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New contributions to the drug profile of TNFα inhibitor SPD 304: affinity, selectivity and ADME considerations

Tumor Necrosis Factor alpha (TNFα) is a relevant clinical target for the treatment of chronic inflammatory diseases such as rheumatoid arthritis. Currently only few small molecules are known as direct inhibitors of TNFα. SPD 304 molecule is considered as a reference molecule in almost all publications describing direct inhibitors of TNFα because its mechanism was demonstrated by He et al in 2005.

In this lecture, we will provide new insights regarding the drug profile, selectivity and ADME considerations of SPD 304 to evaluate its potential as a hit for the structure-based design of novel TNFα inhibitors. ELISA experiments confirmed the inhibition of TNFα/TNRI binding (IC50 = 11 mM). SPD304 was also able to disrupt the binding between TNFα and TNFRI in cellular-based assays resulting with IC50 values of 12.5 and 6.25 mM for L929 and HEK-Blue ™ cell lines respectively. A Surface Acoustic Wave (SAW) experiment highlighted only one binding site with a dissociation constant of 6.1 ± 4.7 nM. Concerning selectivity, SPD304 also inhibited the binding of the cytokines IL-4 and IL-13 to their receptors and showed no direct inhibition on proteins involved in the TNFα pathway (IκB kinases, JNK1, p38 and caspases 3 et 8). Finally, the thermodynamic solubility and Caco-2 cells permeability of SPD304 were experimentally evaluated and ADMET *in silico* predictions will be discussed. The overall physicochemical and pharmacological profile of SPD304 makes it possible to conclude that this hit is of low quality to provide for a drug optimization program based on its chemical structure.

Finally, we will review all the small TNFα inhibitor molecules and show that their drug profile is insufficient to consider their clinical development.

Keywords: TNFα, SPD304, chronic inflammatory diseases, drug profile

Biography:

Marc Port is a chemical engineer graduated from the Ecole Nationale Supérieure de Chimie de Paris. He completed his PhD by carrying out a new total synthesis of trenbolone acetate. He then joined Guerbet company where he became Director of Drug Discovery. He then became Professor of the Pharmaceutical Chemistry Chair at Cnam in 2014 where he is currently the head of the Molecular Chemistry team. His main areas of research focus on medicinal chemistry and on the design of theranostic agents. His research has led to around 80 international scientific publications and 43 international patents