Uncovering the secret life of membrane proteins with mechanistic genetic screening

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Membrane proteins are essential cellular receptors, exchanges of soluble molecules, and channels for ions. Their diverse roles make them essential to the physiology that allows us to perceive and interact with the world around us. While membrane protein physiological roles and complex mechanisms are fascinating, membrane protein biology lags behind the rest of protein science because its role can only be studied meaningfully in the context of the cellular milieu. This gap in knowledge slows down fundamental physiology, the molecular basis of disease, and the development of drugs. Unfortunately, membrane proteins are challenging to study with existing methods, which has resulted in reductionist studies of a receptor with a few mutations, interacting genes, and a couple of phenotypes at a time. We build foundational methods tailored for mechanistically studying membrane proteins in massively parallel genetic screens, which we use to build mechanistic models of how mutations, genes, and stimuli alter membrane proteins across atomistic, molecular, and cellular scales. I will discuss how we (1) developed approaches for exploring new types of genetic variants at scale, (2) extended basic and translation biology of a model potassium channel, and (3) uncovered the mechanistic basis of a drug transporter's folding, function, and pharmacogenomics. Going forward, we will study how membrane proteins underlie physiology, break in disease, and are altered by pharmacology.