1) In vivo analysis of Stat3 activities in intestinal stem cell maintenance and colorectal cancer.

Supervisor: Prof. Francesco Argenton, e-mail: francesco.argenton@unipd.it

Intestinal crypts contain isolated Stat3 responsive cells. For their position at the base of the intestinal crypt, their proliferative phenotype, their persistence from embryonic to adult stages, the phenotype of null mutants and based on the activity of a transcription factor long known to be a stemness marker, we can postulate that these Stat3 responsive cells are either intestinal stem cells or, at least, needed to maintain the intestinal stem cells niche. The PhD student will be involved in: identification and characterization of Stat3 positive cells and their role in colorectal cancer (CRC); epistatic analysis of Stat3 Ser727 phosphorylation in vivo and its role in models of CRC; modelling CRC in organoids and screening of kinase inhibitors acting on Stat3 signaling cascade.

2) Elucidating the role of autophagy in the maintenance of skeletal muscle homeostasis.

Supervisor: Prof. Paolo Bonaldo, e-mail: paolo.bonaldo@unipd.it

Skeletal muscle is an extremely plastic tissue whose remodeling occurs under many different stress conditions (e.g. nutrient starvation, physical exercise, injury). Autophagy is a highly conserved self-degradative pathway, being activated in muscle during these remodeling processes to allow the removal of unnecessary or damaged organelles. We aim at clarifying previously undisclosed aspects of autophagy regulation in skeletal muscle, by mean of different animal models. Our studies will also shed light on autophagy modulation strategies which may have beneficial effects in pathological contexts. The PhD student will characterize conditional knockout mice for different autophagy regulators, and take advantage of mouse and zebrafish models of different muscle diseases to evaluate in vivo the therapeutic potential of autophagy-inducing compounds.

3) CircRNAs in normal and malignant haematopoiesis.

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

Circular RNAs (circRNAs) are highly stable RNA loops generated by that participate to key differentiation and cancer axes, working as efficient miRNA sponges, interacting with RNA binding proteins or being translated into biologically active peptides. Out of 40,000 circRNAs expressed in blood cells, only few have been characterized. The project aims at shedding light on regulatory molecular circuits and on pathogenetic mechanisms involving circRNAs. The PhD student will develop computational methods to study circRNAs, to be used in combination with experimental approaches to detect, validate, and characterize circRNAs in mature and stem blood cell populations and in malignant hematopoiesis. We're looking for a candidate with background in bioinformatics and molecular biology.

4) Development of a metabolic model to investigate the anaerobic digestion system.

Supervisor: Dr Stefano Campanaro, e-mail: stefano.campanaro@unipd.it

Anaerobic digestion, a biologically mediated process, is a worldwide spread technology for biogas production. This process is performed by a complex microbial community in which hundreds of species cooperate in the establishment of a collective organization. As for the majority of the microbiomes, most of the species are difficult to grow in laboratory conditions, for this reason a genome-centric metagenomic approach is needed for their functional characterization. In a cooperative study involving international laboratories, the PhD student will be involved in the development of a metabolic model for this microbiome and in the characterization of the functional roles of the species.

5) ***Modeling human mitochondrial diseases related to APOPT1 in D. melanogaster.***

Supervisor: Prof. Rodolfo Costa, e-mail: rodolfo.costa@unipd.it

Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are severe autosomal recessive disorders associated with decreased mtDNA copy number in clinically affected tissues. Deleterious mutations in *Apoptogenic protein 1* (*APOPT1*) have been recently related with the manifestation of mitochondrial disorders. Clinical manifestations associated with mutations in this gene varied from acute neurometabolic decompensation in late infancy to subtle neurological signs in adolescence. Although COX deficiency represents a typical feature of APOPT1 mutant patients, yet no functional mechanism has been unveiled about APOPT1 involvement in cIV assembly or stability. The PhD project will focus on the functional and molecular characterization the APOPT1 ortholog in *D. melanogaster* (*CG14806*, *dApopt1*), by using genetic, behavioral, biochemical, molecular and genomic approaches.

6) Identification of functional long non-coding RNAs in myofibers of skeletal muscle.

Supervisor: Prof. Gerolamo Lanfranchi, e-mail: gerolamo.lanfranchi@unipd.it

The human and mouse genomes contain tens of thousands of loci that produce long noncoding RNAs (lncRNAs), transcripts that have no apparent protein-coding potential. A subset of lncRNAs have been found to play critical roles in cellular processes, organismal development, disease. Moreover, we demonstrated that they have an expression myofiber specific with a preferential subcellular localization that is dependent on myofiber type. Although these examples are suggestive of the importance and diversity of lncRNAs, the vast majority of lncRNA genes have not been functionally tested. The aim of this PhD project is to develop a CRISPR-mediated interference (CRISPRi) library to identify functionally lncRNAs specifically expressed by fast and slow myofibers that are characterized for a different metabolism. CRISPR/Cas9 nuclease approaches based on introduction of indels are both scalable and useful for targeted loss-of-function studies of protein- coding genes by altering the coding frame, but they are not well suited for the study of lncRNA gene function, as small deletions do not generally disrupt their biological activity. The ideal PhD candidate should have a background in molecular biology or biotechnology interested in non-coding RNA functions and in genomic approaches.

7) Contribution of deregulated miRNAs to the molecular pathogenesis of Arrhythmogenic Cardiomyopathy.

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

Arrhythmogenic Cardiomyopathy (AC) is a leading genetic cause of sudden cardiac death in the young and athletes, characterized by progressive substitution of the myocardium with fibro-fatty tissue. The main research objectives of this project are to assess RNA-based disease mechanisms identifying mRNA targets of selected miRNAs differentially expressed in transgenic mice carrying a mutated human desmoglein-2 protein and to test RNA-therapeutics for AC in transgenic mouse models and in iPS-derived cardiomyocytes from affected patients.

8) Development of bioinformatic tools for the analysis and integration of biological data in advanced stage ovarian cancer.

Supervisor: Prof. Chiara Romualdi, e-mail: chiara.romualdi@unipd.it

The project is aimed at developing a novel methodological and computational infrastructures based on an integrative and functional genomics approach, to study biological alterations characterizing therapy response in advanced-stage high grade serous epithelial ovarian cancers (HGS)-EOC, the most common EOC histological type.

9) Development and application of new technologies enabling complex-genome assembly.

Supervisor: Prof. Giorgio Valle, e-mail: giorgio.valle@unipd.it

Although the recent advances in DNA sequencing technology have been impressive, it is still extremely difficult to assemble complex genomes and it is even more difficult to resolve haplotypes. For overcoming these limitations, new developments and strategies are required for the preparation of NGS libraries and for bioinformatics. The aim of this PhD project is to develop innovative NGS libraries, based on binning, as well as to create suitable algorithms for the processing of the new type of data. The new assembly strategy will be used to improve the reference genome of human and other organisms. The ideal PhD candidate should have a background in molecular biology and a good skill in computer programming.

10) Drosophila melanogaster as a model of neuropsychiatric disease.

Supervisor: Prof. Mauro A. Zordan, e-mail: mauroagostino.zordan@unipd.it

Our group is interested in leveraging the strengths of Drosophila to study the relationship between genetic and/or environmental manipulations leading to disturbances in behavioural and neurophysiological phenotypes which characterize human neuropsychiatric disease. To this end we also collaborate with mathematical physicists and engineers with the intent of implementing machine learning approaches for the classification of locomotor activity/social interaction profiles of groups of (normal/aberrant) flies acting in an enclosed arena.