"Using Genetic Code Expansion Technology to Probe the Functionality of Cryptic Ligand-Binding Pockets in GPCRs"

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Novel methods, including the genetic encoding of unnatural amino acids in mammalian expression systems, have been developed to probe visual pigments, G protein-coupled receptors, channels and other difficult-to-express membrane proteins. A variety of ancillary experimental chemical biology approaches have been adapted recently in the Sakmar laboratory, including targeted photo-crosslinking to map ligand and antibody binding sites, and bioorthogonal labeling reactions to introduce site-specific fluorophores and monoclonal antibody epitopes to facilitate single molecule imaging studies. These strategies can be used in combination with traditional biochemical and biophysical approaches to enhance drug discovery efforts. This lecture will address recently developed experimental approaches to discover and probe "cryptic" ligand-binding sites in GPCRs using a combination of unnatural amino acid mutagenesis, molecular dynamics simulations and medicinal chemistry to create "clickable" drug analogs.