## conferenceseries.com

9<sup>th</sup> International Conference on

## **STRUCTURAL BIOLOGY**

September 18-20, 2017 Zurich, Switzerland

## Structural basis for the cooperative allosteric activation of the free fatty acid receptor GPR40

Stephen M Soisson Merck Research Laboratories, USA

Clinical studies indicate that partial agonists of the G-protein-coupled, free fatty acid receptor GPR40 enhance glucosedependent insulin secretion and represent a potential mechanism for the treatment of type 2 diabetes mellitus. Recently identified, full allosteric agonists (AgoPAMs) of GPR40 bind to a site distinct from partial agonists and can provide additional efficacy. Our recent studies have led to a 3.2-Å crystal structure of human GPR40 (hGPR40) in complex with both the partial agonist MK-8666 and an AgoPAM. Surprisingly, the structure reveals a novel lipid-facing AgoPAM-binding pocket outside the transmembrane helical bundle. Comparison with an additional 2.2-Å structure of the hGPR40–MK-8666 binary complex reveals an induced-fit conformational coupling between the partial agonist and AgoPAM binding sites, involving rearrangements of the transmembrane helices 4 and 5 (TM4 and TM5). These structural rearrangements, along with AgoPAM binding, appear to trigger the transition of intracellular loop 2 (ICL2) into a short helix. These conformational changes likely prime GPR40 to a more active-like state and explain the binding cooperativity between these ligands.



Figure1: Structural basis for the cooperative allosteric activation of the free fatty acid receptor GPR40

## Biography

Stephen M Soisson, PhD is a Director of Biochemical Engineering and Structure at Merck Research Laboratories in West Point, Pennsylvania (USA). With 25+ years of structural biology experience, he has focused research on elucidating the structural aspects of biological regulatory mechanisms, and applying these insights in the area of structure-based drug design. He has served on the scientific advisory boards of the Structural Genomics Consortium, and the GPCR Consortium.

stephen\_soisson@merck.com

Notes: