Role of the protein casein kinase 1 in neurodegenerative disorders: a promising therapeutic target.
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Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration of nerve cells. Many neurodegenerative disorders are characterized by the deposition of toxic proteins in specific brain regions, such as α-synuclein in Parkinson's disease (PD), TDP-43 in amyotrophic lateral sclerosis (ALS), Aβ peptides and Tau protein in Alzheimer's disease (AD). The protein casein kinase 1 (CK1) is a Ser/Thr kinase, ubiquitously expressed in eukaryotic organisms in different isoforms. The CK1δ isoform modulates several physiological processes, such as the circadian rhythm, proliferation, and apoptosis, and its aberrant activity has been described to be associated with central nervous system disorders, including AD, ALS, and PD. For this reason, CK1δ inhibitors might represent a novel therapeutic strategy to slow down the progression of these disorders.

This Ph.D. project aims at investigating the molecular mechanisms linking CK1δ with PD and ALS, by focusing on the hyperphosphorylation of α-synuclein and TDP-43, and on the downstream effects. The impact of potent CK1δ modulators on these pathways will be also assessed, providing proof of concept about this novel treatment strategy. The research will be performed in vivo using specifically designed *Drosophila melanogaster strains,* by exploiting the powerful genetic tools offered by fruit flies, through the use of complementary biochemical assay and state-of-the-art imaging techniques.

Astrocyte phagocytic activity: defining the molecular mechanisms.
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The maintenance of a healthy state of the central nervous system depends on the immediate removal of toxic, obsolete or unwanted material thus preventing inflammatory events. Under certain conditions, astrocytes demonstrate phagocytic capability and cooperate with microglia as an ancillary clerance system in the brain (1,2). However, the molecular machinery recruited for the recognition of specific targets is only in part clarified. In the lab, we identified a very promising class of genes involved in astrocyte-mediated phagocytosis of synapses by performing a cell-based high-throughput approach. The student will validate the selected hits using a plethora of different experimental approaches (imaging and proteomics) and complimentary models (primary astrocyte cells, human iPSC-derived astrocytes, and brain organotypic cultures).

1.Parkinson's Disease-Associated LRRK2 Interferes with Astrocyte-Mediated Alpha-Synuclein Clearance. Streubel-Gallasch L, Giusti V, Sandre M, Tessari I, Plotegher N, Giusto E, Masato A, Iovino L, Battisti I, Arrigoni G, Shimshek D, Greggio E, Tremblay ME, Bubacco L, Erlandsson A, Civiero L. Mol Neurobiol. 2021.
2.Glial phagocytic clearance in Parkinson's disease. Tremblay ME, Cookson MR, Civiero L. Mol Neurodegener. 2019.

Stemness and stem cell niches in the colonial chordate Botryllus schlosseri.
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This project aims to study the stem cell niche organization and stem cell features in the colonial tunicate, *Botryllus schlosseri*. Tunicates, the closest relatives to vertebrates, are invertebrate marine chordates. *B. schlosseri* shows remarkable stem cell mediated processes, such as a cyclical budding and whole body regeneration. Stem cells circulate in the colonial circulatory system and home in specific niches of adult individuals, where they proliferate and differentiate. These niches, differently from the vertebrate ones, are transient structures since, in colonies, buds cyclically substitute the adults that undergo regression. During this phase, stem cells leave the regressing niches to home into the newly forming ones. The molecular pathways driving potency and differentiation of stem cells, and their ability to home in their niches are still enigmatic. In this project, we will induce regeneration, promoting the involvement of stem cells in the development of new tissues, and study the role of factors (such as *soxB1*, *pou2*, *pou3*, *myc*, *vasa*, *piwi*) and pathways (e.g., STAT/JAK) with top programming activity in vertebrate stemness, focusing on the mechanisms controlling cell differentiation and renewal. The work plan will embrace cell sorting, gene expression (RT-qPCR, ISH), functional (RNA interference), behavioral, phylogenetic and morphological (confocal, TEM) analyses.

Mitochondrial DNA as a signal of chemotherapy induced cardiotoxicity.
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Doxorubicin remains an essential component of several anti-cancer regimens, but its use is associated with severe cardiotoxicity that often results in discontinuation of the therapy. Numerous molecular mechanisms have been implicated in doxorubicin-induced cardiotoxicity, with mitochondrial damage playing a major role and ultimately resulting in cardiomyocytes apoptosis.Cardiac endothelium is gaining attention as the potential culprit of doxorubicin cardiotoxicity. Like other anti-cancer drugs, doxorubicin can trigger senescence in endothelial cells with the development of specific inflammatory phenotype strongly affecting the surrounding environment. Inflammatory responses are part of doxorubicin-induced cardiotoxicity but the involvement of senescent endothelium as a source of chronic sterile inflammation remains unexplored. Mitochondria are fundamental hub of innate immunity. In response to cellular stress, they can release mitochondrial DNA molecules engaging different immune sensors in the cytosol, that in turn activate inflammatory pathways. By combining in vitro 2D cell cultures and 3D mini-hearts, unbiased and hypothesis-driven approaches, and in vivo *Danio rerio* (zebrafish) models, the PhD candidate will investigate the role of mitochondrial DNA as a new signaling molecule that drives chemotherapy-induced cardiotoxicity.

Role of redox metabolism in angiogenesis and cancer progression.
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Endothelial and tumor cells exhibit unique plasticity in terms of redox biology and metabolism. Our lab has contributed in the past years in decoding some of these cellular and molecular mechanisms (Mugoni et al., *Cell* 2013; Chen et al. *Cell Reports*, 2017, Facchinello et al., *Nature Metabolism*, 2022; Arslanbaeva et al., *Redox Biology* 2022). By using advanced redox and metabolic platforms, and innovative molecular and genetic approaches in cellular and animal models, we aim to shed light on the role of redox metabolic pathways and antioxidant enzymes in angiogenesis (developmental vs pathological) and cancer disease (breast cancer and melanoma). The ultimate objective is to open the way for the development of innovative therapeutic strategies and complement the existing ones based on genetic and pharmacological manipulation of redox and metabolic state in angiogenic and cancer processes.

Ecophysiology of Antarctic fish.
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Antarctica represents a unique natural laboratory for ecotoxicological studies as it is characterized by low internal pollutants emissions but high external contamination levels. Antarctic organisms have evolved under a peculiar evolutionary pressure, not only represented by low temperatures, but also by the natural presence of metals such as cadmium in coastal areas, where they are present at relatively high concentrations due to geophysical phenomena which occurred millions of years ago. What are the physiological responses that Antarctic fish have evolved to live with this chemical anomaly of their environment? Can the presence of this phenotypic plasticity also protect them from other environmental contaminants, such as hydrocarbons and perfluoroalkyl substances, increasingly present in the Southern Ocean? Are there some evolutionarily favored species within Antarctic fish biodiversity in view of the global changes that are taking place? The potential impact of pollutants on the physiology of Antarctic fish is still largely unknown and therefore one of the main objectives of this PhD research is to gain a greater understanding of the physiological responses, both at the transcriptomic and proteomic level, of Antarctic fish against negative effects of the accumulation of xenobiotics, with particular reference to antistress cell defenses.