LYSOSOMAL DISEASES:

Current and Emerging Enzyme Replacement and Substrate Reduction Therapies

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DISCLOSURES

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Discovery of the Lysosome

Albert Claude, Christian de Duve and George Palade

received the Nobel Prize in Physiology or Medicine in 1974:

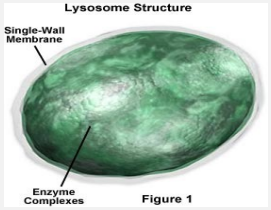
For their discoveries concerning

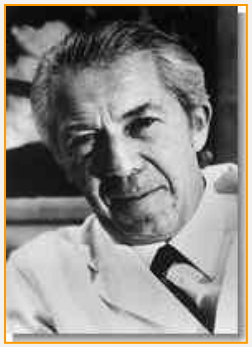
"the structural and functional organization of the cell":

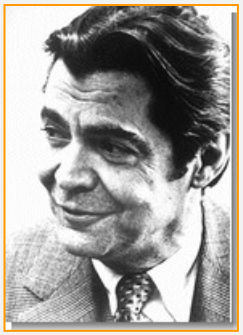
Observation:

Cells Released An Enzyme Called Acid Phosphatase In Much Larger Amounts

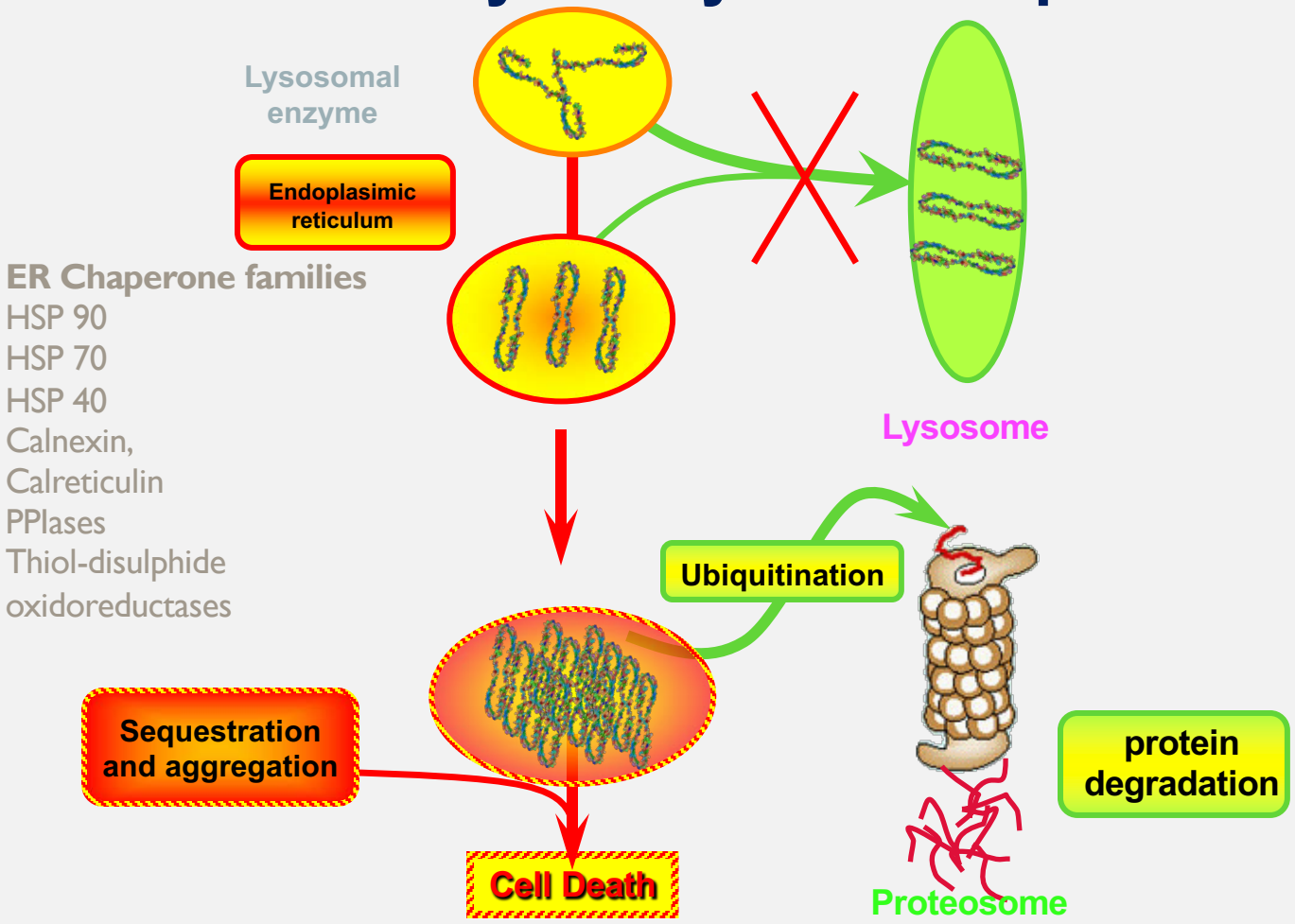
When They Were Repeatedly Frozen And Thawed Before Centrifugation



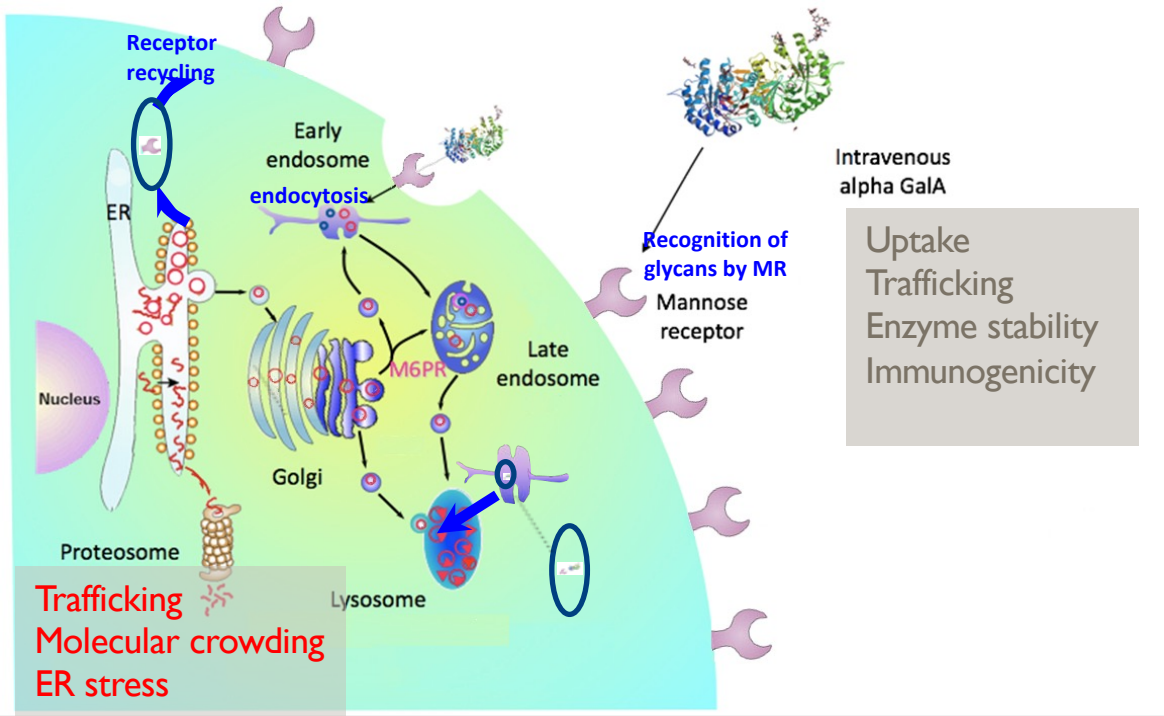




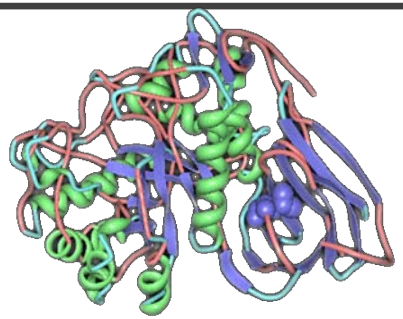
Journey of a lysosomal protein



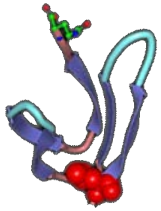
Targeting pathways for treatment of LSDs



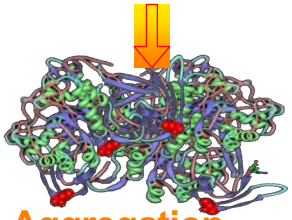
THERAPEUTIC CHALLENGES IN LYSOSOMAL DISEASES



disease–causing mutation



Disease-associated protein (misfolded structure)



Aggregation

- Substrate accumulation **SRT, EET**
- Loss of function **ERT**
- Immune dysregulation and inflammation

- Complex cellular pathology
- Phenotypic heterogeneity within genotype
- Delivery to all systems (CNS, cartilage, bone, lungs)
- Inflammatory component

Speaker's illustration.

EET, enzyme enhancement therapy; SRT, substrate reduction therapy.

THERAPEUTIC APPROACHES FOR LSDS

- Enzyme replacement therapy (ERT)
  - Exogenous recombinant enzymes with M6P "tags"
  - Overcome catabolic pathway block, affect clearance of stored substrate
  - Most do not cross the BBB,
- Small molecules
  - Substrate reduction therapy (SRT)
    - Reduce the production of substrate by inhibiting upstream paths
    - May cross the BBB
  - Chaperone therapy and others
    - Rescue the misfolded protein and deliver to lysosome
    - May cross the BBB
    - Other small molecules (Arimoclomol, cyclodextrin, cysteamine)
- Hematopoietic stem cell transplantation
- Gene therapy: *ex vivo, in vivo*