

## W0063

**Subatomic X-Ray Results on Human Aldose Reductase Inhibitor Complexes.** A. Mitschler<sup>1</sup>, T. Petrova<sup>1</sup>, F. Ruiz<sup>1</sup>, I. Hazemann<sup>1</sup>, M. Van Zandt<sup>2</sup>, S. Ginell<sup>3</sup>, A. Joachimiak<sup>3</sup>, A. Podjarny<sup>1</sup>, <sup>1</sup>IGBMC, CNRS, 1 rue Laurent Fries, 67404 Illkirch, France, <sup>2</sup>IDD, 23 Business Dr., Branford, CT, USA, <sup>3</sup>Bioscience Div., Structural Biology Center and Midwest Center for Structural Genomics, Argonne National Lab., 9700 South Cass Avenue, Argonne, IL, USA.

Human aldose reductase (*h*-AR), implied in the polyol pathway, is thought to be involved in severe diabetic complications such as retinopathy, neuropathy and nephropathy. In despite of their importance, the ALR2 enzymatic and inhibition mechanisms still remain open questions, and the design of potent and selective drugs is a priority. The protonation states of the catalytic residues and the hydration of the catalytic site plays a key role in inhibitor binding.

For studying the relative potency of inhibitors, we have obtained a structure at 0.8 Å resolution showing the simultaneous binding of two charged inhibitors, IDD 594 and Tolrestat. For studying the selectivity against Aldehyde Reductase, we have obtained a structure at 0.9 Å showing the complex of the mutant L300P with Fidarestat.

Both structures will be described during the presentation. A few insights about low temperature X-rays (15K) and neutron Laue diffraction will be also reported.