Proposal for the 2020 International PhD program

Laboratory: Genetic and Development of Cerebral Cortex
Head of laboratory: Alessandra PIERANI
Field of research: Neurodevelopment
Number of students accepted: 1
Supervision: Alessandra Pierani
Project: Programmed Cell Death of Cajal-Retzius cells in the maturation of functional and dysfunctional cortical circuits

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Abnormal brain development participates to the pathophysiology of multiple neurodevelopmental disorders. Neurogenesis, migration, synaptogenesis or myelination are recognized building bricks for circuit formation. Programmed cell death (PCD) is also emerging as a key player in the wiring of cortical circuits. In the developing cerebral cortex, 20-30% of neurons are overproduced and eliminated by PCD. However, only three populations of neurons are present during the construction of neural circuits and completely disappear shortly after birth in mice, namely Cajal-Retzius (CRs) (which come in 3 distinct subtypes), Cortical Plate Transient (CPTs) and Subplate (SPs) neurons. CRs are among the first born cortical neurons and reside in the most superficial layer of the developing cerebral cortex from where they coordinate multiple crucial steps in the construction of functional circuits including neuronal migration, dendritic arborization and synaptogenesis. CRs completely undergo programmed cell death at the end of brain maturation in mice. Persistence of CRs during postnatal life has been detected in pathological conditions such as Temporal Lobe Epilepsy, Ammon's horn sclerosis, polymicrogyria and focal cortical dysplasia, and that of SPs in pharmaco-resistant epilepsy, thereby opening the intriguing possibility that the lack of disappearance of transient cell populations contributes to epilepsies.

Recent work from our laboratory have shown that although all CR subtypes undergo cell death they do so at least through two molecularly distinct pathways. We produced the first mouse model in which one CR subtype survives to adulthood. These animals display neuronal hypertrophy and imbalanced excitatory/inhibitory (E/I) ratio leading to dysfunctional cortical circuits and behavior in addition to increase susceptibility to epileptic seizures. However, it remains to be determined which pathway mediates the other CR subtypes demise.

The aim of the PhD project is to investigate new molecular pathways involved in CR subtype-specific PCD during post-natal development. We will perform an unbiased approach using FACS purification and single-cell transcriptomic analysis of genetically labeled CRs at different post-natal stages. Then functional studies will be done on the potential candidate genes involved in PCD to study their biological effects on CRs survival using mouse genetics and in vitro assays. In parallel, since recent data in the laboratory already established a link between PCD and neuronal excitability, we will also examine how cortical network activity and Cl- imbalance is involved in CR subtype-specific death using conditional knockout mice and Cre-driver lines to specifically target CRs subtypes to analyse CRs persistence and its effects.

This approach should allow us to study how survival of transient neurons in patients might be causally related to pathological phenotypes, provide mouse models to study the underlying molecular mechanisms and bridge developmental studies in mice to pathological conditions in humans. It will also allow to study cortical networks at electrophysiological levels and the possible link between CR persistence and epilepsy.

Lab members

- **1** Team Leader DR1 (CNRS, HDR)

- **2** Professors (AP-HP)

- **2** staff Researchers (INSERM, HDR)

- **2** staff Engineers IE (INSERM/CDD)

- **1** staff Technician AI (Imagine) and 2 students en alternance

- **3** Post-doctoral fellows

- **3** PhD students

- **2** Master students

Major Publications

1: Riva M.[#], Genescu I.[#], Habermacher C.[#], Orduz D., Ledonne F., Rijli F.M., Lopez-Bendito G., Coppola E., **Garel S., Angulo MC., Pierani A**. Activity-dependent death of transient Cajal-Retzius neurons is required for functional cortical wiring. *Elife* (2019) Dec 31;8. pii: e50503. doi: 10.7554/eLife.50503.

2: Arai Y., Cwetsch A.W., Coppola E., Cipriani S., Nishihara H., Kanki H., Saillour Y., Freret-Hodara B., Dutriaux A., Okada N., Okano H., Dehay C., Nardelli J., Gressens P., Shimogori T., D'Onofrio G. and **Pierani A**. Evolutionary gain of Dbx1 expression drives subplate identity in the cerebral cortex. *Cell Reports* (2019) 29:645-658.e5. doi: 10.1016/j.celrep.2019.09.007.

3: Orduz D.[#], Benamer N.[#], Ortolani D.[#], Coppola E., Vigier L., **Pierani A**. and Angulo, M.C. Developmental cell death regulates lineage-related interneuron-oligodendroglia functional clusters and oligodendrocyte homeostasis. *Nature Communications* (2019) 10:4249. doi: 10.1038/s41467-019-11904-4.

4: Causeret F, Coppola E, **Pierani A**. Cortical developmental death: selected to survive or fated to die. *Curr Opin Neurobiol.* (2018), 53:35-42.

5: Freret-Hodara B, Cui Y, Griveau A, Vigier L, Arai Y, Touboul J, **Pierani A**. Enhanced Abventricular Proliferation Compensates Cell Death in the Embryonic Cerebral Cortex. *Cereb Cortex.* (2017), 27(10):4701-4718.

6: Ledonne F, Orduz D, Mercier J, Vigier L, Grove EA, Tissir F, Angulo MC, **Pierani A, Coppola E**. Targeted Inactivation of Bax Reveals a Subtype-Specific Mechanism of Cajal-Retzius Neuron Death in the Postnatal Cerebral Cortex. *Cell Reports.* (2016), 17(12):3133-3141.

7: Barber M, Arai Y, Morishita Y, Vigier L, Causeret F, Borello U, Ledonne F, Coppola E, Contremoulins V, Pfrieger FW, Tissir F, Govindan S, Jabaudon D, Proux-Gillardeaux V, Galli T, **Pierani A**. Migration Speed of Cajal-Retzius Cells Modulated by Vesicular Trafficking Controls the Size of Higher-Order Cortical Areas. *Current Biol.* (2015), 25(19):2466-78.

8: Teissier A, Griveau A, Vigier L, Piolot T, Borello U, **Pierani A.** A novel transient glutamatergic population migrating from the pallial-subpallial boundary contributes to neocortical development. *J Neurosci.* (2010), 30(31):10563-74.

9: Griveau A, Borello U, Causeret F, Tissir F, Boggetto N, Karaz S, **Pierani A.** A novel role for Dbx1-derived Cajal-Retzius cells in early regionalization of the cerebral cortical neuroepithelium. *PLoS Biol.* (2010), 8:e1000440.

10: Bielle F, Griveau A, Narboux-Nême N, Vigneau S, Sigrist M, Arber S, Wassef M, **Pierani A**. Multiple origins of Cajal-Retzius cells at the borders of the developing pallium. *Nature Neurosci.* (2005), 8(8):1002-12.