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Evan O'Brien received his bachelor's degree in chemistry and biochemistry from the University of Pittsburgh, followed by his doctoral work with Dr. Joshua Wand at the University of Pennsylvania. While in Dr. Wand's lab, Evan focused on using structural and dynamic solution NMR methods to probe lipid-protein interactions and fast-timescale dynamics. His work on dynamics and entropy in simple systems drove his interest in exploring these phenomena with more complex human membrane protein systems. To that end, he started his postdoctoral work with Dr. Brian Kobilka at Stanford University in 2018. His early work in the Kobilka lab involved using various fluorescence techniques to interrogate GPCR dynamics, which resulted in a highly multi-disciplinary effort to characterize how unique Family B GPCR structural properties result in distinct signaling behavior. More recent work in the Kobilka lab has continued to focus on combining biophysical techniques with cryoEM to describe and take advantage of allosteric regulatory mechanisms.

Cryo-EM as a tool to characterize & exploit allostery in GPCRs

Allosteric modulation of G-protein coupled receptor (GPCR) activity represents a promising therapeutic avenue for next-generation drugs, yet this type of modulation is complex and understudied relative to more conventional orthosteric signaling. We combined structural data obtained by cryoEM with biophysical approaches such as HDX-MS and smFRET to obtain a more holistic picture of the mechanism of receptor activity modifying protein (RAMP)-induced negative allosteric modulation of a Family B GPCR, the glucagon receptor. We find that RAMP2-binding causes extensive conformational dynamics in the receptor extracellular domain, resulting in loss of agonist affinity and diminished activation at the intracellular face of the receptor. Further, we took advantage of our ability to select for particular receptor ensembles of interest and designed a screening strategy to select for small molecule positive and negative allosteric modulators (PAMs & NAMs) of the μOR. Using cryoEM, we identified our modulator binding sites as novel areas on the receptor responsible for allosteric effects on receptor function. The first identified potent, specific μOR NAM enters the brain and has clear effects on morphine-induced analgesia and side effects, though these effects remain counterintuitive and further study is required.