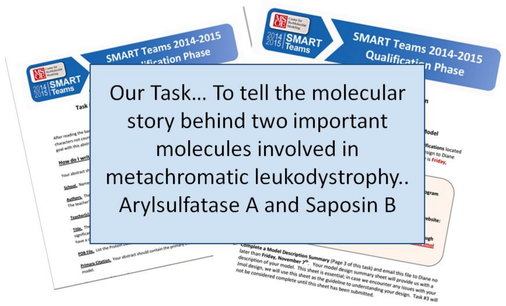
White Matters: MLD., ASA, and Saposin B

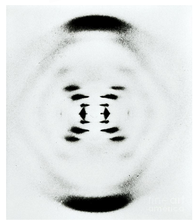
D.C. Everest SMART Team

Poster Created by Emily Adams and Dylan Sebo

SMART Teams 2014-2015 MSOE UNIVERSITY

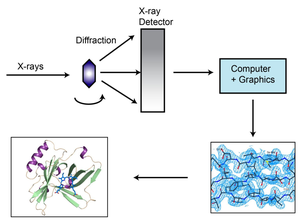


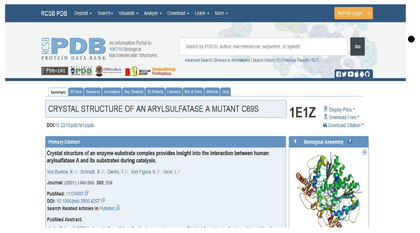
Reading Material: Primary and Popular Sources



- A crystallographer can create a 3D image and determine the (X,Y,Z) coordinates for each atom and their chemical bonds

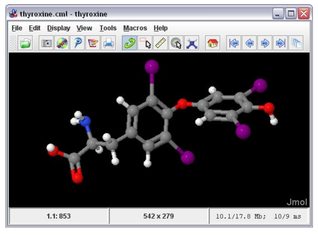
Overview of the X-ray Crystallographic Method





- The Protein Data Bank has a large collection of three-dimensional instructions for molecules mapped by x-ray crystallography

- Jmol allows us to use the instructions from the Protein Data Bank to create a 3D model that we can manipulate and examine closer to find the active site

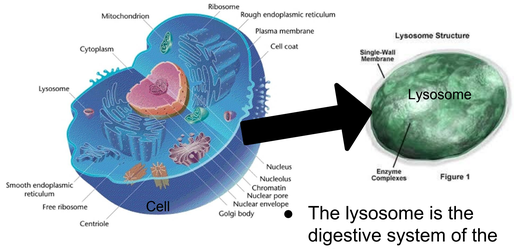


Acknowledgements

- Dr. Diane Munzenmaier
  - MSOE/ Center for Biomolecular Modeling
  - SMART Team Program
- Mr. Heeren
  - D.C. Everest High School
- Dr. Ian Duncan
  - University of Wisconsin - Madison

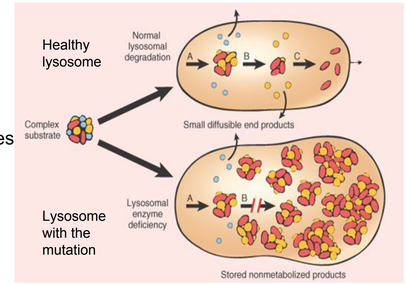
Overview and Myelination

- MLD is a lysosomal storage disorder
- Can be an autosomal recessive disorder
- MLD is a demyelinating disease that stems from a build up of sulfatides in the brain

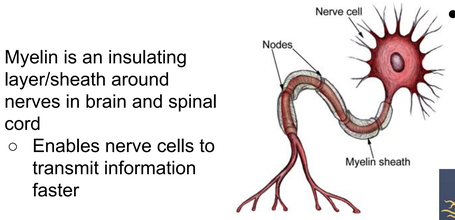


- The lysosome is the digestive system of the cell

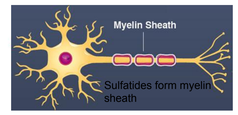
- The lysosome with the mutation in its enzymes causes molecules to build up in the lysosome leading to cellular dysfunction.

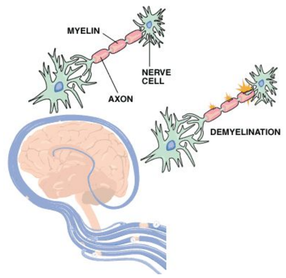


- Myelin is an insulating layer/sheath around nerves in brain and spinal cord
  - Enables nerve cells to transmit information faster



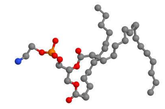
- Sulfatides vital in myelin function
  - Build up as a result of MLD
  - Excess sulfatides cause demyelination



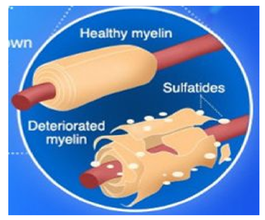


- Sulfatides in MLD
  - Specifics for demyelination is unknown, hypothesized the polarity of blood changes

- Gray carbon are non-polar



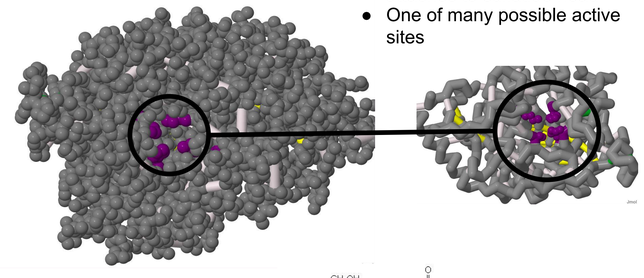
- Demyelination
  - Damage to myelin sheath
  - Nerve impulses slowed and/or stopped
  - Build up of sulfatides causes deterioration of white matter
  - Without myelin, brain would be 2-3 times larger due to need of larger axons



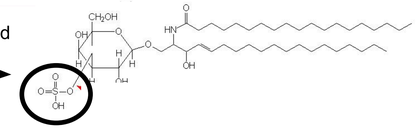
Arylsulfatase A (ASA) Protein

- ASA protein encoded by DNA in 22nd Chromosome
- Protein found within lysosome

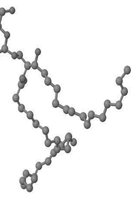
- Active site (shown in purple) attaches to sulfatide head
- One of many possible active sites



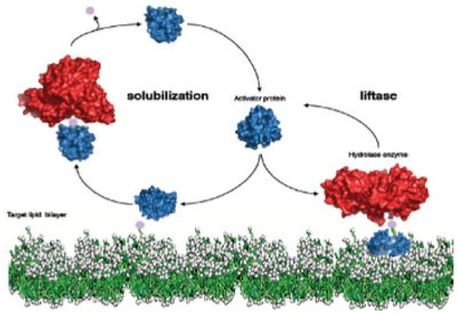
- ASA cleaves off sulfate head of a sulfatide renders them non-functional
- Without cleaving, sulfatides will build up in cell wall
  - Sulfatides break down myelin cell wall
- MLD mutates genes encoding for ASA rendering them non-functional



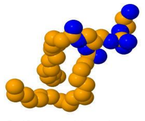
- Sulfate head of the sulfatide



Saposin B

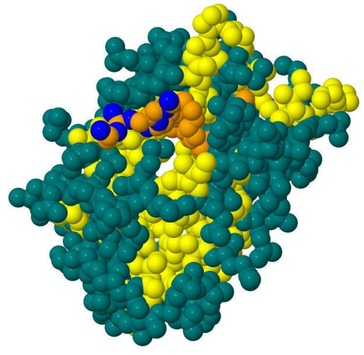


- Saposin B gathers a sulfatide and transports molecule to ASA active site for cleaving
- Saposin B extracts lipids from membranes forming protein-lipid complexes that are recognized by ASA



- Sulfatide with polar labeled orange and nonpolar labeled blue

- Hydrophobic interior of cavity (yellow) attracts and pulls hydrophobic section of lipid (orange) into cavity
- Polar residues (teal) attract to polar sections of lipid (blue)
- Saposin B holds sulfatide, allowing for its interaction with ASA



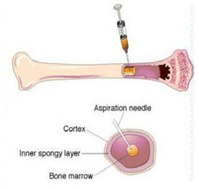
- Saposin B Molecule holding sulfatide within hydrophobic core

Sources used

- http://www.mswatch.ca/en/learn-about-MS/MS-treatment-options/goals-of-MS-treatment.aspx
- 0f86cab0fa9/gaucher-disease-fabry-disease-and-pompe-are-but-a-few-of-the-many-lysosomal-storage-disorders.jpg (Page 13)
- http://plantcellbiology.masters.grkraj.org/html/Plant_Cellular_Structures6-Lysosomes.htm (Page 17)
- https://tspace.library.utoronto.ca/bitstream/1807/31904/1/Popovic_Konstantin_201111_PhD_thesis.pdf (sapison b)
- http://en.wikipedia.org/wiki/sulfatide
- http://www.newluxuryfeed.com/bone-marrow-transplant/(Page 39)
- http://www.heraldextra.com/app/special-sections/campbells/?p=3
- http://www.emedicinehealth.com/myelin_and_the_central_nervous_system/page2_em.htm (Page 21)
- http://medcell.med.yale.edu/systems_cell_biology_old/nervous_system.php
- http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/multiple_sclerosis_ms_and_related_disorders/overview_of_demyelinating_disorders.html

Treatment Options

- No cure for MLD, but there are treatment options
- Enzyme therapy
- Gene therapy
- Bone marrow transplants
  - Slows deterioration of marrow
- Stem cell treatment



Stem Cell & Bone Marrow Transplants

- Patient with mutated DNA is given donor bone marrow
- New bone marrow produces previously mutated enzyme

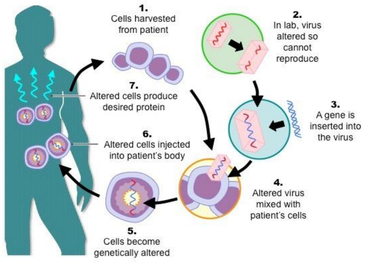
Campbell's Treatment

- The Campbell's used bone marrow transplants to treat MLD
- Out of the three children affected, two survived

Campbell Family

Gene Therapy

- Replace faulty genes with non-mutated genes
- Gene introduced as a vector (virus) to diseased cells
- Uses new genetic information to rebuild RNA and proteins



Enzyme Therapy

- Cells are created containing human DNA
  - These cells produce functioning ASA
- Recombinant human Arylsulfatase A
- Trouble with passing the blood-brain barrier