Analysis of the effect of flavodiiron proteins in crop plants.

Contact: Prof. Alessandro Alboresi, e-mail: alessandro.alboresi@unipd.it

The metabolism of photosynthetic organisms is supported by sunlight that fuels an electron transport, ultimately driving the synthesis of ATP and reducing equivalents (e.g. NADPH). Flavodiiron proteins (FLV) are seminal components of this regulatory machinery in cyanobacteria, eukaryotic green algae, non-vascular plants and gymnosperms while they were lost during the evolution of Angiosperms. This PhD project will contribute to the understanding of the FLV mechanism. FLV heterologous expression in a crop plant (tomato) will allow assessing its impact on growth and development in Angiosperms, also exploring the possibility of using these proteins to improve plant productivity. FLV impact on the photosynthetic capacity will be punctually analyzed by a biophysical approach and extended by a biochemical quantification of the main molecules involved in functional photosynthesis (ATP and NADPH) and in stress response.

Human cardiac microtissues for studying and correcting arrhythmogenic cardiomyopathy.

Contact: Prof. Milena Bellin, e-mail: milena.bellin@unipd.it

We have recently developed a three-dimensional (3D) cardiac microtissue model from human induced pluripotent stem cells (hiPSCs), composed of cardiomyocytes, endothelial cells, and cardiac fibroblasts. In this project, we will use these cardiac cells as well as the 3D cardiac model to study the molecular mechanisms underlying arrhythmogenic cardiomyopathy (ACM). We will focus on mutations of the plakophilin-2 gene (*PKP2*) and we will explore the molecular and cellular mechanisms underlying cardiac disease onset and progression by means of transcriptional, functional, and metabolic analysis. The diseased microtissues will also be used to test potential pharmacological treatments.
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Multi-omics meets artificial intelligence to decipher the role of circular RNAs in leukemias and to find new markers and therapeutic targets: focus on adult Philadelphia and Philadelphia-like acute lymphoblastic leukemia.

Contact: Prof. Stefania Bortoluzzi, e-mail: stefania.bortoluzzi@unipd.it

This PhD position is linked to a project to aiming to explore the role circular RNAs (circRNAs) in leukemogenesis of acute lymphoblastic leukemia (ALL), particularly Philadelphia (Ph+) and Philadelphia-like (Ph-like) ALL.
CircRNAs, a class of pleiotropic RNAs that regulate cellular processes and control key oncogenic axes, are still unexplored in Ph+ and Ph-like ALL, thus representing promising candidates to discover new disease mechanisms and prognostic markers possibly leading to more targeted treatments.

Even if the outcome of adult patients with this aggressive type of leukemia has improved thanks to the introduction of modern combined therapies, a set of patients are not cure and experience disease relapse. Therefore, we aim to to identify circRNAs involved in the biological processes responsible for Ph+ ALL relapse to current approaches.
Moreover, we will develop a refined prognostic algorithms defining allogeneic transplant allocation, by leveraging multi-omics data analysis using Machine learning techniques.
This project will be conducted in the Computational Genomics Laboratory of the Molecular Medicine department of the University of Padova, with expertise in cancer Bioinformatics and circRNA hematological studies, and in collaboration with Dr. Sabina Chiaretti (Università degli Studi di ROMA "La Sapienza") who is a leading expert of in ALL clinics, molecular diagnosis and translational research.

Role of non coding RNAs in the modulation of mitochondrial metabolism during aging.
Contact: Prof. Stefano Cagnin, e-mail: stefano.cagnin@unipd.it

The median life expectancy and proportion of elderly individuals in the human population continue to increase and metabolic changes are the most common symptoms of ageing. Non-coding RNAs participate in metabolic regulation of skeletal muscle and can circulate within blood as messenger for the communication among different tissues. In this project, we will investigate the role of non-coding RNAs in counteracting mitochondrial and metabolic changes induced by ageing in mammalian skeletal muscle. Our objective is to identify age-related markers associated with metabolic alterations by studying secreted noncoding RNAs in old mice and humans subjected to a specific diet or exercise designed for healthy ageing.

Investigating epigenetic reprogramming and mitochondria-driven metabolic rewiring in cancer through multi-omic analysis.
Contact: Prof. Enrica Calura, e-mail: enrica.calura@unipd.it

Targeting respiratory complex I (CI), the largest and rate limiting enzyme of the mitochondrial respiratory chain, has emerged in recent years as a promising anticancer strategy in a wide range of solid tumors. Targeting CI slows down tumor growth, in time it triggers compensatory responses that overcome the metabolic deficit caused by the CI loss, allowing progression to malignancy. Interestingly, CI harnessing increases concentration of α-ketoglutarate and oxygen, both implicated in regulating the activity of the Ten Eleven Translocation (TET) enzymes that catalyze 5mC oxidation promoting cytosine demethylation and are emerging as critical epigenetic regulators of the cancerogenesis processes. We hypothesize TET2 promotes an epigenetic reprogramming that can orchestrate the compensatory responses triggered upon CI inactivation, and we aim to demonstrate that targeting TET2 increases the anticancer efficiency of CI depletion.

The PhD project aim to computationally exploring the links between epigenetic reprogramming and CI-mediated metabolic rewiring in colorectal and ovarian cancers integrating and modelling data from genome editing, metabolic and epigenetic studies, 3D cell culture models, omics analyses, in vivo murine models, and patient samples.
We are seeking dedicated and passionate individuals who aspire to make significant contributions to the computational cancer genomics field. The ideal candidate is a bioinformatician, a computational biology or a statistician formed into multi-omic data analyses, also biologists highly motivated in learning data analysis and computer programming are welcomed.

Improving photosynthetic efficiency by manipulating the redox regulation of carbon fixation - IPERAFIX.
Contact: Prof. Tomas Morosinotto, e-mail: tomas.morosinotto@unipd.it

Global demand for plants biomass for food, feed and energy is steadily increasing, pushing for significant increases in agricultural yields while also increasing the sustainability. Improving plants photosynthetic efficiency is one of the most important innovative approaches to increase yield and respond to the urgent need for new strategies to ensure sustainable food security. The photosynthetic process relies on two interconnected phases, namely light phase and carbon fixing pathway (i.e., Calvin-Benson cycle, CBC), and is limited by environmental and intrinsic factors as well as by complex light-dependent regulatory mechanisms that affect the photosynthetic electron transport chain, the production of ATP, and the CBC.
Photosynthetically derived reductive and oxidative signals are instead expected to be highly impactful in the carbon fixation efficiency in both natural light fluctuations (field agriculture) or artificial continuous light (indoor agriculture). IPERAFIX aims at increasing our mechanistic understanding of how redox signals generated by photosynthesis (or photosynthetic electron flow) impacts carbon fixation efficiency and ultimately primary productivity in depending from environmental conditions. This objective will be pursued by analysing holistically photosynthetic electron transport and carbon fixation, that will be characterized in the same plant genotypes exposed to the same conditions, enabling the clarification of their strong connections. In particular, IPERAFIX aims to connect alteration of photosynthetic electron transport (either by mutations or exposition to various light regimes) with generation of redox signals and ultimately carbon fixation efficiency. The work will employ the moss Physcomitrium patens as model organism, enabling to maximize the test of multiple genetic variants within the three years of the project.

Next generation approaches for dissecting the pituitary-adrenal axi.
Contact: Prof. Gianluca Occhi, e-mail: gianluca.occhi@unipd.it

This is a basic/translational project designed to address some important scientific and clinical issues concerning the etiology and pathogenesis of rare endocrine

tumors. In particular, the main aim is to explore the phenotypic heterogeneity that characterizes these tumors, by both collecting and correlating data on tumoral behavior and histopathological features and perform integrative analysis of epigenomic and transcriptome data combined with functional studies on proper models of the diseases.

A multi-dimensional analysis of cerebrospinal fluid to unravel the conundrum of the silent disease progression in Multiple Sclerosis.
Contact: Prof. Chiara Romualdi, e-mail: chiara.romualdi@unipd.it

Mounting evidence indicates that several patients with relapsing-remitting multiple sclerosis (RRMS) can experience steady progression of disability despite the lack of new inflammatory attacks or brain lesions. Unravelling the pathological drivers underlying such “silent” disease progression is a crucial unmet need that could allow the early identification of those patients with a poor prognosis and guide treatment planning. In this study, using an integrative computational framework that combines transcriptomic single cell RNA-seq of cerebrospinal fluid and brain magnetic resonance images (MRI), we aim to identify potential diagnostic and prognostic biomarkers associated with these “silent” pathological profiles.

Hermetia illucens **as a biotool in organic waste management and valorization: genome editing and nutritional immunology strategies .**
Contact: Prof. Federica Sandrelli, e-mail: federica.sandrelli@unipd.it and/or Prof. Alessandro Grapputo, e-mail: alessandro.grapputo@unipd.it

Hermetia illucens, also known as the black soldier fly, represents one of the most promising insect species for the reduction of organic waste and the sustainable production of animal feed. In order to enhance its use in both sectors, the project will develop and apply genome editing techniques and nutritional immunology strategies. The study will be performed on wild-type strains incorporating genetic, molecular biology and biochemical techniques as well as microbiological and transcriptomic analyses. The results of this project will have a significant impact on both the environment and the feed production, contributing to reduce organic waste impact on the ecosystem and to produce more nutritious animal feed.

The role of potassium channels in cancer.
Contact: Prof. Ildikò Szabò, e-mail: ildiko.szabo@unipd.it

The project in the lab of Prof. Szabo, funded by an AIRC grant, focuses on the elucidation of the role of potassium channels in the context of cancer progression. The Ph.D student will study the behavior of cancer cells lacking specific K+ channels in vitro and in vivo, with special emphasis on tumor growth, metastasis and

chemoresistance. In addition, the role of the same channels will be studied in the cells of the tumor microenvironment, using state-of-the art in vivo genetic models.

Investigating the role of the kinase PAK6 in LRRK2-linked Parkinson's disease.
Contact: Prof. Elisa Greggio, e-mail: elisa.greggio@unipd.it

PAK6 is serine-threonine kinase with expression highly enriched in the brain. Previous work from our team established a physical and functional link between PAK6 and the Parkinson's disease associated kinase LRRK2. PAK6 promotes cytoskeletal-related functions in neurons by reducing the activity of LRRK2 via phosphorylation of 14-3-3 proteins. Our latest unpublished data further established PAK6 as an upstream regulator of Transcription Factor EB (TFEB) nuclear translocation via a mechanisms involving 14-3-3s. Given the established role of LRRK2 in autophagy regulation, this project will investigate the relationship among PAK6, LRRK2 and neuronal autophagy by means of complementary imaging and functional assays harnessing knockout and knockin murine models. In the frame of a cotutelle PhD project, the student will also spend 1 year in the laboratory of Prof. Arjan Kortholt (University of Groningen) to define the physical determinants of the LRRK2:PAK6 complex through biophysical and Cryo-EM approaches.

Role of amyloid aggregation, autophagy dysfunction and neuroinflammation in Mucopolysaccharidosis type II.
Contact: Prof. Enrico Moro, e-mail: enrico.moro.1@unipd.it

Mucopolysaccharidosis type II (MPS II) is a rare lysosomal disorder characterized by behavioral abnormalities and progressive neurodegeneration. While the lysosomal storage of undegraded substrates due to defective enzymatic activity is considered the main trigger of neuronal cell loss, there is no clear evidence which cellular pathways are disrupted in the presymptomatic stage of the disease. In this PhD project the candidate will evaluate potential candidate molecular pathways involved in the early onset of neuroinflammation, by addressing the analysis of autophagic impairment, aberrant proteostasis, oxidative stress and additional underexplored pathways. To achieve this goal an MPS II zebrafish model will be exploited as main experimental tool for the evaluation of proteomic and transcriptomic changes in order to define the hierarchy of molecular defects occurring in the earliest stages of the disease. During the whole project, the rescue of progressive neuronal cell loss and neuroinflammation in the MPS II *in vivo* model will be also investigated by using a novel molecular tool, defined "molecular tweezer".

Targeting fibro-adipogenic precursors in cardiac fibrosis as a new therapeutic option.
Contact: Prof. Alessandra Rampazzo, e-mail: alessandra.rampazzo@unipd.it

Fibrosis is defined as a pathological remodeling of the extracellular matrix that can result from various causes, ranging from acute tissue injury to inherited molecular defects. In the heart, injury of myocardium activates stromal cells towards a fibrogenic program, which ultimately leads to the replacement of contractile tissue with a fibrous scar; these scars can cause severe heart failure, often with life-threatening consequences.
This project aims to study the key cellular and molecular mechanisms that regulate cardiac fibrosis, as well as to identify small molecules potentially capable of blocking the proliferation/pathological differentiation of fibrogenic progenitors. To achieve this, we will couple relevant animal models and human induced pluripotent stem cell (iPSC)-derived cardiac models.

Identification of new therapeutic substrates for ACM by the generation and the characterization of 3D-models.
Contact:
Prof. Martina Calore, e-mail martina.calore@unipd.it
Prof. Alessandra Rampazzo, e-mail: alessandra.rampazzo@unipd.it

Arrhythmogenic cardiomyopathy is a genetic cardiac disorder characterized by fibro-fatty replacement of the myocardium which results in fatal arrhythmias, especially in the young. Currently, there is no effective treatment for the disease. In this PhD project, we aim to develop and characterize novel 2D and 3D in vitro models based on induced-pluripotent stem cells generated from affected patients. These models will be used as a platform to test FDA-approved compounds as well as RNA-based therapies for the disease.

Mechanisms of glia pathology in neurodegeneration.
Contact: Prof. Laura Civiero, e-mail: laura.civiero@unipd.it

Reactive astrocytes refer to astrocytes undergoing morphological, molecular and functional remodelling in response to pathological stimuli. Of note, the activation and differentiation of astrocytes are implicated in the pathogenesis of multiple neurodegenerative diseases. Here the student will take the advantage of a genetic fish and rat model of neurodegeneration to investigate the contribution of astrocyte changes to neuronal dysfunction and cell death. The student will molecularly unravel the astrocyte signature using -omics techniques and apply drug screening to revert specific astrocyte pathological phenotypes.