Research options available for topic B

Research topics a) and b) offered by every Doctoral Course involved in UNIPhD are frameworks within which every applicant has to present an original research project in collaboration with a Supervisor at the University of Padua.

Potential Supervisors at Unipd have proposed the following detailed research options, which are related to the research topic. They are offered as a guideline and should facilitate your contact with potential Supervisors. Supervisors' e-mail is specified in every research option table. You are welcome to contact them directly.

Note that this research option list is not at all exhaustive and, within the topic you have chosen, you are free to propose a different research project.

Doctoral Course	**BIOMEDICAL SCIENCES**
Macro-area	Medical and Biomedical Sciences
Department name	Department of Biomedical Sciences
Webpage	*http://doctorate.biomed.unipd.it/*
Research topic B	**Mitochondria between degenerative diseases and cancer** Rewiring of metabolism enables cancer cells to cope with energy demand required for growth, migration, invasion, and metastasis. Targeting of mitochondrial derangements is under scrutiny to develop innovative anti-tumor strategies. On the other hand, mitochondrial dysfunction has a central role of in neurodegeneration due to alterations in neuronal metabolism and ion homeostasis. Moreover, mitochondrial metabolism modulates astrocyte and microglia reactivity contributing to neuroinflammation.
Link to the UNIPhD Call (Academic Year 2022/2023)	*https://www.unipd.it/en/uniphd*
Latest Update	*11.01.2022*
#Number of available Research Options	*4* *Scroll down to see all the Research Options*

1 Research Option Description

Doctoral Course	**Doctoral Course in Biomedical Sciences**
Department name	Biomedical Sciences
Research topic B	Mitochondria between degenerative diseases and cancer
Research option	Nucleus-mitochondria membrane contact sites at the interface between targeted cancer therapy and neurodegeneration
Supervisor	Prof. Tito Calì tito.cali@unipd.it
Webpage	https://pnc.unipd.it/cali-tito/ https://www.biomed.unipd.it/research-areas/computational-and-structural-biology/protein-crystallography-and-cryoem/people/
Context of the research activity and objectives	Rewiring of metabolism is a general hallmark of tumors and enables cancer cells to cope with the constant energy demand required for growth, migration, invasion, and metastasis. Functional contact sites between organelles are thus the real bottleneck where cell homeostasis can be adjusted to cope with the needs imposed by the environment and are hijacked by cancer cells. In the last year a novel communication between mitochondria and the nucleus emerged (Desai, East et al. 2020). Cancer cells vastly rely on this communication (Wallace 2012) where mitochondria become physically coupled with the nucleus to drive the transcription of prosurvival factors. The mitochondria-nucleus contact is mediated by TSPO, a protein up-regulated in many cancers (Miettinen, Kononen et al. 1995, Maaser, Grabowski et al. 2005, Zheng, Boisgard et al. 2011) also able to transport cholesterol. Therefore nucleus-mitochondria contact sites emerged as a central node where a fine regulation of the cancer cell metabolism is achieved as well as a downstream druggable bottleneck to impede hijacking from cancer cells. Interestingly, cholesterol intermediates are involved in the oncogenic reprogramming [32, 33] but its accumulation and mishandling is also associated with neurological diseases, such as Niemann-Pick type C (NPC), Alzheimer's or Parkinson's disease [34, 35]. We have designed for the first time, contact site sensors (SPLICS) (Cieri, Vicario et al. 2018) to detect disease-relevant organelle contact sites (Vallese, Catoni et al. 2020) in vitro and in vivo. We have now developed a novel SPLICS sensor (SPLICS-P2A^{NU-MT}) for the detection of nucleus-mitochondria contact sites thus paving the way to perform i) drug screening with compounds able to modulate this interface ii) screening of protein targets from siRNA library to identify modulators of the nucleus-mitochondria to be used as novel targets for therapeutic intervention in cancer therapy iii) to understand the link between cancer and neurodegeneration by assessing the role of selected familial Parkinson's or Alzheimer's disease-related proteins in cholesterol trafficking at these contact sites.
Infrastructures	The proponent has access to a fully equipped lab for molecular and cell biology, and several instrumentations, including luminometes and multi-mode plate readers. The host institution has a number of facilities: 2 confocal microscopes (1 Leica SP5-II CW-STED and 1 Zeiss LSM 800). The same building hosts a fully equipped HTS imging facility (https://www.biologia.unipd.it/servizi/servizi-alla-ricerca/servizi-dipartimentali/imaging-facility/high-throughput-screening-facility/).

Skills and competencies for the development of the activity	Cellular and molecular biology and biochemistry techniques (cloning, OCR, DNA extraction and quantification, site directed mutagenesis). Protein expression and purification techniques (WB analysis, IF and confocal microscopy).
Training offer	The doctoral school offer local journal cubs and seminars from internationally recognised speakers. Participation to international conferences is also ensured.
Possible Secondments	Secondments can be spent in a foreign University or Research institute e.g. King's College London (Prof. Alessio Vagnoni) or MRC Mitochondrial Biology Unit, Cambridge (Prof. Julien Prudent). The proponent also established contacts with pharmaceutical industries (Astra Zeneca and Novartis) for the development of the project.

2 Research Option Description

Doctoral Course	**Biomedical Sciences**
Department name	Biomedical Sciences
Research topic B	Mitochondria between degenerative diseases and cancer
Research option	Liquid-liquid phase separation in mis-regulation of mitochondrial functions caused by cancer-mutations
Supervisor	Monika Fuxreiter monika.fuxreiter@unipd.it
Webpage	http://www.biomed.unipd.it/people/fuxreiter-monika/ http://protdyn.med.unideb.hu
Context of the research activity and objectives	Liquid-like, dense state of proteins, generated by liquid-liquid phase separation play fundamental roles in organisation and regulation of cellular processes. Aberrant condensates, caused by familial mutations lead to cancer or neurodegenerative diseases. My group aims to find connections between molecular determinants, biophysical properties of the condensates with health and disease. We apply computational method along with experimental, cell biology and biophysical studies to elucidate this new aspect of cellular regulation and mis-regulation. Note, that most untargetable cancer-genes code proteins, which form condensates. Therefore our premise is to discover novel approaches for identifying pharmaceutical targets.
Infrastructures	Available from January 2022, laboratory equipment and personal computers.
Skills and competencies for the development of the activity	molecular biology techniques, experience in working with cell lines, statistics alternatively: computational biology, bioinformatics, systems biology, structural biology
Training offer	High quality training in protein interactions and condensates
Possible Secondments	Prof. Sonia Longhi "Structural Disorder and Molecular Recognition" Architecture et Fonction des Macromolecules Biologiques (AFMB) UMR 7257 CNRS & Aix-Marseille Université 163, Avenue de Luminy Case 932, 13288 Marseille Cedex 09 Tel ++33 (0)4 91 82 55 80 Email: sonia.longhi@univ-amu.fr http://www.afmb.univ-mrs.fr/Sonia-Longhi?lang=en

3 Research Option Description

Doctoral Course	**Biomedical Sciences**
Department name	Biomedical Sciences
Research topic B	Mitochondria between degenerative diseases and cancer
Research option	Study of the pro-neoplastic functions played by the mitochondrial chaperone TRAP1 in the metabolic rewiring of tumor models.
Supervisor	Andrea Rasola andrea.rasola@unipd.it
Webpage	https://www.biomed.unipd.it/people/rasola-andrea/
Context of the research activity and objectives	Metabolic changes orchestrated by mitochondria promote neoplastic progression, and their targeting is under scrutiny to develop innovative anti-tumor strategies. Our group has established that the mitochondrial chaperone TRAP1 affects mitochondrial bioenergetics in tumor cells, and highly specific allosteric inhibitors developed in the lab display promising anti-neoplastic effects. We are currently focused on a thorough characterization of the pro-neoplastic metabolic rewiring induced by TRAP1, both in tumor cells and in cellular components of the tumor microenvironment. Our ultimate goal is the development of TRAP1 targeting strategies that can lead to selective tumor eradication and can be evolved into next-generation chemotherapeutic regimens.
Infrastructures	The Department of Biomedical Sciences of the University of Padova offers a variety of cutting-edge facilities, including imaging and flow cytometry infrastructures and mouse and zebrafish animal houses.
Skills and competencies for the development of the activity	We are looking for a strongly motivated, curiosity-driven person, with a marked attitude for team work and with some experience in basic cell biology techniques.
Training offer	The PhD student will be part of a team characterized by a blend of cell biology, mitochondrial physiology and molecular oncology competences that integrate in a strongly collaborative group. (S)he will have the opportunity to increase her/his autonomy in drawing and carrying out complex scientific programs. (S)he will participate to lab meetings, journal clubs and international scientific meetings.
Possible Secondments	1. ***Department of Biosciences, Biotechnology and Biopharmaceutics, University of Bari, Italy***, ***Prof. Alessandra Castegna's*** lab, to carry out LC-MS/MS metabolomic investigations. 2. ***Danish Cancer Research Center, Copenhagen, Denmark***, ***Prof. Giuseppe Filomeni's*** lab, to set up advanced 3D cultures of tumor spheroids.

4 Research Option Description

Doctoral Course	**Biomedical Sciences**
Department name	Biomedical Sciences (DSB)
Research topic B	Mitochondria between neurodegenerative diseases and cancer
Research option	The mitochondrion at the centre of Alzheimer's disease pathogenesis. Role of neuroinflammation.
Supervisor	Prof. Paola Pizzo paola.pizzo@unipd.it
Webpage	https://pizzolab.org/; https://www.biomed.unipd.it/people/pizzo-paola/
Context of the research activity and objectives	Alzheimer's disease (AD) is a leading cause of dementia. Evidence has accumulated supporting a central role of mitochondrial dysfunction in AD. Mitochondria actively shape cellular Ca2+ dynamics, contributing to the fine-tuning of neuronal activity. Moreover, defective mitochondrial bioenergetics sensitizes AD neurons to glutamate-induced excitotoxicity, contributing to neurodegeneration. Mitochondrial defects might also affect the function of astrocytes and microglia, key cell types involved in AD, not only as physiological modulators of neuronal activity, but also as main characters in neuroinflammation. Indeed, mitochondrial Ca^{2+} represents an additional signal that drives microglia and astrocyte activation/reactivity, thus determining their role (homeostatic vs reactive/pathologic) in brain function. This project plans to: 1) Unravel the role of mitochondrial Ca^{2+} signal in neurons, astrocytes and microglia of wild type (WT) and AD mice, focusing on its link to neuronal excitotoxicity, hyperexcitability and cell death, as well as to astrocyte/microglia activation and neuroinflammation, during disease progression. 2) Investigate mitochondria-endoplasmic reticulum (ER) contacts and their functional cross-talk in microglia and astrocytes from WT and AD mice; 3) Characterize mitochondrial Ca^{2+} response in brain organoids, containing neurons and glial cells, obtained by reprogramming AD patient-derived fibroblasts, and healthy human control cells, to obtain patient-specific, clinical-grade human induced pluripotent stem cells (hiPSC). The final aim of the project is to identify and modulate early mitochondrial metabolic defects in AD, to specifically validate and characterize altered pathways at early stages, evaluating the potential of mitochondrial bioenergetics as therapeutic target.
Infrastructures	Fully equipped lab for cell/molecular biology and biochemistry; inverted microscopes equipped for in vivo Ca^{2+}, cAMP, ATP imaging; Leica TCS SP5-II STED super-resolution microscope; Leica spinning disk confocal microscope for in vivo FRET-based Ca2+ imaging; Multifunctional Plate reader; Fluorescence Activated Cell Sorter (FACS); XF24 Extracellular Flux Analyzers (Seahorse Bioscience).
Skills and competencies for the development of the activity	Competences in primary culture (neuronal, astrocytic, microglial) preparation/maintenance; molecular biology and biochemistry techniques; Ca^{2+} imaging techniques.
Training offer	DSB seminars and specific Doctoral School courses: Pathophysiology of mitochondria: From energy conservation to disease pathogenesis and therapy, 10h. Astrocytes at the center of the brain of neurons, 10h. Intracellular Ca^{2+} homeostasis in physiology and pathology, 10h. Model

	organisms for biomedical research (in cooperation with Doctorates in Biosciences and Molecular Medicine), 10h.
Possible Secondments	University of Ferrara, Italy (Prof. Francesco Di Virgilio's lab) or Karolinska Institute, Stockholm, Sweden (Prof. Maria Ankarcrona's lab). Venetian Institute of Molecular Medicine (VIMM), Padova, Dr. Onelia Gagliano's BioERA lab.