

## Inserm 2016 Host Laboratories and Research Programs

### 1. Giovanni Marsicano

#### **Role of Mitochondrial Type-1 Cannabinoid Receptors (mtCB1) in Functions: Linking Bioenergetics to Behavior**

Cannabinoid receptors are the targets of the psychoactive component of the plant *Cannabis sativa* (marijuana), delta-9-tetrahydrocannabinol (THC). Type-1 cannabinoid receptors (CB1) are the G protein coupled receptors most abundantly expressed in the brain and mediate most of the effects of THC. Our recent work demonstrated that CB1 receptors are expressed in many different brain cells where they are involved in several functions, including reward, memory, food intake, fear processing, and others.

Brain bioenergetics and behavior: a missing link. The brain weighs only 2% of the body, but it consumes up to 20% of its energy, indicating that bioenergetics processes play a particular role in this organ. However, little is known concerning the direct links between brain bioenergetics and behavior. Besides their classical localization at the presynaptic neuronal terminal plasma membrane, we recently showed that intracellular CB1 receptors are functionally present at mitochondrial membranes of brain cells (mtCB1), where they control respiration and adenosine triphosphate production. This discovery paves the way to a better understanding of the link between brain bioenergetics and behavior.

A cannabinoid link between mitochondria and behavior. We recently developed specific genetic tools to dissociate the functions of mtCB1 receptors from the other pools of CB1 in specific cells of the mouse brain. The postdoctoral project will involve the use of these tools to better understand the role of mtCB1 receptors in behavior and the associated molecular mechanisms.

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### 2. Gonzalez Bruno

#### **Identification of Placental Biomarkers of Neurovascular Defects in the Fetal Brain After *In Utero* Alcohol Exposure**

Fetal alcohol syndrome (FAS) is the most severe form of fetal alcohol spectrum disorders (FASD). However, most children with *in utero* alcohol exposure do not exhibit all features of FAS, and a challenge for clinicians is to make an early diagnosis of FASD to avoid lost opportunities for care. Correct neurodevelopment requires proper angiogenesis, and we previously demonstrated that alcohol impairs fetal brain vasculature. Since the placenta provides angiogenic factors, we hypothesized that it is involved in alcohol-induced brain defects (patent FR1555727, 2015). The objectives of the present project are (1) the demonstration of functional links between placental angiogenic factors and fetal brain angiogenesis, and (2) the characterization of vascular-dependent neurodevelopmental defects induced by *in utero* alcohol exposure.

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### 3. Anne Lise Pitel

#### **Neuropsychology and Neuroimaging of Alcohol Dependence With and Without Korsakoff's Syndrome**

Chronic and excessive alcohol consumption results in brain abnormalities associated with cognitive and motor impairments lying along a continuum from mild to moderate in alcohol-dependent subjects without neurological complications to severe in those with Korsakoff syndrome. The goal of the project is to use neuropsychological testing and multimodal imaging (structural and functional magnetic resonance imaging and FDG-PET) to (1) better understand the specificity of brain dysfunction in Korsakoff patients compared with non-Korsakoff alcoholics, (2) examine whether recovery of brain dysfunction occurs in Korsakoff syndrome, and (3) provide biomarkers that would enable clinicians to detect patients at risk of developing Korsakoff syndrome at an early stage to optimize treatment outcome. Cross-sectional and longitudinal neuropsychological and neuroimaging data have been collected in French alcohol-dependent subjects with and without Korsakoff syndrome.

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### 4. Vincent Vialou

#### **Study of Hevin's Regulation, Mode of Action, and Function in the Normal and Pathological Brain: Focus on Cocaine Addiction**

Matricellular proteins, such as hevin, mediate interaction between cells and the extracellular matrix and are essential regulators of synaptic function and architecture. Hevin's role in resilience, in synaptogenesis, and its presence at excitatory synapses in nucleus accumbens suggests that hevin is involved in the neuroplasticity underlying positive affect and motivation. My main objective is now to understand the regulation and the role of hevin in the adaptation to drugs of abuse. The working hypothesis is that neuronal activity regulates hevin, which in turn affects neuronal identity and the neuronal network.

To grasp hevin's mechanism of action, we will use primary neuronal cultures to determine the mechanism controlling and regulating hevin. Furthermore, to distinguish between pre- and postsynaptic effects, we will use microfluidic devices to reconstruct a neuronal network in collaboration with Dr. Peyrin in our Institute. Cortical and striatal neuronal cultures are grown in a separate but connected compartment. Asymmetric micro-channels impose unidirectional axon connectivity such that only glutamatergic cortical axons connect to striatal GABAergic neurons. Finally, using SNAP-tag technology, we will study the time course of hevin release and action upon neuronal activation using pharmacogenetics.

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## 5. Francois Tronche

### Role of Brahma and BRG1 Chromatin Remodelers in Behavioral Responses to Drugs of Abuse

Clinical and preclinical research strongly suggests that the stress response is a key determinant in the appearance of addiction. Stress release of glucocorticoids activates their receptors (GR). We demonstrated that GR gene inactivation in dopaminergic neurons was sufficient to strongly reduce behavioral responses to a psychostimulant and to block the development of social aversion following repeated aggressions.

Refine anatomical dissection of GR gene functions. To dissociate the effects of GR gene inactivation in the prefrontal cortex from the effects of its inactivation in the nucleus accumbens core, we will generate mice deprived of GR in either one or the other of these structures, using viral delivery of the Cre recombinase.

Understand epigenetic mechanisms underlying GR function. GR controls gene expression in part by recruiting chromatin remodeler complexes containing brahma or BRG1 that shape the chromatin and may be responsible for long-lasting changes in gene expression. We established mouse lines deprived of Brm, BRG1, and both proteins in dopaminergic neurons. Their behavior will be compared with that of GR mutants to reveal whether the interaction of Brm and BRG1 with GR sustains responses to cocaine.

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## 6. Marie-Odile Krebs

### **Stress and Cannabis: Crossed Vulnerability During Adolescence to Long-Lasting Cognitive and Behavioral Impairments in Adults**

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## 7., 8., and 9. Roch Giorgi

### **Epidemiology and Social Sciences in the Field of Addictions**

**Project 7:** OUTSIDER project: An OUTreach Safer Injecting Drugs Education Research to reduce HIV/hepatitis C virus (HCV) risk transmission in people who inject drugs in France. The main objective is to evaluate the impact of a community-based intervention consisting of an individually tailored educational session on injecting practices and provide information about HIV-HCV prevention and care in an outreach context among difficult-to-reach populations of people who inject drugs in France.

**Project 8:** STIMAGO project: A pharmacological study to assess the effective dose of methylphenidate (MPH) in cocaine-dependent individuals using a combination of socio-behavioral and pharmacokinetic approaches preliminarily to a randomized clinical trial to evaluate the efficacy of MPH for cocaine dependence.

**Project 9:** BupIV trial: A clinical trial assessing the efficacy of intravenous buprenorphine for opioid-dependent individuals who have failed with oral opioid substitution treatment.

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## 10. Marcello Solinas

### **Role of Cognitive Training on Cocaine Self-Administration in Rats**

Exposure to environmental enrichment (EE) produces profound positive effects on drug addiction. EE is composed of different types of stimulation including social interaction, physical activity, and cognitive stimulation. In this project, we will investigate whether cognitive stimulation by itself can also be beneficial in animal models of addiction. Our working hypothesis is that training rats in cognitive tasks that require inhibitory control prior to a self-administration session will reduce both active drug taking and risks of relapse. We will use operant cognitive tasks that we have developed in our laboratory and self-

intravenous administration of drugs. In addition, provided that positive results are obtained, we will use molecular techniques to investigate the neurobiological mechanisms involved.

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## 11. Laurence Lanfumey

### Ethanol and Epigenetic Regulations in the Mouse Brain

We have recently shown that chronic and moderate ethanol intake could regulate cell proliferation in the adult C57BL/6J mouse hippocampus. This effect involved chromatin remodeling and brain-derived neurotrophic factor (BDNF) overexpression associated with an increase in transcriptional activity due to an inhibition of histone deacetylases' expression and a hypomethylation of the main CpG islands present within the BDNF gene. Interestingly, while neurogenesis is known to influence hippocampus-dependent learning and memory, we showed that the epigenetic-induced increase in neuroplasticity factors after ethanol intake did not increase hippocampal long-term potentiation. However, memory-related behaviors were affected by ethanol. To further characterize the effects of ethanol, we propose to use novel pharmacological tools, targeting either epigenetic enzymes or the BDNF/TrkB complex to dissect the effects of ethanol.

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## 12. Mickael Naassila

### Looking for a Marker of Alcohol Addiction: Is Loss of Phasic Dopamine Release and Synaptic Plasticity Critical?

The objectives of this proposal are to determine the neural substrates of the alcohol addiction process and especially the changes in phasic dopamine release and synaptic plasticity that may represent the keystone by which alcohol hijacks reward circuits and leads to an overlearning of cues predicting drug availability. Identifying this keystone action of alcohol also targets phasic dopamine release as a potential therapeutic intervention. The present project is aimed at elucidating the neurobiological bases of alcohol addiction using relevant preclinical models of alcohol addiction (using the inhalation procedure to induce both physical and psychological dependence) and the technical approaches such as *in vivo* electrochemical (fast cyclic voltammetry) and *ex vivo* electrophysiological recording techniques.

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### 13. Jocelyne Caboche

#### Epigenetic Regulation in Addiction: Role of miR128b

Addiction is a chronic disease characterized by a loss of control over use and compulsive drug taking, in spite of adverse effects on health and psychological state. It is now well established that this pathology relies on neuroadaptative processes in specific brain areas: the «reward circuitry». This project will study the molecular mechanisms that underlie cocaine-induced neuroadaptation in the striatum, with a particular emphasis of the short noncoding RNA: miR128b. We will collaborate with Dr. Anne Schaefer (anne.schaefer@mssm.edu), assistant professor at Icahn School of Medicine at Mount Sinai in New York, who generated a transgenic mouse that can overexpress miR128b. This miRNA controls the neuronal excitability and locomotor activity; miR128b will be overexpressed in striatal neurons expressing D1 receptors specifically. We will study in these mice cocaine-induced long-term behavioral responses (locomotor sensitization, conditioned place preference). Postmortem, on striatal slices, we will study intracellular signaling pathways (MAPkinase/ERK; Elk-1 CREB) and gene regulation induced by cocaine. This study will provide new therapeutic avenues in addiction.

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### 14. Jean-Louis Laplanche and Bruno Mégarbane

#### Addiction Properties of the New Synthetic Cathinones: A Behavioral and Molecular Approach

The use of synthetic cathinones in the recreational scene is exponentially spreading. However, only limited experimental data support their potential for abuse. The objective of this project is to investigate the addictive potential of different cathinones in comparison to cocaine and amphetamine in a rodent model of addiction and study their involvement on dopamine in reward-related behaviors through the mesolimbic dopaminergic pathway using an *in vivo* microdialysis approach. The contribution of different monoamines and specific transporters at the blood-brain barrier will be studied. In this proposal, we will combine behavioral, neurochemical and pharmacokinetic approaches after acute and repeated administration, to better understand the mechanisms involved in cathinone abuse.

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## 15. Jean-Louis Laplanche and Frank Bellivier

### **Mutation Screening, Genetic Association and Gene-Gene Interaction Modeling Studies in Addiction**

Our research team is involved in clinical phenotyping and biological sampling of cohorts of drug abusers (mainly of cocaine and opiates). We use a variety of approaches such as transcriptional profiling, molecular genetics, and genome-wide epigenetics in combination with extensive clinical characterization to study vulnerability factors to addictions as well as factors influencing illness course. Ongoing projects on cocaine addiction include next-generation sequencing of a large cohort of cocaine addicts and controls, targeting a pathway possibly involved in cocaine dependence according to preclinical studies. In addition, a single nucleotide polymorphism-based gene association study is ongoing in patients with complex addiction (polydependence) regarding the subjective effects of first cocaine use. The objective of the project is to establish gene association and gene-gene interaction modeling studies in addiction based on a large and complex set of data.

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## 16. Jean-Luc Martinot

### **Outcome of Cannabis and Other Addictions: Multidisciplinary Database of Adolescents**

Substances of abuse such as cannabis have deleterious effects on the brain maturation at adolescence that can be tackled by multimodal magnetic resonance imaging techniques acquired in the context of an international cohort. Participants were assessed for psychometry, neuropsychology, and genome-wide association study, and their parents completed questionnaires. INSERM Unit 100 is a partner in this unique resource database, which includes multidisciplinary data from >2,000 14-year-old adolescents who were followed up. Outcome data at ages 16 and 18 might be available for analysis.

Raising specific hypotheses on the relationships between these brain images and psychobehavioral or genetic data, and performing the analyses would be part of the research exchange. This might be of interest for further French–U.S. collaboration as regards brain imaging and bioinformatics applied to addiction.

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