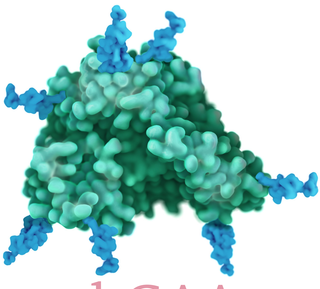
POMPE DISEASE: Advances in ERT

Second-generation enzyme-replacement therapies (ERTs) are engineered to have increased cellular uptake compared with the first-generation enzyme.

1st GENERATION
Alglucosidase alfa

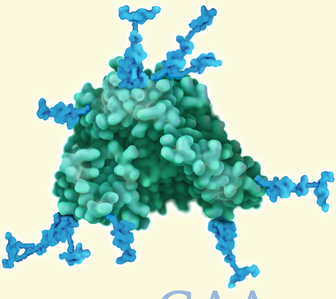


rhGAA
Recombinant human alglucosidase alfa

- Addition of manose-6-phosphate (M6P) permits endocytosis into cells and targeting to lysosomes
- Main challenge:
  - Variability in the response of skeletal muscle to treatment
  - Cellular uptake is more efficient in cardiac muscle than skeletal muscles
  - Long-term survivors continue to experience symptoms
- Safety warning: potential for anaphylaxis, hypersensitivity and immune-mediated reaction, and risk of cardiorespiratory failure

Approved for the treatment of all patients with Pompe disease (PD)

2nd GENERATION
Avalglucosidase alfa

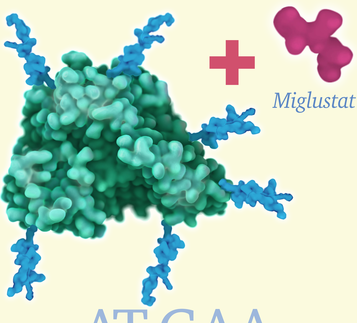


neoGAA
Avalglucosidase alfa

- Greater number of M6P neoglycans to increase cellular uptake
- Preclinical studies showed 1000x higher binding affinity to receptors vs rhGAA
- Safety warning: potential for hypersensitivity reactions including anaphylaxis, infusion-associated reactions, and risk of acute cardiorespiratory failure

Approved August 2021 in the United States for the treatment of late-onset PD in patients who are ≥1 year of age

2nd GENERATION
Cipaglucosidase alfa + miglustat



AT-GAA
Cipaglucosidase alfa

- More M6P neoglycans to increase cellular uptake
- Miglustat, a chaperone molecule, provides enzyme stability
- Safety: clinical data indicate a safety profile similar to alglucosidase alfa

This investigational therapy has not yet been approved

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