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### **Nuclear Receptor Signalling and Design of Modulators**

One of the major challenges for nuclear receptor drug discovery in recent years is the ability to develop compounds that can discriminate between desired pharmacological effects versus potential liabilities. This approach is best exemplified through the development of Selective Estrogen Receptor Modulators (SERMs) and is now being extended to other members of the nuclear receptor family. The Liver X Receptor (LXR)  $\alpha$  and LXR $\beta$  are nuclear receptors that bind to oxysterols and regulate the expression of target genes involved in cholesterol metabolism and transport (ABCA1), inflammation (COX2, iNOS), and gluconeogenesis (PEPCK, G6P). These effects on gene expression are manifested *in vivo* as first generation LXR agonists GW3965 and T1317 show beneficial effects in multiple animal models for atherosclerosis and diabetes. However, the LXRs have also been shown to induce the expression of genes that control fatty acid and triglyceride metabolism, primarily through SREBP-1c. As a result, accumulation of triglycerides in the liver as well as an adverse lipid profile is observed in rodents following chronic treatment with GW3965 or T1317. LXR modulators that retain the beneficial effects and lack triglyceride liability will be required for progression to the clinic. Our efforts directed towards the identification of LXR modulators with improved therapeutic indices will be described in this presentation.