Development of highly potent and selective inhibitors for GRK5

G protein-coupled receptor kinases (GRKs) regulate cell signaling by **Development of highly potent and selective inhibitors for GRK5**triggering receptor desensitization via phosphorylation on G protein-coupled receptors (GPCRs). There are seven human GRKs (GRK1−GRK7) where GRK5 and GRK6 are structurally closely related. GRK5 is required for cancer progression in various cancer types. Depletion of GRK5 has been shown to suppress prostate cancer, breast cancer, and non-small-cell lung cancer. GRK6 is highly abundant in immune cells and is overexpressed in multiple myeloma (MM). Knocking down GRK6 has been shown to cause apoptosis of MM cells. Therefore, targeting GRK5 or 6 is considered a potential strategy for cancer treatment. Currently, we are developing a series of inhibitors for GRK5/6 based on a lead compound derived from sunitinib and utilizing Cys474 residue unique in GRK5/6 to enhance selectivity by covalent capture. In collaboration with Dr. Arun Ghosh lab, we have been exploring different inhibitor warheads for improving potency and selectivity without potentially toxic functional groups. So far, we have identified several highly potent and selective GRK5 inhibitors. Recently, I have developed a pipeline of crystallization of GRK5 available for soaking various ligands and have solved a preliminary structure of novel inhibitor-bound GRK5. The structural details of inhibitor binding have substantially facilitated our understanding of the inhibition mechanisms and the next step of optimizing drug design.