How the human brain evolved to ensure complex cognitive functions is one of the most fundamental and fascinating questions in biology. The increased number of neurons and henceforth the expanded complexity of the human brain is believed to underlie the enhancement of our intellectual skills.

Brain is composed of two major cell types: neurons which transmit electrical stimuli and glial cells including (i) astrocytes, which ensure the proper homeostasis, (ii) oligodendrocytes which form the myelin sheath, and (iii) microglia which are a type of immune cells that help defend brain tissue in inflammation.

Synapses are specialized structures allowing specific and fast intercellular communication between neurons. Remarkably, in addition to traditional housekeeping functions, astrocytes are essential for proper functioning of synapses. Without astrocytes there can be no higher-level brain activity, no neural plasticity, and hence no learning or memory.

Astrocytes are heterogenous in form and function. Nonetheless, we can distinguish five major groups of astrocytes in the brain cortex and the white matter. These include protoplasmic, fibrous, varicose projection, radial, and interlaminar astrocytes. Remarkably, the interlaminar (ILA) and varicose projection astrocytes are present only in primates. The distribution of ILA in the brain suggests their implication in higher level brain functions. However, very little is known about ILAs, notably we do not yet know which genes are expressed in these cells and what ILAs can teach us about brain evolution and the acquisition of features specific to human brain. The research of ILA is extremely difficult from obvious ethical reasons. However, the recent development of techniques relying on induced stem cells largely circumvents the need of providing tissue material. Instead, we can recapitulate ILAs in lab conditions.

By and large, all neurological disorders feature dysfunctions of astrocytes: from excessive reactivity to degeneration. Brains of patients with Down syndrome or Alzheimer's disease (AD) show profoundly altered ILA populations with the most striking phenotype in the AD patients, where ILAs are severely altered or disappear altogether. Therefore, in this project we hypothesize that by **determining genes defining biology of ILAs in primates, we will provide critical new insights into mechanisms that safeguard brain homeostasis and provide new understanding of the principles of brain evolution**. We will take advantage of the cutting-edge technologies to obtain stem cell derived human, chimpanzee and macaque ILAs in the laboratory conditions. We will deploy imaging and single cell molecular biology techniques to characterize ILAs from these primates. We will perform computational analyses to evaluate the possible implication of genes expressed in ILAs in neurological disorders. We will perturb the most relevant candidate genes using CRISPR-Cas9 and test the impact of the perturbation on ILAs. **The data generated in this project will shed new light on the genetic base of brain evolution and likely lead to new insights into neurological disorders, including Alzheimer's disease.**