Présentation des projets financés au titre de l'édition 2010 du Programme « ERA-Net NEURON – Maladies Mentales »

Programme « ERA-Net NEURON – Maladies Mentales »

Edition 2010

	AMRePACELL Développement de nouveaux modèles expérimentaux pour le retard mental et l'autisme par la technologie IPS : génération de neurones humains affectés et de modèles animaux par reprogrammation des fibroblastes de peau et tests de correction des gènes à l'aide de modèles in vitro et in vivo
Résumé	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.
Partenaires	IRCCS Foundation, National Neurological Institute Carlo Besta, Milano, Italie Leibniz Institute for Neurobiology, Magdeburg, Allemagne Institut Cochin, Paris, France International Institute of Molecular and Cell Biology, Warsaw, Pologne
Coordinateur	Carlo Sala (Italie) Correspondent français : Pierre Billuart

Aide de l'ANR	159 000 k€ (partenaire français)
Début et durée	Février 2011 - 36 mois
Référence	ANR-10-NEUR-001

Programme « ERA-Net NEURON »

Edition 2010

	AUSZ_EUCan De l'autisme à la schizophrénie : étude des mécanismes génétiques dans les dysfonctionnements du cerveau et les phénotypes dans la schizophrénie et les troubles du spectre autistique
Résumé	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.
Partenaires	INSERM Université Paris Descartes, Hôpital Sainte-Anne, Paris, France Université de Montréal, Montréal, Canada Universitat de Barcelona, Barcelona, Espagne Hospital General Universitario Gregorio Marañón, Madrid, Espagne Max Planck-Institute for Experimental Medicine, Goettingen, Allemagne
Coordinateur	Marie-Odile Krebs (France)

Aide de l'ANR	198 969 k€ (partenaire français)
Début et durée	Février 2011 - 36 mois
Référence	ANR-10-NEUR-002

Programme « ERA-Net NEURON »

Edition 2010

	EUHFAUTISM Réseau Européen sur l'autisme de haut niveau : Recherche translationnelle sur un échantillon bien caractérisé phénotypiquement
Résumé	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.
Partenaires	Institut Pasteur, Paris, France INSERM, Créteil, France INSERM, Paris, France JW Goethe University Frankfurt, Frankfurt, Allemagne University of Seville, Seville, Espagne
Coordinateur	Thomas Bourgeron (France)
Aide de l'ANR	440 000 k€ (partenaires français)
Début et durée	Mars 2011 - 36 mois
Référence	ANR-10-NEUR-003

Programme « ERA-Net NEURON »

Edition 2010

	NICO-GENE Modélisation chez la souris des polymorphismes humains impliqués dans la dépendance à la nicotine
Résumé	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.
Partenaires	Institut Pasteur, Paris, France Istituto Di Ricovero e Cura a Carattere Scientifico, Pozzilli, Italie Universitat Pompeu Fabra, Barcelona, Espagne
Coordinateur	Uwe Maskos (France)
Aide de l'ANR	198 000 k€ (partenaire français)
Début et durée	Janvier 2011 - 36 mois
Référence	ANR-10-NEUR-004

Programme « ERA-Net NEURON »

Edition 2010

	STNDBS-ICD Stimulation cérébrale profonde du noyau sous-thalamique pour le traitement des troubles compulsifs
Résumé	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.
Partenaires	CNRS, Marseille, France University of British Columbia, Vancouver, Canada FIMA, Pamplona, Espagne
Coordinateur	Christelle Baunez (France)
Aide de l'ANR	218 853 k€ (partenaire français)
Début et durée	Mars 2011 - 36 mois
Référence	ANR-10-NEUR-005

Programme « ERA-Net NEURON »

Edition 2010

	SuppHab Amélioration de la dépression résistante au traitement par la suppression de l'activité de l'habenula latérale
Résumé	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.
Partenaires	Central Institute of Mental Health, Mannheim, Allemagne University of Strasbourg, Strasbourg, France Hadassah Hebrew University, Jerusalem, Israël Otto v. Guericke University, Magdeburg, Allemagne
Coordinateur	Alexander Sartorius (Allemagne) Correspondent français : Jean-Christophe Cassel
Aide de l'ANR	221 932 k€ (partenaire français)

Début et durée	Mars 2011 - 36 mois
Référence	ANR-10-NEUR-006