

## E0058

**Atomic Resolution X-ray Diffraction Studies of *E. coli* Dihydrofolate Reductase.** Brad Bennett, Anna Gardberg, Elizabeth Howell, and Chris Dealwis, Dept. of Biochemistry, Cellular and Molecular Biology, Univ. of Tennessee- Knoxville, Knoxville, TN.

Hydrogen constitutes a large percentage of the atoms in biological molecules, and their contribution in noncovalent interactions and in biochemical reactions underlie all aspects of biology at the molecular level. High resolution X-ray and neutron crystallography can provide direct and accurate positions of hydrogens within macromolecules. We have applied this methodology to *E. coli* Dihydrofolate Reductase in order to better understand its catalytic mechanism. DHFR homologs have been identified in organisms representative of the whole biosphere and are essential for multiple biosynthetic pathways, including the production of thymidylate and methionine. Despite exhaustive investigation of its proton donation mechanism, controversy persists for ecDHFR and clarification is possible if ligand and residue protonation states as well as precise solvent structures were elucidated. To this end, we have solved the structure of DHFR bound to the anticancer drug methotrexate (MTX) to 0.95Å. Though still in the process of refinement, a number of interesting features have been observed in the electron density maps, including alternate side chain conformations and density peaks which may be attributed to hydrogen.