MASTER 2 Neurosciences Fondamentales et Cliniques
UCB Lyon 1, Lyon, France

Internship proposal 2020-2021
(internship from January to end of May 2021)

Host laboratory:
Centre de Recherche en Neurosciences de Lyon
Inserm U1028, CNRS UMR5292, Université Lyon 1
Centre Hospitalier Le Vinatier – NeuroCampus, Bât 452
95, Boulevard Pinel
69500 Bron

Host team :
GenDev – Genetics of neurodevelopmental anomalies, directed by Patrick Edery
https://crnl.univ-lyon1.fr/index.php/fr/Recherche/Equipes/21

Internship supervisors :
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Project title :
Exploring the effects of human *POC5* mutations on brain and spine morphogenesis in zebrafish

Project summary :
Our group is interested in the genetics and pathogenic mechanisms of idiopathic scoliosis (IS), a multifactorial disorder with autosomal dominant genetic traits. In the past years, the group has gathered a cohort of large families with IS, allowing the identification of the first gene, *POC5*, associated to IS in humans. More recently, a homozygous mutation of *POC5* has been reported in patients with retinitis pigmentosa (RP), short stature and microcephaly, thus suggesting a pleiotropic effect of this gene. To address this point, we propose to study the effects of the IS variants and RP mutation on POC5 function both *in vitro* and *in vivo* in zebrafish. POC5 is a centrosomal protein involved in centriole maturation, important for cell cycle progression, and cilia formation. Cilia are microtubule-based organelles, present at the surface of almost all vertebrate cells. They act as extracellular antennae sensing key signaling factors (Hh, PDGF, Wnt…), essential for development and tissue homeostasis. Motile cilia also function to generate a flow, propelling for example the cerebrospinal fluid (CSF) in the central nervous system. Recently, a strong link has been established between cilia function, CSF and IS, notably in zebrafish that turned out to be an excellent model to study IS.
During his/her internship, the student will analyse the morphology of the spine, brain and retina of zebrafish POC5 models (transgenic and knock-out models) and investigate using

confocal/spinning disk microscopy the link between *POC5* mutations and cell division or cilia formation/function, both *in vitro* (engineered cell lines) and *in vivo*. With this project, the host team is in close contact with other zebrafish labs (C. Wyart, ICM, Paris; S. Schneider-Maunoury, IBPS, Paris) and the student will have the opportunity to go and learn technics in these labs (CSF flow, CSF-contacting neuron activity).

3-5 recent publications :

Dupont MA, Humbert C, Huber C, Siour Q, Guerrera IC, Jung V, Christensen A, Pouliet A, Garfa-Traoré M, Nitschké P, Injeyan M, Millar K, Chitayat D, Shannon P, Girisha KM, Shukla A, Mechler C, Lorentzen E, Benmerah, A, Cormier-Daire V, Jeanpierre C, Saunier S, Delous M. Human IFT52 mutations uncover a novel role for the protein in microtubule dynamics and centrosome cohesion. *Hum Mol Genet*., 28(16):2720-2737 (**2019**).

Reilly ML, Stokman MF, Magry V, Jeanpierre C, Alves M, Paydar M, Hellinga J, Delous M, Pouly D, Failler M, Martinovic J, Loeuillet L, Leroy B, Tantau J, Roume J, Evans CG, Shan X, Filges I, Allingham JS, Kwok BH, Saunier S, Giles RH, Benmerah A. Loss of function mutations in KIF14 cause severe microcephaly and kidney development defects in humans and zebrafish. *Hum Mol Genet*. 28(5):778-795 (**2018**).

Ryan R, Failler M, Reilly ML, Garfa-Traoré M, Delous M, Filhol E, Reboul T, Bole-Feysot C, Nitschké P, Baudouin V, Amselem S, Escudier E, Legendre M, Benmerah A, Saunier S. Functional characterization of tektin-1 in motile cilia and evidence for TEKT1 as a new candidate gene for motile ciliopathies. *Hum. Mol. Genet*., 27(2):266-282 (**2018**).

Grampa V, Delous M*, Zaidan M*, Odye G, Thomas S, Elkhartoufi N, Filhol E, Niel O, Silbermann F, Lebreton C, Collardeau-Frachon S, Rouvet I, Alessandri JL, Devisme L, Dieux-Coeslier A, Cordier MP, Capri Y, Khung-Savatovsky S, Sigaudy S, Salomon R, Antignac A, Gubler MC, Benmerah A, Terzi F, Attié-Bitach T, Jeanpierre C and Saunier S. Novel NEK8 mutations cause severe syndromic renal cystic dysplasia through YAP dysregulation. *PLoS Genet*., 12(3):e1005894 (**2016**). *co-authors

Patten SA, Margaritte-Jeannin P, Bernard JC, Alix E, Labalme A, Besson A, Girard SL, Fendri K, Fraisse N, Biot B, Poizat C, Campan-Fournier A, Abelin-Genevois K, Cunin V, Zaouter C, Liao M, Lamy R, Lesca G, Menassa R, Marcaillou C, Letexier M, Sanlaville D, Berard J, Rouleau GA, Clerget-Darpoux F, Drapeau P, Moldovan F, Edery P. Functional variants of *POC5* identified in patients with idiopathic scoliosis. *J Clin Invest*. 125(3) :1124-8 (**2015**).

Edery P, Margaritte-Jeannin P, Biot B, Labalme A, Bernard JC, Chastang J, Kassai B, Plais MH, Moldovan F, Clerget-Darpoux F. New disease gene location and high genetic heterogeneity in idiopathic scoliosis. *Eur J Hum Genet.* 19(8):865-9 (**2011**).