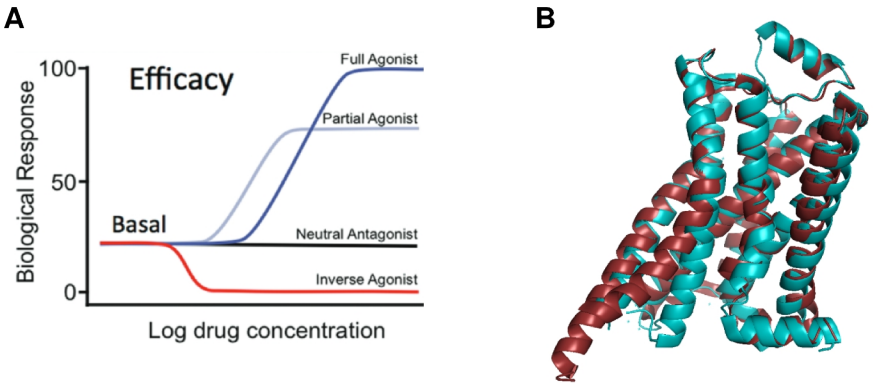
Computer-aided design of ligands with tailored efficacies for the β_2-adrenergic receptor

Magdalena M. Scharf, Peter Kolb

Department of Pharmaceutical Chemistry, Philipps-Universität Marburg

G protein-coupled receptors (GPCRs) are one of the pharmacologically most important classes of proteins with more than 800 genes in humans encoding them. Due to their function as universal signal transduction entities, they are involved in a large number of physiological processes. Therefore, GPCRs are a target for 1/3rd of present-day marketed drugs and, consequentially, highly interesting targets for the design of future drugs. [1],[2]
Ligands binding to a GPCR might have different effects on the signal transmitted into the cell (see Fig. A, [3]), acting as agonist, antagonist or inverse agonist. Hence, ligands with different efficacies have different impact on the body when used as a drug.



We aim to find new ligands with predicted efficacies for the β_2-adrenergic receptor by docking molecule libraries to this receptor. It is involved in smooth muscle relaxation processes and, therefore, useful for e.g. treating asthma. Furthermore, the β_2-adrenergic receptor offers great perspectives for *in silico* studies due to the high number of available crystal structures (e.g. Fig. B: In blue pdb 3NY9, in red pdb 3SN6).
I will show preliminary results from docking calculations against inactive and active conformations of the β_2-adrenergic receptor. In total, 3.7 million molecules were docked in each docking campaign. From these, a total of 49 molecules were selected. The chosen molecules have been or will be tested in biological assays to determine their efficacies.
The insights gained from these studies not only help to understand the effect different ligands have upon binding to the β_2-adrenergic receptor, but can potentially be applied to other GPCRs as well. Thereby, our findings can contribute to our knowledge of function and mechanism of these fascinating proteins.

[1] C. N. Cavasotto, D. Palomba, *Chem. Commun.*, **2015**, *51*, 13576-13594.
[2] J. A. Salon, D. T. Lodowski, K. Palczewski, *Pharmacol. Rev.*, **2011**, *63*, 901-937.
[3] B. Kobilka, *Nobel Lecture*, **2012**, 195-213.