Selective Small-Molecule Probes for TNF Receptors

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Tumor Necrosis Factor-α (TNF-α) is a pleiotropic cytokine that plays a major role in the immune system homeostasis. It is involved in many inflammatory diseases such as rheumatoid arthritis, psoriasis, or Alzheimer's [1]. Thus, TNF-α is a very relevant pharmacological target, and biologics (etanercept/adalimulab) have already been developed to modulate its inflammatory signaling cascade. However, these biologics come with several side effects and expensive production costs [2]. TNF-α trimer selectively binds to two transmembrane receptors: TNFR1 and TNFR2. They assemble into trimers upon binding and are responsible for the transmission of the inflammatory signal inside the cell. Soluble TNF-α binds to TNFR1 and activate apoptosis, whereas membrane-bound TNF-α binds to TNFR2 and can activate cell survival. Due to these opposing effects, it is believed that selective blocking of TNFR1 and/or activation of TNFR2 will lead to more efficient treatments with fewer side effects compared to general TNF blocking [3]. Hence, we are aiming to find selective small-molecule binders for these receptors that will have an impact on TNF signaling. In order to achieve this goal, we are using Fragment-Based Ligand Discovery through the screening of fluorinated fragments by 19F Nuclear Magnetic Resonance. Validation and optimization of the hits was carried out via Surface Plasmon Resonance and X-ray crystallography.

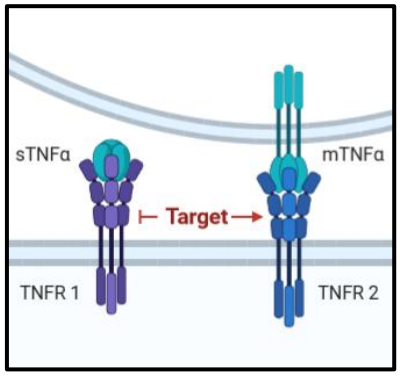

Figure 1. Targeting TNF-α signalling via TNF receptors

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[2] J. Li, Z. Zhang, X. Wu, J. Zhou, D. Meng, and P. Zhu, Front. Pharmacol. 12, 746396 (2021)
[3] N. Ortí-Casañ, Y. Wu, P. Naudé, P. De Deyn, I. Zuhorn, and U. Eisel, Front. Neurosci. 13, 49 (2019)