Molecular recognition is an important part of signaling, and occurs when membrane-spanning receptors physically interact with a stimulus on the outside of the cell and activate downstream effectors. We are performing structural analysis of several model systems to identify how protein interactions contribute to molecular recognition.

Cellular Bioenergetics and Respiration

The physiological process of respiration couples oxidation-reduction reactions to the synthesis of ATP. Members of the complex II superfamily contribute to the process of respiration in all kingdoms of life. We use the E. coli complex II homolog quinol:fumarate reductase (QFR) as a model system to study catalysis, assembly, inhibition, covalent modification, and chemotactic signaling.

**Figure 3**: Orthoester synthases
A. Orthosomycin chemical structures. B. X-ray crystal structures of orthoester synthases. C. AKG coordinates the metal center of orthoester synthase, shown here in 1.4Å resolution. D. Hygromycin B binding in the HspX active site.

Pathogenic bacteria commonly recognize cell surface carbohydrates to bind specific tissue as the first step in infection. Various pathogens use serine-rich repeat surface receptors to bind platelets and salivary proteins. We study the molecular details of how these receptors bind.

**Figure 4**: Serine-Rich Repeat Receptor, GspB
A. Crystals of a subdomain of the receptor GspB (GspB_Cytb) from A. thaliana shares ~37% sequence identity with both Dcytb and Cgcytb from human.
B. A zoomed-in view of the orthosomycin binding region where the orthosomycin (cyan) is shown with electron density (green mesh).
C. Structure of surface glycoprotein GspB_Cytb.

Ascorbate as a Redox Co-Factor in Cytochrome B₅₆₁

Among the plethora of functions that ascorbic acid (vitamin C) fulfills in human metabolism, maintenance of redox homeostasis in the blood is one of the most important. Duodenal cytochrome B₅₆₁ (Dcytb) has been linked to uptake of dietary iron via the oxidation/reduction of ascorbate. Additionally, the adrenal chromaffin granule cytochrome B₅₆₁ (Cgcytb) uses ascorbate to transport reducing equivalents to dopamine-betahydroxylase in the production of catecholamine synthesis. Cyt b₅₆₁ from A. thaliana shares ~37% sequence identity with both Dcytb and Cgcytb from human.

**Figure 5**: Crystal structure of cytochrome b₅₆₁ from A. thaliana
A. The extramembrane and cytosolic membrane are shown as red and blue dotted spheres, respectively. Cyt b₅₆₁ was revealed to be a dimer in the crystal structure with one protomer of Cyt b₅₆₁ shown as light blue and the other gray. Each protomer has six transmembrane helices with two homologous regions (pink) positioned in the intra-membrane region. B. Ascorbate (green sticks) is shown positioned next the heme groups outside of the membrane region.

**Receptor Mediated Recognition**

G protein-coupled receptors (GPCRs) mediate information transfer in eukaryotic cells. Interactions between GPCRs and their binding partners modulate the signaling process. For example, the interaction between GPCR and cognate arrestin terminates G protein-mediated signaling. We are interested in identifying how different conformations of receptors influence protein interactions with signaling partners.

**Figure 2**: Role of arrestin-1 in rhodopsin signaling
Upon light activation, rhodopsin changes conformation to the active state. Its cognate G protein, transducin, binds to the active rhodopsin and initiates downstream signaling. Active rhodopsin is phosphorylated at multiple sites by GRK1. Arrestin-1 binds to active phosphorylated rhodopsin, blocking further transducin activation.

**Antibiotic Development**
Novel antibiotic scaffolds can contain unusual structural features, sometimes implicated in activity. The orthosomycin antibiotics are defined by having at least one orthoester linkage between sugar groups.