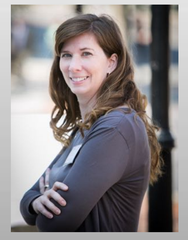
THE STRUCTURAL BASIS FOR MOLECULAR RECOGNITION



Iverson Laboratory

Departments of Pharmacology and Biochemistry, Vanderbilt Institute for Chemical Biology, and the Center for Structural Biology,
460 & 464 Robinson Research Building
Vanderbilt University Medical Center, Nashville, TN 37232-6600
https://medschool.vanderbilt.edu/iverson-lab

VANDERBILT UNIVERSITY


Kathryn McCulloch, Ph.D


Qiuyan Chen


Nicole Perry


Chrystal Starbird


Lioudmila Loukachevitch


Izumi Yamakawa

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 flavinylation, and chemotactic signaling.

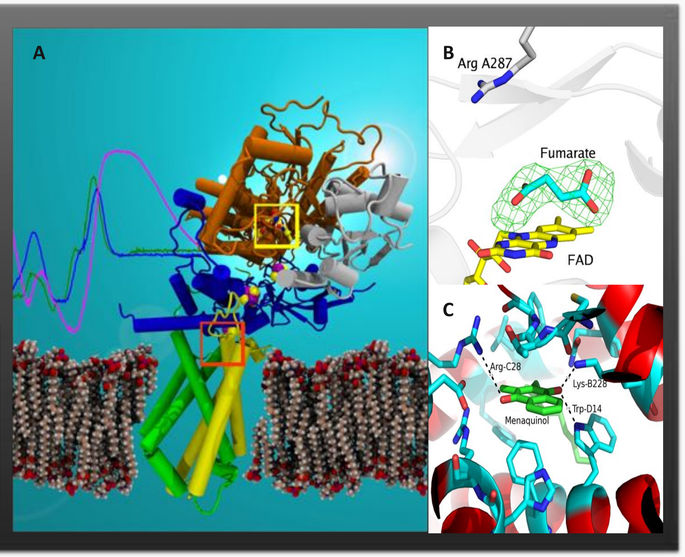


Figure 1: Quinol:fumarate reductase structures
A. The *E. coli* QFR is a heterotetramer with two soluble subunits (shown in orange, gray, and blue) and two membrane subunits (yellow and green). Two coupled active sites, boxed in yellow and red, bind the substrates fumarate and menaquinol, respectively. B. A zoomed-in view of fumarate binding site where fumarate (cyan) is shown with electron density (green mesh). C. A zoomed-in view of the menaquinol bindng region where the menaquinol (green) is shown with neighboring amino acids (cyan).

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.

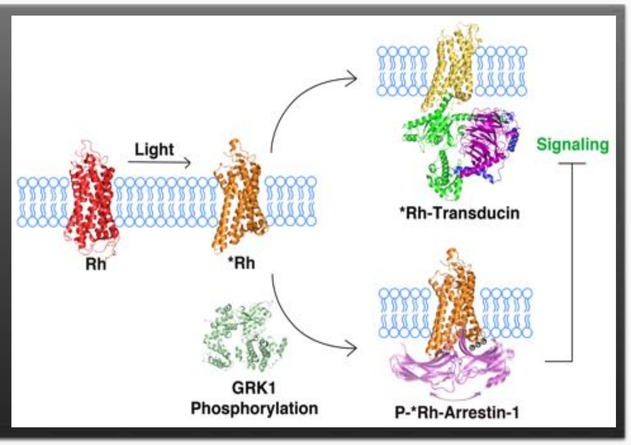


Figure 2: Role of arrestin-1 in rhodopsin signaling

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.

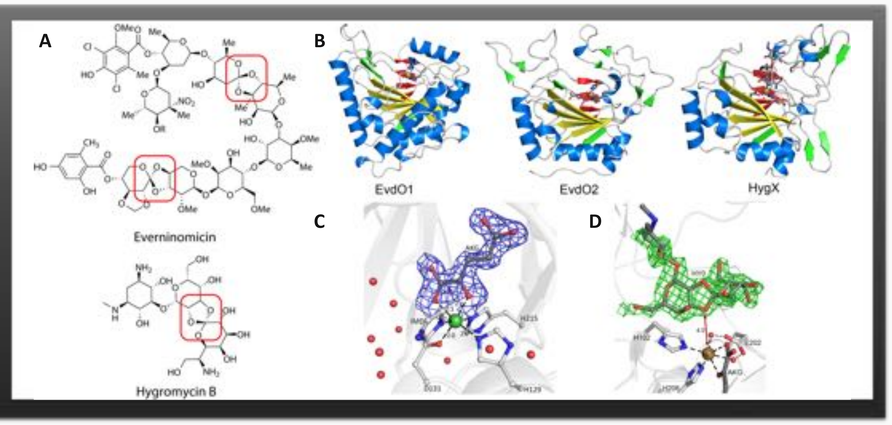


Figure 3: Orthoester synthases
A. Orthosomycin chemical structures.
B. X-ray crystal structures of orthoester synthases.
C. AKG coordinates the metal center of orthoester synthases, shown here in EvdO2.
D. Hygromycin B binding in the HygX active site.

The Role of Surface Receptors in Pathogen Invasion

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.

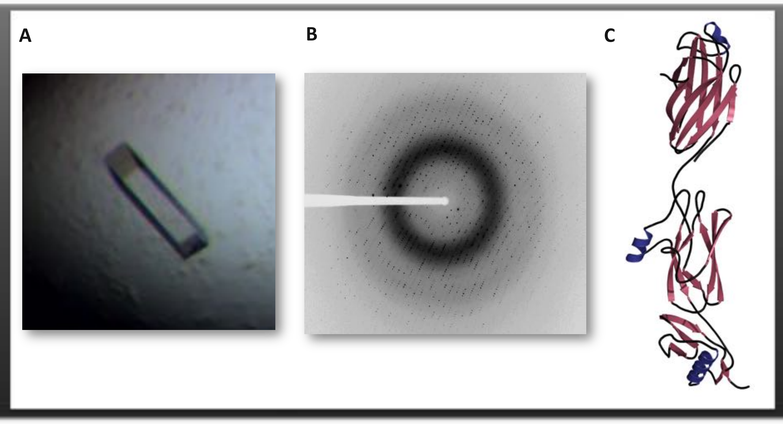


Figure 4: Serine-Rich Repeat Receptor, GspB

A. Crystals of a subdomain of the receptor GspB ($GspB_{BR}$)
B. A sample X-ray diffraction image of a $GspB_{BR}$ crystal. Diffraction was observed to 1.4Å resolution.
C. Structure of surface glycoprotein $GspB_{BR.}$

Ascorbate as a Redox Co-Factor in Cytochrome B_{561}

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 b_{561} (Dcytb) has been linked to uptake of dietary iron via the oxidation/reduction of ascorbate. Additionally, the adrenal chromaffin granule cytochrome b_{561} (CGcytb) uses ascorbate to transport reducing equivalents to dopamine-beta-hydroxylase in the production of catecholamine synthesis. Cyt b_{561} from *A. thaliana* shares ~37% sequence identity with both Dcytb and Cgcytb from human.

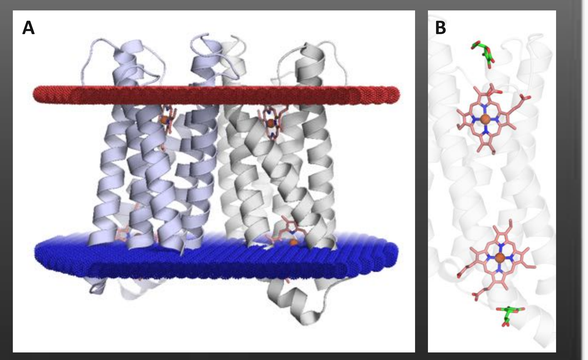


Figure 5: Crystal structure of cytochrome b_{561} from *A. thaliana*
A. The extracellular membrane and cytosolic membrane are shown as red and blue dotted spheres, respectively. Cyt b_{561} was revealed to be a dimer in the crystal structure with one protomer of Cyt b_{561} is shown as light blue and the other grey. Each protomer has six transmembrane helices with two heme groups (pink) positioned in the intra-membrane region. B. Ascorbate (green sticks) is shown positioned next the heme groups outside of the membrane region.