Organelle contact sites remodeling in physiology and pathology.
Contact: Prof. Marisa Brini, e-mail: marisa.brini@unipd.it

Many physiological processes are regulated by the functional and physical interaction between cellular organelles. Active and bidirectional exchange of molecules, lipids and ions through contact sites occurring between mitochondria, ER, lysosomes and nucleus is not only essential to furnish material for metabolic reactions but also represents an important signaling pathway to coordinate different cellular processes, such as survival, metabolism, sensitivity to cell death or proliferation.
Organelles proximity represents a critical hub for the transfer of information and its dysregulation is linked to different pathological conditions, including many neurodegenerative diseases.
Our research is focused on the understanding of the mutual crosstalk in contact sites remodeling upon manipulation of proteins whose mutations are linked with familial Parkinson disease (i.e., alpha-synuclein, PINK1, Parkin and DJ-1) by applying biochemical, molecular and cellular biology approaches. Live cell imaging and confocal microscopy using contact sites sensors based on splitGFP and bimolecular fluorescence complementation (BiFC) will be employed. A special attention will be devoted to monitor Ca^{2+} signalling with organelles targeted recombinant probes.

Targeting class IIa HDACs to reset super-enhancers activity in cancer cells: a biomolecular approach towards selective epigenetic therapies.
Contact: Prof. Laura Cendron, e-mail: laura.cendron@unipd.it

DNA mutations are the main cause of cancer occurrence and progression. To sustain cell proliferation and tumor aggressiveness, mutations in oncogenes and tumor suppressor genes must hijack transcriptional programs, through extensive epigenome restructuring. These modifications operate within spatial defined organization of the genome through typical enhancers (TE) and super-enhancers (SE), that act as major regulatory elements shaping gene expression and defining cell identity. TE and SE are transcriptional hubs, essentials for coordinating complex transcriptional programs to drive the tumorigenic process. Class IIa HDACs are epigenetic modulators that monitor the activity of TE and SE, thus representing promising and quite unique drug targets. They are characterized by a large molecular weight, 120-135 kDa, organized in different domains that are essential for interaction with various transcription factors, including members of the Myocyte Enhancer Factor 2 family and other co-repressors. In this contest, the protein-protein interaction (PPI) disruption represents a promising and still poorly investigated strategy. In fact, Class IIa HDACs exert their role as molecular platforms, binding multiple partners including other co-repressors and targeting the catalytic activity per se may not be sufficient to abolish their repressive influence. To discover novel inhibitors capable of disrupting the interaction between class IIa HDACs and key regulators, we will explore an innovative approach based on i) rational design and selection of protein-protein disruptors, to be used as probes for the ii) screening of small peptide macrocycles. The discovered inhibitors will be validated and characterized by biochemical and biophysical techniques and then tested in cell culture models in collaboration with international research teams.

Regulation of mitochondria dynamics in amyotrophic lateral sclerosis.
Contact: Prof. Marta Giacomello, e-mail: marta.giacomello@unipd.it

Recent evidence suggest that changes in mitochondria dynamics and functions fundamentally contribute to the onset and progression of several neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS). Cells activate many mechanisms to cope with mitochondria dysfunctions and to maintain proper cellular physiology and viability. Mitophagy, e.g., the removal of damaged mitochondria, is one of the main homeostatic processes. Interestingly, it has been shown that mitophagosomes form at the sites of contacts among mitochondria and the Endoplasmic Reticulum, that are in turn controlled by post-translational modifications such as phosphorylation and ubiquitination. However, it is not yet clear how the latter contribute to the aetiology of ALS. We are particularly interested clarifying this point, thereby highlighting new targets for the development of effective therapeutical strategies.

Organelles contact sites in cancer.
Contact: Prof. Luigi Leanza, e-mail: luigi.leanza@unipd.it

Mitochondria are organelles not only involved in cellular respiration but also in several other pathways important for cell life and death. Mitochondria are not isolated within the cells but are closely

interconnected with other organelles, among which the Endoplasmic Reticulum (ER) and the lysosomes. Defective ER-mitochondria crosstalk and ER stress impacts on several cellular functions as well as on important intracellular pathways that promote the cancer development. The present project is aimed to clarify whether the modulation of ER-mitochondria-lysosome contacts could have a role in cancer development and resistance to pharmacological therapy by impacting on cellular bioenergetics and metabolism, thus unveiling new possible oncological targets.

Engineering of algae photosynthesis for improved productivity.
Contact: Prof. Tomas Morosinotto, e-mail: tomas.morosinotto@unipd.it

Global demand of biomass is continuously expanding and new sustainable technologies are needed to avoid overexploitation of natural resources, reduce environmental footprints and greenhouse-gas emissions. Algae represent a valuable alternative for the production of several bio-commodities such as food. feed and chemicals. Despite this potential, algae large scale cultivation still present several limitations and only a few algae-based products are currently present on the market.
This project aims at investigate molecular bases of photosynthetic yield in algae and use this knowledge to generate genetically improved strains with higher biomass productivity. Algae strains development efforts must fully consider the seminal influence on productivity of regulatory mechanism of photosynthesis as well as of cultivation parameters like cells concentration, light distribution in the culture, mixing, nutrients and carbon dioxide availability. Mathematical models will be exploited to account for the complex influence of all environmental parameters and identifying the genetic targets for improved algae strains.

Genome editing of peptide hormone-related genes for disentangling networks controlling growth and development of fruit in horticultural plants.
Contact: Prof. Livio Trainotti, e-mail: livio.trainotti@unipd.it

Peptide hormones (PHs) are signalling molecules involved in short and long distance cell-to-cell communication to integrate endogenous developmental processes with environmental conditions and in mediating responses to pathogens. The project aims to shed light on the role that endogenous plant PHs have on controlling reproduction of species producing fleshy fruit. Genome editing of genes encoding PHs and their receptors in model and horticultural plants, as Arabidopsis and tomato, will be produced and analysed to gain functional data on the network(s) in which these signaling molecules are involved. Effects on development, growth, ripening and shelf life on fleshy fruits will be evaluated in GE plants.

Plant adaptation to changing environmental conditions: key role of mitochondria as stress sensors.
Contact: Prof. Michela Zottini, e-mail: michela.zottini@unipd.it

Rapid climate change increasingly exposes plants to novel environmental conditions that are outside of their physiological limits and beyond the range to which they are adapted. For this reason, it is of primary importance to better understand the cellular and molecular processes that are involved in environmental stress response. In this context mitochondria play a major role being the powerhouse of the cell and an important hub with essential metabolic processes occurring within the organelle itself and several other pathways either emanating from or converging on mitochondria. Properly functioning mitochondria, indeed, can be seen as an early checkpoint before cells commit to any developmental or stress-response processes. Maintenance of organelle integrity, in term of functionality, morphology and dynamics, crucial for cellular homeostasis and proper responses to environmental challenges, is provided through anterograde and retrograde signaling. Mitochondrial Unfolded Protein Response (mtUPR) is suggested to be a major retrograde response activated in plants by a variety of different conditions that can lead to the accumulation of misfolded or unfolded proteins. mtUPR is still a poorly understood process and this PhD project aim to characterize it, identifying the molecular components and pathways that act as signals between the organelles and the nucleus, by using an integrated molecular, physiological, and imaging approach.