G protein-coupled receptors (GPCRs) constitute the largest family of human cell surface receptors. A detailed understanding of GPCR structure and function is thus of central importance for the development of drugs against numerous diseases. However, structural studies of these receptors are hampered by their low native expression levels, intrinsic flexibility and inherent instability. To facilitate the difficult structure determination process of GPCRs, we developed new protein engineering methods to overcome these hurdles. Application of these methods allowed us to determine several high-resolution crystal structures of therapeutically important GPCRs.

I will demonstrate our engineering efforts on the example of the parathyroid hormone 1 receptor (PTH1R), a class B GPCR which is critically involved in the regulation of serum calcium homeostasis and bone metabolism, and is a major target for the treatment of osteoporosis. I will present the first crystal structure of human PTH1R in complex with a peptide agonist, which allowed us to delineate the agonist binding mode for this receptor and revealed molecular details within conserved structural motifs that are critical for class B receptor function. I will show how this structure provides insight into the function of PTH1R and adds to the understanding of the therapeutically important class B of GPCRs.

Date & time: Friday, March 6, 2020 at 4:00 pm
Location: Lecture Hall Y03-G-95, UZH Irchel

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