Irreversibly-binding GPCR Ligands and slowly diffusing analogs

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Aim:
We aim for the development of irreversibly binding GPCR ligands to chemically restrain a given receptor in a desired and predefined conformation and consequently to observe and control the receptor's structure and biological activity.

Methodology:
The formation of covalent complexes of functional proteins and specific ligands enables us to observe and control the receptor's biological activity. The doctoral student will combine design and chemical synthesis of highly specific molecular probes displaying covalent receptor binding based on a disulfide exchange reaction and slowly diffusing analogs (Gmeiner lab), which will yield pharmacologically relevant GPCRs in a controlled ligand-induced conformation or monomer / dimer composition. As an example, we aim to design and synthesize inverse agonists for the neurotensin NTS1 receptor for the crystallization of a receptor-ligand complex and an analysis of allosteric modulation. Because ligand – induced receptor conformations and dynamics have substantial impact on biological activity, this work will be of particular relevance for mechanistic investigations (Lohse lab), the generation of novel assay systems and the construction of receptor ligand complexes suitable for the generation of high resolution X-ray crystal structures (Grisshammer lab, Kobilka lab).

Collaborators:
Reinhard Grisshammer (NIH, Rockville), Brian Kobilka (Stanford University)

Project goals:
This project will lead to covalent GPCR ligands taking advantage of our recently described irreversible agonist FAUC50 as a lead compound. High resolution GPCR-ligand X-ray structure is envisioned.

Key publication:

Rosenbaum DM, Zhang C, Lyons JA, Holl R, Aragao D, Arlow DH, Rasmussen SGF, Choi H-J, DeVree BT, Sunahara RK, Chae PS, Gellman SH, Dror RO, Shaw DE, Weis WI, Caffrey M, Gmeiner P, Kobilka BK (2011) Structure and function of an irreversible agonist-beta2 adrenoceptor complex. Nature 469, 236.