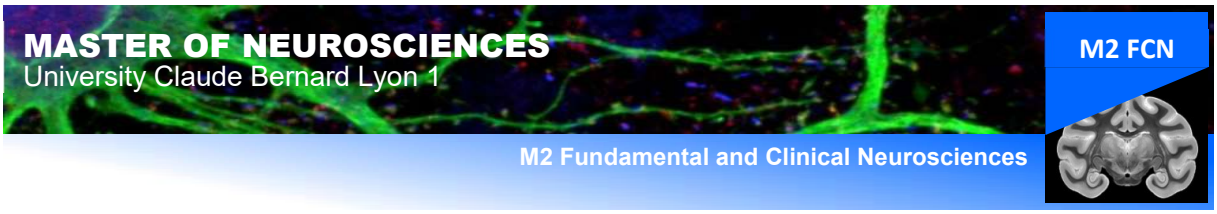

MASTER 2 Fundamental and Clinical Neurosciences

Internship proposal 2022-2023

(internship from January to June 2023)

Host laboratory:
Centre de Recherche en Neurosciences de Lyon
Inserm U1028, CNRS UMR5292, Université Lyon 1
Centre Hospitalier Le Vinatier – Bât. 462 NeuroCampus
95, Boulevard Pinel - 69500 Bron

Host team :
Equipe GENDEV – Génétique des anomalies du neurodéveloppement
Institut IDEE
59, Boulevard Pinel - 69500 Bron
https://www.crnl.fr/fr/equipe/gendev

Internship supervisor : DELOUS Marion, marion.delous@inserm.fr

Project title: Deciphering the physiopathological mechanisms of microcephalic syndromes linked to defective minor splicing

Project summary:
Splicing of pre-messenger RNAs is a crucial step in gene expression. For the majority of species, it is ensured by two distinct machineries, the major and minor spliceosomes. In 2011, the GENDEV team showed that mutations in the U4atac component, specific to the **minor spliceosome** that removes minor introns in ~750 genes in the human genome, are responsible for the **microcephalic** dwarfism syndrome, called Taybi-Linder (TALS). Two other pathologies, presenting similar characteristics but less severe, were then also associated with U4atac. Since the identification of the gene, our team has been working to understand the pathophysiological mechanisms of these syndromes, and why different mutations in the *RNU4ATAC* gene lead to phenotypic variability. Recently, the team uncovered a fourth U4atac-related pathology, the Joubert syndrome (JBTS), a well-known ciliopathy with cerebral anomalies, which suggests an unexpected link between TALS, minor splicing and **the primary cilium**. This link has been confirmed *in vitro* in patients' cells and *in vivo* in a **zebrafish** model we engineered. During his/her internship, the student will study one of the two models we generated, the zebrafish model or the induced pluripotent stem cells (iPSC)-derived **cortical organoids**. The objective of the internship will be the characterization of the cerebral anomalies (global morphology of brain structures and cellular processes known to be involved in microcephaly (proliferation/apoptosis, asymmetric cell division, cell migration,…)). This approach, mostly based on confocal imaging, will be combined to analyses of molecular aspects, i.e. retention of minor introns in candidate genes (qRT-PCR).

3-5 recent publications:
- Khatri D*, Putoux A*, Cologne A, Kaltenbach S, Besson A, Bertiaux E, Guguin J, Fendler A, Dupont M A, Benoit-Pilven C, Grotto S, Ruaud L, Michot C, Castelle M, Guët A, Guibaud L, Hamel V, Bordonné R, Leutenegger A-L, Attié-Bitach T, Edery P, Mazoyer S§ and Delous M§. Deficiency of U4atac snRNA results in ciliary defects. *medRxiv*, doi.org/10.1101/2021.12.12.21266616 (2021)

Please send your proposal to marion.richard@univ-lyon1.fr for publication on the Master of Neuroscience website.

- Benoit-Pilven C, Besson A, Putoux A, Benetollo C, Saccaro C, Guguin J, Sala G, Cologne A, Delous M, Lesca G, Padgett RA, Leutenegger AL, Lacroix V, Edery P[§] and Mazoyer S[§]. Clinical interpretation of variants identified in *RNU4ATAC*, a non-coding spliceosomal gene. *PLoS One*, 15(7):e0235655 (2020)
- Cologne A, Benoit-Pilven C, Besson A, Putoux A, Campan-Fournier A, Bober MB, de Die-Smulders CEM, Paulussen ADC, Pinson L, Toutain A, Roifman C, Leutenegger AL[§], Mazoyer S[§], Edery P[§], Lacroix V[§]. New insights into minor splicing - A transcriptomic analysis of cells derived from TALS patients. *RNA* 25(9):1130-1149 (2019)
- Putoux A, Alqahtani A, Pinson L, Paulussen ADC, Michel J, Besson A, Mazoyer S, Borg I, Nampoothiri S, Vasiljevic A, Uwineza A, Boggio D, Champion F, de Die-Smulders CE, Gardeitchik T, vanPutten WK, Perez MJ, Musizzano Y, Razavi F, Drunat S, Verloes A, Hennekam R, Guibaud L, Alix E, Sanlaville D, Lesca G, Edery P. Refining the phenotypical and mutational spectrum of Taybi-Linder syndrome. *Clin Genet* 90(6):550-555 (2016)
- Edery P, Marcaillou C, Sahbatou M, Labalme A, Chastang J, Touraine R, Tubacher E, Senni F, Bober MB, Nampoothiri S, Jouk PS, Steichen E, Berland S, Toutain A, Wise CA, Sanlaville D, Rousseau F, Clerget-Darpoux F, Leutenegger AL. Association of TALS developmental disorder with defect in minor splicing component U4atac snRNA. *Science*. 332(6026):240-3 (2011).