Longitudinal cancer studies by NGS and multi-omics to define the molecular alterations and the clone dynamics underlying relapses and metastasis.
Contact: Prof. Stefania Bortoluzzi, e-mail: stefania.bortoluzzi@unipd.it

The identification of the molecular alterations acquired during cancer progression, also due to the effects and the selective pressure of therapy, has the potential to disclose the biological features underlying the most deadly evolution of cancer, the relapses. In leukemias, the exploration of the clone evolution dynamics tracking the mutational profile changes will inform the basis of chemotherapy resistance and help the refinement of clinical treatments. In solid tumours, single-cell DNA sequencing data of circulating tumour cells will be used to increase our understanding of metastasis development mechanisms and possibly open new opportunities to acquire early warnings of disease progression with non invasive tests. The Phd student activity will entail the development of bioinformatics methods to study tumor clonal evolution by NGS and multi-omics profiling of patient sample series collected during disease progression (e.g. diagnosis, remission, relapse and post-therapy follow-up points) and the biological interpretation of the results.

Combining metagenomic data with flux balance analysis to investigate the equilibrium of key metabolic compounds in the gut.
Contact: Prof. Stefano Campanaro, e-mail: stefano.campanaro@unipd.it

Genome-centric metagenomics and metabolic flux balance are two powerful approaches for the study of the uncultivable members of microbial communities. The target of this study is the development of bioinformatic methods to interpret the information derived from metagenome-assembled genomes and their transcriptomes through genome-scale metabolic models. These methods will be applied to the investigation of microbial interactions in anaerobic environments such as the gut.

Drosophila melanogaster **as model to investigate the link between circadian clock, cellular metabolism and Parkinson Disease.**
Contact: Prof. Gabriella Mazzotta, e-mail: gabriella.mazzotta@unipd.it

Parkinson disease (PD) is one of the most common neurodegenerative disorders and among the manifestations of PD are sleep problems that have a great impact on the quality of life. Circadian dysfunction is proven to accelerate the neurodegenerative process and light
treatment has been shown to improve sleep in PD patients. In this project, a Drosophila model of PD will be used to explore the molecular mechanisms by which circadian light input can influence the etiology and progression of this neurodegenerative disease.

The combination of genetic and novel functional approaches for the identification of the pathogenetic mechanisms underlying still unsolved Endocrine familial cancers.
Contact: Prof. Gianluca Occhi, e-mail: gianluca.occhi@unipd.it

Familial cancers represent a major challenge mainly due to heritability recognition that has a great impact on disease prevention, early detection, and clinical outcomes. In some endocrine disorders, a quasi-mendelian inheritance has been recognized and tumoral implicated genes identified (e.g. Multiple Endocrine Neoplasia Type-1, Medullary Thyroid Cancer). Conversely, in several other neoplasias of endocrine glands, although clear evidence of familial clustering, no recurrent mutated genes are known. We aim at discovering new mutations driving familial non-medullary thyroid cancers (FNMTCs), a tumor subtype having a steadily increasing prevalence. Our preliminary data, based on NGS analysis on several FNMTCs families, possibly suggests that the combination of rare germline and somatic variants may play a primary role in tumoral transformation. To reach our goal we intend to combine genomic and transcriptomic data, together with *in vivo* or *in vitro* experimental approaches. Genome editing systems (e.g. Crispr/Cas9) will be leveraged to obtain mutants and the functional readout will be assessed.

Pharmacologic strategies to reduce cardiac fibro-fatty replacement in mouse models of arrhythmogenic right ventricular cardiomyopathy.

Contact: Prof. Alessandra Rampazzo, e-mail: alessandra.rampazzo@unipd.it

The pathological hallmark of arrhythmogenic right ventricular cardiomyopathy (ARVC) is fibrofatty replacement of myocardium, which leads to ventricular arrhythmias; we recently reported that cardiac fibroadipogenic precursors (cFAPs) are the main source of fibrofatty deposition in ARVC hearts. The main research objectives of this project are to investigate at the transcriptional level the molecular mechanisms underlying cFAPs activation and to assess the efficacy of pharmaceutical compounds in preventing fibrofatty infiltration in ARVC mouse models.

Circadian clocks, microbiota, and gut infections in *Drosophila melanogaster.*

Contact: Prof. Federica Sandrelli, e-mail: federica.sandrelli@unipd.it

The circadian clock is an endogenously maintained timing mechanism that regulates molecular, cellular, physiological, immunological and behavioral processes, and provides a periodicity of about 24 h. Environmental signals, such as daylight, reset the clock, enabling animals to adapt to environmental changes in phase with the 24h day of the Earth. This project will characterise the relationships between the light-dark cycle, the circadian clock, and the influence of gut microbiota on immune responses in Drosophila melanogaster following oral infection with bacteria. The study will be performed in wild-type and clock mutant strains incorporating genetic, biochemical, microbiological, next generation sequencing, and histological techniques.

Analysis of Polg/Polg2-related disorders and drug-mediated rescue in zebrafish.

Contact: Prof. Natascia Tiso, e-mail: natascia.tiso@unipd.it

This project aims at modeling Polg/Polg2 mitochondrial disorders in zebrafish, using this organism as a system to screen a panel of candidate molecules for therapeutic treatment.
The project will imply:
- Crispr/Cas9-production of Polg and Polg2 zebrafish mutant lines; genotyping and line maintenance;
- Phenotypic characterization of the Polg/Polg2 mutants by mtDNA content and mutation rate analysis, WISH, IHC, transgene and pathway reporter imaging, confocal microscopy and TEM, metabolic analysis and behavioral assays;
- Drug treatment and phenotypic rescue.

Collaborations will be in place to compare the results with yeast-, worm- and mammalian-based models.