Extracellular vesicles (EVs) are key players in cell-to-cell communication, both in physio- and pathological conditions, released by virtually all cell types in the microenvironment. EVs are a heterogeneous class of circulating membranous nanostructures – including exosomes and microvesicles – with different size and biogenesis. They are involved in the exchange of a broad range of bioactive molecules (e.g., nucleic acids, proteins, etc.), with a great potential as source of new biomarkers and for the development of advanced cell-free nanotherapeutics. However, much remains to be elucidated with regard to their roles in the brain. During my professional experience, I studied the mechanisms of intercellular signaling mediated by neural stem cell (NSC)-derived EVs in the context of neuroinflammation. With my work I contributed to demonstrate that: (i) mRNA and protein sorting in NSC-EVs is regulated by inflammatory cytokines; (ii) IFN-γ/Ifngr1 complex on EVs promotes the intercellular induction of Stat1 signaling; (iii) NSC-EVs are metabolically active and alter enzymatically the metabolic environment; (v) mouse and human NSC-EVs are enriched in L-asparaginase activity (via Asrg1 enzyme).

Taken together these results revealed a mechanism of cell-to-cell communication by which NSCs may signal with the microenvironment via EVs. This is potentially relevant both in physiological conditions (e.g., neurogenesis) and in the context of neurodegenerative diseases. More recently, I focused on the role of EVs in the context of Parkinson’s disease (PD). PD is characterized by the progressive loss of DAergic neuronal cell bodies in the ventral midbrain (VMB), and their terminals in the striatum (STR). In PD, astrocytes (AS) can have either destructive or beneficial effects. Again, the complex intercellular signaling between glia and neurons has not been fully elucidated, yet. My lab demonstrated that AS from the VMB and STR release a population of small-EVs (~100 nm) in a region-specific manner, with VMB-AS secreting the highest rate of EVs.

Functional studies revealed that AS-EVs recover mitochondrial complex I functionality injured by MPP+ neurotoxin. Interestingly, only VMB-AS-EVs ameliorate ATP production, supporting a regional specificity in targeting mitochondrial dysfunction. To investigate the molecular mechanism(s) of neuroprotection exerted by AS-EVs, we are modelling how AS-EVs enter target neurons and which are the AS-EV molecular cargoes. The AS-EV content was characterized via small RNA-sequencing and mass spectrometry (MS). Interestingly, the RNA content of VMB-AS-EVs revealed that an important portion (25%) of sRNAs corresponds to tRNA-derived fragments, some of which were recently identified as significantly upregulated in PD patients. MS analysis shows the presence of both cytosolic and mitochondrial proteins, related to neuroprotective pathways, and known to be affected by aging. By identifying key molecular players involved in this complex cell-to-cell communication, our findings may pave the way for targeted therapeutic interventions to tackle PD.