

W0409

Inhibition Studies and Crystallization of Human Maltase-glucoamylase (MGA). Lyann Sim^a, Elena J. Rossi^a, Douglas A. Kuntz^b & David R. Rose^{a,b}, ^aDept. of Medical Biophysics, Univ. of Toronto and ^bDiv. of Molecular and Structural Biology, Ontario Cancer Inst., Toronto, ON, Canada.

Human maltase-glucoamylase (MGA) is a Family 31 glycoside hydrolase responsible for catalyzing the final glucose releasing step in mammalian starch digestion. Inhibitors targeting α -glucosidases such as MGA are currently used in the treatment of Type II diabetes to delay glucose production following digestion. Human MGA was cloned, expressed and purified from *Drosophila* S2 cells in suitable quantities allowing for kinetic and preliminary crystallization trials. Inhibition kinetics of MGA was conducted with 4 prospective α -glucosidase inhibitors modeled after the natural occurring α -glucosidase inhibitor, salacinol. With each of the 4 inhibitors, inhibition constants (K_i) were determined to be in the range of 0.2-0.5 μ M, making these inhibitors promising candidates for anti-diabetic drugs. Preliminary crystallization trials are currently underway in order to gain a structural perspective on the mechanism of inhibition of MGA. Protein modification approaches, such as deglycosylation and reductive methylation, have been used to improve MGA crystallization.