

## W0116

**Crystal Structure of *E. coli* Dihydrofolate Reductase Bound to a Novel Potent Inhibitor.** Rachael Summerfield, Murray Junop, Dept. of Biochemistry, McMaster Univ., Hamilton, ON, Canada.

Dihydrofolate reductase (DHFR) catalyzes the NADPH-dependent reduction of 7,8-dihydrofolate to 5,6,7,8-tetrahydrofolate (THF). THF is, in turn, essential for the synthesis of purines, pyrimidines and several amino acids. DHFR has been a long-standing drug target due to its necessity in DNA synthesis and there are currently several drugs on the market that target this enzyme. Some of these drugs include pyrimethamine, an antimalarial agent, trimethoprim, an antibacterial agent and methotrexate, an anticancer agent. However, the emerging resistance of DHFR to known drugs necessitates the discovery of new inhibitors of this target. High-throughput screening of *E. coli* DHFR identified several novel inhibitory compounds, the most potent of which has a  $K_i$  of 17.9 nM and was termed Compound 10. The crystal structure of DHFR complexed with Compound 10 and NADPH was determined to 1.89 Å resolution. This structure appears to most closely resemble the structure of DHFR bound to methotrexate and NADPH (PDB ID: 1RX3). Based upon the mode of binding for Compound 10 several second-generation inhibitors were designed and synthesized in an attempt to improve its affinity and specificity. The structure of one of these compounds was determined in the presence of DHFR and NADPH to 2.37 Å resolution and is also reported here.