The Cholecystokinin Type 1 Receptor (CCK1R) is a pharmaceutically relevant target for the treatment of obesity resulting from chronic caloric surplus. The process of caloric assimilation is governed in part by the activity of the neuroendocrine peptide cholecystokinin (CCK), which influences function in a range of gastrointestinal tissues and the associated peripheral nervous system (PNS). CCK has attracted attention from pharmaceutical companies for its activity in the PNS, where CCK activation of CCK1R suppresses appetite. CCK1R accomplishes its function via activation of Gαq signalling, which has been identified as a target for appetite modifying therapeutics.

The first candidate was SR146131. Despite excellent *in vitro* capacity relative to CCK, the mechanism of SR146131 activity has been reported as both orthosteric and allosteric. This molecule was withdrawn from Phase 1 clinical trial in 2004, in France. The results of this clinical trial have not been released but SR146131 has subsequently been used as an investigative molecule. Despite this there exists considerable disagreement on the mechanism or mechanisms by which SR146131 achieves CCK1R agonism, with some interpretations favouring orthosteric activity while others favour allosteric modes.

This project used single particle cryo-EM to determine the structure of CCK1R in complex with SR146131 to 3.2Å, showing the agonist bound in the orthosteric pocket, with receptor architecture closely mirroring that of CCK bound receptors.