational and statistical tools to identify the new causative genes, as well as gene networks, digenic and oligogenic approaches.

Another main challenge in the future is the development of specific treatment, instead of relying on solely controlling known risk factors, such as hypertension and age. Thus, a strong focus on mechanistic studies is highly required, in order to allow the translation from basic work to preclinical studies and to the necessary understanding of the pathogenic mechanisms.


Prof Martin Dichgans

## Stroke genetics: Discovery, biology, and clinical implications

# Prof Martin Dichgans

Institute for Stroke and Dementia Research, Ludwig-Maximilians-Universität, Munich, Germany

Not only did recent achievements of genetics allow us to differentiate disorders that were previously considered a single one in traditional classification, they also allow us to dive deeper into the investigation of the underlying mechanisms for these diseases. This paves the way for new approaches in terms of targeted treatments. As an example, studies in recent years provided a better understanding of the role of extracellular matrix molecules in small vessels diseases, such as collagens Col4A1/A2 in CARASAL, Cathepsin A in HANAC, Notch3 in CADASIL, or HTRA1 in CARASIL. Identifying the genes implicated in these disorders provided mechanistic insights and allowed to pinpoint an overlap of genes. In this regard, Genome-Wide Association Studies (GWAS) can prove exceedingly useful to explore drug targets, by identifying genes implicated in multiple strokes or small-vessels diseases and highlighting loci that are significantly enriched for drug targets.

The GWAS data also allows exploring other aspects, such as causal relationship with risk factors, drug responses or even side effects, using mendelian randomization and other approaches. This would enable performing in silico trials before actually moving to clinical trials, saving both money and efforts. By using informative genetic datasets, we can obtain a situation very similar to a clinical trial, with a robust methodology to test the association of genetic variants with an outcome such as stroke. This enables gathering converging evidence from human genetics (through mendelian randomization), observational data (from studies on cardiovascular outcomes) and experimental data from previous studies, in a sort of triangulation of evidence that would be a strong starting point for drug development.

Lastly, there is the important topic of genetic risk prediction. Instead of using solely established risk factors for vascular diseases, vascular endpoints, and vascular risk factors reflected for example by the Framingham stroke risk score, there are opportunities in developing Genome-Wide Polygenic Scores. Such scores would allow quantification of the genetic risk factors, as illustrated in a recent study showing a comparable risk for people with either high genetic risk but favourable lifestyle or low genetic risk and intermediate lifestyle. This is an important finding, since it proves that with relevant genetic risk information, it is possible to counteract risk factors by intervening early enough. Still, many challenges remain for the development of polygenic risk scores, their implementation and their clinical use, and it is important to foster efforts in this direction.

Prof Anna Maria Planas

## State of the art of preclinical research on stroke

# Prof Anna Maria Planas

Institute for Biomedical Research, Spanish Research Council, Barcelona, Spain

The blood-brain barrier plays an active role in the injury and the progression of damages following ischemic stroke, with several mechanisms of this role now being identified. For that reason, we need to move away from the neuron-centric approaches and to protect not only neurons but also endothelial cells and the complex junctions of the blood-brain barrier from the changes that take place following a stroke.

Interesting targets have been identified and studied in preclinical research as means to ensure such protection. First of all, several molecules involved in the repair response of tissues proved to be partly responsible for the post-ischemic blood-brain barrier breakdown. Matrix metalloproteinases, cytokines, chemokines, and growth factors have been identified as having a role in increasing the barrier permeability during the acute phase, and are regarded as potential therapeutic targets. Oxidative stress also proved to be highly related to protection of the blood-brain barrier, since superoxide generation leads to the activation of matrix metalloproteinases and consequent disruption of the barrier. Animal studies have notably shown protective effects of uric acid, as a potent scavenger of peroxynitrite, even though clinical studies in this direction have remained unsatisfactory.

Another target of interest for stroke therapy is the complement system, since its activation can trigger mechanisms leading to damages of the blood-brain barrier and to vascular permeability. Inhibition of the lectin pathway or of C3 activation, in particular, have shown promising results in terms of drug development.

The excitotoxicity of glutamate has also gathered some attention, because of the rapid glutamate release caused by ischemic stroke, leading to critical effects on postsynaptic and to oxidative stress. Interesting strategies have been explored targeting postsynaptic proteins to inhibit the NMDA-mediated excitotoxic signalling. Other approaches, which focused on blood intervention, have shown interesting results in preclinical research, such as scavenging glutamate or using blood substitution therapy.

However, despite many promising preclinical advances, translation towards the clinic remains a major challenge. While exploratory research is critical to explore new ideas, strong efforts are needed for reproducibility and validation of these studies before moving on towards clinical trials. It will be decisive for the future of stroke research to come up with strategies to address methodological issues in this direction and to encourage performing preclinical studies in a more collaborative manner.

Prof Joanna Wardlaw

## Imaging for vessels and stroke

# Prof Joanna Wardlaw

University of Edinburgh, United Kingdom

Imaging on cerebral vessels historically focused on visible lesions, such as White Matter Hyperintensities (WMH), lacunae and microbleeds. Yet, since 2013, new technological advances have emerged that are important to consider for future research. Technological developments of MRI systems allow us to observe consequences of the diseases that were previously difficult to discriminate among and enable the development of more sophisticated detection methods and quantitative measures.

Critical progress in the field led to a change in paradigm regarding the evolution of lesions such as WMH: while these lesions were thought to be permanent, it has since been highlighted that they can both increase or decrease in size over time. For WMH, these lesions shrink in an estimated 25% of patients after 1 year, associated with fewer new neurological events and less cognitive decline. Although the mechanisms underlying these changes remain unknown, it is an increasingly important topic to investigate in the future. This is also related to increased perivascular spaces, another key aspect of cerebrovascular diseases that can be measured in MRI and is associated with a large number of risk factors. In this respect, computational measures for perivascular spaces characteristics are becoming increasingly important to capture even the smallest features as accurately and quantifiably as possible.

Investigating vascular dysfunction is also critical for exploring cerebrovascular diseases, with measures such as vasoreactivity and vascular pulsatility. A large number of studies suggested a protein leakage in the blood-brain barrier that increased with age and could predict cognitive decline and worsening of functional outcomes after stroke. Measurement of the blood-brain barrier permeability is thus of particular interest, such as leakage quantification using gadolinium. Yet, there are technical barriers to overcome to allow a more generalized use of this technique.

As previously mentioned, there is a strong need to develop automated computational assessing of these cerebrovascular measures, since there are still many subtleties that remain difficult to detect for computational analysis. Still, we need to remember that manual checking is also necessary to keep noticing new features and to further advance in the field.

It is also essential to consider small vessel diseases, not as just focal lesions, but rather as global diseases that affect other components of the brain. We need to think in a more global way and from a multimodality perspective. Lastly, there is another challenge, which is developing faster, yet accurate, methods that would allow the investigation of larger sample sizes.

Prof Netanel Korin

## New technologies in cerebral vessels

# Prof Netanel Korin

Technion - Israel Institute of Technology, Haifa, Israel

The development of better therapeutic strategies for cerebrovascular diseases requires a proper understanding of the interactions of the constitutive components of the neurovascular unit and, despite exciting advances in animal models, important challenges remain in translating preclinical findings to the clinical setting. Human in vitro models may prove to be instrumental in this regard, thanks to important technological advances in the field of 3D in vitro models.

Moving from 2D to 3D models allows to replicate more physiological features of the human blood-brain barrier in normal or disease conditions, investigating outputs such as transepithelial electrical resistance and permeability. Thanks to new techniques, such as membrane-based barrier models that simulate different compartments, or 3D hydrogel self-assembled models using iPS cells to form physiologically-relevant neurovascular units, we can further investigate the mechanisms involved in the blood-brain barrier.

Additionally, there has been some interesting focus on tissue engineering to replicate large vessels. These vessel models allow for new methods to study disease conditions such as aneurysm.

Technological developments are also instrumental in investigating new therapeutic strategies. In particular, the use of nanoparticles as carriers enabled new innovative approaches for thrombolytic treatment of stroke. Deformable carriers, for example, allow for long-acting treatments. On the other side, endogenous stimuli responsive carriers (based on a local stimulus, such as the mechanic environment) and carriers coupled with affinity molecules allow for targeted drug delivery. This can lead to new paradigms for treatments, for instance, on the critical time of intervention: with long-acting treatments, we could consider using safer yet less efficient drugs in the earlier stages following embolic stroke to reduce the initial brain damage, before a more adapted treatment is carried out.

Lastly, drug-free interventions also benefit from technological innovations, as we can see with the example of aneurysm. Traditional strategies suffer from important disadvantages, ranging from risk of injuring the vessels to the need for antiplatelet medications, raising the question of whether to intervene. Improvements in the fields of expandable devices or injectable biomaterials have led to new therapeutic approaches that may prove critical in the future.

Prof Andreas Luft

## Rehabilitation and compensatory mechanisms for cerebrovascular diseases

# Prof Andreas Luft

Stroke Center, University Hospital of Zurich, Switzerland

The rehabilitation after stroke relies heavily on active training, since it is a key step in inducing the mechanisms of plasticity required to deal with the deficits caused by brain lesions. Plasticity, as broadly defined, is indeed necessary for both true neurological recovery and for compensation (the use of the existent body structures to overcome the deficit). The development of better care strategies for stroke and other brain lesions thus rely on improving the intervention to foster an increased brain plasticity.

Motivation has been shown to be a key factor for successful recovery in a large number of studies, which modulate the patient's adherence and investment in training therapies. Various studies demonstrated, for example, how dopaminergic projections in the motor cortex mediated a long-term potentiation of the motor cortical field potential that is essential for motor task learning, a very important part of stroke rehabilitation. There is, however, a critical challenge to overcome, because of the post-stroke depression syndrome observed in stroke patients, with deficits of the dopaminergic system that impair their motivation. Potential strategies need to be investigated in this regard, such as the use of Levodopa or designing the training therapy to include rewards.

Another topic of interest for future investigations is the consolidation of the training, and the important role of sleep in this regard. There are consistent results showing that with specific intervention applied during sleep (for example musical cuing during both training and sleep), we can actually improve the consolidation of the task and reach better outcomes after stroke.

Lastly, the timing of the intervention may be critical to reach better outcomes. Studies in rat models highlighted a long-term potentiation in the motor cortical field occurring 14 days after stroke, suggesting a time window of enhanced plasticity. Training immediately after this period showed improved learning in rats. While the existence and timing of a similar time window in humans remains to be confirmed, this suggests that active training needs to fall on a ground that is well prepared for its pro-plastic effects to be optimal, allowing for better recovery or compensation.