

## A novel pharmacogenetic strategy to study the regulation of glucose and energy homeostasis by distinct GPCR signaling pathways

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G protein-coupled receptors (GPCRs) play critical roles in maintaining proper glucose and energy homeostasis. During the past few years, clozapine-N-oxide (CNO)-sensitive designer GPCRs have emerged as valuable new tools to dissect the in vivo roles of distinct G protein signaling pathways in specific cell types or tissues. Structurally, these novel receptors (alternative name: designer receptors exclusively activated by designer drugs; DREADDs) are mutant muscarinic acetylcholine (ACh) receptors that are unable to bind the endogenous ligand, ACh. However, DREADDs can be activated by CNO with high potency and efficacy. Importantly, CNO is otherwise pharmacologically inert. We recently started to use DREADD technology to assess the in vivo roles of distinct GPCR signaling pathways in regulating glucose and energy homeostasis. Specifically, we generated and analyzed transgenic mice that express different DREADDs in distinct, metabolically relevant cell types such as pancreatic beta-cells, adipocytes, hepatocytes, or distinct neuronal subpopulations of the hypothalamus. For our studies, we are using various DREADDs that differ in their G protein-coupling properties (Gq, Gs, Gi, etc.). For example, using this strategy, we found that chronic CNO treatment of mice expressing a Gq-coupled DREADD in pancreatic beta-cells only greatly improves beta-cell function. More recently, we developed a novel DREADD that is unable to activate G proteins but can selectively recruit proteins of the arrestin family. This new construct represents an important novel tool to explore the physiological roles of arrestin-dependent signaling pathways in various metabolic functions.

### Biography

Jurgen Wess is the Chief of the Molecular Signaling Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, Bethesda, Maryland, USA. He received his Ph.D. in Pharmacology from the Johann Wolfgang-Goethe University in Frankfurt/Main (Germany) and subsequently worked as a Postdoctoral Fellow at the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS), NIH, Bethesda, Maryland, USA. One major focus of Dr. Wess' lab is to explore the roles of G protein-coupled receptors (GPCRs) in maintaining proper glucose and energy homeostasis.

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