

UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA
DOTTORATO DI RICERCA IN Tecnologie Convergenti per i Sistemi
Biomolecolari – XLII CICLO

Research Topic ID: XLII – 1.3

Project Tutor: Ferdinando Chiaradonna

Project Supervisor/s: Cinzia Bragato / Barbara La Ferla

Project Title: Innovative inhibitors of Hexosamine Biosynthetic Pathway as novel therapy in pancreatic and breast cancers

Scientific background & Objectives

The efficacy of chemotherapy is constrained by the emergence of resistance, a multifaceted process in which a pivotal role is attributed to cancer metabolism rewiring. Pancreatic and breast cancers are characterized by an increased flux through the glucose-dependent Hexosamine Biosynthetic Pathway (HBP), which plays a key role in protein glycosylation (1). Both N- and O-glycosylation are markers of epithelial-mesenchymal transition (EMT), metastasis, cell proliferation and plays an important role in the DDR mechanism as well as in chemoresistance. Our published results indicate that FR054, a specific inhibitor of HBP, reduces *in vitro* and *in vivo* tumor growth with negligible side-effects. In this contest we recently patented four novel inhibitors characterized with a major anticancer effect. Therefore, it is important to fully-characterize these novel inhibitors in *in vitro* cellular models as well as in *in vivo models*, including Zebrafish, a powerful model for oncology drug discovery.

Project's Networks, Sustainability & Mobility

- a) the coherence of the suggested project with competences/tools of the hosting lab
- b) intradepartmental or external collaborations
- c) at least one pertinent research article published by the proposer/s
- d) 1 (or more) putative foreign institutions for achieving the required ordinary mobility (6 months)

a) The project is fully aligned with the laboratory's expertise, encompassing both its experimental methodologies and conceptual framework. All the essential equipment and resources required to carry out the project are readily available within the proponent's department.

b) Barbara La Ferla (Department of Earth and Environmental Sciences, University of Milano-Bicocca, Milano). La Ferla is coinventor of the 4 novel molecules. She will be involved in chemical synthesis.

Cinzia Bragato (Department of Earth and Environmental Sciences, University of Milano-Bicocca, Milano), will be the collaborator for *in vivo* experiments to test cytotoxicity, tumor growth and metastasis upon drug treatment. Both collaborations are currently ongoing and actively progressing.

c)
- PGM3 inhibition shows cooperative effects with erastin inducing pancreatic cancer cell death *via* activation of the unfolded protein response. Zerbato B, Gobbi M, Ludwig T, Brancato V, Pessina A, Brambilla L, Wegner A, **Chiaradonna F**. *Front Oncol*. 2023 May 16;13:1125855.

- Hexosamine pathway inhibition overcomes pancreatic cancer resistance to gemcitabine through unfolded protein response and EGFR-Akt pathway modulation. Ricciardiello F, Gang Y, Palorini R, Li Q, Giampà M, Zhao F, You L, La Ferla B, De Vitto H, Guan W, Gu J, Zhang T, Zhao Y, Chiaradonna F. *Oncogene*. 2020 May;39(20):4103-4117.

d) Dr. Sara Sdelci, Centre for Genomic Regulation, Barcelona, Spain. Connection between metabolism and DNA repair machinery in the nucleus. Proteomic and microscopy techniques.