

## Structural basis of diverse substrate recognition by PMM/PGM from *P. aeruginosa*

### Abstract:

*P. aeruginosa* is an opportunistic human pathogen that produces life-threatening infections in cystic fibrosis patients, burn victims, and immunocompromised individuals. The bacterium is known to form antibiotic resistant biofilms, and its infections are further complicated by the production of exoproducts that contribute to its virulence. The enzyme phosphomannomutase/phosphoglucomutase (PMM/PGM) participates in the biosynthesis of three virulence factors from *P. aeruginosa*: alginate, rhamnolipid and lipopolysaccharide. Enzyme-substrate complexes of PMM/PGM reveal the structural basis of the enzyme's ability to use four different substrates in catalysis. High-resolution structures with glucose 1-phosphate, glucose 6-phosphate, mannose 1-phosphate, and mannose 6-phosphate show that the position of the phosphate group of each substrate is held constant by a conserved network of hydrogen bonds. This produces two distinct, and mutually exclusive, binding orientations for the sugar rings of the 1-phospho and 6-phospho sugars. Specific binding of both orientations is accomplished by key contacts with the O3 and O4 hydroxyls of the sugar, which must occupy equatorial positions. Dual recognition of glucose and mannose phosphosugars uses a combination of specific protein contacts and nonspecific solvent contacts. The ability of PMM/PGM to accommodate these four diverse substrates in a single active site is consistent with its highly reversible phosphoryl transfer reaction and allows it to function in multiple biosynthetic pathways in *P. aeruginosa*.