UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

Tutor's Name	Monica Montopoli
Cotutor's Name	

1) Project title

Cancer Metabolic Rewiring in Drug Resistance: A Multidisciplinary Approach to Identify Novel Therapeutic Targets

2)Abstract (max 500 words)

Chemotherapy resistance remains one of the most critical obstacles in oncology, leading to disease relapse, treatment failure, and poor patient outcomes. Tumors can exhibit either intrinsic resistance — driven by genetic characteristics — or acquired resistance, developed upon drug exposure. Understanding the mechanisms underlying this phenomenon is essential to design more effective therapeutic strategies.

Confirmed evidence highlights that cancer cells actively rewire their metabolism in response to chemotherapeutic agents, exploiting metabolic flexibility to survive in hostile conditions. Key pathways involved include glycolysis, the pentose phosphate pathway (PPP), lipid and glutamine biosynthesis, and mitochondrial function remodeling.

Our research has shown that cisplatin-resistant ovarian cancer cells display enhanced glucose uptake and upregulation of Glucose-6-Phosphate Dehydrogenase (G6PDH), a key PPP enzyme. Combined treatment with G6PDH inhibitors and cisplatin — including a novel lyophilized stealth liposomal formulation designed to reduce systemic toxicity — demonstrated selective cytotoxic activity against resistant cells and improved pharmacokinetics *in vivo*.

Additionally, we identified mitochondrial dysfunction and increased mitophagy as mechanisms of resistance in both cisplatin-resistant ovarian cancer and osteosarcoma cells, as well as in doxorubicin-resistant osteosarcoma models. Targeting autophagy pathways restored chemosensitivity, reinforcing the central role of mitochondria in acquired resistance.

This PhD project aims to:

- Map altered metabolic pathways in chemoresistant cancer cells
- Identify novel prognostic and predictive biomarkers of chemoresistance
- Develop innovative pharmacological approaches to sensitize resistant tumors to conventional chemotherapy

By integrating metabolomics, cell biology, and drug delivery strategies, this project has the potential to translate metabolic vulnerabilities into actionable clinical targets, ultimately improving therapeutic outcomes for patients with refractory cancers.

Tutor's Name	Monica Montopoli
Cotutor's Name	Andrea Alimonti

1) Project title
Natural Compounds as Modulators of Inflammaging: Identification and Characterization of Novel Anti-inflammatory and Geroprotective Agent
2)Abstract (max 500 words)
Aging is inevitably associated with a chronic, low-grade, sterile inflammatory state known as "inflammaging", a term coined to describe the progressive increase in pro-inflammatory markers observed in older individuals. This phenomenon represents a major driver of age-related diseases, including cardiovascular disorders, neurodegeneration, metabolic syndrome, and cancer. Despite its clinical relevance, effective pharmacological strategies to counteract inflammaging remain limited, and the search for safe, well-tolerated modulators is a pressing research priority. Natural compounds — including polyphenols, terpenoids, alkaloids, and flavonoids — have long been recognized for their pleiotropic biological activities, particularly their ability to modulate inflammatory pathways with limited side effects. However, a systematic investigation of their mechanisms of action in the context of inflammaging, as well as rigorous preclinical validation, is still largely lacking. This PhD project aims to screen and identify natural compounds with significant anti-inflammaging activity through *in vitro* and *in silico* approaches, and to elucidate the molecular mechanisms underlying their activity. Particular attention will be devoted to key inflammatory pathways such as NF-κB signaling, NLRP3 inflammasome activation, mTOR regulation, and the senescence-associated secretory phenotype (SASP). Mitochondrial dysfunction and oxidative stress, as interconnected and upstream drivers of inflammaging, will also be investigated, evaluating the capacity of selected compounds to restore cellular homeostasis and delay the onset of senescence. By combining biochemistry, molecular biology, and pharmacology, this project seeks to bridge the gap between traditional knowledge on natural products and modern aging biology, ultimately contributing to the development of innovative nutraceutical or pharmacological strategies to promote healthy aging.