



NEWS FROM ERA NET NEURON

ERA-Net NEURON has just started its fifth year of activity. All partners are participants to the submission of a new proposal NEURON II to the EC for another funding period. In addition, Belgium, Iceland, Portugal, and Turkey joined in the proposal.

In January 18, 2011, ERA Net NEURON published the fourth Joint Transnational Call for applications: "European Research Projects on Cerebrovascular Diseases". The submission deadline for pre-proposals was March 9, 2011. Decisions on pre-proposals will be announced in May 2011, and the deadline for full proposals submission is June 15, 2011.

In the next newsletter we will publish a summary on the workshop on Transfer Technology which took place in Montréal in January 2011

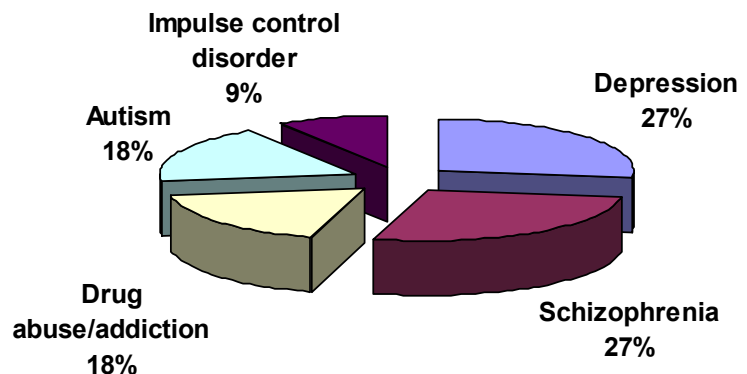
European research projects on Mental Disorders

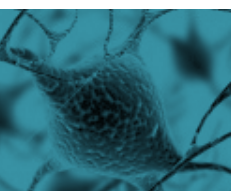
In January 2010, ERA-Net NEURON launched a joint transnational call for proposals focused on Mental Disorders.

The aim of the call was to enable multi-national collaborative research projects addressing major issues relating to mental disorders.

Proposals received in response to the Call covered a wide spectrum of issues: from understanding basic mechanisms of mental disorders to proof-of-concept clinical studies in man. Among those were research projects on depression and bipolar disorders, schizophrenia and psychotic disorders, phobia and anxiety disorders, substance use disorders, autism and mental retardation and other mental disorders. 103 consortia comprising 402 research groups from 11 countries submitted their proposals. Of these, 11 applications were approved for funding with a total volume of about 10 million €. These are briefly described on the following pages.

Distribution of diseases in 11 proposals selected for funding





AMRePACELL \ \ DEVELOPMENT OF NEW EXPERIMENTAL MODELS FOR MENTAL RETARDATION AND AUTISM BY IPS TECHNOLOGY: GENERATION OF HUMAN AFFECTED AND ANIMAL MODEL NEURONS BY REPROGRAMMING SKIN FIBROBLASTS AND TESTING GENE CORRECTION USING IN VITRO AND IN VIVO MODELS.

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SUCCESSFUL PROJECTS

Most proteins encoded by genes involved in mental retardation (MR) and autism disorder (AD) are associated with the synaptic junction between neurons. Studying the function of these proteins, as model of MR and autism, will not only help to better understand the molecular mechanisms of synapse formation, plasticity and learning and memory processes, but will also open the possibility of future therapeutic approaches for such invalidating disorders. Previous efforts to decipher the pathophysiological mechanisms of MR rely on the functional characterization of mouse models. Here we propose to use a new technology based on the genetic reprogramming of human somatic cells from patients carrying a mutation in MR and AD genes to derive cells that are pluripotent (iPS). In vitro differentiation of these iPSs toward the neuronal cell fate will lead to both excitatory and inhibitory neurons, which we will use for an exhaustive and multidisciplinary analysis including morphological, biochemical and functional assessment of the synaptic activity and gene expression profile. Finally, we will also explore in mouse the possibility to use iPS cells for assessing lentivirus-mediated site-specific integration of cDNA constructs into defect genes and into gene-correct mutant iPS as possible cell therapy.



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AUSZ_EUCan \ \ FROM AUTISM TO SCHIZOPHRENIA : STUDY OF THE GENETIC MECHANISMS. UNDERLYING BRAIN DYSFUNCTION AND STRUCTURAL PHENOTYPES IN SCHIZOPHRENIA AND AUTISTIC SPECTRUM DISORDERS

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SUCCESSFUL PROJECTS

Schizophrenia (SCZ) and autistic spectrum disorders (ASD), two severe disorders, share symptomatology and neurocognitive conditions. Distributed structural brain abnormalities are described in both disorders, involving cortical and sub-cortical anomalies, suggesting that they could reflect 'dysconnectivity' within cortical networks. We propose an integrative approach combining comprehensive cognitive assessments, high-resolution genetics and brain imaging with a translational approach in mouse models.

Our objectives are: i) to compare developmental clinical features, brain anatomy and neurocognitive functions in a large sample of patients with early- and adult-onset SCZ or ASD and their respective relatives and controls; ii) to study the variant of genes involved in brain development in relation to brain structural variations, white matter architecture, myelination, connectivity, cortex morphology and gyrification as well as rare genetic variations in genome wide scans for Copy Number Variations and de novo mutations; iii) to study novel animal models with developmental abnormalities of the subcortical white matter. This project, which involves 5 partners in Europe and Quebec, will improve the identification of the biological basis of ASD and schizophrenia and will, in turn, improve therapeutic interventions in mental and cognitive disorders.

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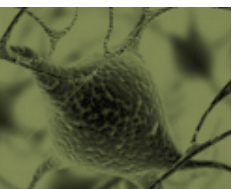
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DBS_F20rat \\ DESCRIBING PATHOPHYSIOLOGY TO PROMOTE FOCAL THERAPY IN TREATMENT OF SCHIZOPHRENIA – AN ANIMAL EXPERIMENTAL STUDY.

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SUCCESSFUL PROJECTS

Schizophrenia is characterized by profound disruptions in cognition and emotion. Despite pharmacotherapeutic progresses, a considerable percentage of patients has no or only partial response to treatment. Development of more effective treatments is indispensable but crucially depends on an advanced elucidation of the progressive pathophysiological mechanisms underlying schizophrenia. Given methodological and ethical limitations of human studies, the use of appropriate animal models is a promising tool for such endeavours. The present project uses the maternal immune stimulation rat model of schizophrenia and deep brain stimulation (DBS) as an investigative tool to modulate neural activity of selected brain areas and associated networks in order to i) correlate the emergence of a schizophrenic phenotype with the development of dysfunctions at different levels of neurobiological integrity; ii) study bi-directional consequences of DBS of selected brain areas and iii) study the preventive potential of presymptomatic activity-modulation of selected brain areas on the emergence of behavioral and neurobiological abnormalities. The project will foster our understanding of dysfunctional neural circuitries in schizophrenia and set a strong interdisciplinary foundation for the translational application and advancement of DBS as a novel focal and causative strategy in the treatment of therapy-resistant schizophrenia.



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EUHFAUTISM \ \ EUROPEAN HIGH-FUNCTIONING AUTISM NETWORK: TRANSLATIONAL RESEARCH IN A PHENOTYPICALLY WELL CHARACTERISED SAMPLE.

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Autism spectrum disorders (ASD) are heterogeneous neurodevelopmental disorders affecting up to 1 in 100 persons. ASD have no cure or effective treatment, representing a major health problem. ASD represent a continuum of symptoms, ranging from profound intellectual impairment to above average intellectual functioning. Given the added complexity of studying a heterogeneous disorder such as ASD, the characterization of more homogeneous subgroups of patients can facilitate clinical and genetic approaches. Here, we propose to study the subgroup of high-functioning ASD (HF-ASD) patients. With the aim of understanding the causes of HF-ASD, we have assembled a multidisciplinary European team that brings together expertise in the clinical diagnosis of ASD, human genetics and neurobiology. We will define a common standardized assessment of the patients and use whole genome genotyping and gene sequencing to identify the major risk factors for HF-ASD. We expect that the studies proposed here will advance our knowledge of the mechanisms leading to ASD, and thus, in the development of precise diagnostic and therapeutic strategies.

SUCCESSFUL PROJECTS

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NeuConnect \\ NOVEL STRATEGIES FOR THE TREATMENT OF SCHIZOPHRENIA BASED ON GENETIC VARIATION OF THE NEURAL CELL ADHESION MOLECULE NCAM AND ENZYMES INVOLVED IN ITS POSTTRANSLATIONAL MODIFICATIONS

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SUCCESSFUL PROJECTS

Schizophrenia is a devastating psychiatric disease characterized by substantially disturbed cognition and emotion, affecting the most fundamental human features: language, thought, affect, perception, and sense of self. Even though medication is available to improve the symptoms of schizophrenia, not all patients benefit from these drugs. Current research revealed that the susceptibility to schizophrenia may be caused by disturbed brain development and maturation. A relevant molecule in this context is the neural cell adhesion molecule NCAM. The appearance of NCAM during brain development is subject to complex genetic and enzymatic control. The structures affecting the modulation of these control systems represent promising targets for innovative therapeutics for schizophrenia. The NeuConnect consortium will use a unique patient database to identify disease-related variations of NCAM and translate them into animal models. Investigations on the molecular causes and consequences of dysregulated NCAM in animal and cell models will be used to generate and test novel pharmaceuticals for their capacity to restore brain function and to improve clinical symptoms of schizophrenia. The interdisciplinary group of involved scientists and clinicians is perfectly suited to combine expert knowledge on genetic, molecular, neurobiological, and clinical aspects in order to establish new treatment strategies for schizophrenic patients.

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NICO-GENE \ \ MODELING HUMAN POLYMORPHISMS FOR NICOTINE ADDICTION IN MICE

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SUCCESSFUL PROJECTS

Every year, more than five million people worldwide die from the consequences of smoking. These deaths, principally from lung cancer, are avoidable. A formidable obstacle to the prevention of these deaths is that tobacco contains nicotine — the major, if not sole, compound responsible for driving the strong addiction to smoking. The actions of nicotine are mediated by nicotinic acetylcholine (ACh) receptors (nAChRs). Human genetic studies have recently identified alterations in the sequence of some of the genes coding for subunits of nAChRs. These mutations are correlated with a higher incidence of lung cancer and smoking. To increase our understanding of the contribution of different nAChR oligomers to nicotine addiction, new strategies will be developed. These include the detailed study of deletions in mice of nAChR subunit genes, the re-expression of a deleted gene by stereotaxic injection of a lentiviral vector carrying the missing gene, and the quantitative analysis of the behaviours elicited by nicotine in these mice. We aim to bridge the gap from genes to cognition in the understanding of nicotine addiction, on the basis of our recent advances in the molecular biology of nAChRs, and of animal models with modified nAChR gene expression.



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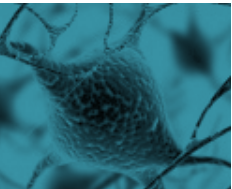
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PADRE \ PHARMACOGENOMICS OF ANTIDEPRESSANT DRUG RESPONSE (PADRE): TENTATIVE DRUG RESPONSE BIOMARKERS FROM HUMAN LYMPHOBLASTOID CELLS.

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SUCCESSFUL PROJECTS

Although several classes of antidepressant drugs are now available for treating major depression, no tools are available for selecting the most appropriate drug for the individual patient. This project aims to develop and validate a functional antidepressant drug response assay, based on an individual's genomic and transcriptomic information, for assessing pharmacogenomic variability between individuals. Growth inhibition by different classes of antidepressants will be compared systematically in human lymphoblastoid cell lines (LCLs) of the Israel National Laboratory for the Genetics of Israeli Populations. Since the antidepressant drug-mediated growth inhibition effect of an individual LCL has been shown to be stable, and to reflect drug class-specific differences, we aim to use this tool to study individual variability in molecular drug effects. Candidate genes derived from this approach together with candidate genes from the recent genome wide clinical antidepressant drug response studies will be functionally characterized and differences in transcriptomics will be compared in LCLs and primary blood lymphocytes from individual patients clinically characterized for antidepressant drug response. Tentative biomarkers of drug response will then be transformed to a pharmacogenetic diagnostic test which will be studied and validated in large cohorts of patients characterized for antidepressant drug response.

This project is situated in the gap between the complex clinical situation of antidepressant drug therapy, and modern genome-wide tools for functional pharmacogenetic assays. It serves the need to predict which of the several available antidepressant drug classes will work most likely in an individual depressed patient.



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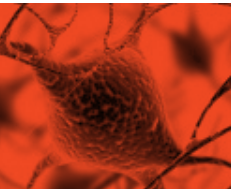
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POSEIDON \ PRE-, PERI- AND POSTNATAL STRESS IN HUMAN & NON-HUMAN OFFSPRING: A TRANSLATIONAL APPROACH TO STUDY EPIGENETIC IMPACT ON DEPRESSION

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

SUCCESSFUL PROJECTS

Exposure to early life stress (ELS) has been associated with a prospectively increased risk for depression. Epigenetic regulation of gene expression may mediate this effect, but windows of vulnerability, candidate stressors, methylation profiles, time course, persistence and functional significance of the effects of ELS on the methylome remain unclear.

The POSEIDON study will focus on these questions in a cross-species (rodent, primate, humans) approach covering different tissues (brain, T-cells, buccal cells, saliva), stressors (prenatal stress, perinatal asphyxia, maternal care) and time points of adversities (pre-, peri-, postnatal) and follow-up (infancy, adulthood). We will study methylation of candidate genes and do methylome analysis. The functional relevance will be examined in expression studies and using discovery-based systems biology approaches. The rodent studies will provide information on type and time point of stressors leading to effects on adult phenotype, gene expression and methylome. The non-human primate study will investigate maternal vs. nursery reared rhesus monkeys. Using a whole genome methylation strategy, expression studies and systems biology approaches, candidate genes and functional gene pathways will be identified in T-cells and neurons. The human study will prospectively examine ELS and its effect on methylation patterns at birth and at 6 month postpartum. Candidate genes and stressors identified in the animal studies will be analyzed in humans. In the end, POSEIDON will contribute to identifying DNA methylation signatures in a convergent approach that could serve as predictive and diagnostic markers also as guidance for prevention and intervention of psychiatric disorders in adulthood.



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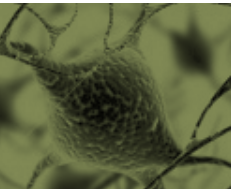
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STNDBS-ICD \ \ SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION FOR THE TREATMENT OF IMPULSE CONTROL DISORDERS

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

SUCCESSFUL PROJECTS

Impulse Control Disorders (ICD), also termed “behavioural addictions” include drug addiction, pathological gambling, shopping, etc. Dopaminergic treatments in Parkinson’s disease (PD) are associated with ICD in 13 % of patients. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been applied to these patients with success. In rats, STN lesions increase impulsive action in various tasks, but can also reduce impulsive choice and motivation for cocaine.

The aim of the present project is to better understand the effects of STN DBS on different forms of impulsivity that could relate to ICD in rats and in PD patients.

We will aim at understanding the contribution of STN in impulsive choice by testing STN DBS in the delay-discounting and the rat gambling tasks in intact or parkinsonian rats. We will then study how STN DBS can possibly decrease addiction to cocaine (model of escalation). In parallel, the effects of STN DBS will be studied in PD patients suffering or not from ICD and tested in similar tasks to those used in the rat and paralleled with electrophysiological recordings and PET imaging.

Taken together the various aims of the project should lead to a better understanding of ICD and eventually to future therapeutic tools for various forms of ICD.



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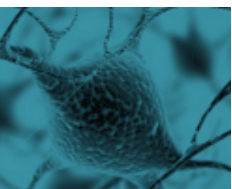
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SuppHab \ \ IMPROVEMENT OF TREATMENT RESISTANT DEPRESSION BY SUPPRESSION OF LATERAL HABENULA ACTIVITY

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

SUCCESSFUL PROJECTS

A significant proportion of patients with major depression is treatment-refractory, presenting a major clinical and societal challenge. Recently, deep brain stimulation (DBS) was tested as a new therapeutic approach for these severely ill patients. DBS, working with thin electrodes, which stimulate very specific brain regions, has been shown to improve motor symptoms in Parkinson's disease patients. It is nowadays a procedure with comparatively low risk due to its reversibility. Here we propose a well-controlled study, in an animal model of depression, to test the clinical therapeutic benefits of DBS of the lateral habenula (LHb). This little brain structure has recently been associated with stress responses, reward and emotional processing. Based on our and other preliminary results, we believe that hyperactivity of this structure plays a central role in depression by inhibiting dopaminergic and serotonergic transmission. This hypothesis will be tested by means of magnetic resonance imaging in a well-known animal model of depression and additionally, and identically, in depressed patients. To test the hypothesis we will first assess if activation and levels of dopamine and serotonin are altered, using imaging and microdialysis techniques, and second, whether these can be restored with DBS of the LHb.

We anticipate that the results of our study will be applicable to humans, since we have successfully performed DBS of the LHb on a first patient who achieved sustained remission.



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TRANSALC \\ TRANSLATIONAL NEUROIMAGING IN ALCOHOLISM: IDENTIFICATION OF ALTERED BRAIN CONNECTIVITY AND TREATMENT EFFICACY PREDICTORS

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SUCCESSFUL PROJECTS

Alcohol addiction or alcoholism is estimated to affect 23 million Europeans (5% of men, 1 % of women) in any given year, making it probably the most prevalent neuropsychiatric disorder afflicting our society today. This disorder can best be defined as a pathological behavioural syndrome, characterised by compulsive drug seeking (craving) with repeated relapses into heavy drinking. These events may occur even after long periods of abstinence, in spite of obviously disastrous consequences for the individual concerned, including fatality. Available medications for relapse prevention do not meet the extensive clinical needs.

Promising new molecular targets have been put forward by animal models, but several clinical trials aimed to exploit this potential have fallen short to expectations. One strategy to improve the predictive validity of animal tests is to use translational biomarkers, i.e. disease-related responses that are largely homologous between humans and animals. TRANSALC aims to identify brain responses to pharmacotherapy that are comparable between patients and animal models of alcoholism by employing cutting-edge magnetic resonance imaging (MRI) techniques for investigation of morphological and functional connectivity in the living brain.

We put together an international consortium with highly complementary expertise in the fields of alcoholism and neuroimaging seeking to reveal alcoholism-specific connectivity maps and knowledge about their modification by clinical reference compounds in humans and animals. Based on this information, we expect to better predict the effects of experimental drugs proposed for treatment of alcoholism in human patients.

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