MASTER 2 BMC- PARCOURS GENOPATH
ANNÉE 2018-19

Titre du sujet de stage :
Exploring the effects of human POC5 mutations on cilia function and spine morphogenesis in zebrafish

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Sujet de stage :
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 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, cerebrospinal flow (CSF) and IS, notably in zebrafish that turned out to be an excellent model to study IS.

During his/her internship, the student will establish knock-down (siRNA/morpholino) or mutant (CRISPR/Cas9) cell and zebrafish lines for POC5, and will use confocal/spinning disk microscopy to study the link between cell division, cilia formation/function (*in vitro/in vivo*), and morphology of the spine, brain and retina in zebrafish.

Mots clés : Idiopathic scoliosis, cilia, zebrafish, spine

Publications du groupe/encadrant :

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

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. (**2015**) Functional variants of *POC5* identified in patients with idiopathic scoliosis. *J Clin Invest*. 125(3) :1124-8.

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, Saunier S. (**2016**) Novel *NEK8* mutations cause severe syndromic renal cystic dysplasia through YAP dysregulation. *PLoS Genet*., 12(3):e1005894.

Macia M, Halbritter J*, Delous M*, Bredrup C, Gutter A, Filhol E, Christensen Mellgren A, Leh S, Braun D, Gee H, Silbermann F, Krug P, Bole-Feysot C, Nitschké P, Joly D, Nicoud P, Paget N, Haugland H, Brackmann D, Ahmet N, Sandford R, Cengiz N, Knappskog P, Boman H, Linghu B, Yang F, Oakeley E, Saint-Mézard P, Sailer A, Johansson S, Rødahl E, Saunier S, Hildebrandt F, Benmerah A. (**2017**) Mutations in *MAPKBP1* cause late onset cilia-independent nephronophthisis. *Am J Hum Genet*, 100(2):323-333.

Ryan R, Failler M, Reilly ML, Garfa-Traore M, Delous M, Filhol E, Reboul T, Bole-Feysot C, Nitschké P, Baudouin V, Amselem S, Escudier E, Legendre M, Benmerah A, Saunier S. (**2018**) 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.