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Comparison of Inhibitor Binding Modes to Aldose Reductase at Subatomic Resolution. T. Petrova¹, F. Ruiz¹, A. Mitschler¹, I. Hazemann¹, A. Podjarny¹, M. Van Zandt², S. Ginell³, A. Joachimiak³, IGBMC, CNRS, 1 rue Laurent Fries, 67404 Illkirch, France, IDD, 23 Business Dr., Branford, CT, \USA, Bioscience Div., Structural Biology Center & Midwest Center for Structural Genomics, Argonne National Laboratory, 9700 South Cass Ave. Argonne, IL, USA.

Aldose Reductase (ALR2; EC 1.1.1.21), a 35 kDa monomeric member of the Aldo keto reductase superfamily, is the first and rate determining step in the polyol pathway, an alternative route for the glucose phosphorylation. This pathway processes one third of the total cellular glucose under hyperglycemia conditions. The acceleration of the ALR2 activity has been linked with the development of diabetic complications such as retinopathy, neuropathy and nephropathy. One of the possible options in the pharmaceutical development of compounds against these pathologies is to block the activity of ALR2. In despite of their importance, the ALR2 enzymatic and inhibition mechanisms still remain open questions. One of the key points to be determined is the protonation state of several residues in the active site; observation of these states is crystallographically possible only at ultra-high resolution. Several ALR2-inhibitor complex structures are currently available in our group at atomic and sub-atomic resolution, including complexes obtained with different inhibitors (IDD594, IDD676, IDD552, IDD393), crystallographic conditions (pH 5, pH 8) and measurement temperatures (15, 60, 100 and 300 K). Here we present the comparison of the active site of such complexes structures, pointing out the most important aspects for the enzymatic mechanism and inhibition.