Project 2

Project title: Perinatal microglia-neuron crosstalk in circuit development

Lead group: Cornelius Gross (EMBL Rome)
Partner group: Francesco Papaleo (IIT Genova)

Rationale: Genetic and environmental factors both play a role in the pathogenesis of psychiatric disorders. Increasing evidence points to inflammatory brain processes in the interaction of these factors, in particular for neurodevelopmental disorders such as ADHD, autism, and schizophrenia. Recently, copy number variation in one of the complement cascade component genes known to regulate microglia-dependent synaptic pruning has been associated with schizophrenia, suggesting a specific molecular mechanism by which immune and genetic variation can interact to impact brain maturation. At the same time, rare hemizygous deletions of chromosome 22 (22q11.2DS) are associated with increased risk for schizophrenia and present with immune defects. Moreover, a mouse model of 22q11.2DS presents brain inflammation during the perinatal and adolescent phases, suggesting that microglia-dependent brain inflammation may play a common role in risk for schizophrenia.

Aims: The aim of this project is to investigate the structural and molecular events regulating microglia-neuron interaction in the early postnatal stages of brain development and their long-lasting impact on the development of brain circuits and the cognitive and social behaviors they control.

Objectives:

- Use genetic editing and tagging approaches to selectively manipulate and monitor perinatal microglial/neuron signaling and causally relate it to circuit development and behavior.
- Highlight critical time-windows of vulnerability and responses to pharmacological treatments as a perspective for early intervention.

Integration of expertise of partners:
The candidate will benefit from the integration of knowledge and approaches in the partner laboratories. Francesco Papaleo (IIT Genova) will contribute access to genetically modified mouse models, behavioral assessment focused on cognitive and social processes, and *in vivo* mechanistic tools (optogenetics, fiber photometry, miniscopes). Cornelius Gross (EMBL Rome) will contribute expertise in microglia-synapse interactions and molecular genetic, viral-based neural manipulation tools (CrispR knock out/in) as well as the development of axonal pruning sensors.