SCI 2024
Chemistry
ELEMENTS OF FUTURE
XXVIII National Congress
MILANO,
26 - 30 August 2024
Società Chimica Italiana

FAR-PO-038

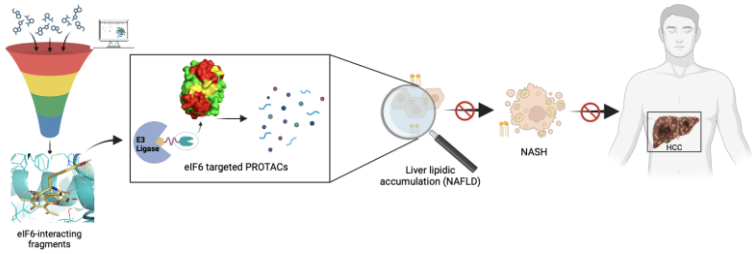
Tackling Hepatocellular Carcinoma with Targeted Degraders of eIF6

A. Colleoni,[a] Enrico M. A. Fassi,[a] A. Miluzio,[b] M. Albani,[a] D. Lecchi,[a] M. De Amici,[a] G. Grazioso,[a] S. Biffo,[b,c] C. Matera[a]

[a]*Department of Pharmaceutical Sciences, University of Milan, 20133 Milan, Italy*
[b]*National Institute of Molecular Genetics, Fondazione Romeo ed Enrica Invernizzi, INGM, 20122 Milan, Italy*
[c]*Department of Biosciences, University of Milan, 20133 Milan, Italy*
alessio.colleoni@unimi.it

Translational control is the selective and regulated translation of specific mRNAs from the pool of the transcribed mRNAs. According to several studies, it is the major regulator of gene expression. eIF6 is a translation initiation factor that acts downstream the insulin pathway. Seminal work from Biffo's group has shown that mice heterozygous for eIF6 fail to upregulate protein synthesis in postprandial conditions, and simultaneously show a reduction in the accumulation of white fat. Subsequent studies have shown that translation factors amplify lipid accumulation by acting at the translational level. Increased lipid accumulation in the liver is known as non-alcoholic fatty liver disease (NAFLD), a prevalent condition in Western countries. Notably, fatty liver is the fastest growing cause of liver failure and hepatocellular carcinoma (HCC), the second leading cause of cancer-related death worldwide. Recently, it was observed that genetic eIF6 inhibition reduces lipid metabolism and the progression of NAFLD to HCC.

We hypothesize that eIF6 inhibition is an effective strategy for impairing the pathological evolution from a fatty liver (NAFLD) to non-alcoholic steatohepatitis (NASH) and then HCC, and the progression of HCC. To challenge this hypothesis, we aim to generate a set of small molecules able to selectively degrade eIF6, based on the emerging proteolysis targeting chimera (PROTAC) technology. Docking, molecular dynamics simulations and ligand binding free energy (by MM-GBSA approach) have been accomplished on compounds displaying promising in vitro activity on eIF6. The top scoring candidates are currently under development. The design strategy, chemical synthesis, and pharmacological investigation of this novel class of targeted protein degraders will be presented and discussed.



References:
[1] A. Scagliola, A. Miluzio, G. Ventura, S. Oliveto, C. Cordiglieri, N. Manfrini, D. Cirino, S. Ricciardi, L. Valenti, G. Baselli, R. D'Ambrosio, M. Maggioni, D. Brina, 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.