Project 6:

TITLE OF THE COLLABORATIVE PROJECT

PATTERNS OF NEUROCIRCUITRIES MODIFICATION IN ALCOHOLISM: IN VIVO ASSESSMENT IN MOUSE MODELS OF ALCOHOL ADDICTION

Brigitte Kieffer, IGBMC, University of Strasbourg

Jürgen Hennig, BCF, University of Freiburg

1. PARTNERS INVOLVED IN THE COLLABORATION

Lead Higher Education Institute (HEI 1)

Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), University of Strasbourg, France

Name and laboratory address of the thesis advisor at HEI 1

Prof. Brigitte Kieffer - Institut de Génetique et de Biologie Moleculaire et Cellulaire (IGBMC), Dep. Of Neurobiology and Genetics, 1 rue Laurent Fries BP 10142, F-67404 ILLKIRCH FRANCE - Email: briki@igbmc.fr

Partner Higher Education Institute (HEI 2)

Bernstein Center Freiburg at the University of Freiburg, Germany

Name and laboratory address of the thesis advisor at HEI 2

Prof. Dr. Jürgen Hennig **-** Advanced Molecular Imaging Center, Medical Physics - Department of Radiology, University Medical Center, Breisacher Straße 60, PH2a, D-79106, Freiburg, Germany

Email: juergen.hennig@uniklinik-freiburg.de

2. DESCRIPTION OF THE COLLABORATIVE PROJECT

Neuroimaging studies enabled the examination of the alcoholism's dynamic course and its effects on the brain microstructure and function during periods of drinking and sobriety. Modifications in the brain fibers integrity and disruption of different neural circuitries1 were noticed. However, the alcohol induced modifications can vary with multiple factors overtime, including sex[2], genetic[3], age at alcohol exposure[4], etc. Such factors are only possible to control and document in longitudinal animal studies designed for identifying and tracking the relative contribution of the relevant variables. In this context, the aim of our project is to combine brain magnetic resonance imaging (MRI), genetic and molecular approaches for examining the brain adaptations to alcohol exposure, in validated animal models of alcoholism[5]. Using structural and functional brain MRI, we will study the pathological brain neurocircuitry changes in mouse models that mimic the various stages of alcohol addiction cycle. Recreational alcohol drinking, excessive alcohol drinking and alcohol intoxication models are currently developed in the Strasbourg Lab. (IGBMC) and will be included in our experimental paradigms. To test the hypothesis that the endogenous opioid system[6,7] as well as other novel candidate genes for alcoholism (Nr4a1 and Gpr88), contribute to modification of brain connectivity during alcohol addiction we will also image knockout mice for the genes of interest (provided by IGBMC). Cutting edge mouse brain imaging approaches will be applied using the knowledge and technology available in the Freiburg Lab. In-vivo non-invasive mouse brain DTMRI and fiber tracking[8] will be used to map the structural connectivity fingerprints and to check the brain fibers integrity overtime in the same individuals, at different stages of the addiction cycle. The functional relevance of any identified alterations will be assessed by implementing the functional connectivity (fcMRI) methodology (resting state fMRI) for the mouse brain and by using parallel behavioral tests. All the mouse brain imaging experiments will be carried-out in Freiburg where two high field (9.4 T and 7 T) MRI scanners, dedicated for small animal research are available, along with latest mouse brain adapted CryoProbe, known to provide increased sensitivity and to improve both temporal and spatial resolution for brain imaging. This study will expand our understanding on the brain adaptations to alcohol exposure overtime and will give insight about the implication of novel genes in alcohol intoxication, intake and dependence at molecular and neuronal network level.

We estimate equal mobility periods, shared by the PhD student between Strasbourg (for the animal models generation) and Freiburg Lab (for the brain imaging part). The project provides multidisciplinary training using state-of-the-art techniques and therefore the successful candidate will be well placed for a future career in biomedical and neuroimaging sciences.

1. Sullivan, E.V. and A. Pfefferbaum. 2005. Neurocircuitry in alcoholism: a substrate of disruption and repair. Psychopharmacology (Berl),
180(4): p. 583-94.
2. Pfefferbaum, A., et. Al, 2001. Sex differences in the effects of alcohol on brain structure. Am J Psychiatry, 158(2): p. 188-97.
3. Edenberg, H.J., et. al., 2008. Association of NFKB1, which encodes a subunit of the transcription factor NF-kappaB, with alcohol dependence. Hum Mol Genet, 17(7): p. 963-70.
4. Riley, E.P., et al., 2003. Neurobehavioral consequences of prenatal alcohol exposure: an international perspective. Alcohol Clin Exp Res, 27(2): p. 362-73.
5. Contet C, Gardon O, Filliol F, Koob GF and **Kieffer BL.** (2011) Identification of genes regulated in the mouse extended amygdala by excessive ethanol drinking associated with dependence Addiction Biology 16, 615-9.
6. Contet C. S, **Kieffer B. L.** and Befort K. (2004) Mu opioid receptor: a gateway to drug addiction. Curr. Op. Neurobiol. 14, 1-9.
7. Le Merrer J, Becker JAJ, Befort K and **Kieffer BL** (2009) Neural Bases of Addictive Behaviors: Brain Sites for Expression, Activity and Regulations of the Opioid System. Physiol. Rev 89, 1379.
8. Harsan, L.A., et. Al., 2010. In vivo diffusion tensor magnetic resonance imaging and fiber tracking of the mouse brain. NMR Biomed, 23(7): p. 884-96.

3. REQUIREMENTS FOR THE FELLOWSHIP

Applicants should have a BSc in biology/physics/biomedical science and a MSc in Neuroscience, Medical Physics, Computational Neuroscience or Bioengineering (or in a related field), with a particular interest in imaging techniques to study biological systems. Expertise and training in either molecular biology, biophysics, imaging or animal model is desirable. Strong intrinsic motivation and an interest to study neuroscience from cellular function to neurocircuitry formation are required. An interest in using MatLab routines for MRI data analysis would be advantageous.