



## NEWS FROM ERA Net NEURON

On January 19, 2010, ERA Net NEURON announced the publication of its third Joint Call for application: "European Research projects on mental disorders". Over 100 application involving 400 scientists from 11 participating countries submitted pre-proposals to the Joint Call secretariat. Decisions on pre-proposals will be announced in May 2010, and the deadline for full proposals submission is June 15.

Final funding decisions will be made on October 2010, and funding of selected projects will start in early 2011.

## European research projects on "Development and advancement in methods and technologies towards the understanding of brain diseases"

In January 2009, the ERA-Net NEURON launched a joint transnational call for proposals focussed on innovative technologies in neuroscience. The scope of this call was not the funding of pure technology development per se. Research projects had to be hypothesis-driven and combine cutting-edge technological developments with a clear, substantial research question. There was no sharp restriction concerning the specific technologies or methodologies used in the applications. These could include imaging techniques (including optical, MR and PET techniques), molecular and genetic approaches, stem cells and neural differentiation in relation with cell therapy, gene targeting in the brain, electrical and magnetic brain stimulation, molecular modelling techniques and others. 81 consortia comprising 325 research groups from 10 countries submitted their proposals. Of these, 10 consortia have started working since February 2010, supported by a funding volume of about 10 million euros. The 10 funded projects are briefly described on the following pages.



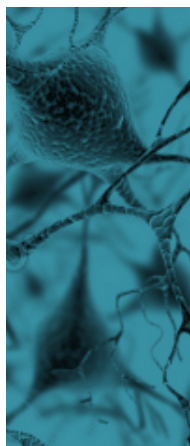
More information can be found in our web page  
<http://www.neuron-eranet.eu/index.php>

## 2p-Imaging: High-speed two-photon imaging for *in vivo* analysis of brain disease

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

**Project Description** Nerve cells exchange electrical signals at high speed. If this signal exchange is disturbed, neurological diseases result. For example, in epilepsy too many nerve cells are active at the same time, so proper information processing is disturbed, and seizures ensue. Similarly, in Alzheimer's disease, nerve cells fail to properly communicate: some fall silent, while others show abnormal levels of activity. Even altered rhythms of activity cause problems, such as the tremors seen in movement disorders.

The central challenge in understanding failures in nerve cell communication is to reveal disturbed activity with single-cell resolution in large networks of nerve cells inside the intact brain. In order to accomplish this, large volumes of brain tissue have to be examined at many sites simultaneously. To do so, novel fast imaging methods need to be developed. Our project aims to meet this challenge for animal models of disease: We want to develop advanced methods of microscopy (known as "two-photon imaging") that can in parallel reveal the activity of hundreds of cells inside the brain of living mice. We will combine two-photon imaging with dyes that convert changes in brain signalling into optical signals. We will develop mouse models of disease with tailored light-based reporters to study the pathomechanisms of Alzheimer's disease, epilepsy and tremor.



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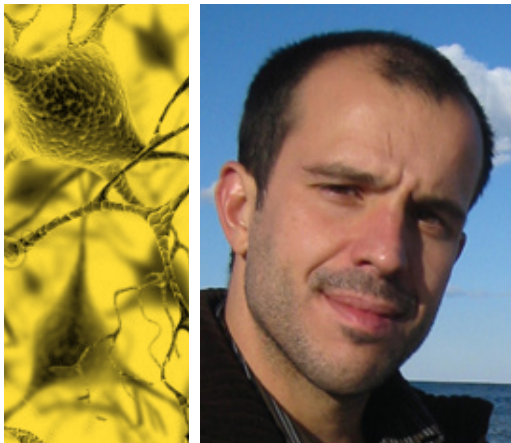
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## BEYONDIS “When attention meets perception”: Non invasive Neurostimulation technologies to boost visual perception in intact subjects and cerebrally damaged patients

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

**Project Description** Our ability to consciously discriminate what we see, hear or feel emerges out of well-defined large-scale brain networks. Studies suggests that those systems are not deterministically sculpted in stone and that can be dynamically fine-tuned and adapted to novel demands. It is such flexibility that allows us to benefit from practice to learn new skills, improve performance, and after lesions, provide patients with chances to recover. Increasing evidence indicates that our ability to orient attention in space, i.e., to concentrate our perceptual resources- in specific areas of the visual environment, holds the power to modulate visual systems and influences the odds to detect, categorize, discriminate or identify objects, faces and events occurring in attended regions of the space. BEYONDIS will use neuroimaging to explore the architecture and temporal dynamics of the brain networks involved in attentional orienting able to induce ameliorations in conscious visual performance. For both, healthy participants and patients afflicted by visual field defects, we will develop novel training/ rehabilitation strategies that based on the use of non-invasive brain neurostimulation technologies alone or combined with traditional endogenous or exogenous cuing might allow for an efficient manipulation of attentional networks and drive significant performance increases in conscious vision.



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## DISCover- interdisciplinary project investigating chronic mental disease from single molecules to behavioral analysis in animal models

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

**Project Description** Little is known on the biological mechanisms leading to chronic mental diseases (CMD) like schizophrenia or recurrent affective disorders. Recent genetic linkage analyses have highlighted the significance of the disrupted-in-schizophrenia 1 (DISC1) protein in the genesis of CMD. However, investigations have focussed on the dysfunction of mutant DISC1 found in familial DISC1 disorders.

Here, we propose to investigate the role of DISC1 and its molecular interactors within the DISC1/NDEL1/centrosomal protein complex in the majority of non-familial cases of CMD. With a team of multidisciplinary scientists, each with different expertises, we propose to investigate this protein complex with novel cutting-edge technologies on the levels of single proteins, its molecular interactors (protein biochemistry and proteomics), its function in neurons and in the development of the nervous system (live cell imaging and in utero electroporation techniques), and animal behavior (in vivo dialysis, episodic memory tests, and others). Results from investigating the biology of this protein complex at different levels from single molecules to behavior will provide insights that ultimately translate into much-needed progress in clinical psychiatry: for example, detection methods to establish biological testing or novel pharmacological targets.



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## EpiNet: Understanding and manipulating epileptic networks with optical stimulation and advanced population recording techniques



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

**Project Description** Epilepsy is one of the most common neurological disorders (~8.000.000 patients in the EU). The cardinal symptom of epilepsy - seizures - consists of synchronized neuronal discharges. So far, the complexity of neuronal networks has hampered the investigation of the cellular basis of seizures using conventional electrode-based stimulation and recording techniques. We will use novel light based recording and stimulation techniques that allow to analyze the activity of hundreds of nerve cells in a network simultaneously while stimulating individual synaptic connections, or defined populations of neurons. Together with novel morphological approaches to reconstruct neuronal microcircuits, this will permit us to dissect functional changes in neuronal circuitry underlying neurological disorders such as epilepsy. We will focus our work on the role of inhibitory neurons, which powerfully control neuronal excitability and rhythmogenesis. In addition, we will transfer these studies to the in-vivo level. We will determine changes in neuronal excitability and synaptic inputs in awake behaving animals using extracellular and intracellular recording techniques and utilize light based stimulation in-vivo to control epilepsy and seizures. In addition to understanding the network basis of epilepsy, we expect these paradigms to be useful to study the neuronal and network basis of other common neurological disorders.



Prof. Dr. Heinz Beck (coordinator)

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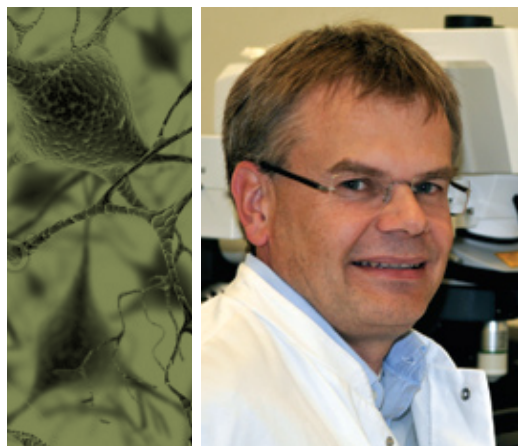
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## ImageNinND: Imaging Neurogenesis in Neurodegenerative Disease: *In vivo* imaging of dopaminergic adult-born neurons in the olfactory bulb of animal models of Parkinson's disease.

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

**Project Description** With advancing age, the ability of humans to detect and discriminate odorous molecules declines. Deficits in olfactory function cause a decrease in the quality of life and can affect appetite and thereby impact the nutritional status of elderly individuals. Decreased olfactory function during ageing is paralleled by decreases in other brain functions that occur in the absence of obvious disease states, such as changes in other sensory functions and cognition (memory loss, depression, etc.). Olfactory deficits are also very common in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. These deficits may be partly due to alterations in the maturation of adult-born neurons which incorporate into the neuronal network of the olfactory bulb.

We aim to apply cutting-edge technologies to study the basic mechanisms of the survival and maturation of dopaminergic neuronal precursor cells in the olfactory bulb throughout ageing and in Parkinson's disease. Overall, we seek to establish an *in vivo* assay that allows the testing of compounds aimed at promoting the maturation of adult-born neurons in altered neuronal networks. Such an assay may not only be relevant for neurodegenerative diseases with early olfactory dysfunction including Alzheimer's disease and Parkinson's disease but may also be relevant for other brain diseases of different origin where the integration of adult-born neurons in altered neuronal networks is a potential therapeutical option.



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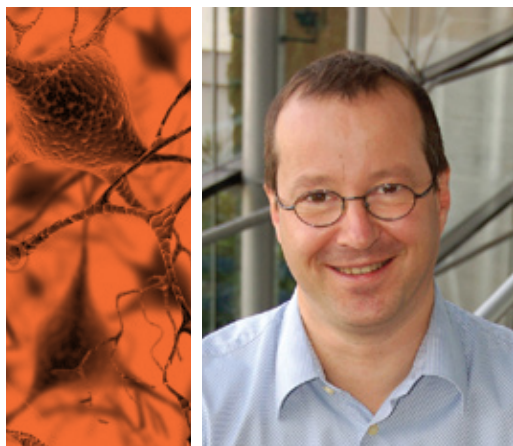
## MODDIFSYN: Development of new chemical and optical tools to study and modulate glutamate receptor surface trafficking in synaptic transmission in different models of neurodegenerative diseases

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

**Project Description** Dysfunction of neurotransmitter trafficking is likely to be at the basis of the abnormal synaptic transmission and plasticity observed in several neurodegenerative and neurological diseases. Surface trafficking has recently emerged to be a key process to regulate ionotropic glutamate receptor numbers at excitatory synapses and to control fast excitatory synaptic transmission. At present no tools are available to specifically modulate receptor surface trafficking in intact tissues. We selected glutamate receptors themselves and extracellular matrix proteins (ECM) as lead targets to achieve this modulation.

We put together an interdisciplinary consortium with a good balance of technology development and application of this technology to the understanding of the molecular mechanisms of brain disease. Aims will be to develop new ways to label and immobilize receptors, new methods to visualize receptor trafficking and new approaches to measure protease activity on the ECM.

We will use these tools to study the fundamental role and modulation of AMPA and NMDA glutamate receptor surface trafficking in normal fast synaptic transmission as well as apply these knowledge and tools to study and correct the defects in receptor trafficking in different neurodegenerative and neurological diseases such as Alzheimer's and Parkinson's disease as well as temporal lobe epilepsy.



Daniel Choquet (coordinator)

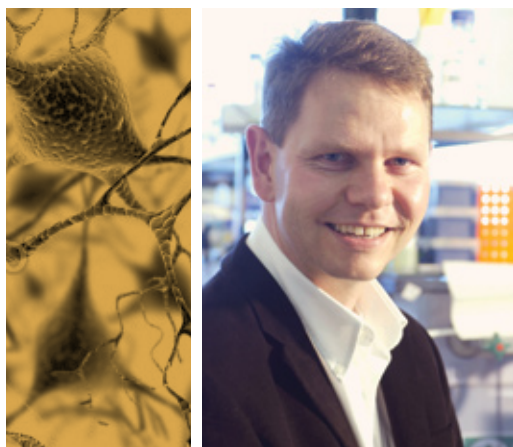
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## NanoBrain: Alzheimer drugs incorporated in nanoparticles for specific transport over the blood brain barrier

Austria Canada Finland France Germany Italy Israel Luxemburg Poland Romania Spain

**Project Description** The number of people suffering from Alzheimer's disease (AD) is estimated to be around 11.2 million Europeans by the year 2050. Any drug for AD prevention needs to fulfill two critical requirements. First, the drug should target underlying molecular and biological mechanisms responsible for initiation or initial steps of the disease process. Second, the drug should have minimal side-effects and the potential to enter the brain. Evidence from large retro- and prospective epidemiological studies has documented that long-term medication with non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk and delays the onset of AD significantly. Unfortunately these drugs do not penetrate the blood brain barrier (BBB) very well and therefore are not useful for immediate treatment approaches. Therefore the overall objective of this project is the development of a novel drug delivery systems based on nanoparticles over the BBB. The successful discovery and development of new therapeutic approaches have been increasingly aided through the use of appropriate in vitro model systems. In this project we will focus on the development of an in vitro assay to monitor drug transport through nanoparticles over the BBB which will be subsequently transferred into animal models to establish a new therapeutic approach to fight Alzheimer's disease.



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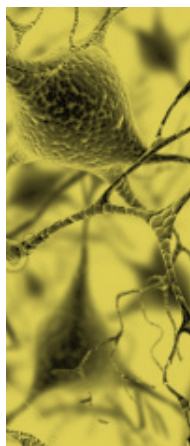
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## NANOSYN: Manipulation of synapses with nanotechnologies to study molecular mechanisms of neurodegeneration

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

**Project Description** Brain function relies on regulated communication between neurons at contact points called synapses, where nerve terminals release chemical transmitters. Degeneration of nerve terminals is a hallmark of severe neurological human diseases. Our goal is to understand the mechanisms that maintain nerve terminals up-and-running and protects them from degeneration. Our study is focused on a mouse model with fragile nerve terminals that become degenerated at early adulthood. Those mice lack a protein (Cysteine String Protein-alpha) that probably is a chaperone that helps other synaptic proteins to be functionally active. Here, in cultured neurons, we will apply new technologies attempting to prevent or to recover nerve terminals from degeneration. NANOSYN will use nanotechnologies to engineer microcapsules loaded with fresh proteins to either substitute damaged proteins within the terminal or to invigorate protein repair. We will implement microscopes with laser illumination to open microcapsules and to achieve temporal and spatial control of protein release within neurons. We will visualize neuronal function with advanced microscopy approaches. In addition, NANOSYN will investigate the potential role of astrocytes in preventing neurodegeneration. We expect to open new possibilities to study and to interfere with molecular mechanisms of neurodegeneration in models of human diseases using nanoparticles-mediated protein delivery.



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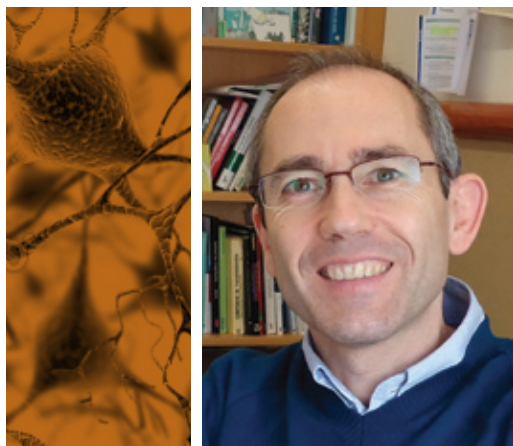
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## PANS – Probing the auditory novelty system

Austria Canada Finland France Germany Italy Israel Luxemburg Poland Romania Spain

**Project Description** Hearing it is one of the most amazing human capacities. It is at the basis human speech and communication, and thus constitutes a prerequisite towards cognitive development. A key principle in cognitive auditory function is the ability of the auditory system to extract the implicit regularity in the acoustic environment. Animal studies have identified neurons along the auditory pathway that show strong stimulus-specific adaptation but that fire vigorously to novel acoustic events. Also, human studies based on a deviance-related EEG response, the mismatch negativity (MMN), have suggested that novelty detection is paramount to auditory function. Yet, a unified picture of these two lines of research is lacking. Our project aims at the understanding of the auditory novelty system, while providing a new testing protocol of cognitive dysfunction in pre-term born infants. This will be achieved by a multidisciplinary approach encompassing the recording of human (EEG, MEG) and animal (single unit, multi unit, local field and epidural) novelty responses elicited at multiple levels of the auditory system to common experimental protocols. The results will guide the design of new testing protocols for assessing cognitive sequelae of prematurity that should guide the rapid implementation of preventive measures.



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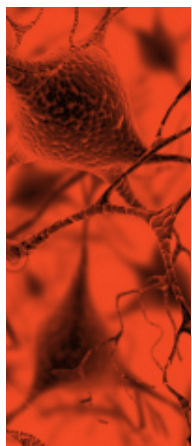
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## REPark : Modeling Parkinson's disease by iPS technology: generation of human affected dopaminergic neurons and gene disease correction by site-specific integration

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





**Project Description** Parkinson's disease (PD) is a disorder of old age with characteristic impairments of movement. Ever increasing numbers of PD in our aging society constitute a major burden to the health systems.

To develop new medications, it is critical to gain a full understanding of the cellular and molecular mechanisms of PD. However, despite a tremendous wealth of new information about the molecular basis of the disease, the lack of faithful cellular and animal models is delaying the development of new therapeutics. Thus, we are going to employ an innovative technology which uses patient skin cells and genetically reprograms them into brain nerve cells where different stages of disease progression and therapeutics can be studied over time. We plan to use an induced Pluripotent Stem cell (iPS) approach to generate dopaminergic neurons, which contain the diverse genetic factors that triggered PD. This technology will provide us with unlimited amounts of viable human cells derived from sporadic or monogenic PD patients which can be differentiated into electrically active nerve cells where the disease vulnerability can be studied during life. We plan to validate this pioneering in vitro system and to identify the cellular and molecular dysfunctions induced by PD mutations.



Vania Broccoli (coordinator)

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