Proposal for the 2020 Imagine International PhD program

Laboratory: **Developmental Brain Disorders Lab**
Head of laboratory: Vincent Cantagrel
Project and student supervisor: Cantagrel Vincent (HDR)
Number of HDR in the lab: 3
Field of research: Neurogenetics
Number and names of PhD students currently in the lab in 2020: One : Ekin Ucuncu 4th Year-FRM/INSERM
Number and names of PhD students under the Imagine program: None (Ekin is an Ex-PhD international).
Project Title: Genetic and pathological mechanisms involved in cerebellar developmental defects

Project description (Max 2 pages including abstract and publications)

Genetic and pathological mechanisms involved in cerebellar developmental defects

This project aims to decipher the molecular defects underlying pediatric neurological disorders affecting the cerebellum structure and function with consequences on psychomotor development. This project will focus more specifically on a disease called **pontocerebellar hypoplasia** (PCH). Affected children have a smaller cerebellum (hypoplasia) with a decreased volume of the ventral pons, a part of the brainstem. The clinical features include a very limited motor and cognitive development, swallowing and feeding difficulties along with limb spasticity. This condition is usually lethal within the first 10 years of life, and no treatments exist. The genetic bases are only partially known and clear hypothesis are lacking about its pathogenesis. The leading hypothesis is an **excess of cell death affecting neural progenitors and neurons during cerebellum development**. Several pathways have been identified including RNA processing and degradation, protein translation regulation and inositol phosphate metabolism. Yet, how disruption of genes ubiquitously expressed specifically affects cerebellar and pontine cells remains puzzling. Moreover, the exact defect at the cellular level has not been clearly characterized yet.

Aim 1: Identifying new molecular causes and mechanisms for PCH and other Cerebellar developmental defects using Next-Generation Sequencing techniques (NGS). A cohort of patients from Necker hospital is currently being genetically characterized using high-throughput sequencing of the coding part of the genome (a technique called "Whole-exome sequencing") or the full genome (called "Whole-genome sequencing"). In addition to these genomic data, a transcriptomic data set from patient's cells, including iNeurons (see aim2) will be used to help the interpretation of regulatory mutations. This approach will allow the identification of new mutations and genes involved in this defect.

Aim 2: Characterize new developmental mechanisms involved in pontocerebellar hypoplasia. We have recently identified new candidate and validated genes involved in PCH. Some of these genes are predicted to play a key role in cerebellum and brainstem neuron differentiation and for others the role during hindbrain development is completely unknown. To study the cellular consequences of the disruption of these genes, human neuronal stem cells (NSCs) or potentially induced neurons (iN) with patient's mutation will be studied. He/she will use live cell imaging to study cell proliferation, survival or differentiation in NSCs or iN. In parallel, a transcriptomic approach will be undertaken to understand how the cell differentiation program is affected and could cause neural cell death.

This project should enable a better diagnosis of patients and allow deeper understanding of the molecular and cellular mechanisms that govern the development of the cerebellum.

Lab members

Research scientists and clinicians: Valérie Malan**;** Anne Philippe**;** Giulia Barcia**;** Marlène Rio**;** Karthyayani Rajamani**;** Lydie Burglen.
M2 and PhD Students: Romain Nicolle (M2), Lotte Philippen (M2), Ekin Uçünçü (PhD)
Research assistant: Karine Siquier-Pernet

***Major Publications* (Bold: Lab PhD students)**

1- **Medina-Cano D**, **Ucuncu E**, Nguyen LS, Nicouleau M, Lipecka J, Bizot JC, Thiel C, Foulquier F, Lefort N, Faivre-Sarrailh C, Colleaux L, Guerrera IC, Cantagrel V (2018).
High N-glycan multiplicity is critical for neuronal adhesion and sensitizes the developing cerebellum to N-glycosylation defect.
eLife. 2018 Oct 12;7.

2- Chemin J, Siquier-Pernet K, Nicouleau M, Barcia G, Ahmad A, **Medina-Cano D**, Hanein S, Altin N, Hubert L, Bole-Feysot C, Fourage C, Nitschk√© P, Thevenon J, Rio M, Blanc P, Vidal C, Bahi-Buisson N, Desguerre I, Munnich A, Lyonnet S, Boddaert N, Fassi E, Shinawi M, Zimmerman H, Amiel J, Faivre L, Colleaux L, Lory P, Cantagrel V (2018).
De novo mutation screening in childhood-onset cerebellar atrophy identifies gain-of-function mutations in the *CACNA1G* calcium channel gene.
Brain. 141(7):1998-2013.

3- D Mircsof*****, **M Langouet***, M Rio, S Moutton, K Siquier-Pernet, C Bole-Feysot, N Cagnard, P Nitschke, L Gaspar, M Znidari, O Alibeu, Ak Fritz, Dp Wolfer, A Schröter, G Bosshard, M Rudin, C Koester, F Crestani, P Seebeck, N Boddaert, Jm Fritschy, A Munnich, J Amiel, Sa Brown, Sk Tyagarajan, L Colleaux (2015).
Mutations in NONO are a novel cause of syndromic intellectual disability and inhibitory synaptic defects.
Nature Neuroscience, 18 :1731-36

4- Akizu N, Cantagrel V et al. (2015)
Biallelic mutations in SNX14 cause a syndromic form of cerebellar atrophy and lysosome-autophagosome dysfunction.
Nature Genetics ;47:528-34

5- Akizu N*, Cantagrel V* et al. (2013).
AMPD2 regulates GTP synthesis and is mutated in a potentially treatable neurodegenerative brainstem disorder.
Cell. 154(3):505-17

6- Cantagrel V et al. (2010).
SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder.
Cell. 2010 Jul 23;142(2):203-17.