

## W0264

**Inter-domain Signaling in Histidine Biosynthesis.** V. Nagarajan, R.S. Meyers, V.J. Davisson, J.L. Smith, Dept. of Biological Sciences & Dept. of Medicinal Chemistry & Molecular Pharmacology, Purdue Univ., W. Lafayette, IN, 47907.

Imidazole glycerol phosphate synthase (IGPS) catalyzes the two-step reaction of histidine biosynthesis at the bifurcation point with the *de novo* purine pathway. Ammonia produced in a glutaminase active site (step 1) is channeled through a 30 Å internal tunnel to a cyclase active site (step 2) (Bernali *et al.*, Structure, 9, 987, 2001). Glutaminase activity is impaired in the resting enzyme and stimulated by substrate (PRFAR) binding in the cyclase active site. PRFAR binds across the top of the  $(\beta/\alpha)_8$  barrel, with the AICAR end of PRFAR binding to helical insertion  $\alpha 4'$  and the ImGP end binding to  $\alpha 8'$ . The  $\alpha 8'$  side of the site has greater affinity for substrates, analogs and products. Binding in this sub-site stimulates a catalytic residue in the glutaminase active site docked at the bottom of the  $(\beta/\alpha)_8$  barrel. The bases for glutamine specificity and for glutaminase impairment in the resting enzyme are inferred from the structure of an IGPS-glutamine analog complex.