Characterization of the spatial and temporal heterogeneity of ovarian cancer and its tumor microenvironment using single cell sequencing.
Contact: Dr Enrica Calura, e-mail: enrica.calura@unipd.it
(curriculum in Genetics, Genomics and Bioinformatics).

The PhD project is focused on the study of ovarian cancer, which is a highly lethal female malignancy, usually diagnosed at late stages with extensive and frequent chemoresistant metastases. The tumor is a complex ecosystem composed of healthy and malignant cell types, which mediate tumor progression, drug delivery and affect chemoresistance. The PhD candidate will study the ovarian cancer microenvironment through computational analyses of single cell RNA sequencing data, defining the cell components and their cross-talk in multiple metastases before and after chemotherapy.

Study the role of Neuroblastoma-derived Exosomes in cancer dissemination.
Contact: Prof. Elisa Cimetta, e-mail: elisa.cimetta@unipd.it
(curriculum in Biochemistry and Biotechnology).

The research activities will be focused on the characterization of Neuroblastoma-derived Exosomes and on the analysis of their role in tumor progression and on its metastatic dissemination. This highly multidisciplinary project will also involve the use of microfluidic platforms and microscale technologies more in general. These techniques are unique in their capability of recreating conditions mimicking the in vivo microenvironment, where standard approaches might fail.

Role of tumor-associated macrophages (TAM) in immune evasion in colorectal cancer.
Contact: Dr Gaia Codolo, e-mail: gaia.codolo@unipd.it
(curriculum in Cell Biology and Physiology).

Tumor-associated macrophages (TAMs) are one of the major immune cells that infiltrate the tumor. In the tumor microenvironment TAMs orchestrate various dynamics that culminate in the inhibition of the antitumor immune response, allowing tumor cells to evade the immune system. In many tumors, including colorectal cancer (CRC), a high infiltration of TAMs is usually associated with a poor prognosis.
This project is aimed at dissecting the mechanism of immune evasion in colorectal cancer. It will study the molecular pathways and molecules that switch-off the ability of macrophages to counteract tumor growth. Some of these molecules could act as immune-checkpoint; the final goat of this project is to pave the way toward the design of novel approaches for the TAMs-targeted immunotherapy.
Different approaches will be adopted to identify pathways leading, for example, to the impaired antigen presentation process: primary cells isolation and culture from blood and other tissues, intestinal organoids/macrophages co-culture, FACS analysis, transcriptome analysis, biochemistry, metabolomics.
In parallel, for this study a novel mouse models will be generated to understand the mechanisms that regulate the unsuccessful antigen presentation in.

Regulation of intracellular signaling pathways by tuning of mitochondrial metabolism in cancer cells.
Contact: Prof. Luigi Leanza, e-mail: luigi.leanza@unipd.it
(curriculum in Biochemistry and Biotechnology).

Mitochondria are central organelles in cell physiology. Their role in several intracellular processes related either to cell life or cell death has been clearly delineated. In this scenario, we have recently discovered that fine pharmacological tuning of mitochondrial fitness caused the downregulation of Wnt signaling. We have proved that ER-stress is involved as a key step in the molecular pathway. This research project builds up from this background and will be focused on correlate the new mitochondria-Wnt axis in cancer cells, in particular melanoma and breast cancer. We will use *in vitro* models to try to discover new possible ways to modulate Wnt signaling and to avoid tumor development, progression and migration.

Modulation of intracellular signaling pathways in animal models for cancer.
Contact: Prof. Luigi Leanza, e-mail: luigi.leanza@unipd.it
(curriculum in Biochemistry and Biotechnology).

Mitochondria are central organelles in cell physiology. Their role in several intracellular processes related either to cell life or cell death has been clearly delineated. We have recently linked mitochondrial fitness to modulation of intracellular Wnt signaling by tuning mitochondrial ATP synthesis. The mito-Wnt axis has been observed in colorectal cancer cells as well as on cells from patients harboring a defect on mitochondrial respiratory chains complex III. These observations were mostly performed in *in vitro* systems. This research project builds up from this background and will be focused on apply this new paradigm regarding mito-Wnt axis also to *in vivo* preclinical mouse and zebrafish models for melanoma, breast and colorectal cancers.

Computational approaches to dissect ovarian cancer heterogeneity.
Contact: Prof. Chiara Romualdi, e-mail: chiara.romualdi@unipd.it
(curriculum in Genetics, Genomics and Bioinformatics).

Stage I epithelial ovarian cancer (EOC with tumor confined to the ovary) represents about 10% of all EOCs and although characterized by good prognosis, 20% of patients relapse with incurable disease. As it occurs less frequently than advanced-stages, stage I EOC molecular features have not been thoroughly investigated, thus, the identification of the cell mechanisms involved in tumour progression and the definition of new biomarkers is an urgent need. The project will use an integrative network-based approach to combine genomic, transcriptomic and methylomic data to dissect tumour-immune interaction and to improve patient stratification with the aim to predict their risk of relapse and to identify potential therapeutic targets.

Characterize the impact of mitochondrial dynamics on nuclear epigenome and pancreatic carcinogenesis.
Scientific Director: Prof. Luca Scorrano
Contact: Dr Alessandro Carrer, e-mail: alessandro.carrer@unipd.it
(curriculum in Cell Biology and Physiology).

The candidate will interrogate the role of mitochondrial dynamics in pancreatic cancer. Using autochthonous mouse models of spontaneous carcinogenesis, the candidate will examine how activating mutations of *Kras* impact mitochondrial morphology and rewire mitochondrial-derived metabolites, with a focus on citrate and its export in the nucleo-cytoplasmic compartment.
Breeding lines of transgenic animals the candidate will develop tools to interrogate the role of *Optic Atrophy Protein 1* (OPA1) in $KRAS^{G12D}$-induced carcinogenesis.
Finally, the candidate will test whether alterations in mitochondrial morphology influence the nuclear epigenome to facilitate cancer initiation.

Studying the role of ion channels is the tumor microenvironment.
Contact: Prof. Ildikò Szabò, e-mail: ildiko.szabo@unipd.it
(curriculum in Biochemistry and Biotechnology).

The Ph.D. fellowship is financed from a grant of the Italian Association for Cancer Research (AIRC) aiming to exploit ion channel modulators against cancer. Ion channels are emerging as promising oncological targets. The group where the Ph.D. student will work is studying some of the mitochondrial channels in a way to trigger apoptosis of cancer cells only, by modulating these proteins. The Ph.D. student will investigate the effect of novel channel modulators and will characterize a mouse model with tissue-specific deletion of a specific ion channel. In particular, tumor growth and the tumor microenvironment will be studied. The Ph.D. student will have to possibility to acquire a solid background in cancer research, ion channels, cell biology and immunology.

Study of the effect of redox cyclers on mitochondrial diseases.
Contact: Prof. Ildikò Szabò, e-mail: ildiko.szabo@unipd.it
(curriculum in Biochemistry and Biotechnology).

The Ph.D. student will work in the context of an approved Telethon project that focuses on mitochondrial diseases. In particular, we study pathologies linked to deficit of respiratory chain complexes and are still incurable. The Ph.D. student will investigate the effect of some small molecule with redox activity in cell's of patients as well as in genetic mouse models. The Ph.D. student will have the possibility to work in a dynamic group and learn various techniques linked to bioenergetics, cell biology and pharmacokinetics. Furthermore, the student will be involved in ongoing collaborations with experts of mitochondrial diseases.

Topics "Biological Signals"

The topic of these projects will coincide with one of the topics presented in each Curriculum.