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Fragment based screens of the α-D-phosphohexomutases as an initial step for inhibitor design

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Enzymes in the α-D-phosphohexomutases superfamily frequently play a role in the biosynthesis of carbohydrates and glycolipids, critical for bacterial virulence and growth. α-D-phosphohexomutases are being increasingly shown to play key roles in microbial infections, including enzymes from several major human pathogens. Successful inhibition of enzymes in the α-D-phosphohexomutases superfamily may result in decreased bacterial growth rates, decreased virulence and greater susceptibility to traditional antibiotic treatment. As an initial step toward inhibitor design, we are conducting fragment-based screens of two structurally characterized members of the enzyme superfamily: P. aeruginosa phosphomannomutase/ phosphoglucomutase (PMM/PGM) and S. typhimurium phosphoglucomutase (PGM). Fragment based screening is a relatively new method that has been effectively used in the design of drug-like inhibitors for many systems. Crystals of PMM/PGM and PGM have been soaked with cocktails of small molecules (typical molecular weight 100-300 Da) to determine their sites of interaction with the proteins. X-ray diffraction data will be collected on these soaked crystals and the binding sites analyzed to determine the optimal interactions for effective inhibition.