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SPECIAL SEMINAR - 15 July, 4:00 PM AEST

Dr. Dietmar Weichert

Principal Scientist, Structural Research, Global Medicinal Chemistry, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

Dr. Dietmar Weichert is a Principal Scientist in the Structural Research Group at Boehringer Ingelheim. His work focusses on the structure and function of integral membrane proteins and the support of drug discovery projects. As a pharmacist by training, Dietmar received his PhD in Medicinal Chemistry at Erlangen University, which included research work on G protein-coupled receptors (GPCRs) biochemistry and structural biology at Stanford University. Following his postdoctoral work in membrane protein structure and function at Trinity College, Dublin, Dietmar joined Boehringer Ingelheim in 2020.

Dr. Tobias Claff

Structural Research, Global Medicinal Chemistry, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

Dr. Tobias Claff is a pharmacist and postdoctoral researcher in the Structural Research unit of Boehringer Ingelheim's Medicinal Chemistry department. Dr. Claff earned his doctorate in Pharmacy from the University of Bonn where he worked in the Pharmaceutical & Medicinal Chemistry group of Prof. Christa Müller. Dr. Claff's work is at the intersection of structural biology and drug discovery, with a strong focus on GPCRs. He gained expertise in membrane protein structural biology during a research stay in Ray Stevens' lab in Shanghai, where he determined agonist-bound crystal structures of the delta-opioid receptor. His doctoral studies focused on X-ray crystallography of adenosine receptors, contributing to a deeper understanding of receptor-ligand interactions. Currently, at Boehringer Ingelheim, Dr. Claff is using cryo-electron microscopy and structure-based drug design to study GPCRs. He is particularly interested in lipid-activated orphan GPCRs such as GPR55.

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Enabling Structure-based Drug Discovery for Membrane Proteins: Insights Into Lipid-mediated Activation of GPR55

GPR55 is an understudied class A orphan G protein-coupled receptor (GPCR). It has sparked considerable interest when it was shown that GPR55 can be activated by cannabinoid ligands[1]. However, its classification as an atypical cannabinoid receptor remains controversial. In addition, GPR55 was found to be activated by lysophosphatidylinositol lipids, the putative endogenous ligands of this receptor[2]. The fact that GPR55 is physiologically highly relevant and has been associated with inflammation[1], metabolic disorders[3] and cancer[4] has led to drug discovery efforts that identified synthetic ligands, which, however, have yet to be optimized to become potential drug candidates[5].

To strengthen our capabilities in the enablement of membrane protein biophysics and structure determination to support our drug discovery pipeline, GPR55 was used as a case study.

We determined high-resolution cryo-electron microscopy structures of the activated GPR55 in complex with a heterotrimeric G 13 protein and two structurally distinct ligands:
(1) the putative endogenous agonist, 1-palmitoyl-2-lysophosphatidylinositol and
(2) the synthetic agonist, ML184.

Our work sheds light on (endogenous) ligand recognition at GPR55, G protein coupling and receptor activation. Furthermore, an opening connecting the ligand binding site to the membrane, which is conserved in other lipid binding GPCRs, is observed[6]. Our work is corroborated by mutagenesis and functional experiments as well as molecular dynamics simulations.

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5. Kotsikorou, E. et al. Biochemistry, 50: 5633–5647, 2011.
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