SMART Teams 2014-2015 Research and Design Phase

Grafton High School SMART Team

Robyn Ahrenhoerster, Amber Amenda, Eli Bolker, Brittany Cassel, Chloe Lichosik, Rebecca Milliken, Andrew Mosin, Nick Pavelic, Ashleigh Perry, Hannah Weber, Sara Zimmerman
Teacher: Dan Goetz, Fran Grant

Mentors: James Miller, MD/PhD Candidate
Medical College of Wisconsin, Department of Biochemistry

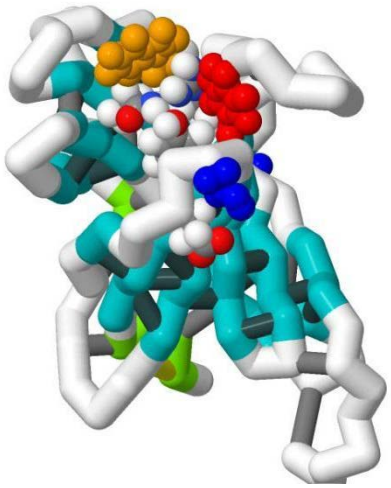
CI-MPR: The Lysosomal Enzyme Receiving Superstar

PDB: 2KVA

Primary Citation: Linda J. Olson, Francis C. Peterson, Alicia Castonguay, Richard N. Bohsack, Mariko Kudo, Russell R. Gotschall, William M. Canfield, Brian F. Volkman, and Nancy M. Dahms. (2010). Structural Basis for Recognition of Phosphodiester- Containing Lysosomal Enzymes by the Cation-Independent Mannose 6-Phosphate Receptor. PNAS. 107: 12,493-12,498.

Format: Alpha carbon backbone

RP: Zcorp with plaster



Description:
Fabry disease is X-linked and occurs from a deficiency of α-galactosidase A, a lysosomal enzyme that normally degrades the ganglioside globotriaosylceramide (Gb3). Lysosomal accumulation of Gb3 results in cardiovascular, renal, and neurological pathologies, and hemizygous males with Fabry disease tend to have the most severe presentations. The cation-independent mannose 6-phosphate receptor (CI-MPR) recognizes lysosomal enzymes bearing a mannose 6-phosphate (M6P) tag, via the amino acids Gln644, Arg687, Glu709, and Tyr714 in its fifth domain, and transports these enzymes from the trans-Golgi network to the lysosome. Four out of CI-MPR's 15 domains are able to bind M6P or M6P conjugated to N-acetylglucosamine. CI-MPR is also present at the cell surface, and this localization can be exploited to deliver exogenous M6P-tagged biomolecules (i.e., α-galactosidase A) to the lysosome. Intravenous enzyme replacement therapy (ERT) for Fabry disease is extremely expensive, inefficient, and immunogenic. Determining the 3-D structure of CI-MPR is crucial in improving the efficiency of Fabry ERT because this knowledge will allow for the rational design of recombinant α-galactosidase A with optimally placed M6P moieties. The Grafton SMART (Students Modeling A Research Topic) Team will create a physical model of CI-MPR domain 5 using 3-D printing technology, which is made possible by a grant from NIH-CTSA. Further structural studies of CI-MPR will not only lead to a reduction in ERT cost, but will also improve the lives of those suffering from Fabry disease.

Specific Model Information:

- Backbone is colored white.
- Alpha helices are colored chartreuse.
- Beta Sheets are colored dark turquoise.
- Hydrogen bonds are colored dark slate grey.
- Disulfide bonds (Cys592-Cys628, Cys-636-Cys643, and Cys690-Cys724) are colored yellow.
- Struts are colored grey.
- Amino acids that bind M6P (Gln644, Arg687, Glu709, and Tyr714) are colored cpk.
- Trp653 (which positions the mannose ring so that it interacts with Gln644 and Arg687) is colored orange.
- Tyr679 (which binds the methyl group of N-acetylglucosamine) is colored red.
- N-linked glycosylated sites (Asn591 and Asn711) are colored blue.

http://cbm.msoe.edu/smartTeams/

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