Proposition de sujet de thèse à l’appui d’une demande de contrat doctoral 2019-2020

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Titre du sujet proposé :
Recherche de biomarqueurs interindividuels dans les processus d’entrée dans la psychose à l’adolescence : focus sur la voie de signalisation Wnt
Inter-individual biomarkers for psychosis onset at adolescence: focus on Wnt signalling

Département:
- [ ] Biologie Cellulaire et moléculaire, Physiologie et Physiopathologie
- [ ] Immunologie
- [✓] Développement Génétique Neurobiologie et Vieillissement
- [ ] Infectiologie, Microbiologie

Summary (5 lines maximum) :
Molecular changes occurring during psychosis onset could correspond to biomarkers, crucial to predict the evolution toward schizophrenia (SCZ) and could open on new personalized therapies. Wnt signalling factors are great candidates for SCZ pathophysiology and our recent results show their involvement the onset of the disease. Using multiscale approaches, changes in Wnt pathways at adolescence in animal models for SCZ will be explored and targeted for rescue of the behavioural abnormalities.
Schizophrenia (SCZ) is a frequent disabling psychotic disorder with considerable human and social burden. It usually appears at adolescence, a period of time where brain maturation is still very active and is subject to various environmental insults, such as drug consumption or stress. Early therapeutic intervention has been shown to ameliorate long-term prognosis. Therefore, biomarkers to detect as early as possible the disease and more personalised and targeted treatments are urgently needed.

In pioneering studies, the host lab showed that psychosis onset is associated with longitudinal change during adolescence in gene involved in synaptic functions. These changes could be used as biomarkers if they are confirmed to be associated with the disease onset and represent promising targets for personalised therapeutic approaches when they are dysregulated. Among candidates that regulate neurodevelopment and synaptic structure and function, the Wnt signalling pathway has already been put forward as involved in the pathophysiology of SCZ. However, which component of this pathway, its concrete involvement and whether Wnts are involved in any forms of the pathology remain to be established.

In the PhD program, the student will study different animal models for SCZ, to account for the heterogeneity of the pathophysiology and the origin of the disorder. Double hit models will be favoured (e.g. prenatal methylazoxypethanol (MAM) exposure or maternal immune activation models followed by THC or stress exposure during adolescence). In the first Work Packages (WP1), longitudinal correlates between behavioural assessments and brain expression patterns of a wide network of genes constituting Wnt signalling will be explored. WP2 will address in vivo whether targeting these dysregulated Wnt components, using either modulation by genetic modification or existing drugs targeting Wnt pathways developed for other diseases, can reverse or prevent the development of SCZ-like behavioural abnormalities in rat models for SCZ. This translational project is based on the expertise of the supervisors on animal models for SCZ and Wnt signalling and will take advantages of the great access to state of the art behavioural and molecular technological platforms at IPNP. It will contribute to understand the role of Wnt component changes in SCZ onset and guide new therapies development.