

## W0420

**Crystal Structure of *E. coli* ClpP in Complex with a Peptidyl Suicidal Inhibitor** Agnieszka. Szyk, Michael R., Maurizi, Laboratory of Cell Biology, National Cancer Institute, Convent Drive Bldg. 37, Rm. 2128, Bethesda, MD 20892 USA

Clp proteins are proteasome-like assemblies that constitute the proteolytic component of the ATP-dependent ClpAP or ClpXP chaperone/protease complexes. Bacterial ClpP's are composed of 14 subunits arranged in two stacked heptameric rings. The active sites in ClpP are enclosed within an aqueous chamber accessible through narrow axial channels. ClpP's belong to the family of serine proteases with Ser97, His122, and Asp171 forming the catalytic triad. Here, we present the 1.9 Å crystal structure of ClpP from *E. coli* bound to the peptidyl inhibitor, Z-Leu-Tyr-chloromethylketone (Z-LY-CMK). Covalent complex between the Z-LY and Ser97 and His122 of ClpP mimics a natural intermediate. Binding 14 molecules of Z-LY-CMK does not change the relative orientations of the ClpP subunits as compared to the active enzyme. Root-mean-square deviation for the equivalent C $\alpha$ -atoms in the complexed and uncomplexed enzyme is 0.44 Å. In the active site only the orientation of the Ser97 side chain is affected by the binding of Z-LY-CMK, which replaces 5 water molecules in the unliganded enzyme. Conformation of the Z-LY fragment in the ClpP active site is stabilized by 5 hydrogen bonds to the enzyme's backbone atoms and by hydrophobic interactions between the Tyr of inhibitor and P1 substrate pocket of the enzyme.