EuReCa International PhD Program

PhD thesis project

2021 Call for application

Acentrosomal microtubule organization in neural stem cells

General information

Call	2021
Reference	2021-01-BAFFET
Keyword(s)	Neural stem cells; microtubules; brain malformations; human cerebral organoids; polarized transport

Director(s) and team

Thesis director(s)	Alexandre Baffet
Research team	Cell Biology of Mammalian Neurogenesis
Research department	UMR 144 - Cell Biology and Cancer

Description of the PhD thesis project

Neurons of the neocortex are generated by neural stem cells called radial glial cells. The relative abundance of these cells varies greatly across species. In particular, they are highly amplified in humans and believed to be critical players in the massive size expansion of the human brain. These polarized cells extend a long basal fiber that acts as a scaffold for neuronal migration.

We recently characterized the organization of the microtubule cytoskeleton in the basal process of mouse and human RG cells (Coquand et al, 2020, BioRxiv, doi: https://doi.org/10.1101/2020.03.16.993295).
We showed that microtubules in the basal fiber display a mixed polarity, reminiscent of the mammalian neuronal dendrite, and identified acentrosomal microtubule organizing centers localized in membrane swellings of the basal fiber.

In this project, we will identify the factors controlling the generation and organization of this acentrosomal microtubule network, and test for the consequences of altered organization on cerebral development. Using iPS-derived human cerebral organoids, as well as mouse models, we will test for the function of factors controlling microtubule severing, minus end capping or acentrosomal nucleation.

We will analyze the consequences on microtubule organization and polarized transport of secreted molecules. Using mutant cerebral organoids, we will test how alteration of these processes affects neural stem cell proliferation, fate, and the development and growth of the cerebral tissue.

The Baffet lab investigates mouse and human brain development with a strong focus on neural stem cells. In particular, we address how cytoskeletal organization and motor proteins, which are severely altered in many patients with brain malformations, are regulated and control polarized transport and asymmetric cell division.
Our lab highly relies on in situ live imaging methods, allowing us to address these questions in real time and within the tissue.

International, interdisciplinary & intersectoral aspects of the project

For this project, we will collaborate with the group of Silvia Cappello (Max Planck, Munich), who has expertise in the genetics of brain malformations.
In particular, her group has recently identified mutations in the LGALS3BP gene as a cause of cerebral heterotopia. Using KO cerebral organoids, they uncovered the role of this secreted factor for proper cerebral development.

In order to image RG cells at a higher resolution, we have developed, in collaboration with Catherine Villard, biophysicist at IPGG, a method for their in vitro culture, coupled to their alignment on micropatterns of adhesion.
This enables us to mimic their in vivo elongated morphology, and study the subcellular localization of regulators of microtubule organization within the basal fiber, with very high resolution.

Recent publications

1. Jacopo A. Carpentieri, Amandine Di Cicco, David Andreau, Laurence Del Maestro, Fatima El Marjou, Laure Coquand, Jean-Baptiste Brault, Nadia Bahi-Buisson, **Alexandre D. Baffet** (2020) Endosomal trafficking defects alter neural progenitor proliferation and cause microcephaly. BioRxiv doi: https://doi.org/10.1101/2020.08.17.254037

2. Coquand L.*, Victoria G. S.*, Tata A., Brault J.B., Guimiot F., Fraisier V., **BAFFET AD** (2020) A dendritic-like microtubule network is organized from swellings of the basal fiber in neural progenitors. BioRxiv doi: https://doi.org/10.1101/2020.03.16.993295

3. Vargas-Hurtado D, Brault JB, Piolot T, Leconte L, Da Silva N, Pennetier C, **BAFFET A**, Marthiens V, Basto R. (2019) Differences in Mitotic Spindle Architecture in Mammalian Neural Stem Cells Influence Mitotic Accuracy during Brain Development. Curr Biol. 29(18):2993-3005.e9.

4. Brault JB, Khou C, Basset J, Coquand L, Fraisier V, Frenkiel MP, Manuguerra JC, Pardigon N, **BAFFET AD**. (2016) Comparative Analysis Between Flaviviruses Reveals Specific Neural Stem Cell Tropism for Zika Virus in the Mouse Developing Neocortex. EBioMedicine 10, 71-76.

5. **BAFFET AD**, Hu D, Vallee R. (2015) Cdk1 activates pre-mitotic nuclear envelope dynein recruitment and apical nuclear migration in neural stem cells. Dev Cell. 33, 1-14.

Expected profile of the candidate

Applicants should have a strong desire to explore cell biological phenomena in an in vivo context, and should show solid capacity for independent and creative thinking.

Background in cell biology, developmental biology and/or stem cell biology is strongly recommended.

The project highly relies on microscopy and live imaging techniques, for which the applicant should have either experience or a strong motivation to learn.