Modelisation:
Structural study of the dynamic catalysis in class II FBP aldose

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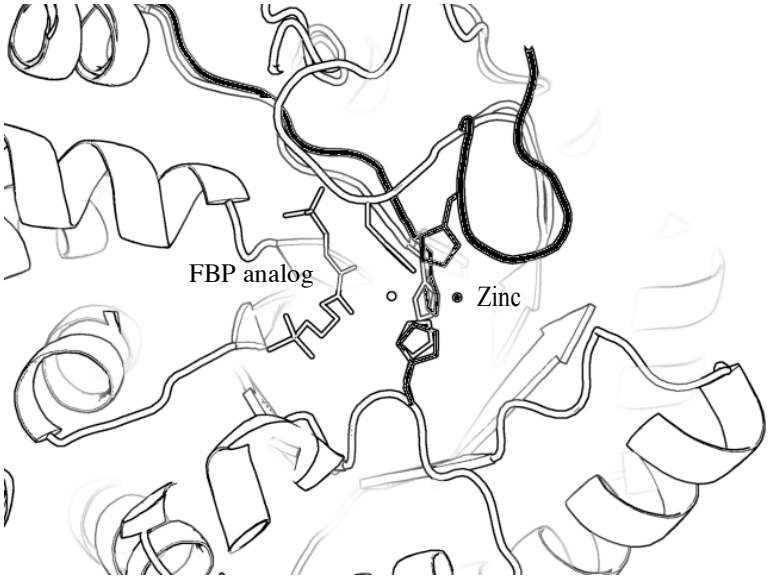
The class II Fructose-1,6-bisphosphate (FBP) aldolase (Fba) is a bacterial enzyme that is central to glycolysis. Our goal is to describe reaction mechanism of class II aldolases at the molecular level using protein crystallography, site directed mutagenesis and molecular dynamics. A secondary goal is to design antimicrobial drugs targeting this essential glycolytic enzyme.

We have succeeded in solving several enzymatic complexes by soaking reactants and ligands into aldolase crystals and cryo-trapping the resultant enzymatic complexes for crystallographic analysis. These structures provided detailed insight into the catalytic mechanism. Two proton transfers occur during this reversible reaction and were examined in detail. However enzyme flexibility and dynamics limits our experimental approaches as to the underlying structural events that accompany these transfers. Molecular dynamic simulations were thus performed and results obtained were experimentally validated in order to reach a new level of understanding of how these transfers take place at the structural level.

Through collaborations and based on our structural data, we have characterized several potent inhibitors of glycolytic aldolases that corroborate our understanding of the reaction mechanism.



Conformational changes induced upon binding of substrate analog in H.pylori aldolase. Loops and catalytic zinc ion which undergo positional changes are shown in black for the native Fba structure .Bound Fba structure is in white.