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Investigating the Catalytic Mechanism of Golgi alpha-mannosidase II: A Possible Target for Cancer Chemotherapy. N. Shah, D.A. Kuntz, D.R. Rose, Dept. of Medical Biophysics, Univ. of Toronto, Ontario Cancer Inst., University Health Network, Toronto, ON M5G1L7 Canada.

A feature typical of many cancerous cells is their altered cell surface glycosylation. Golgi alpha-mannosidase II (GMII, 125 kDa) catalyzes the committed step of complex N-glycan formation in the N-glycosylation pathway. Inhibition of GMII by small molecule inhibitors is known to reduce metastasis in cancer patients and generally improve clinical outcome. GMII catalyzes the hydrolysis of two different mannose-mannose bonds converting $GnMan_5Gn_2$ to $GnMan_3Gn_2$. Its catalytic action is highly specific and unique.



Our laboratory has previously solved the crystal structure of GMII from *Drosophila melanogaster* and has studied many potential inhibitors against this enzyme. Through current work, we aim to gain insight into the catalytic mechanism of GMII. The objective of my work is to study the enzyme interacting with its natural substrate. Isolation of this complex, branched polysaccharide has been a challenging task. We are attempting to purify the GMII natural substrate by exploiting a strain of *Pichia pastoris* that has its host N-glycosylation system knocked out, followed by introduction of certain elements of the human N-glycosylation system. Our progress to this end will be presented.