

ERA-Net Neuron

NEWSLETTER 13



News From ERA-Net NEURON

THE KICK OFF MEETING OF ERA-Net NEURON II WILL TAKE PLACE IN PARIS JANUARY 17-18, 2012

In ERA-Net NEURON II, 3 new partner organizations from Iceland, Portugal and Belgium, will join the 18 funding organizations of ERA-Net NEURON I.

Adjacent to the kick-off NSC meeting, a scientific workshop on 'Neuroinflammation' will be held, with 5 invited speakers.

TOWARDS THE ANNOUNCEMENT ON JOINT TRANSNATIONAL CALL 2012

ERA-Net NEURON NSC chose "Novel Methods and Approaches towards the Understanding of Brain Diseases" as the topic of the 5th joint call. This joint call will be managed in the framework of ERA-Net NEURON II. It will be published on January 20, 2012 and submission deadline for pre-proposals is March 09, 2012.

European Research Projects on Cerebrovascular Diseases

Damaged blood vessels in the brain can give rise to a stroke and can lead to permanent neurological damage with serious consequences for the patients and the entire health care system. A stroke is the leading cause of adult disability and the second leading cause of death worldwide. In order to support research into this devastating disorder, the 2011 Joint Transnational Call launched by the NEURON consortium was dedicated to the field of cerebrovascular diseases. The call aimed at promoting multinational collaborative research projects on the pathogenesis of cerebrovascular diseases and on novel strategies for their diagnosis, therapy, and rehabilitation. 57 multinational research consortia including nearly 230 research groups submitted their applications in response to the call. After a two-step peer review process, the top ten proposals were chosen for funding. More than 40 research groups all over Europe, Israel and Canada will collaborate in these projects and will be granted about 10 million € in total.

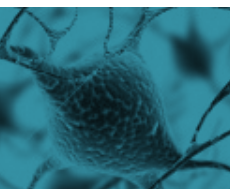
Thematically, six projects will focus on stroke, two projects will treat small vessel disease, and one project will focus on cavernous malformation and vascular cognitive impairment, respectively. The projects encompass the broad range from fundamental biomedical research into disease mechanisms to patient-oriented clinical research and rehabilitation studies.

We hope that the results from the NEURON-funded projects will help to understand stroke and related diseases and can be translated into measures that benefit the affected patients and their families and carers.

Find out more about each project on the subsequent pages.



More information can be found in our web page
<http://www.neuron-eranet.eu/index.php>



BIODVAS \ NEUROIMAGING AND MOLECULAR BIOMARKERS OF VASCULAR COGNITIVE IMPAIRMENT.

Austria \ Canada \ Finland \ [France](#) \ [Germany](#) \ Italy \ Israel \ Luxembourg \ Poland \ Romania \ [Spain](#)

Vascular cognitive impairment (VCI) affects 7% of the population over 65 years of age and nearly 50% of those aged 80 years, which makes it the second leading cause of dementia after Alzheimer's disease. This prevalence is expected to double in the next 30 years, which will make VCI a priority for health services. Clinicians will be under pressure to achieve faster diagnosis and find effective treatments. This will be a challenge because VCI is poorly understood. Urgent developments in neuroimaging are necessary in order to improve diagnosis, and a better understanding of disease mechanisms is absolutely necessary if a potential therapy is to be developed. The current proposal aims to make significant advances in both respects. We will develop and characterize experimental animal models of chronic hypoperfusion that are thought to contribute to VCI using sophisticated magnetic resonance imaging (MRI) and cognitive behavioural testing. We will test pharmacological therapies that improve blood flow and inhibit the inflammatory response to gain mechanistic insight into the disease. We will also use transgenic animal models to investigate the role of the inherent brain microglia.



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Imagerie par Résonance Magnétique Médicale et Multi-Modalités, Orsay, France

CCM \\\ CEREBRAL CAVERNOUS MALFORMATIONS. FROM PATHOBIOLOGY TO THERAPEUTIC STRATEGIES.Austria \ Canada \ Finland \ **France** \ **Germany** \ Italy \ Israel \ Luxemburg \ Poland \ Romania \ **Spain**

Cerebral Cavernous Malformations (CCM) are among the most common blood vessel malformations of the brain, particularly in young people. Such cavernomas can give rise to epileptic seizures and brain hemorrhages (stroke). CCM lesions which are located deep in the brain stem or the spinal cord may lead to severe morbidity and novel pharmacological approaches are desperately needed for those severe forms of the disease which do not benefit from neurosurgery.

The genes responsible for the hereditary CCM form have been identified. However, there are still many unknowns about the function of the CCM genes and consequently about the biology of this disease. Our teams have contributed to the understanding of CCM biology, and propose now to decipher the functions of CCM proteins using an integrated approach. We will study all three CCM genes at a time, and combine in vitro approaches and advanced animal models. This way, we intend to assess possible therapeutic strategies that could be implemented in human patients afterwards.



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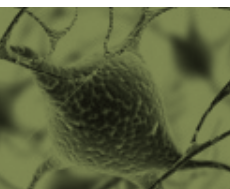
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COGSTROKE \\ COGNITIVE RECOVERY AFTER STROKE. TRANSLATIONAL APPROACH TO NEW THERAPIES OF HIGHER MOTOR DEFICITS.

Austria \ Canada \ Finland \ France \ Germany \ Italy \ Israel \ Luxemburg \ Poland \ Romania \ Spain

Stroke is a major cause of chronic motor disability in humans. The human brain has a remarkable capacity to reorganize in response to such injury, yet the complex mechanisms underlying recovery are still not well understood and evidence based standards for the rehabilitation of motor or cognitive-motor functions after stroke are not well established. The aim of the present project is to translate, test and optimize laboratory protocols into effective treatment protocols for the recovery from motor deficits after stroke respectively to bring together experimental and clinical research on neural and behavioural aspects of motor learning and motor skill re-learning in healthy older adults (the age group in which stroke is a major concern) and in stroke patients with limb apraxia.

Our translational, transnational project COGSTROKE is expected to result in innovative and ecologically valid therapeutic training programs for both healthy older adults and stroke patients with limb apraxia by incorporating multiple parameters and procedures. Especially, this will be the first project to prove the impact of sleep on motor skill learning in healthy elderly and stroke patients with limb apraxia. COGSTROKE will also provide new insights into the learning mechanisms of the elderly brain and contribute to the understanding of motor system reorganization after stroke.

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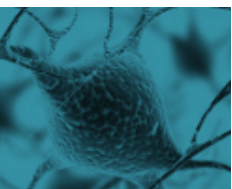
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GINA \ BIOMATERIALS SCAFFOLDING FOR BRAIN RECONSTRUCTION IN STROKE

Austria \ [Canada](#) \ Finland \ France \ [Germany](#) \ [Italy](#) \ Israel \ Luxembourg \ Poland \ Romania \ [Spain](#)

Stroke in mammals, including humans, is followed by proliferation and migration of stem cells into the penumbra and core ischaemic zones. However, this process is followed by massive cell death at the core zone, clinically resulting in incomplete recovery in many cases. We hypothesize that this is due to an inadequate milieu at the necrotic area and/or insufficient stimulation of stem cell proliferation and migration. Thus, implantation of biocompatible scaffolding materials permitting cell survival and differentiation along with angiogenesis within them, associated with electric stimulation to promote neurogenesis and cell integration, may improve cell colonization and survival and lead to functional improvement of the neurologic condition in animal models of stroke.

In our consortium, one group in Valencia will make biocompatible materials, and a group in Mainz will test “in vitro” the ability of these to preserve survival of neurons and the development of angiogenesis. Two groups in Madrid and Venezia-Padova will apply these biomaterials and neurostimulation to animal stroke models. A group in Toronto will test those hypotheses in a different model of stroke (hippocampal ischaemia). These results will probably lead to clinical trials using implant of biomaterials and neurostimulation for the reconstruction of brain defects due to stroke.

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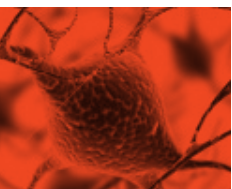


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COORDINATOR | JUÁN ANTONIO
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MEMS - IRBI \\ MRI NAVIGATED ENHANCEMENT OF MESENCHYMAL STEM CELL (MSC). HOMING TOWARD STROKE LESION – EVALUATING AN IMPACT ON ANIMAL RECOVERY WITH BEHAVIORAL TESTING AND IMAGING.

Austria \ Canada \ **Finland** \ France \ **Germany** \ Italy \ Israel \ Luxemburg \ **Poland** \ Romania \ Spain

FUNDED PROJECTS

Stroke is a major reason of death and the leading cause for permanent disability of patients. Positive effects of mesenchymal stem cell (MSC) transplantation were seen in animal models. However, pilot clinical trials did not result in functional improvement in patients. Low efficiency of MSC therapy could be increased by facilitating MSC homing towards the brain lesion. Our project aims to develop such an approach, to investigate its feasibility and efficacy in relevant cell culture and animal models and to collect the information for safe translation into a clinical testing. In a first phase, MSC will be engineered to overexpress VLA-4 protein, which enhances cell homing to the lesioned brain. In a second phase, MSC will be labeled with iron particles and tracked by means of magnetic resonance imaging (MRI) in animals. This reveals data on MSC distribution in the brain at high resolution and confirms safety of the approach. Behavioral tests will be used to reveal efficacy of the approach in rodent models of stroke. In a third phase, the approach will be verified in a close-to-practice large animal model offering anatomical conditions being comparable to humans. In case of success, the modified MSC would be in case of success, the modified MSC would be ready to be produced for early patient studies.



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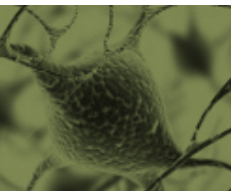
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MESCOG \ MECHANISMS OF SMALL VESSEL RELATED BRAIN DAMAGE AND COGNITIVE IMPAIRMENT: INTEGRATING IMAGING FINDINGS FROM GENETIC AND SPORADIC DISEASE.

Austria \ Canada \ Finland \ France \ Germany \ Italy \ Israel \ Luxembourg \ Poland \ Romania \ Spain

We hypothesise that CADASIL, a hereditary small vessel disease (SVD), and common sporadic forms of SVD have shared mechanisms and that integrating imaging data from both conditions will allow defining key mechanisms of small-vessel related brain damage and associated cognitive impairment. MESCOG investigators will use their combined patient, family and population-based resources and apply state of the art image post-processing and analytical tools to address the following scientific aims in a collaborative effort:

- delineate the mechanisms of incident lacunar infarcts and their consequences on anatomically connected brain regions.
- identify strategic locations for subcortical ischemic lesions and cognitive performance.
- explore the mechanisms and clinical impact of cortical changes in patients with SVD.
- provide a detailed account of microstructural changes in the normal appearing brain and their imaging and cognitive correlates.
- provide integrated models predicting cognitive impairment in SVD.

Our approach builds on two prospective observational cohorts collected by MESCOG PIs with longitudinal data already available: 320 patients with CADASIL and 820 community-dwelling middle aged and elderly participants.

Using machine learning processes data will be integrated into joint models to identify general mechanisms of small vessel related brain damage and cognitive impairment. Validation of the final models will then be performed in external cohorts. Our ultimate goal will be to provide novel predictive instruments, markers and targets for therapeutic trials.



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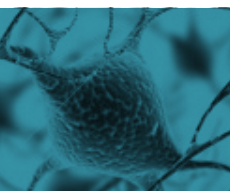
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NanoStroke \ \ ROLE OF DANGER SIGNALS IN STROKE AND THERAPEUTIC TARGETING BY NANOBODIES.

Austria \ Canada \ Finland \ France \ [Germany](#) \ [Italy](#) \ Israel \ Luxembourg \ Poland \ Romania \ [Spain](#)

In acute stroke, the size of the initial brain lesion can further increase over the first hours and days after the ischemic event. This 'infarct growth' is a significant clinical problem because it is related to worsening of neurological deficits and poor functional outcome. Recent lines of evidence directly link local inflammatory and immune reactions with the degree of stroke-associated brain damage and secondary infarct growth. What exactly triggers this inflammatory response and how the immune reaction amplifies damage is unknown. Likely candidates for immune activation are danger signals such as adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NAD), and high-mobility group box 1 protein (HMGB1) that are released from dying cerebral tissue after stroke.

In this project, we will investigate the pathophysiological role of danger signals in acute and subacute stroke. We will take a therapeutic approach using specific nanobodies to perturb danger signal receptors in vitro and in vivo. We will design different versions of nanobody complexes to achieve an optimal function and avoid the immunogenicity and toxicity characteristic of classical antibodies. These modifications will be critical for clinical application in the future. As a step towards a novel treatment option for patients, we will test if nanobody suppression of inflammatory cell activation under ischemic conditions can be extended to the human system using in vitro and ex vivo preparations.

The consortium consists of Anna Planas, Barcelona, Christoph Kleinschnitz and Guido Stoll, Würzburg, Carlos Matute, Bilbao, Andrea la Sala, Rome and Friedrich Koch-Nolte and Tim Magnus, Hamburg.

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PROTEA \\\ INFLUENCE OF PROTEASES BEFORE, DURING AND AFTER STROKE.Austria \ Canada \ **Finland** \ **France** \ Germany \ **Italy** \ Israel \ Luxembourg \ Poland \ Romania \ **Spain**

Every day, 1000 Europeans die from a stroke and about twice that number survive but are disabled. Despite tremendous progresses in our understanding of the pathophysiology of stroke, translation into effective acute therapies has largely failed, apart from tissue-type plasminogen activator (tPA)-induced thrombolysis. Nevertheless, strict inclusion criteria for eligibility restrict thrombolytic opportunity to only 2-5% of stroke patients. Thus, it is an emergency to look for new and possibly combined therapies within and beyond the acute phase of stroke to increase the proportion of treated patients. Proteases, especially plasminogen – plasminogen activators and metalloproteinases, critically control several stages in the evolution of stroke lesions. Emerging concepts suggest that these proteases can influence the fate of all cell types of the “neurovascular unit”, through both extra- and intra-cellular mechanisms/signalling(s). These neurovascular perturbations contribute to the risk of thrombosis, blood-brain barrier leakage, excitotoxic neuronal death, oedema, haemorrhage, inflammation and repair processes, over hours or even days, weeks and months after stroke. Protea proposes to characterize the influence of these proteases before, during, and after stroke and to point out novel diagnostic/therapeutic avenues that may result from this knowledge. To achieve these goals, we will perform an extensive pre-clinical and clinical stroke related proteasomic analysis, investigate whether proteases conveyed by microparticles may be messengers of cell activation/damage in the neurovascular unit, validate combined strategies to improve stroke recovery and thus determine the influence of the plasminogen/tPA/metalloproteinases triad at the different stages of stroke.



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REVIS \ RESTORATION OF VISION AFTER STROKE.

Austria \ Canada \ Finland \ France \ Germany \ Italy \ Israel \ Luxembourg \ Poland \ Romania \ Spain

About 1/3 of stroke patients, i.e. 2.1 Mio new cases annually, suffer damage to the brain's vision processing centres which leads to serious visual impairments in everyday life activities such as reading, orientation in space and visually-guided mobility. Because the resulting blindness does not improve, new treatments options are urgently needed to help restore vision. However, surviving, residual visual tissue at or near the lesion can be activated by repetitive activation which helps the brain to adapt in process called post-lesion "neuroplasticity".

The aim of REVIS is to find new stimulation protocols to activate residual vision by inducing brain plasticity using non-invasive brain alternating (AC) or direct (DC) current stimulation. AC was already shown to improve vision after optic nerve damage and therapeutic DC effects have been studies in different neurological disorders.

Four European research centres and a commercial partner from Germany, Finland, Italy and Poland now join efforts to better understand the neuronal mechanisms of brain plasticity after visual field loss (hemianopias) and to find appropriate protocols to restore vision in stroke patients and experimental animals using non-invasive AC and DC current stimulation. The aim is to increase activation by inducing lasting synchronization changes in the brain of neuronal networks and functional connectivity patterns.

If successful, the project will uncover new ways to activate residual visual capacities after stroke which then provides the basis for a novel, non-invasive current stimulation medical device to help patients restore some of the lost vision and improve quality of life in lasting ways.

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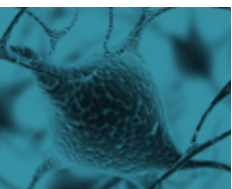
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**SDSVD \\\ SPREADING DEPOLARIZATION IN SMALL VESSEL DISEASE.**Austria \ Canada \ [Finland](#) \ France \ [Germany](#) \ Italy \ Israel \ Luxembourg \ Poland \ Romania \ [Spain](#)

There are presently no neuroprotective drugs with efficacy to improve outcomes after lacunar stroke. Fundamental challenges to advancing treatment of lacunar stroke are its heterogeneity in terms of cause, pathology, and the lack of mechanistic endpoints in clinical studies. Mechanistic endpoints, necessary for appropriate targeting of treatment, have been lacking due to our limited ability to validate and monitor relevant pathologic processes in clinical populations. Nonetheless, understanding mechanisms contributing to neuronal and vascular disruption and developing mechanistic endpoints on the basis of this understanding holds great promise to unravel the heterogeneity of lacunar stroke, assign treatments appropriately, and detect significant treatment effects when they exist. Spreading depolarizations are a pathology of cerebral gray matter that originate spontaneously in injury foci where they seem to facilitate cellular damage. Whether or not they are deleterious seems to be intimately linked to the composition of the brain extracellular microenvironment and to the level of brain perfusion. In our project “spreading depolarization in small vessel disease” (SDSVD), we will investigate the role of spreading depolarizations in an animal model for small vessel disease. This will provide the basis to develop spreading depolarizations as a mechanistic endpoint for clinical studies of lacunar stroke.



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