*Project Tutor: Prof. Alfonso De Simone, Dept. of Pharmacy*

*Project Co-Tutor: Prof. Bruno Catalanotti, Dept. of Pharmacy*

**Title: A Multi-Omics Graph Neural Network Framework for Systematic Discovery and Drug-Oriented Validation of Synthetic Lethal Interactions in Triple-Negative Breast Cancer**

**Project overview and objectives**: Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer, characterised by poor prognosis and resistance to conventional treatments. Due to the absence of estrogen, progesterone, and HER2 receptors, standard targeted therapies are ineffective. In this context, synthetic lethality represents a transformative therapeutic strategy, enabling the selective elimination of tumour cells by targeting genes that become lethal only in the presence of specific oncogenic mutations. However, clinical translation remains hampered by the vast combinatorial space of possible gene interactions, the limitations of current predictive methods, and the disconnect between target identification and effective druggability. In light of this, this project aims to develop an integrated computational framework for the discovery, prioritisation, and structural validation of novel synthetic lethal interactions in TNBC. The main objectives are to identify tumour-specific genetic vulnerabilities, elucidate their molecular mechanisms, assess their druggability through advanced structural simulations, and ultimately discover novel therapeutic candidates with the potential to improve precision treatment strategies for patients with TNBC.

**Innovation of the project:** This doctoral project proposes an innovative computational framework based on multi-omics graph neural networks for the systematic discovery and validation of novel synthetic lethal interactions specific to TNBC. The approach is structured in three phases: training a predictive model to identify synthetic lethal gene partners while providing mechanistic explanations; identifying TNBC-specific gene pairs by integrating expression data and mutual exclusivity patterns; and structurally validating prioritised targets through AI-enhanced molecular dynamics simulations. This last phase overcomes the limitations of traditional docking by capturing protein conformational flexibility and identifying cryptic binding sites. For each validated target, a dedicated drug discovery pipeline will be implemented, integrating ensemble docking, MM/GBSA free energy calculations, and drug repurposing screening against approved compound libraries, with the aim of identifying small molecules ready for experimental testing. This approach builds on established strategies combining computational and biophysical methods to identify effective ligands for cancer-relevant targets. The project will deliver a validated list of novel therapeutic targets for TNBC together with structurally characterised drug candidates, bridging the gap between computational discovery and clinical application through rigorous thermodynamic and structural simulations.

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**COLLABORATIONS**

The project will be carried out in collaboration with two experimental research groups: the IBB-CNR guided by Prof. Emilia Pedone, and the Department of Molecular Medicine and Medical Biotechnology guided by Prof. Antonio Feliciello.