Molecular Basis of Biased Signaling in the

Angiotensin II Type 1 Receptor

G protein-coupled receptors (GPCRs) are a large family of membrane proteins formed by seven α-helical segments. GPCRs undergo conformational changes in response to a broad palette of extracellular signals that trigger either the canonical or the noncanonical intracellular signaling cascade. The fact that ligands can choose between these two subtypes of signaling pathways makes them biased, and the process it self is called biased signaling or functional selectivity.

My project concerns the study of biased signaling in the angiotensin II type 1 receptor (AT1R), a GPCR involved in the renin-angiotensin system that regulates blood pressure and fluid homeostasis. Since hypertension is the cause of many medical conditions, finding a way of controlling it is very important. One way to control it is to understand the activation mechanism of AT1R, since it directly influences new drug designs.

By applying different computational techniques, with the focus on enhanced sampling methods, we elucidated the biased signaling by detecting different conformational changes in the receptor upon activation with the natural and biased ligand. In addition, we suggest a way to improve the ligands in order to make them more selective for one or the other signaling pathway.