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GENE THERAPIES

Therapeutic Approaches in Pompe Disease

This Disease Education Brochure is for Healthcare Professionals Only

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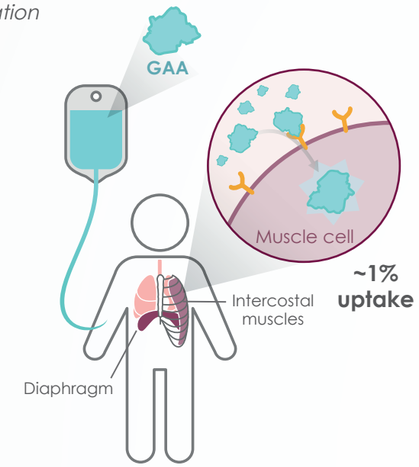
Current Standard of Care

Pompe disease *is a rare, severe, autosomal recessive, metabolic disease with progressive muscle degeneration caused by mutations in one gene that encodes the lysosomal enzyme, acid alpha-glucosidase (GAA).*[1]

- Currently available therapies include **Enzyme Replacement Therapy (ERT)**, which aims to correct the deficiency with exogenous GAA[2]
- ERT has **improved clinical outcomes** for patients, including motor and respiratory function, and survival[3]
- Approximately **1% of ERT is taken up** into skeletal muscle after intravenous bolus administration,[4] requiring infusions **at least every other week**[5,6]
- **Second-generation ERT therapies** with a **muscle specific tag** (avalglucosidase alfa* or neo-GAA) have been developed to **increase GAA uptake in the muscle**[7,8]

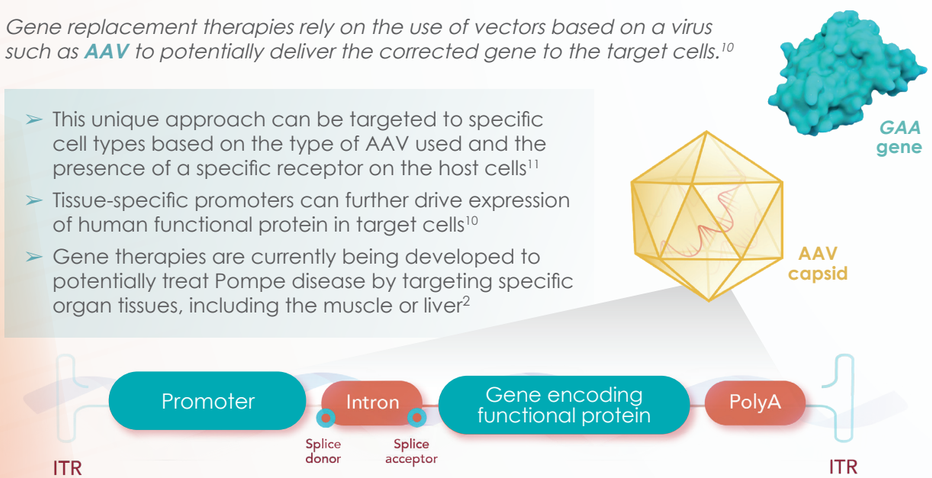


*Approved for use in the United States in August 2021[9]

Adeno-associated Virus (AAV)-mediated Gene Therapy

Gene replacement therapies rely on the use of vectors based on a virus such as ***AAV*** *to potentially deliver the corrected gene to the target cells.*[10]

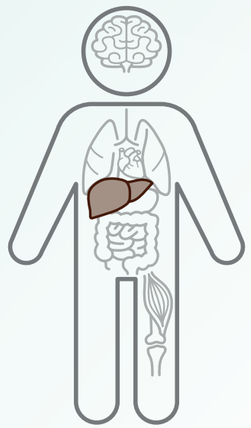
- This unique approach can be targeted to specific cell types based on the type of AAV used and the presence of a specific receptor on the host cells[11]
- Tissue-specific promoters can further drive expression of human functional protein in target cells[10]
- Gene therapies are currently being developed to potentially treat Pompe disease by targeting specific organ tissues, including the muscle or liver[2]



ITR, inverted terminal repeat; polyA, polyadenylation signal.

Tissue-specific Targeting in Gene Therapy

Liver-directed Gene Replacement Therapy

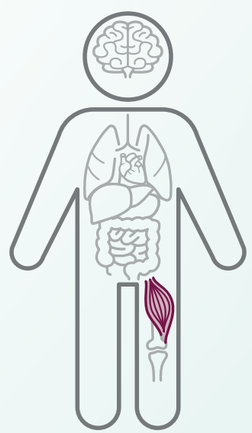


The liver is a highly vascularized organ, specialized for protein expression and secretion, and requires low doses of AAV vector for efficient organ transduction[8,12]

- The liver may serve as a **depot** for GAA before it enters circulation[13]
- Circulating GAA enters muscle cells via **cross-correction** — extracellular protein is taken up and targeted to the lysosomes of otherwise enzyme-deficient cells[8,12,13]
  - However, biodistribution of GAA from liver to muscle may be limited due to the **need for efficient cross-correction** of the circulating enzyme[8,12]
- Liver-directed gene expression may result in **immune tolerance** via antigen-specific regulatory T-cells[14]

Muscle-directed Gene Replacement Therapy

- Aims to **express GAA** in cardiac and skeletal muscles, the primarily affected tissues in Pompe disease[12]
- Effective transduction of muscle cells may facilitate **production of GAA directly in muscle cells** and reduce glycogen storage[12,15]
- **Immune tolerance** and **absence of immune responses** were observed in non-human primates with species-specific muscle-directed expression[15]



Liver- and muscle-directed gene replacement therapies are currently being investigated in clinical trials to determine whether organ-directed GAA transgene expression may lead to benefits in clinical outcomes