The neocortex is the center for higher brain functions, such as perception, decision-making and language. Our group focuses on the mechanisms governing neocortex development, with a strong interest on the role and regulation of the neural stem cells.

We want to understand how neural stem cell proliferation is tightly controlled, both spatially and temporally, to allow for the efficient formation of the highly organized neocortex. In addition, we wish to characterize how variations in neural stem cells behavior may account for the large expansion of the human brain, but also how alterations may lead to pathological brain development.

During development, neural stem cells called the apical radial glial (aRG) cells give rise, directly or indirectly, to all neocortical neurons, most glial cells and to the adult neural stem cells. aRG cells are highly elongated, extending a basal process all the way to the pial surface of the developing brain and an apical process that remains in contact with the ventricular surface (Fig. 1). They can divide symmetrically to produce two self-renewing aRG cells or asymmetrically to produce one aRG cell and one intermediate progenitor that will divide to produce two neurons. Following cell division, the newly generated neurons migrate towards the cortical plate along the basal processes of aRG cells. Therefore, aRG cells serve both as neural stem cells and as tracks for neuronal migration, positioning them at the very centre of neocortical development.
aRG cells undergo fascinating cell cycle-dependent nuclear oscillations, a process known as Interkinetic Nuclear Migration (INM) (**Fig. 1**). During G1 phase, basal migration of the nucleus requires the plus-end-directed microtubule motor Kif1A, while during G2 phase, apical migration requires the minus-end-directed motor dynein. Cell division always occurs at the apical surface and when nuclear migration is inhibited, cells fail to enter mitosis, leading to dramatic developmental defects. We recently indentified the mechanism for G2, dynein-dependent apical nuclear migration, which involves a Cdk1-triggered recruitment of dynein to the nuclear pore complex (Baffet et al., *Dev. Cell*, 2015; Hu*, Baffet*, Nayak* et al., *Cell*, 2013). INM is not limited to the developing brain but occurs in a wide variety of epithelia. However, the role of this phenomenon in the developing brain or other tissues is currently unknown.

To investigate neocortex development, we use *in utero* electroporation, coupled to live imaging of embryonic brain slices (**Fig. 2**). 1-4 days following DNA injection and electroporation, embryonic brains are dissected, sliced, placed on a filter in culture medium and live imaged over night (Baffet et al., *Methods Cell Biol.*, 2015). The remarkable size expansion of the human neocortex is thought to partly arise from a second pool of neural stem cells, called the basal Radial Glial (bRG) cells (**Fig. 1**). bRG cells are not specific to the human brain but their abundance strongly correlates with the degree of folding of the cerebral cortex. Indeed, bRG cells are very rare in the smooth mouse brain (lissencephalic) and very abundant in the folded macaque and human brains (gyrencephalic). Gyrencephaly allows for the packing of a much greater surface of cortical tissue in the limited volume of the skull and is therefore thought to play a major role in the development of higher cognitive functions. Because of the rarity of bRG cells in rodent models, the mechanisms controlling proliferation and self-renewal of these neural stem cells remain largely unexplored.

Perturbations at multiple steps of neocortex development lead to cortical malformations. These pathologies are associated with neuronal disorganization or abnormal brain size, and are characterized by intellectual disability and drug-resistant epilepsy. A large number of these cortical malformations remain unexplained, both because causative mutations have yet to be identified and because the function of some of the identified genes remains poorly characterized.
Key publications

Year of publication 2016

Jean-Baptiste Brault, Cécile Khou, Justine Basset, Laure Coquand, Vincent Fraisier, Marie-Pascale Frenkkel, Bruno Goud, Jean-Claude Manuguerra, Nathalie Pardigon, Alexandre D Baffet (2016 Jul 26)
Comparative Analysis Between Flaviviruses Reveals Specific Neural Stem Cell Tropism for Zika Virus in the Mouse Developing Neocortex.
EBioMedicine : DOI : S2352-3964(16)30323-1


Year of publication 2015

Cdk1 Activates Pre-mitotic Nuclear Envelope Dynein Recruitment and Apical Nuclear Migration in Neural Stem Cells.
Developmental cell : 703-16 : DOI : 10.1016/j.devcel.2015.04.022

Year of publication 2014

Alexandre D Baffet (2014 Jan 30)
[Nuclear migration in neuronal progenitors: when the brain plays yo-yo].
Médecine sciences : M/S : 30-2 : DOI : 10.1051/medsci/20143001009

Year of publication 2013

Dynein recruitment to nuclear pores activates apical nuclear migration and mitotic entry in brain progenitor cells.
Cell : 1300-13 : DOI : 10.1016/j.cell.2013.08.024

Year of publication 2012

Alexandre D Baffet, Béatrice Benoit, Jens Januschke, Jennifer Audo, Vanessa Gourhand, Siegfried Roth, Antoine Guichet (2012 Aug 3)
Drosophila tubulin-binding cofactor B is required for microtubule network formation and for cell polarity.

*Molecular biology of the cell* : 3591-601 : DOI : 10.1091/mbc.E11-07-0633