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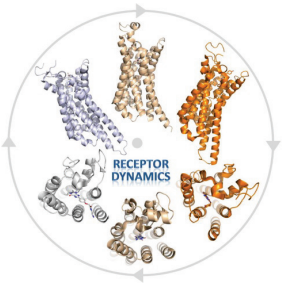

Temporal dynamics of GPCRs: ligand-dependent stabilization of receptor conformations, residence time and insurmountable antagonism

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Aim:
Functionally selective GPCR ligands are supposed to be capable of activating distinct signalling pathways such as G-proteins and beta-arrestin successively, in parallel, to a different extent or exclusively. Stabilization of a GPCR in an active or an inactive state, respectively, is closely related to the concept of functional selectivity. The project is aiming at a better understanding of ligand-dependent molecular mechanisms and the time-courses of processes resulting in discrepancies in receptor binding, activation or inhibition of GPCR signaling pathways.

Methodology:
In an interdisciplinary approach, covering medicinal chemistry, molecular pharmacology, bioanalytics and biophysics, the PhD student will preferably investigate neuropeptide Y (NPY) and/or histamine receptor subtypes as prototypical peptidergic and aminergic GPCRs. Classes of ligands, previously identified as insurmountable antagonists and assumed to induce ligand-selective conformations, will be further explored, structurally optimized, functionally modified (covalently binding and dimeric compounds, fluorescent tracers), investigated with regard to biased cellular signaling, the interaction with or recruitment of associated proteins and time-dependent influences on second messenger levels. The project will be pursued in collaboration with experts in special methods to study GPCRs and signaling pathways in live cells. Fluorescently labeled ligands and receptors in combination with single-molecule microscopy methods and superresolution imaging will be used to analyze the localization and dynamics of GPCRs.

Collaborators:
C. Hoffmann (Würzburg), D. Larhammar (Uppsala), T. Ozawa (Tokyo), groups involved in the Research Training Group “Medicinal Chemistry of Selective GPCR Ligands” (GRK1910)

Project goals:
Identification of molecular mechanisms of ligand-dependent stabilization of GPCR conformations, irreversible and pseudo-irreversible binding (slow dissociation), resulting in insurmountable antagonism and biased signaling, using NPY and histamine receptors as models.

Key publications:

1) Keller M, Erdmann D, Pop N, Pluym N, Teng S, Bernhardt G and Buschauer A (2011) Red-fluorescent argininamide-type NPY Y_1 receptor antagonists as pharmacological tools. *Bioorg Med Chem* 19:2859-2878.

2) Birnkammer T, Spickenreither A, Brunskole I, Lopuch M, Kagermeier N, Bernhardt G, Dove S, Seifert R, Elz S and Buschauer A (2012) The bivalent ligand approach leads to highly potent and selective acylguanidine-type histamine H_2 receptor agonists. *J Med Chem* **55:** 1147-1160.

3) Pluym N, Baumeister P, Keller M, Bernhardt G and Buschauer A (2013) [^{3}H]UR-PLN196: A Selective Nonpeptide Radioligand and Insurmountable Antagonist for the Neuropeptide Y Y_2 Receptor. *ChemMedChem* 8:587-593.