Communication and transport across lipid membranes control a large variety of cellular processes but remain poorly understood, largely because membrane proteins are difficult to study experimentally. The scarcity of high-resolution membrane protein structures and mechanistic insights hinder the development of effective therapeutics, with membrane proteins estimated to represent around 60% of possible cellular drug targets. To address these challenges, we have recently developed an ensemble of integrated computational/experimental approaches to accurately model and design membrane protein structures and functions. With our methods, we can (1) successfully predict the functional consequences of membrane protein sequence variations, (2) uncover new molecular determinants of membrane protein structure and function, and (3) rationally design membrane receptors with novel biophysical and signaling properties. We leverage these combinatorial approaches to engineer biosensors, as well as reprogram and create novel signaling pathways for applications in synthetic, systems biology and personalized medicine, including immunotherapeutic interventions.