## OS06-1 Medicinal chemistry of farnesoid X receptor ligands

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The nuclear receptor farnesoid X receptor (FXR) has emerged as a highly promising target in preclinical development in recent years. A significant amount of research has been conducted and, although none has reached clinical use, many synthetic ligands of FXR have been described.

In its function as a ligand-activated transcription factor, the farnesoid X receptor (FXR) is, besides its primary role in bile acid homeostasis, involved in the regulation of genes related to metabolic processes. It is primarily expressed in the liver, kidneys, intestine and adrenal glands, where it is activated by its physiological ligands, the bile acids. Chenodeoxycholic acid (CDCA) is the most potent physiological FXR ligand, while the other bile acids are less active and ursodeoxycholic acid (UDCA) is not an FXR agonist.

The role of FXR as a bile acid sensor was first reported in 1999 when three groups found that certain bile acids activate FXR and modulate expression of its target genes. Since then, FXR has gained a lot of academic and industrial interest. New physiological roles of FXR were discovered leading to reasonable hope that the nuclear receptor could serve as a pharmacological target in several pathophysiological conditions.

At the time of writing, there are more than twenty co-crystal structures of the LBD of FXR (FXR–LBD) with several ligands including steroidal and nonsteroidal structures but no physiological ligand has been co-crystallized yet. For some structural classes the co-crystal structures give many insights into the SARs of FXR ligands (1).

Due to the high potential for side effects of steroidal compounds, the search for nonsteroidal FXR ligands started soon after the discovery of FXR. The first identified nonsteroidal high-affinity ligand of FXR, GW4064, is still one of the most important chemical tools to study the molecular and physiological characteristics of FXR *in vitro* and *in vivo* (2). However, due to poor bioavailability and toxicological issues, especially concerning the stilbene moiety, it is not suited for clinical use.

The available knowledge about the SAR of FXR ligands – especially agonists – and their co-crystal structures indicate that the development of new FXR ligands has to consider that there are few polar interactions possible and that the FXR–LBD requires quite hydrophobic ligands. This makes the design of ligands with drug-like properties a challenging topic.

(1) Merk, Steinhilber, Schubert-Zsilavecz, Medicinal chemistry of farnesoid X receptor ligands: from agonists and antagonists to modulators. *Future Med Chem*, **2012**, 4(8): 1015-1036

(2) Merk, Steinhilber, Schubert-Zsilavecz, Characterizing ligands for farnesoid X receptor - available in vitro test systems for farnesoid X receptor modulator development. *Expert Opin Drug Discov*, **2014,** 9(1): 27-37