AGENCE NATIONALE DE LA RECHERCHE

Presentation of the funded projects in 2010 for the « ERA-Net NEURON – Mental Disorders » Programme

« ERA-Net NEURON – Mental Disorders » programme

YEAR 2010

	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
Abstract	Most of proteins encoded by genes involved in mental retardation (MR) and autism disorder (AD) are associated to 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 open the possibility of future therapeutic approaches for such invalidating disorders. Previous efforts to decipher the pathophysiological mechanisms of MR lay on the functional characterization of mouse models. Here we propose to use a recent 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 that 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 assess lentivirus-mediated site-specific integration of cDNA constructs into defect genes and to gene-correct mutant iPS as possible cell therapy.
Partners	IRCCS Foundation, National Neurological Institute Carlo Besta, Milano, Italy Leibniz Institute for Neurobiology, Magdeburg, Germany Institut Cochin, Paris, France International Institute of Molecular and Cell Biology, Warsaw, Poland
Coordinator	Carlo Sala (Italy) French correspondant: Pierre Billuart
ANR funding	159 000 k€ (French partner)

Starting date and duration	February 2011 - 36 months
Reference	ANR-10-NEUR-001

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YEAR 2010

	AUSZ_EUCan FROM AUTISM TO SCHIZOPHRENIA: Study of the genetic mechanisms underlying brain dysfunction and structural phenotypes in schizophrenia and autistic spectrum disorders
Abstract	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.
Partners	INSERM Université Paris Descartes, Hôpital Sainte-Anne, Paris, France Université de Montréal, Montréal, Canada Universitat de Barcelona, Barcelona, Spain Hospital General Universitario Gregorio Marañón, Madrid, Spain Max Planck-Institute for Experimental Medicine, Goettingen, Germany
Coordinator	Marie-Odile Krebs (France)
ANR funding	198 969 k€ (French partner)

Starting date and duration	February 2011 - 36 months
Reference	ANR-10-NEUR-002

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YEAR 2010

	EUHFAUTISM European High-functioning Autism network: Translational research in a phenotypically well characterised sample
Abstract	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.
Partners	Institut Pasteur, Paris, France INSERM, Créteil, France INSERM, Paris, France JW Goethe University Frankfurt, Frankfurt, Germany University of Seville, Seville, Spain
Coordinator	Thomas Bourgeron (France)
ANR funding	440 000 k€ (French partners)
Starting date and duration	March 2011 - 36 months
Reference	ANR-10-NEUR-003

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YEAR 2010

	NICO-GENE Modeling human polymorphisms for nicotine addiction in mice
Abstract	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 the 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.
Partners	Institut Pasteur, Paris, France Istituto Di Ricovero e Cura a Carattere Scientifico, Pozzilli, Italy Universitat Pompeu Fabra, Barcelona, Spain
Coordinator	Uwe Maskos (France)
ANR funding	198 000 k€ (French partner)
Starting date and duration	January 2011 - 36 months
Reference	ANR-10-NEUR-004

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YEAR 2010

	STNDBS-ICD Subthalamic Nucleus Deep Brain Stimulation for the treatment of Impulse Control Disorders
Abstract	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.
Partners	CNRS, Marseille, France University of British Columbia, Vancouver, Canada FIMA, Pamplona, Spain
Coordinator	Christelle Baunez (France)
ANR funding	218 853 k€ (French partner)
Starting date and duration	March 2011 - 36 months
Reference	ANR-10-NEUR-005

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YEAR 2010

	SuppHab Improvement of treatment resistant depression by suppression of lateral habenula activity
Abstract	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 assess, using imaging and microdialysis techniques, first, if activation and levels of dopamine and serotonin are altered and, second, if those can be restored with DBS of the LHb. Additionally, we will assess within the rat model the behavioral and cognitive responses to 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.
Partners	Central Institute of Mental Health, Mannheim, Germany University of Strasbourg, Strasbourg, France Hadassah Hebrew University, Jerusalem, Israel Otto v. Guericke University, Magdeburg, Germany
Coordinator	Alexander Sartorius (Germany) French correspondant: Jean-Christophe Cassel
ANR funding	221 932 k€ (French partner)
Starting date	March 2011 - 36 months

and duration	
Reference	ANR-10-NEUR-006