SMART Teams 2015-2016 Research and Design Phase

Laconia High School SMART Team

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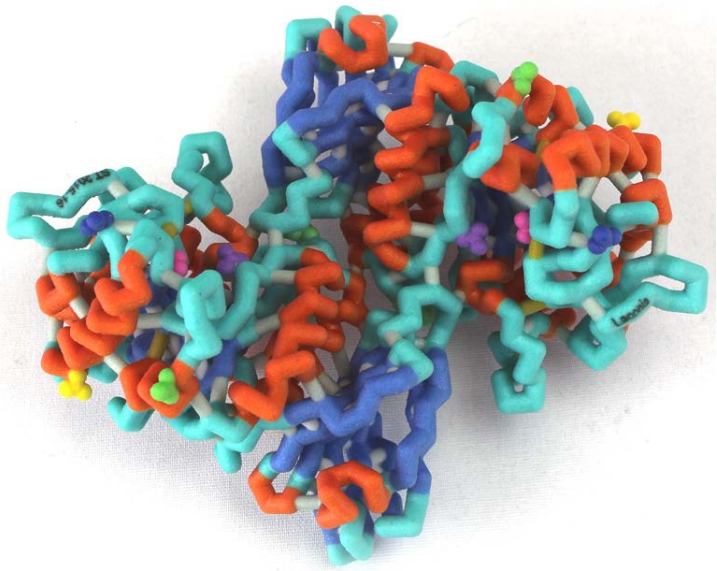
Modeling α-Galactosidase A to Improve Fabry Disease Treatment

PDB: 3HG5

Primary Citation: Guce, A.I., Clark, N.E., Salgado, E.N., Ivanen, D.R., Kulminskaya, A.A., Brumer III, H., Garman, S.C. (2010). Catalytic mechanism of human α-galactosidase. *J. Biol. Chem.* 285(6): 3625-3632.

Format: Alpha carbon backbone

RP: Zcorp with plaster



Description:
Fabry disease is a debilitating lysosomal storage disease. Early in life, patients with Fabry disease experience extreme pain, especially in the extremities (acroparesthesias). Patients are eventually at risk of developing kidney disease, heart failure, and strokes, all of which may lead to a premature death. The prevalence of Fabry disease in its severest form is estimated at 1:40,000; however, the prevalence of milder, later-onset forms may be as high as 1:3,600. Fabry disease is caused by mutations in the X chromosomal *GLA* gene, which encodes the lysosomal enzyme, α-galactosidase A (α-Gal A). When α-Gal A activity is deficient, glycolipid substrates accumulate within lysosomes, leading to cellular, tissue, and organ pathology. To treat Fabry disease, patients are given enzyme replacement therapy (i.e., bi-weekly intravenous infusion of recombinant α-Gal A). Enzyme replacement therapy costs up to $300,000 per patient per year and commonly causes dangerous immune reactions in patients. A more cost-effective and safer treatment is desperately needed. The Laconia SMART (Students Modeling A Research Topic) Team used 3D printing technology to generate a model of α-Gal A. To be trafficked to lysosomes and to optimally degrade glycolipids, α-Gal A must be glycosylated and must dimerize. Therefore, critical residues are highlighted in the model, such as those involved in catalysis (Asp170, Asp231), N-linked glycosylation (Asn139, Asn192, Asn215), and dimerization (Phe273). Disulfide bonds, which stabilize α-Gal A tertiary structure, are also shown. Studying the structure of α-Gal A is critical in the design of a more potent therapy, which has the potential to reduce the cost and immunogenicity of Fabry disease treatment.

Specific Model Information:

- Backbone colored dark turquoise
- Beta Sheets colored slate blue
- Helices colored red
- Hydrogen Bonds colored alice blue
- Disulfide Bonds colored dark golden rod
- Asn 215 colored lime
- Asn 139 colored midnight blue
- Asn 192 colored yellow
- Phe 273 colored medium spring green
- Asp 170 colored magenta
- Asp 231 colored purple
- Struts colored silver

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

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