The Mechanism of T. Cruzi FPPS Involves a Substrate Induced Conformational Change

Sandra B. Gabelli, Jason S. McLellan, Andrea Montalvetti, Eric Oldfield, Roberto Docampo, L. Mario Amzel, *Dept. of Biophysics and Biophysical Chemistry, Johns Hopkins School of Medicine, Baltimore, MD 21205, USA*. E-mail: sandra@groucho.med.jhmi.edu

Typanosoma cruzi, the causative agent of Chagas disease, has recently been shown to be sensitive to the action of the bisphosphonates currently used in bone resorption therapy. These compounds target the mevalonate pathway by inhibiting farnesyl diphosphate synthase (farnesyl pyrophosphate synthase, FPPS), the enzyme that condenses the diphosphates of C_5 alcohols (isopentenyl and dimethylallyl) to form C_{10} and C_{15} diphosphates (geranyl and farnesyl). The structures of the *T. cruzi* FPPS (*Tc*FPPS) alone and in two complexes with substrates and inhibitors reveal that following binding of the two substrates and three Mg^{2+} ions, the enzyme undergoes a major conformational change consisting of a hinge-like closure of the binding site. In this conformation, it would be possible for the enzyme to bind a bisphosphonate inhibitor that spans the sites usually occupied by dimethylallyl diphosphate (DMAPP) and the homoallyl moiety of isopentenyl diphosphate. In addition, the structures provide an important mechanistic insight: after its formation, geranyl diphosphate can swing without leaving the enzyme, from the product site to the substrate site to participate in the synthesis of farnesyl diphosphate.

Keywords: enzyme mechanism, inhibitor design, farnesyl diphosphate synthase