

**Dr. Lizbeth Hedstrom**  
**Brandeis University**

Thursday, April 24, 2008  
11:30 a.m.  
101 Biochemistry

**IMP dehydrogenase and the dynamics of drug selectivity**

**Research in the Hedstrom Laboratory**

Inosine monophosphate dehydrogenase (IMPDH) is an important immunosuppressive, antiviral and anticancer target. This enzyme catalyzes the oxidation of inosine monophosphate to xanthosine monophosphate with the concomitant reduction of  $\text{NAD}^+$ , thus controlling the entry of purines into the guanine nucleotide pool. IMPDH displays several unusual mechanistic features, including a large conformational change in mid-catalytic stream, an Arg residue that acts as a general base catalyst and a dynamic monovalent cation site. IMPDH is also a promising target for drugs against *Cryptosporidium parvum*, a major cause of the "vicious cycle of diarrhea and malnutrition", an important AIDS pathogen and potential bio-terrorism agent. Moreover, the IMPDH gene was obtained from bacteria by lateral gene transfer. We exploited the unexpected evolutionary divergence of parasite and host enzymes by designing a high throughput screen to target the most diverged portion of the IMPDH active site. We have identified four parasite-selective IMPDH inhibitors that display antiparasitic activity with greater potency than paromomycin, the current "gold standard" for anticryptosporidial activity.

**References**

Hedstrom, Lizbeth and Gan, Lu. *IMP dehydrogenase: structural schizophrenia and an unconventional base*. *Current Chemical Biology* 10, 520-525 (2006).

Umejiego, Nwakaso N.; Gollapalli, Deviprasad; Sharling, Lisa; Volftsun, Anna; Lu, Jennifer; Benjamin, Nicole N.; Stroupe, Adam H.; Riera<sup>1</sup>, Thomas V.; Striepen, Boris; Hedstrom, Lizbeth. *Targeting a prokaryotic protein in a eukaryotic pathogen: identification of lead compounds against Cryptosporidiosis*. *Chem. Biol.* 15, 70-77 (2008).

