ERA-NET NEURON

NEWSLETTER 41

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Announcements from NEURON

DON'T MISS
2023 Calls for Proposals on:

"Resilience and Vulnerability in Mental Health"

Pre-proposal submission deadline:
7 March 2023 | 14:00 CET

"Neuroethics"

Submission deadline:
4 May 2023 | 14:00 CEST

DON'T MISS

Opportunity for JTC2022 funded projects!

2023 Spring School on Open Science

April 19th-21st, Berlin, Germany
More on page 3

From the desk of the coordinator | January 2023

Dear All,

We at the ERA-Net NEURON are happy to begin a new year of continued devoted efforts to fund, support and encourage excellent, innovative and collaborative neuroscience research.

In this issue of the ERA-Net NEURON newsletter we focus on the 14 consortia that are funded under our Joint Transnational Call 2022 (JTC2022) on 'Cerebrovascular Diseases including Small Vessel and Brain Barrier Dysfunction'. Read more about the call, its outcomes and the funded projects on page 4.

In the past year we have accentuated the topic of mental health in our various activities, on occasion of this year's JTC2023 topic: 'Resilience and vulnerability in mental health'. Amongst

The NEURON Cofund2 project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964215.

More information can be found on our website
http://www. neuron-eranet.eu/index.php
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the activities that focused on mental health were two webinars, given in the framework of the ERA-Net NEURON lecture series for lay audience. This lecture series demonstrates ERA-Net NEURON's dedication to involve and inform the public in order to raise awareness to various neurological and mental disorders and illuminate the great importance of brain research and the investment in it.

In the first webinar that took place in the year 2022, Prof. Philip McGuire from King's College London discussed the topic of 'Prevention in Mental Health' (watch a recording of the webinar here). In the second webinar, which took place on October 21st, Dr. Livia de Picker from University Psychiatric Hospital Duffel, Belgium, talked about the various implications of the Covid19 pandemic on mental health (a recording of the video can be found here).

This webinar ended with a special presentation of the winning video from our video competition for the young researchers of the JTC2018 on the topic of "Mental Disorders". This competition was launched in order to provide early career researchers with the stage to present their collaborative research project. The winning video was produced by the DiSCoVeR project young researchers' team, working together from around the world on an innovative home-based non-invasive brain stimulation protocol that aims to alleviate depression with the help of a cognitive control videogame. Following the presentation of the video, a representative from the DiSCoVeR young researcher team gave a short presentation about the project.

Finally, but very importantly, this year, 2023, two calls for proposals were launched by ERA-Net NEURON on January 9th – one on the topic of 'Resilience and vulnerability in mental health' (more details on the call here) and a second one on 'Neuroethics' (more details can be found here).

Please keep up with our website, follow us on twitter and join our LinkedIn group in order to join our community and not to miss further information about our various calls, activities and events.

Sincerely yours

OPEN SCIENCE SUPPORT FOR FUNDED PROJECTS OF JTC2022 ON 'CEREBROVASCULAR DISEASES'

The ERA-Net NEURON supports excellent, innovative and collaborative neuroscience research, and, thus, organizes and invites the coordinators of the JTC2022 funded projects on 'Cerebrovascular Diseases' for a workshop on Open Science. **The 2.5 days workshop will take place as a physical event on April 19th-21st, 2023, and is organized in cooperation with the BIH QUEST Center – Charité University Hospital in Berlin, Germany**.

In December 2020, the European Commission published a reproducibility report following the growing recognition in the past decade for the need to address inefficiencies of the research process. The main motivations are as follows:

- To avoid useless and costly repetition – and this is a most important item for funding organisations, as those invest taxpayers' money in research. Moreover, it is regarded unethical to sacrifice small numbers of animals several times instead on one confirming approach.
- To prevent the propagation of mistakes, and to facilitate the translation of results into innovations.

These objectives can be pursued by increasing the openness and the transparency of all steps of the research process, to increase the likelihood that research & development results will be valid, and therefore, reliable and reusable. Any lack of reproducibility has a negative impact on public trust in the conclusions of science. The trustworthiness of research results is crucial for scientists and indispensable for citizens.

- To not foster negative perceptions of science it is of utmost importance to implement open science and the FAIR data principle, a set of old and new practices aimed at enhancing the scientific process.
- To address and promote open science in research it is necessary to broadly inform and support the research community in the implementation of (future) pre- and clinical research that is credible, contributory, communicable, and conforming.

Therefore, as the implementation of Open Science requires compliance of preclinical and clinical research with standards and guidelines on design, conduct, analysis and reporting, the ERA-Net NEURON supports the researchers in their efforts to implement this approach.

NEURON Joint Transnational Call 2022:
"Cerebrovascular Diseases including Small Vessel and Brain Barrier Dysfunction"

Cerebrovascular diseases contribute to 85% of deaths associated with neurological conditions, globally, and stroke represents, by itself, the second leading cause of death. The relative contribution to health burden of these neurological disorders is near twice as important in Europe as compared to other regions in the world, representing 45 billion euros of expenditure including care and a heavy societal burden. Although the pathophysiological mechanisms leading to specific cerebrovascular diseases are not completely understood, changes of cerebral small vessels and the malfunction of brain barriers as well as other changes such as immune responses have been identified as conditions frequently associated to the development of stroke and vascular cognitive dysfunction. Focused translational research in these areas is thus a priority in order to promote healthy living in Europe and worldwide.

Fourteen multinational research consortia were selected for funding under JTC2022 on the topic of 'Cerebrovascular Diseases including Small Vessel and Brain Barrier Dysfunction'. In total, 56 research groups from 14 NEURON partner countries collaborate in these research projects, which cover various aspects of ischemic stroke and cerebral small vessel diseases using numerous methodological approaches. The total funding volume of the call amounts to about 11.7 M€.

As part of ERA-Net NEURON's mission to actively involve patients in the biomedical research process, proposals of the Joint Transnational Call 2022 underwent a patient review as part of the evaluation process. International patient experts reviewed the full proposals from the perspective of patients and carers. Besides providing a full written evaluation to the applicants, the patients actively participated in the discussion at the review panel meeting to advocate for their appraisals and concerns.

We wish all the funded consortia success and significant achievements and hope their outcomes may one day assist in the prevention, diagnosis and/or therapy of cerebrovascular diseases!

Jocelyne Bloch

ANCE4STROKE

Autologous neurovascular cell ecosystems (ANCE) to repair ischemic stroke in mice, primates, and humans

Project Coordinator:
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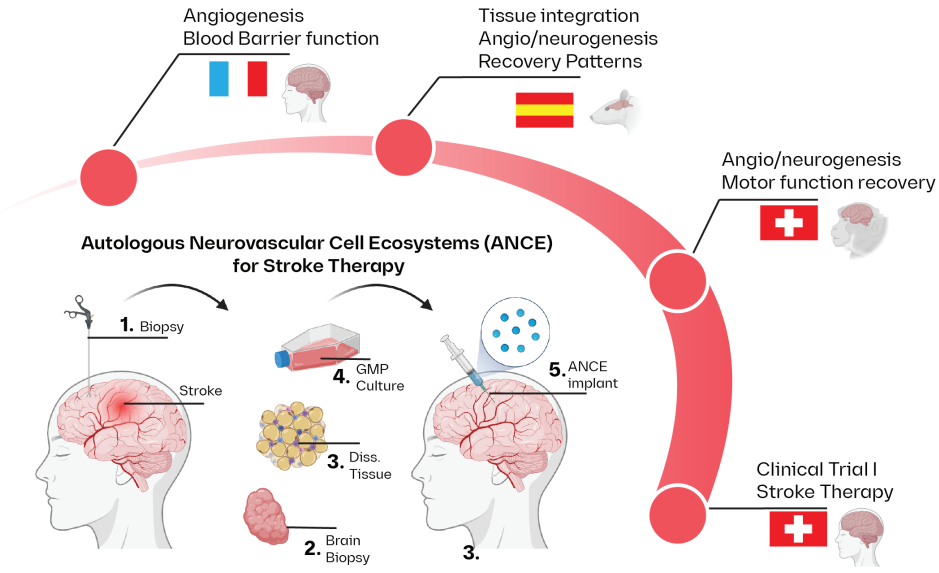
Project Partners:
Gregoire Courtine, Institut Neuro-X, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, Switzerland

Stephane Germain, DR2 INSERM, CIRB, College de France, Paris, France

Adam Ranson, Faculty of Medicine and Health Sciences, Universitat International de Cataluña, Madrid, Spain

Over 100 million people worldwide suffered from stroke. Following a stroke event, the affected brain region is deprived of blood supply, leading to the death of the neural tissue associated with irreversible cognitive and motor impairments. To circumvent the loss of tissue and function, we previously developed a cell therapy termed Autologous Neural Cell Ecosystems (ANCE). The ANCE are grown from a small brain sample of the patient, offering a safe and effective approach for re-implantation into the brain. We previously showed that implanting ANCE into the brain of nonhuman primates alleviates motor deficits due to Parkinson's disease and cortical lesion. ANCE implants are thought to promote the formation of new blood vessels and neural repair tissue. These features are particularly relevant in the context of a stroke. In this project, we will combine in vitro and preclinical models together with cutting-edge techniques to uncover the mechanisms through which ANCE implants mediate tissue repair and improve recovery after a stroke. This knowledge will allow us to refine the design and delivery of ANCE implants. Following the completion of this first phase, we will conduct a clinical trial to test the safety and early feasibility of implanting ANCE therapy in patients with chronic stroke to improve motor recovery. Our goal is to establish a path toward a pivotal clinical trial to demonstrate the efficacy of ANCE implants to improve brain repair and motor recovery following a stroke in humans.



Corinne Benakis

BiotaBB

Modulation of brain barrier function by microbiota-derived factors in cerebral ischemia

Project Coordinator:
Corinne Benakis, Institute for Stroke and Dementia Research (ISD), LMU Hospital, Munich, Germany

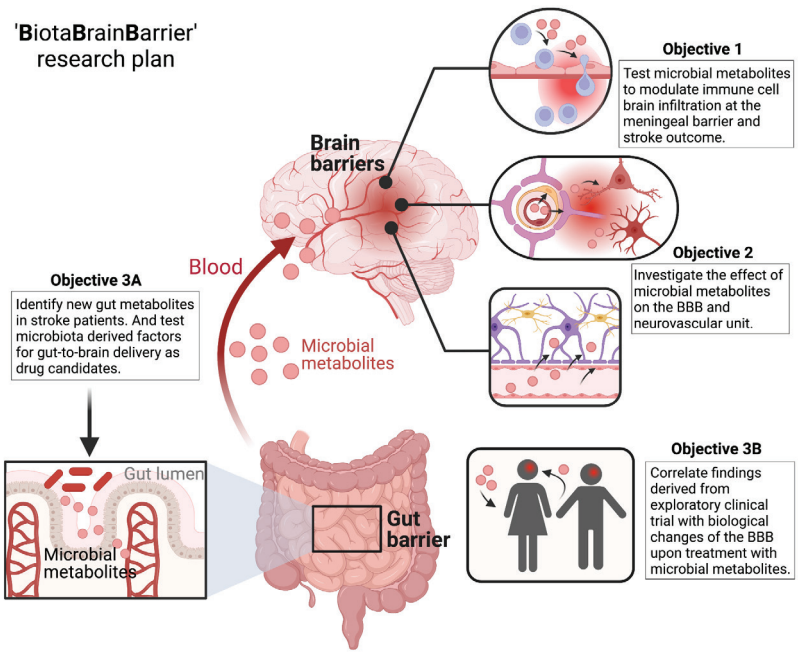
Project Partners:
Nur Mustafaoglu, Faculty of Engineering and Natural Sciences, Sabanci University, Istanbul, Turkey

Lorenz Hirt, Centre Hospitalier Universitaire Vaudois (CHUV), Dep of Clinical Neurosciences and Dep of Fundamental Neurosciences (DNF), Lausanne, Switzerland

Stroke is one of the leading causes of death and the most common cause of long-term disabilities, worldwide, with very few therapeutic options. Hence, there is an enormous need for new therapeutic options for stroke patients.

When a stroke happens, the brain's blood vessels are damaged, causing inflammation and injury to neurons. This can lead to permanent trouble in walking, speaking and to impaired memory. Blood vessels inside the brain are not only important for providing oxygen and nutrients to neurons, but they also prevent harmful substances from entering the brain, acting like a selective barrier that protects neurons. In this project, we want to understand how we can prevent the damage to this blood brain barrier, in order to save neurons.

Recent research has discovered that bacteria in our gut - called the microbiota - can communicate with cells in our body via small molecules that only the microbiota produces. These bacterial molecules can travel everywhere in our body, including the brain, and they can change the function of the cells they interact with. Here, we had the novel idea to test whether these molecules formed by the gut microbiota can protect the brain barriers, preventing inflammation and neuronal damage caused by stroke. By understanding better how microbial molecules work, it should be possible in the future to offer treatment to people at risk of stroke; they could drink a solution of beneficial bacteria, or beneficial molecules produced by bacteria and ultimately save neurons from being damaged after a stroke.



Christoph Harms

CH-Stroke

Clonal Haematopoiesis in Ischemic Stroke

Project Coordinator:

Christoph Harms, Charité-Universitätsmedizin Berlin, Center for Stroke Research Berlin, Dep of Experimental Neurology, Berlin, Germany

Project Partners:

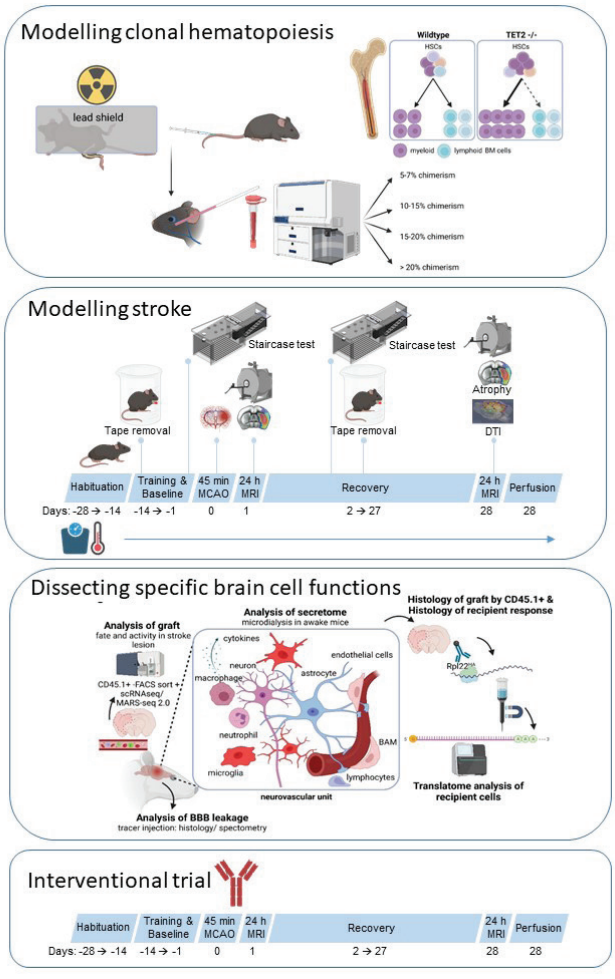
Daniel Lewandowski, CEA/DRF/Institut de Biologie François Jacob, Fontenay-aux-Roses Cedex, France

Steffen Jung, Dept of Immunology and Regenerative Biology, Weizmann Institute of Science, Rehovot, Israel

Anna Malik, Cellular Neurobiology Research Group, Faculty of Biology, University of Warsaw, Warsaw, Poland

Matthias Endres, Charité Universitaetsmedizin Berlin, Klinik für Neurologie mit Abteilung für Experimentelle Neurologie, Germany

Stroke is one of the leading causes of death worldwide and often leads to lifelong disability. In this research consortium, we will explore a possible link between stroke and an age-related imbalance of circulating blood cells that occurs since proliferating hematopoietic stem cells mutate. People displaying this so-called clonal haematopoiesis are at higher risk for tumour development as well as strokes, heart attacks, and death. Specifically, we have recently shown that patients who have suffered a first ischemic stroke and display a hematopoietic Tet2 mutation are at higher risk for a second vascular event or death in the future. It is unknown, however, whether the mutated blood cells invade the brain and proliferate, thus damaging it after a stroke, and if patients with clonal hematopoiesis would benefit from an anti-inflammatory treatment. To tackle these questions, we will develop an experimental model to dose or «titrate» mutant cells and thereby establish a link between clonal haematopoiesis, stroke pathology, and outcome. Through a comprehensive analysis of both mutant cells and affected brain tissue, we will gain deep insights into the underlying mechanisms that can be targeted to interfere with the stroke pathology. Finally, we expect to establish the feasibility of therapeutic interventions. If successful, these findings will help to better prevent strokes and treat patients in the future.



Charlotte Cordonnier

COHDICH

COnsequences of Haemostatic Defects after IntraCerebral Haemorrhage

Project Coordinator:
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Project Partners:
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Kufner Anna, Charité–Universitätsmedizin Berlin, Center for Stroke Research Berlin, Germany

Tsai Hsin-His, Dept. of Neurology, National Taiwan University College of Medicine, Taiwan

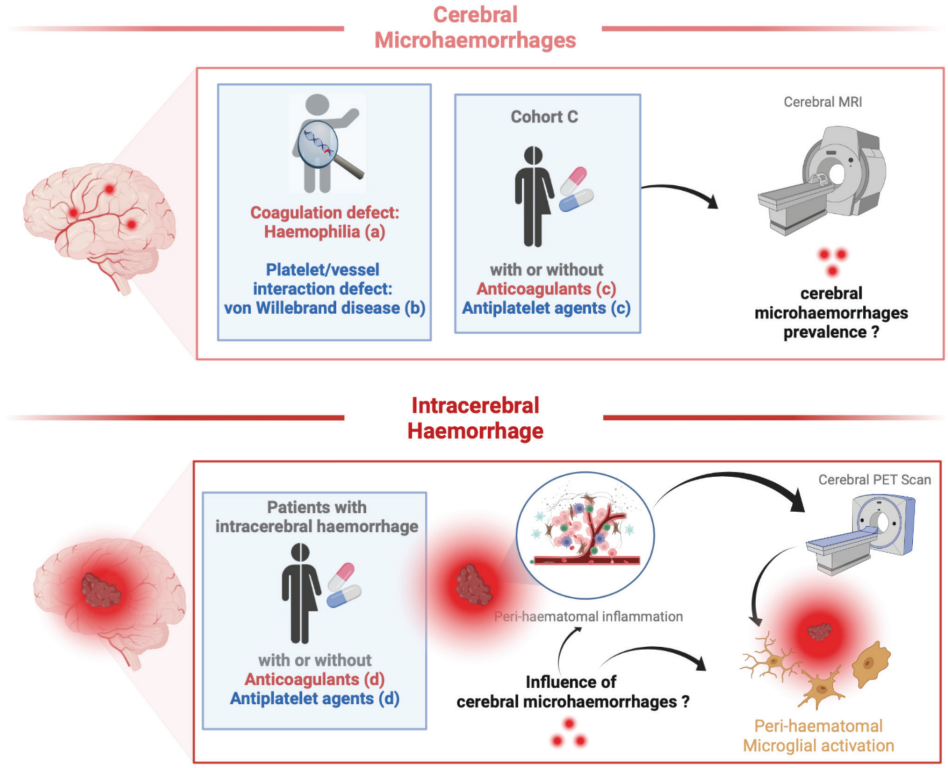
Cerebral microhaemorrhages (CMHs) are tiny bleedings seen on brain MRI. People with these tiny bleedings can develop intracerebral haemorrhages that are the most devastating type of stroke. Most studies have considered that CMHs are due to an ongoing disease in the brain small vessels. However, besides the fragility of the vessels, some disorders in the blood coagulation may influence the transformation of CMHs into big bleeds. Genetic disease such as haemophilia and von Willebrand disease (VWD) are unique situations: patients have no known fragility of their brain small vessels but their blood does not coagulate properly and in them, major big bleeds are frequent and devastating.

Hypothesis: In the setting of CMHs, the existence of a blood disorder modifies the ability of the brain to fight against brain bleeds.

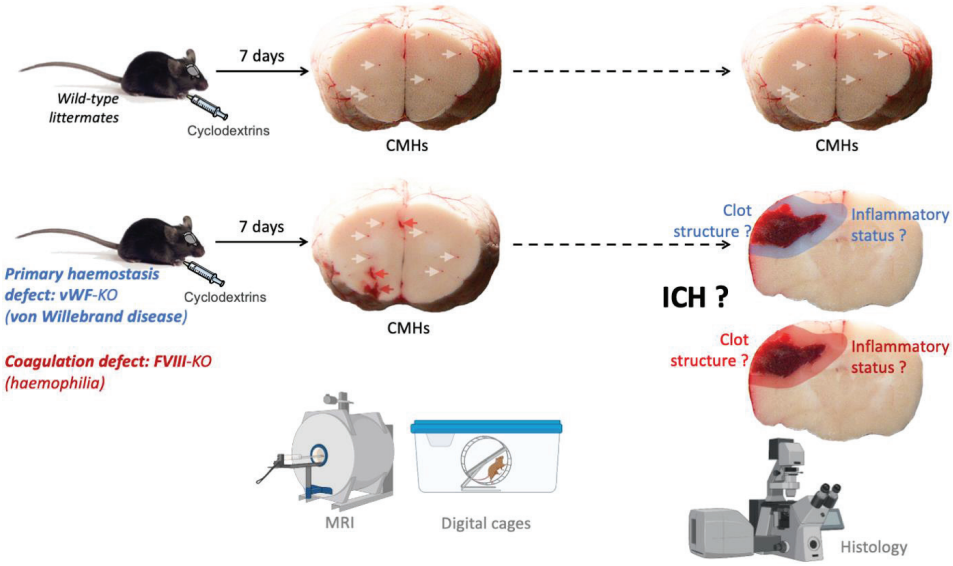
Methods: translational approach to study brain bleeds in animal models and in patients with blood disorders.

In part1, we will determine how often patients with haemophilia and VWD exhibit CMHs on the MRI. We will also look at inflammation in the brain when a large bleed occurs. In part2, we will induce CMHs in mouse models of haemophilia and VWD. We will try to understand what happens when CMHs become larger in terms of blood coagulation and inflammation.

Relevance to public health: Being able to identify who is at risk of large brain bleeds could be helpful, especially in people with genetic disease such as haemophilia. Indeed, in situations at risk, doctors could modify their protective treatment. From a rather caricature scenario of rare genetic diseases, this new knowledge may also benefit to patients with other blood coagulation disorders (for example when people take oral anticoagulants).



Graphical abstract part 1



Graphical abstract part 2

Gerrit M. Grosse

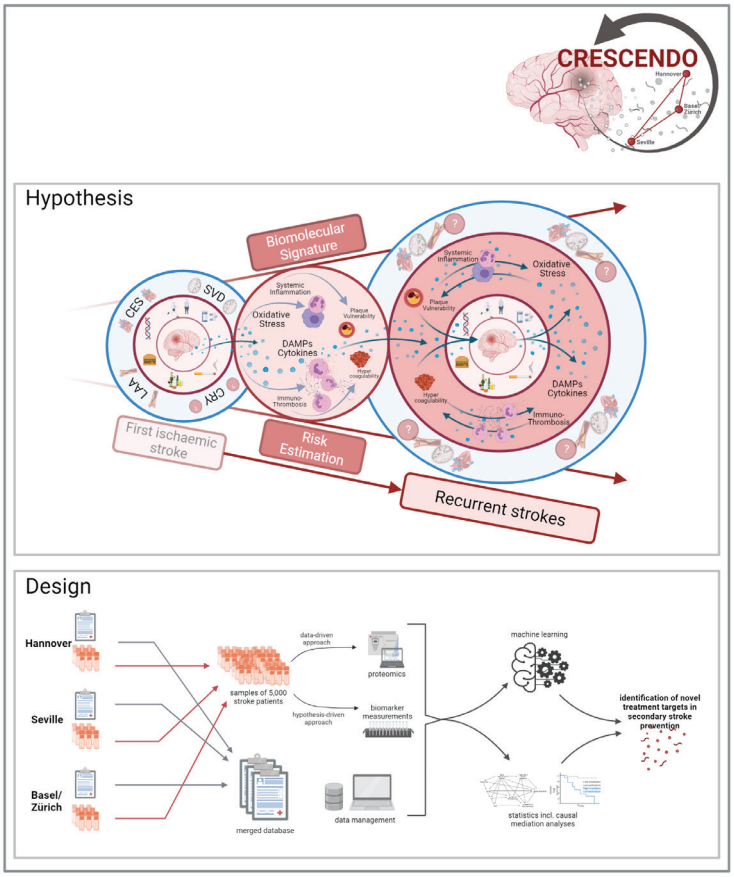
CRESCENDO

CiRculating mEdiators of Stroke reCurrENce anD aetiOlogies

Project Coordinator:
Gerrit M. Grosse, Hannover Medical School, Hannover, Germany

Project Partners:
Mira Katan, University Hospital Basel & University Hospital Zürich, Switzerland
Joan Montaner, Macarena Hospital & Institute of Biomedicine, Seville, Spain

Patients who have suffered an ischaemic stroke are at high risk for a recurrent cerebrovascular event, with a subsequent increase in morbidity and mortality. Therefore, innovative concepts and strategies in secondary stroke prevention are of major relevance. Currently, measures of stroke prevention are essentially based on the presumed aetiology which is commonly defined according to categories. This concept, however, does not sufficiently reflect the complex pathophysiology. Rather, it appears probable that circulating mediators related to the extent of acute and chronic brain damage in concert with aetiological mechanisms and underlying comorbidities influence the risk for recurrent cerebrovascular events. Knowledge of these circulating mediators may open novel avenues in therapeutic approaches for secondary stroke prevention. With the CiRculating mEdiators of Stroke reCurrENce anD aetiOlogies (CRESCENDO) consortium, we therefore aim to initiate a paradigm shift towards an integrated pathophysiology-based evaluation of cerebrovascular risk. CRESCENDO is a transnational consortium using existing large-scale biosample collections of stroke patients with deep phenotyping in order to identify and validate molecular targets for prevention of stroke recurrence. The three consortium partner sites in Hannover (Germany), Seville (Spain) and Basel/Zürich (Switzerland) will provide their specific methodological expertise and contribute samples of in total over 5,000 patients with acute ischaemic stroke. On the one hand we will investigate well-characterized biomarkers of inflammation, immunothrombosis, and stress in a hypothesis-driven approach and, on the other hand, additionally search for predictive targets of interest via a data-driven omics approach. CRESCENDO will consequently advance our understanding of stroke pathophysiology.



Lydia Sorokin

DeCoDis

Deciphering Cellular and Acellular Barrier Dysfunction in Cerebrovascular Diseases

Project Coordinator:
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Project Partners:
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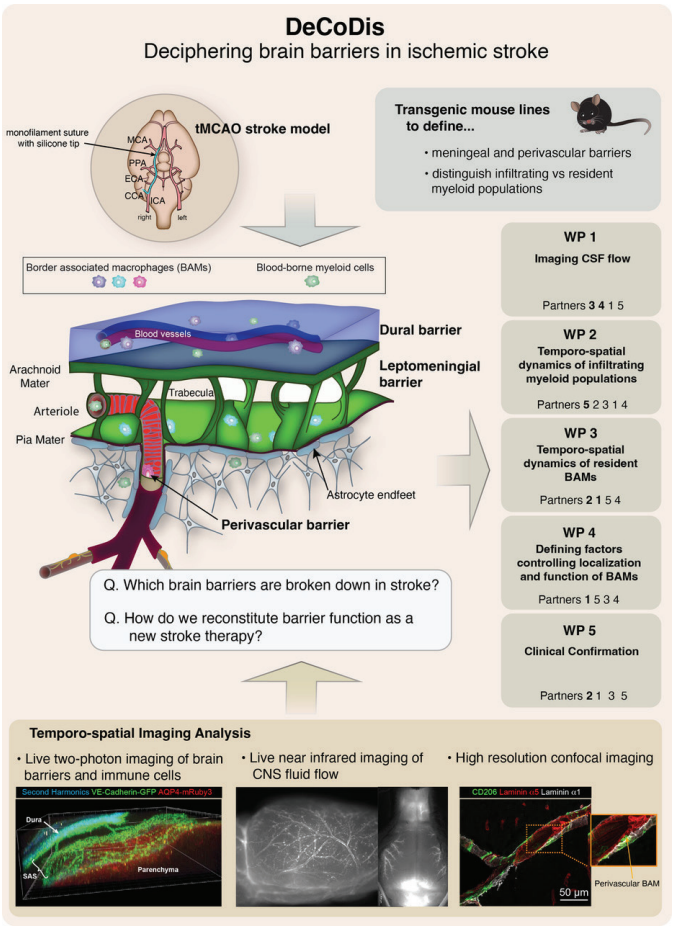
Steven T. Proulx, University of Bern, Theodor Kocher Institute, Bern, Switzerland
Rejane Rua, Centre d'Immunologie de Marseille Luminy Affiliation, CNRS UMR7280, INSERM U1104, Marseille, France

Several barriers at the brain surface and around blood vessels protect the brain from harmful factors from the outside. Breakdown of brain barriers after stroke allows uncontrolled entry of damaging white blood cells and blood components and contributes to brain swelling and damage. Stroke therapies to date have aimed at blocking entry of circulating white blood cells into the brain, with little success. Our approach is different - we will elucidate which of the brain barriers are compromised by ischemic stroke and determine how we can restore the integrity of these barriers after stroke.



We have special genetically modified mice that allow us to see and distinguish the brain barriers, the immune cells that reside at these barriers, and immune cells infiltrating from the blood in the brain of live anesthetized animals. Changes occurring at these barriers as they occur during stroke will be visualized by specialized microscopic techniques, called "intravital microscopy". Only in this way can factors changing brain barrier properties be identified and validated in human stroke samples.

We expect to identify which of the brain barriers change in function after ischemic stroke. We will further define how these barrier(s) contribute to the entry of potentially damaging immune cells or blood factors after stroke and how their dysfunction contributes to fluid build-up (brain edema). Understanding these mechanisms will permit design of novel therapeutic strategies to stabilize the function of the right barrier after ischemic stroke and, thus, reduce brain damage after stroke and improve the outcome for patients.

Abraham Martin

IMatrix

Theragnostic targeting of extracellular matrix metalloproteinases and blood brain barrier disruption in subacute ischemic stroke

Project Coordinator:
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Project Partners:
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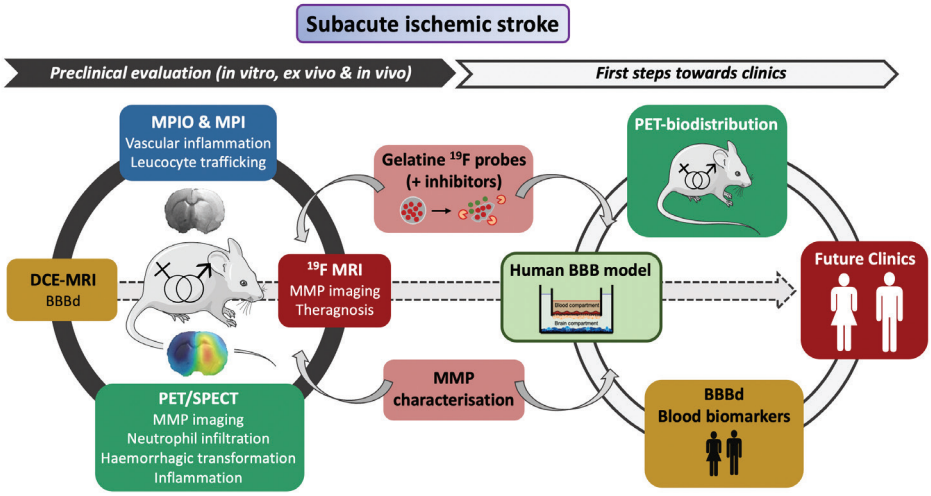
Maxime Gauberti, Normandie University, UNICAEN, INSERM UMR-S U1237, Caen, France
Marie-Pierre Dehouck, Université d'Artois, Faculté des Sciences Jean Perrin, Artois, France
Domokos Máthé, Hungarian Centre of Excellence for Molecular Medicine, Budapest, Hungary

Stroke kills more than 500,000 people each year in the European Union alone and is also the leading cause of permanent disability. Due to the demographic age shift, these numbers will increase continuously. The clinical management of the acute stroke is nowadays well stablished with both thrombolysis and mechanical thrombectomy. However, the subacute ischemic stroke care has received little attention due to lack of efficient therapies. Thus, there is an urgent medical need for the establishment of novel diagnostic and treatment strategies focused in the subacute ischemic stroke. Based on the observation that matrix metalloproteinases (MMPs) exert control on the secondary ischemic damage after preclinical stroke, we propose these MMPs as promising targets for subacute stroke therapy. In the framework of IMatrix, we want to explore and validate the diagnostic and therapeutic potential of MMPs using smart 19F nanoprobes as theragnostic systems together with the imaging evaluation of the secondary ischemic damage. To this end, magnetic resonance and nuclear imaging techniques with specific radiotracers and microparticles conjugated with antibodies will be used to gain knowledge on the secondary neurovascular damage after preclinical stroke. We will also investigate the clinical subacute ischemic damage using brain imaging and blood biomarkers from patients suffering stroke. Hence, our project proposes a translational research approach with a strong economic potential and interest for clinical neurology.



Anne Joutel

MatriSVDs

Multidimensional interrogation of microvascular matrisome abnormalities in cerebral small vessel diseases

Project Coordinator:
Anne Joutel, Institute of Psychiatry and Neurosciences of Paris, Inserm UMR1266, Université Paris Cité, Paris, France.

Project Partners:
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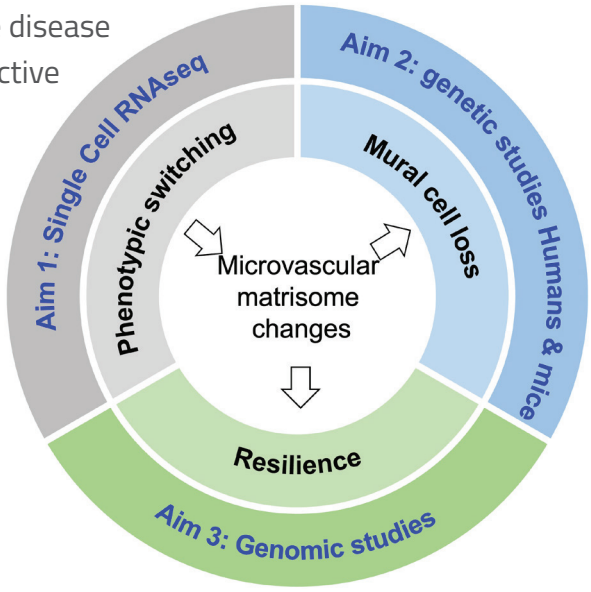
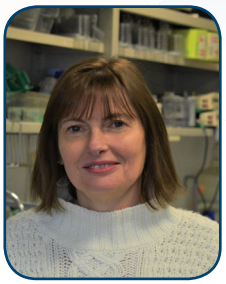
Annika Keller, University of Zürich, Dept. of Neurosurgery, Switzerland

Aniket Mishra, Bordeaux Population Health Research Centre – Inserm UMR1219, Bordeaux, France

One quarter of ischemic stroke, the vast majority of spontaneous intracerebral hemorrhage and about one third of dementia cases world-wide are caused by diseases affecting these small brain vessels, also called cerebral small vessel diseases (cSVDs). cSVD is an heterogeneous group of diseases and currently there is no understanding of what goes wrong and therefore these diseases lack an effective treatment. Cells that make up the vessel wall are embedded in a complex mesh of proteins called the matrisome. Altered levels of matrisome proteins can lead to small vessel lesions, the underpinning of cSVDs. Our hypothesis is that matrisome changes in small brain vessels take center stage in cSVDs. This project aims at addressing the 3 following questions: 1) What drive these matrisome changes in cSVDs? 2) How do changes in the levels/activity of HTRA1, a matrisome protein and key player in cSVDs, contribute to disease manifestations and death of contractile vascular cells and 3) conversely, can some matrisome modifications have a protective role, preventing the occurrence of disease manifestations? Altogether, the information obtained from our study can be used to get an inspiration for future studies to develop therapeutics - either directly to interfere or correct the disease pathway or to stimulate existing protective pathways.





Eva Faurobert

MECACCM

Preclinical study targeting cationic channels for Cerebral Cavernous Malformations therapy and early diagnosis

Project Coordinator:
Eva Faurobert, Institute of Advanced Biosciences INSERM U1209 CNRS 5309 University Grenoble Alpes, Grenoble, France

Project Partners:
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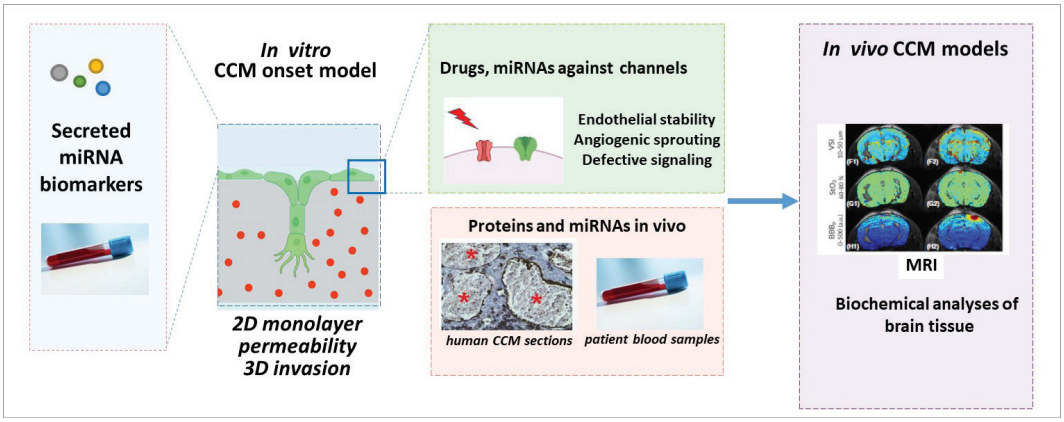
Souvik Kar, International Neuroscience Institute, Hannover, Germany
Luigi Battaglia, University of Turin, Dept of Pharmaceutical Science and Technology, Torino, Italy
Emmanuel Barbier, Grenoble Institute of Neurosciences INSERM U1216 University Grenoble Alpes, Grenoble, France
Adriana Adameova, Centre of Experimental Medicine SAS and Faculty of Pharmacy, University in Bratislava, Slovakia

Cerebral Cavernous Malformations (CCM) are vascular malformations occurring in the venous capillaries of the brain. One person out of 200 can develop such malformations consisting of stacks of dilated and hemorrhagic blood vessels resembling a mulberry. These lesions can occur either sporadically and their cause is usually not known, or in family of patients who carry mutations on either one of 3 identified genes. Numerous lesions form in the brain of these patients throughout their life. The consequences are devastating as they provoke epilepsy, stroke and many neurological disorders such as paralysis or cognitive disorders. There is no therapeutic treatment yet for the many patients who cannot be operated. The goal of our project is to test new therapeutic drugs against certain cationic channels that, as we recently discovered, are not functioning correctly in the diseased state. Our hypothesis is that their dysfunction is a triggering event that initiates the formation of the CCM by causing vessels leakiness and excessive growth. Using different in vitro and in vivo models of the disease, we will test whether blocking these channels stops the formation of CCM. This preclinical study will help to find a preventive therapeutic treatment for the familial patients and also to identify specific biomarkers that could be used to predict the occurrence of a new lesion.



Vivien Denis

MeniSPYs

The meninges as a new player in post-stroke

Project Coordinator:

Vivien Denis, Caen-Normandy University, Dept of Innovation in Diagnosis and Therapeutics, Caen Hospital, Blood and Brain Caen Normandie Institute, Caen, France

Project Partners:

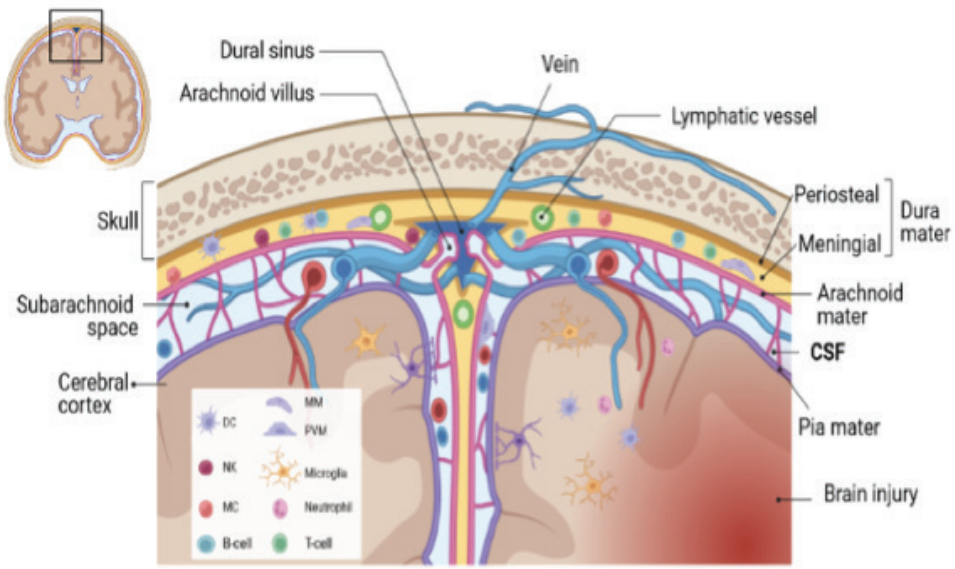
Karoline Degenhardt, Experimental Research in Stroke and Inflammation, Neurology Dept, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Arthur Liesz, Institute for Stroke and Dementia Research, LMU University Hospital Munich, Munich, Germany

Adam Denes, Institute of Experimental Medicine, Budapest, Hungary

The meninges have been described as an important cerebral invasion route in primary autoimmune diseases and also important in regulating cerebral blood flow, antigen drainage to the systemic immune compartment and recirculation of leukocytes from brain to blood. However, little is known about the role of meninges in ischemic stroke. Based on this knowledge, we postulate that a better understanding of the routes and mechanisms by which inflammatory cells invade the brain following stroke will open new avenues for stroke care. To address this issue, the present proposal utilizes a collaborative effort combining the latest tools in imaging, experimental models, cell- and tissue manipulation approaches and clinical research. We will focus on meningeal gateways to understand the key mechanisms controlling meningeal inflammation and inflammatory cell recruitment with particular emphasis on the role of meningeal inflammatory actions on unfavourable outcomes after stroke that could be therapeutically targeted for the benefit of patients.

The meninges as an immune hub at the brain borders



Jasmin Hefendehl

MICRO-BLEEDs

MICROglia as modulators of brain BLEEDs

Project Coordinator:

Jasmin Hefendehl, Goethe University, Institute for Cell Biology and Neuroscience and Buchmann Institute for Life Sciences, Frankfurt am Main, Germany

Project Partners:

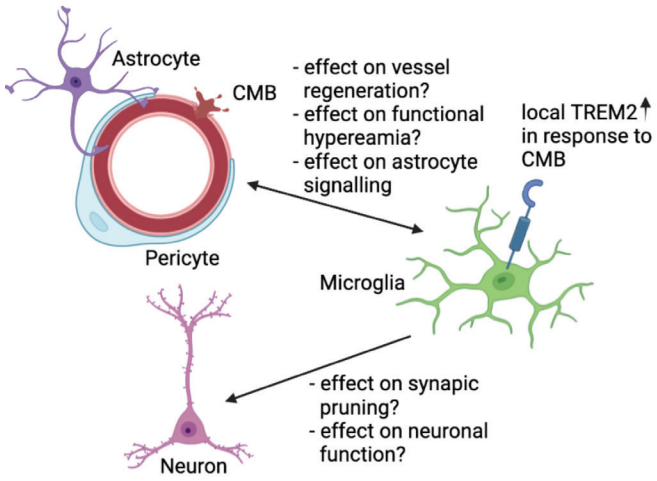
Ravi Rungta, Université de Montréal, Faculty of Dental Medicine and CNS Research Group, Montréal, Canada

Gabor Petzold, University Hospital Bonn, German Center for Neurodegenerative Diseases, Bonn, Germany

Michela Matteoli, Humanitas University, Humanitas Clinical and Research Center, Milan, Italy

Pablo Blinder, Neurobiology, Biochemistry and Biophysics School and Sagol School for Neuroscience, Tel Aviv University, Tel Aviv, Israel

Cerebral microbleeds (CMBs) are small chronic brain bleedings which are caused by pathological fragility of the small blood vessels of the brain. They can be observed in individuals with stroke and cognitive impairment and in apparently healthy elderly individuals. Because of their small size, CMBs usually do not cause any acute symptoms, but insidiously, they trigger delayed and persistent nerve cell death and long-term problems such as memory decline and dementia. The mechanisms at the basis of this brain tissue damage are currently unclear. Hence, there is an unmet need to identify the molecular pathways contributing to brain damage after CMBs, and to test the potential of modulating these pathways as a new therapeutic approach. Importantly, CMBs lead to a local activation of the brain's resident immune cells, called microglia. In general, microglia can have a protective or deleterious role for the brain, with the microglial gene TREM2 representing a main switch controlling these opposing functions. However, whether and how microglia and TREM2 are involved in the damage imposed by CMBs is still unknown. Our MICRO-BLEEDs consortium will gather an interdisciplinary group of clinicians and researchers internationally recognized in the field of cerebral small-vessel diseases as well as the normal function of brain cells including microglia and TREM2. The team will exploit advanced technologies to define the role of microglia and TREM2 in brain tissue damage occurring in mouse models of CMBs. We will specifically investigate how TREM2 activation controls microglial function, and how this may lead to changes in the function of blood vessels, synapses and different brain cell types. Importantly, we will also test whether antibodies that modulate the activity of TREM2 can be harnessed to ameliorate the damage caused by CMBs, with the final goal to identify novel targets for CMB prevention and treatment that can be moved forward into clinical trials.



Highlighted Methods

WP I

Role of TREM2 in the microglial response to CMBs

- Lead PIs: P1 & P4 in collaboration with all partners
- Use of TREM2-KO mouse to investigate microglial-, monocytes and perivascular fibroblasts changes in CMBs
- Use of TREM2-KO to investigate long-term vessel fate and BBB integrity

Highlighted Methods:
- In vivo 2-Photon imaging
- Imaging mass cytometry
- RNAscope in situ hybridization
- Immunohistochemistry

WP II

Effects of TREM2 on BBB patency, vascular function and the multicellular functional response to CMBs

- Lead PIs: P3 & P2 in collaboration with all partners
- Use of TREM2-KO mouse to investigate impact on astroglial and neuronal calcium activity and BBB integrity.
- Use of TREM2-KO to analyse pericytes and smooth muscle cells response in CMBs

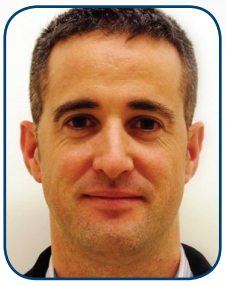
Highlighted Methods:
- In vivo 2-Photon imaging
- Wide field and 2-Photon calcium imaging
- Neurovascular in vitro model

WP III

Modulation of synaptic pruning, refinement and network activity after CMBs by TREM2

- Lead PIs: P4 & P3 in collaboration with all partners
- Use of TREM2-KO to analyse neuronal and synaptic damage
- Analysis of synaptic pruning by microglia in relation to CMBs
- Correlation to data from imaging mass cytometry

Highlighted Methods:
- In vivo 2-Photon imaging
- imaging mass cytometry
- In vivo 2-photon STED microscopy
- Immunohistochemistry



Pablo Herrero Gallego

STROKE-POC

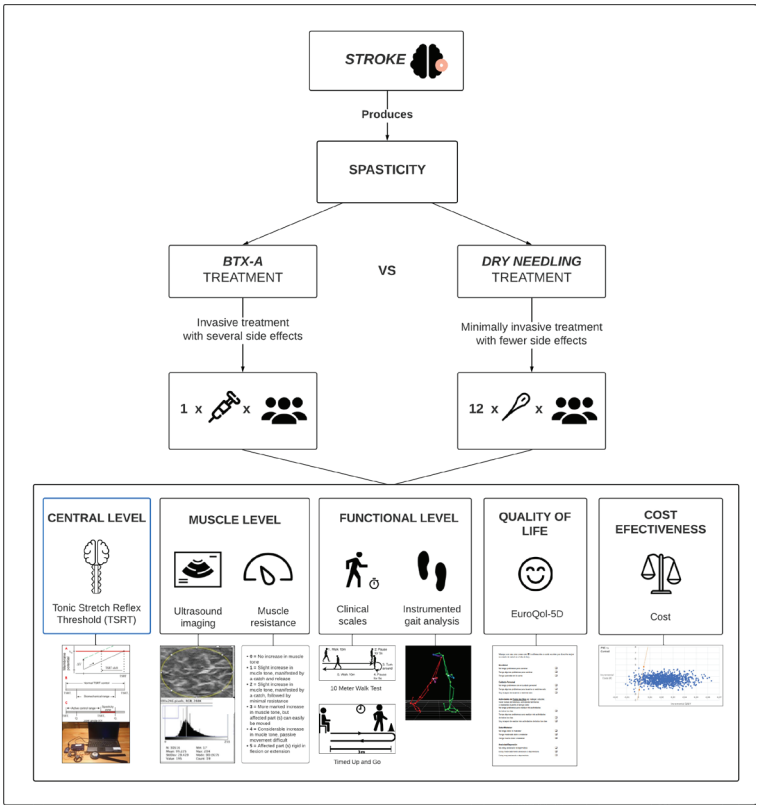
Comparative study of the mechanism of action of Dry Needling and Botulinum Toxin type A as a treatment for lower limb post-stroke spasticity: a proof of concept controlled trial

Project Coordinator:
Pablo Herrero Gallego, Faculty of Health Sciences, University of Zaragoza, Spain

Project Partners:
Mindy Levin, School of Physical and Occupational Therapy, McGill University and Director of the Sensorimotor Control and Virtual Reality Laboratory at the Jewish Rehabilitation Hospital Site of the Centre for Interdisciplinary Research in Rehabilitation, Montreal, Canada

Wim Saeys, University of Antwerp, Belgium

Stroke is a leading cause of disease, disability, and economic loss. As populations grow and people live longer, cases of stroke are likely to increase. Stroke affects the central nervous system and interferes with mobility and walking. One consequence of stroke is muscle spasticity (stiffness) that affects half of stroke victims within six months, causing discomfort and hindering recovery. One of the most effective treatments for spasticity is the injection of Botulinum Toxin type A (BTX-A), which is considered 'invasive' and has been linked to several side effects. 'Dry needling' (DN) is a relatively new treatment for spasticity with comparable effectiveness as BTX-A. DN is minimally invasive and has fewer side effects. However, it is not usually applied in current clinical practice. While studies have reported the effects of these two techniques on muscle and mobility, the effects on the whole system have not been systematically studied.



We propose: DN and BTX-A will have comparative effects on decreasing spasticity, but DN will have fewer side effects and be more acceptable to patients and their families. We will study this by examining the effects of each treatment on ankle muscles in two groups of subjects. One group will have a series of 12 DN sessions and the other will have one BTX-A injection. We will evaluate effects on spasticity at different levels – muscle structure, reflex activity, motor ability, quality of life, acceptability, and cost-effectiveness. We will use novel methods to help clinicians, patients, and families make more informed spasticity treatment choices.

Carmen Ruiz de Almodóvar

TACKLE-CSVD

Targeting autophagic networks and the lysosome in cerebral small vessel disease

Project Coordinator:
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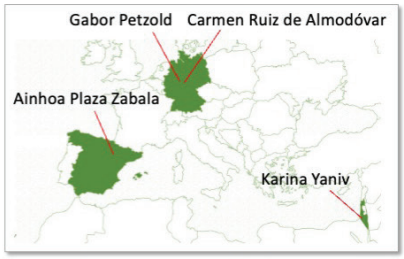
Project Partners:
Karina Yaniv, Department of Immunology and Regenerative Biology, Weizmann Institute of Science, Rehovot, Israel

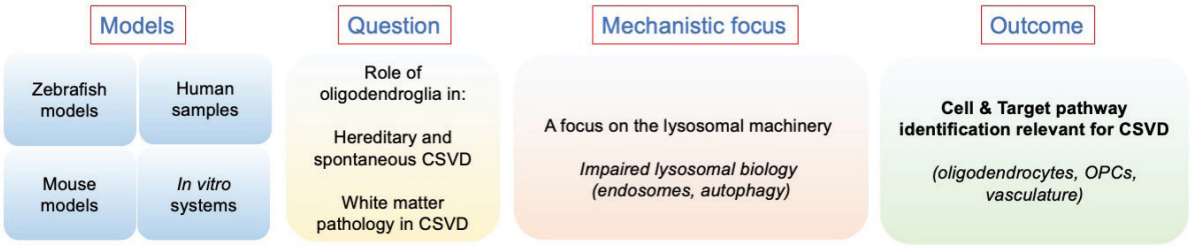
Ainhoa Plaza Zabala, Dept Pharmacology, University of the Basque Country - UPV/EHU, Spain

Gabor Petzold, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Cerebral small vessel disease (CSVD) is caused by dysfunction of small blood vessels particularly in a part of the brain called the white substance, in which nerve cells are enwrapped by an insulating sheath called myelin that is produced by cells called oligodendrocytes. CSVD causes a breakdown of myelin, but the reasons for this are unclear. We hypothesize that CSVD does not only arise from defects in blood vessels of the brain, but that oligodendrocyte dysfunction contributes to initiation and progression of the disease. This project will answer the question of what is the role of oligodendrocytes in CSVD. A particular focus will be on lysosomes, which are cellular organelles that allow cells to degrade and recycle their components, but which we hypothesize to be perturbed in oligodendrocytes, leading to their dysfunction.

In this project, we will characterize at the cellular and molecular level how oligodendrocyte dysfunction contributes to CSVD pathology. We expect to gain a deeper understanding of the molecular mechanisms contributing to the dysfunction of lysosomes in oligodendrocytes and the development of the disease. Through this, we aim to identify molecules that can be tested as new targets for potential therapies.





Nikolaus Plesnila

VasOx

Role of oxidative stress for neuro-vascular function

Project Coordinator:
Nikolaus Plesnila, University of Munich Medical Center, Institute for Stroke and Dementia Research (ISD), Munich, Germany

Project Partners:
Emrah Eroglu, Faculty of Engineering and Nat. Sciences, Sabancı University, İstanbul, Turkey

Pierre Gressens, U1141 Inserm-Université de Paris, Hôpital Robert Debré, Paris, France

Blockage of a cerebral artery causes injury to the brain, a disorder termed "ischemic stroke", which affects many millions of people every year worldwide. Medical doctors reopen the blocked artery to minimize brain damage from ischemic stroke. However, the sudden reopening of the blocked artery may cause additional brain damage by flooding the brain with oxygen. Too much oxygen results in the formation of "reactive oxygen species" (ROS) and "free radicals" thereby causing further damage to brain tissue. The high reactivity of ROS and the lack of suitable tools to monitor and quantify ROS undermined to study when and where cells produce ROS after stroke. The applicants of the current project developed a genetic tool that permits simultaneous generation and detection of ROS in individual cell populations of living tissue. The current experimental program aims to take advantage of these "chemogenetic" tools to identify the cells which produce ROS after ischemic stroke, to uncover the genes activated by ROS production, and to screen antioxidant compounds which inactivate ROS. This knowledge will pave the way for developing specific drugs against ROS-induced brain damage after stroke.