Enzyme Replacement Therapy

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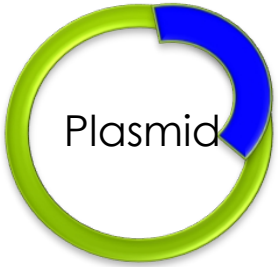
Lysosomal Storage Diseases (LSD)

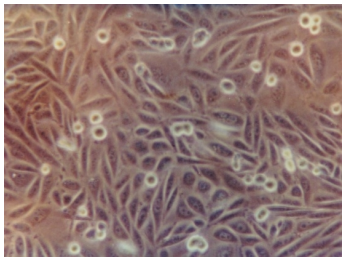
- Lysosome = organelle responsible for catabolyzing macromolecules
- Characterized by deficiency of lysosomal enzyme
- Group of over 40 diseases
- Most are autosomal recessive
- Combined incidence of 1:6500 – 7500 live births

Enzyme Replacement Therapy (ERT)

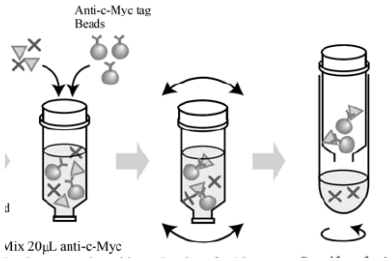
- Cultivate missing enzyme outside the human body and then administer it to patients as treatment
- Can be used for diseases besides LSD
- First suggested in 1960s by Roscoe Brady
- Treats the cause, not just the symptoms

Creation of ERT





Chinese Hamster Ovary Cells



Purification

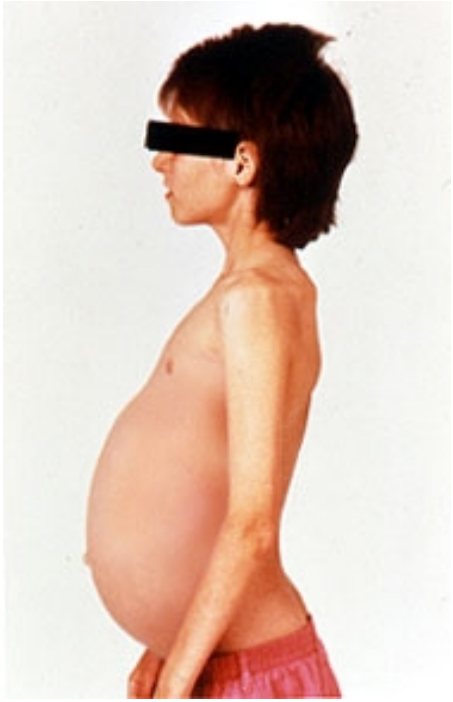
Animal models

Clinical Trials

- Currently ERT for 6 Lysosomal storage diseases

Gaucher's Disease

- 1st developed ERT
- Most common of the lysosomal storage diseases
- Deficient enzyme: Glucocerebrodase (catabolyzes glucoceramide)
- Affects spleen, liver & bone marrow
- 3 clinical subtypes
- Gaucher Disease type 1: lethal by 2 years old
- Cerezyme
- ERT reverses pathologies → near normal lives



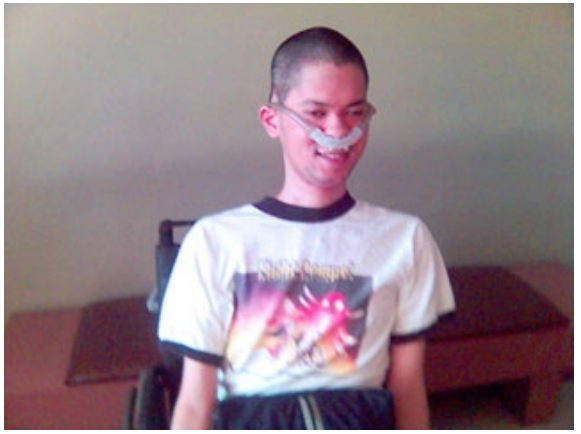
http://geneticpeople.com/?p=276

Fabry Disease

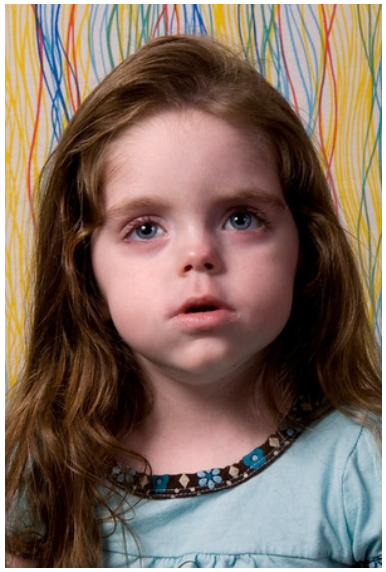
- X-linked inheritance
- Deficient enzyme: α-galactosidase (catabolyzes globotriaosylceramide)
- Symptoms:
  - Usually begin in adolescence
  - Acroparesthesias
  - Pain and gastrointestinal problems
- Fabrazyme
- Prevents but does not reverse damage
- Pain remains

Pompe Disease

- A.k.a. Glycogen storage disease type II
- Deficient enzyme: a-glucosidase
- Onset infant – adulthood
- Skeletal muscle problems
- Myozyme
- ERT prolongs infant life, increases motor abilities
- Clinical trials still in process for late onset Pompe



http://www.fightpompe.com/article/45/fight-pompe-around-the-world



http://www.joemcdowellphotography.com/Haley/Haley/1903403_Mpc3n/3/97982714_W9w3V#97982714_W9w3V

Mucopolysaccharidoses (MPS)

- Group of 6 diseases
- Glycosaminoglycans accumulate
- 3 types have treatment
- MPS I
  - Hurler or Hurler-Scheie syndrome
  - a-L-iduronidase
- MPS II
  - Hunter syndrome
  - X-linked inheritance
  - Iduronate sulfatase
- MPS VI
  - Maroteaux-Lamy syndrome
  - Arylsulfatase

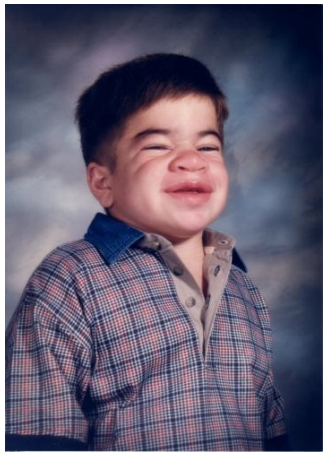
Mucopolysaccharidoses

- Common symptoms: coarse facies, deafness, cardiac disease, delayed development, neurologic problems (I & VI)

Hurler

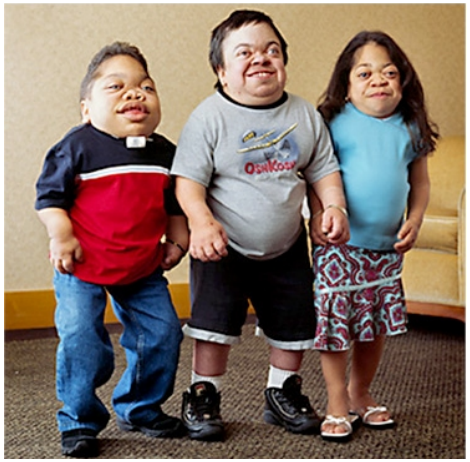
http://www.metabolica.org/start/node/8

Hunter



http://chad-pyper.last-memories.com/?

Maroteaux-Lamy



http://www.maroteaux-lamy.com/English/hcp/AboutMPS.aspx

- Bone marrow transplant (Hurler)
- Enzyme replacement therapies
  - Aldurazyme (Hurler) – 2003
  - Elaprase (Hunter) – 2006
  - Naglazyme (Maroteaux-Lamy) – 2005

Non lysosomal storage diseases

- Can correct symptoms, not disease
  - Cystic fibrosis – has problems with pancreatic ducts that prevents enzymes from reaching gastrointestinal tract
  - Pancreatitis
  - Pancreatic and periampullary cancer

Shortcomings of ERT

- Admistered via IV once every 2 weeks
  - Infusions last 2 – 6 hours
- Side Effects
  - Allergy symptoms, respiratory distress
  - Long term effects not yet known
  - Gaucher's: treated for 15 – 20 years with no severe side effects
- Antibody responses
  - IgG – binds to drugs → allergy symptoms
  - IgE – increased risk of anaphylactic reaction
- Cost = $200,000 - $300,000 per year
  - Can max out health insurance in 2 – 5 years
- Affects employment

Sources

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