Artificial intelligence and deep learning-assisted design of novel Peroxisome Proliferator-Activated Receptors ligands for the treatment of non-alcoholic steatohepatitis (NASH)

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and control important metabolic functions; they are mainly implicated in lipid and glucose homeostasis, insulin sensitivity, and energetic metabolism. The PPARs family comprises three different subtypes: α, β/δ and γ, whose expression and actions differ according to subtype, organ and tissue cell type.[1] These receptors are valuable targets for the treatment of metabolic syndrome, a group of risk factors for cardiovascular disease and type 2 diabetes mellitus (T2DM).
Metabolic syndrome is a risk factor for non-alcoholic steatohepatitis (NASH), one of the most studied hepatic dysfunctions with increasing prevalence worldwide. Many drugs being actively pursued for NASH are medicines that are already approved or in development to treat T2DM and obesity.[2] Among the most advanced drug candidates, the modulators of PPARs appear to be the most promising. The development of more balanced drugs interacting with PPARs, devoid of the side effects showed by the currently marketed PPARγ full agonists, is considered a major challenge. To overcome these issues, research efforts have been ultimately directed toward the design of selective PPAR modulators (SPPARMs), able to induce distinct agonistic and antagonistic responses depending on the cellular context and specific transcriptional signatures, as well as PPARα/γ dual agonists or PPARα/γ/δ pan-agonists, eliciting a balanced activation on all the three subtypes.[3,4] Hence, the goal of this project is to identify novel PPARs modulators by combining structure-based virtual screening with deep learning approaches.[5] Building on the wealth of structural information available for PPARs in public databases, such as the Protein Data Bank (PDB), we will exploit generative models suitable for multiobjective de novo drug design, in order to design compounds endowed with multiple target properties.[6] In addition, we will explore innovative docking approaches based on deep learning architectures,[7] to accomplish faster screening of ultralarge chemical libraries with better accuracy. The Hight Performance Computing (HPC) infrastructure, already available at the Department of Pharmacy of the University of Naples "Federico II", will be leveraged to perform computationally intensive calculations. The most promising candidates will be selected for efficacy studies (e.g. transactivation assays) and will be assessed further in steatosis-induced cells to evaluate their effects on the hallmarks of NASH. Then, lead optimization efforts will take place, involving in silico design, acquisition of structural analogues and synthesis, informed by biological assays outcomes.

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