Targeted degraders of eIF6: a novel strategy to remodulate liver pathological lipidic metabolism

Alessio Colleoni[a,b], Enrico Mario Alessandro Fassi[a], Annarita Miluzio[c], Marco Albani[a], Davide Lecchi[a], Giorgia Tempra[a], Marco De Amici[a], Giovanni Grazioso[a], Stefano Biffo[b,c], and Carlo Matera[a]

[a] *Department of Pharmaceutical Sciences, University of Milan, Via Mangiagalli 25, 20133, Milan, Italy*
[b]*Department of Biosciences, University of Milan, Via Celoria 26, 20133 Milan, Italy*
[c]*National Institute of Molecular Genetics, Fondazione "Romeo ed Enrica Invernizzi", 20122, Milan, Italy*

E-mail: alessio.colleoni@unimi.it

Among the crucial mechanisms involved in gene expression, translational control has proved to play a pivotal role. eIF6, a translation initiation factor that operates downstream of the insulin pathway, has recently emerged as a potential drug target: mice heterozygous for this factor reduce the upregulation of protein synthesis under postprandial conditions and exhibit reduced white fat accumulation [1]. It is well-known that increased lipid accumulation in the liver leads to non-alcoholic fatty liver disease (NAFLD), which can progress to non-alcoholic steatohepatitis (NASH) and eventually to hepatocellular carcinoma (HCC), a leading cause of cancer-related death worldwide. Notably, fatty liver is the fastest-growing cause of liver failure and HCC. Recent studies have shown that genetic inhibition of eIF6 reduces lipid metabolism and impedes NAFLD to HCC progression [2].

Based on these studies, inhibiting eIF6 could represent an effective strategy to prevent the pathological development of NAFLD, its progression to NASH, and subsequently to HCC, as well as the progression of existing HCC. To test this hypothesis, we designed selective degraders of eIF6 based on the molecular skeleton of known eIF6 binders previously identified and applied the emerging "proteolysis targeting chimera" (PROTAC) strategy. Thus, an *in silico* study of a set of degraders of eIF6 was performed, combining docking, molecular dynamics simulations and ligand binding free energy (MM-GBSA) approaches. The top scoring candidates are currently under development: the design, synthesis and characterization of these novel, putative PROTACs will be presented and discussed.

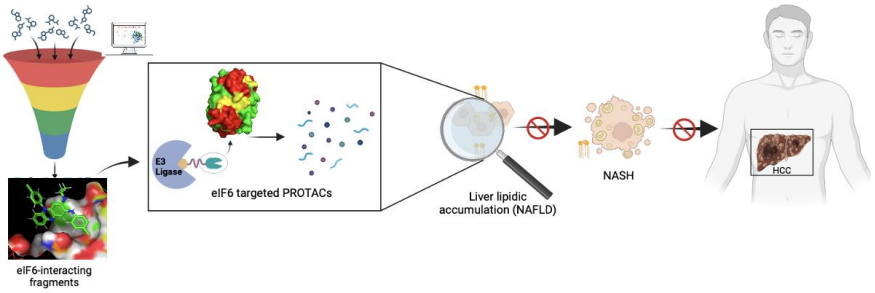

Figure 1. Project workflow.

References:

[1] A. Scagliola, A. Miluzio, G. Ventura, S. Oliveto, A. Bresciani, S. Biffo. Nat. Commun. 2021, 12(1), 4878.
[2] A. Scagliola, A. Miluzio, G. Mori, S. Ricciardi, S. Oliveto, N. Manfrini, S. Biffo S. Int. J. Mol. Sci. 2022, 23(14), 7720