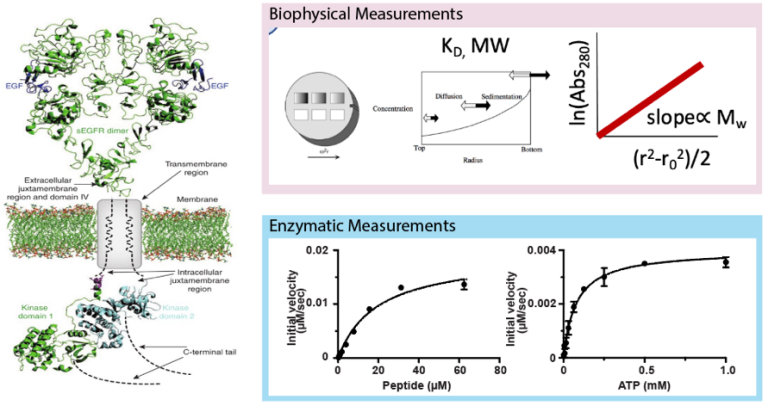
BIOPHYSICAL TRAINING GRANT | RESEARCH IN PROGRESS TALKS

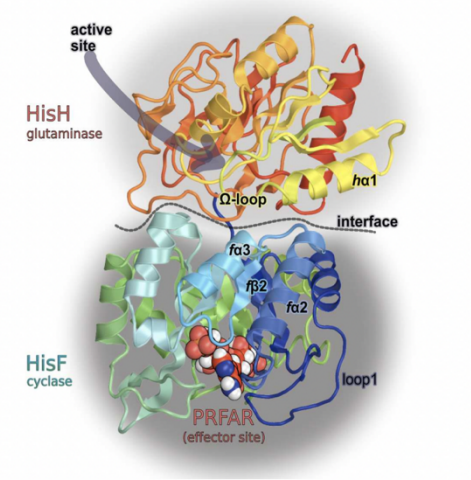
Zaritza Petrova



EGFR intracellular kinase dimerization contributes weakly to receptor dimerization but strongly activates kinase catalytic activity

AND

Olivia Enny



Investigating allosteric enzymes through the use of NMR spectroscopy

Friday, February 9, 2024 at 12 pm
BASS 305
Coffee and snacks will be provided

Zaritza Petrova is an 8th year graduate student in the laboratory of Mark Lemmon. Her project has focused on biophysical and biochemical studies of the activation mechanism of the EGF receptor, a long-standing and important clinical target. Prior to Yale, she worked for 4 years as a technician in the laboratory of Graham Hatfull at the University of Pittsburgh, exploring mycobacteriophage genomics and the infection mechanism of *M.tuberculosis* and its non-pathogenic relatives. She holds a B.A. in Biology from Dartmouth College. Outside of lab, she dances tango, goes for runs, and adds books to her reading list that she wishes someday to read.

Abstract: EGFR is a receptor tyrosine kinase with ubiquitous expression in various tissues. It normally functions during development to relay signals for cell growth and proliferation. Oncogenic driver mutations in the kinase domain of EGFR are associated with 20% of non-small cell lung carcinoma (NSCLC) cases. To understand the process of oncogenic activation, it is essential to develop a solid grasp of the natural mechanism of EGFR activation. Broadly, it involves the binding of growth factor ligands, dimerization at both the extracellular and intracellular regions, mediated entirely by receptor-receptor contacts, and activation of the catalytic function of the kinase domain to phosphorylated downstream substrates. Whereas the strength of the extracellular domain dimer has been directly measured, the strength of the intracellular dimer has been indirectly inferred. Thus, there is no clear comparison between the two interacting regions to delineate which dimer drives the activation process. Furthermore, EGFR kinase dimerization is necessary for unlocking catalytic function by stabilizing an active conformation state, whereas other kinases rely on a slightly different mechanism. I provide an enzymatic characterization of a dimerized EGFR kinase domain to demonstrate that, when properly activated, its activity is comparable to the activity of other receptor tyrosine kinases.

Olivia Enny is a second-year graduate student in the Chemistry Department. She works in the Loria lab, focusing on studying allostery in enzymes through the use of NMR spectroscopy.

Abstract: Allostery is a ubiquitous regulatory mechanism responsible for the modulation of activity of countless numbers of enzymes. However, there is still much that is unknown about allostery and its role in enzyme function. Gaining a deeper understanding of allostery at the fundamental level will pave the way for new opportunities and advancements in protein engineering and drug discovery. One enzyme in particular that is useful in this context is imidazole glycerol phosphate synthase (IGPS). IGPS is an enzyme that is responsible for the biosynthesis of histidine and purines in plants, bacteria, and fungi. Our approach uses nuclear magnetic resonance (NRM) spectroscopy and kinetic studies to elucidate structural, dynamical, and binding information about IGPS and various mutations of this enzyme.