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How has successful ERT treatment in IOPD changed the phenotype?

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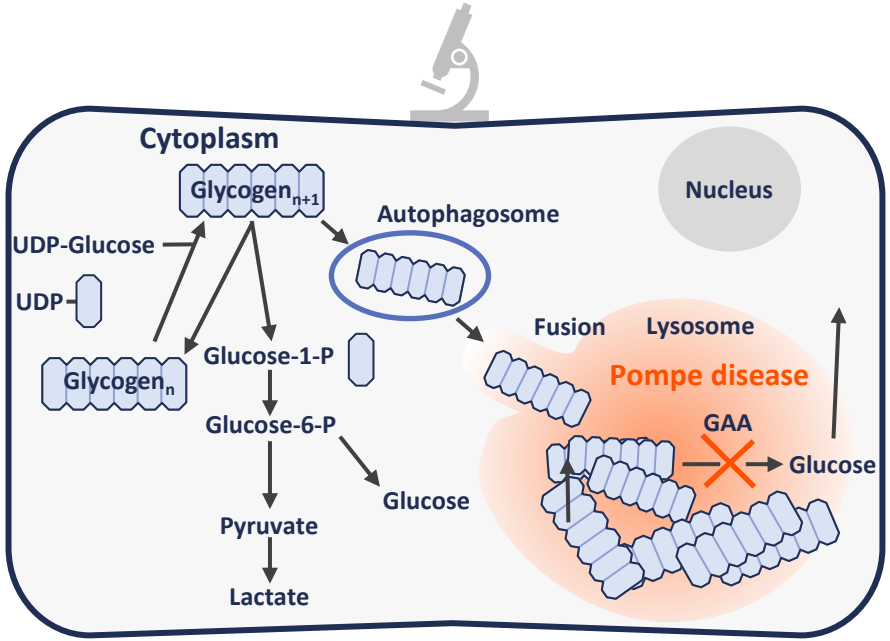
Pathophysiology of Pompe disease[1–3]

Autosomal recessive genetic disorder leading to GAA enzyme deficiency and impaired glycogen metabolism



cytoplasmic + lysosomal glycogen accumulation in…

…striated and smooth muscle cells

myopathies

- Cardiomyopathies
- Respiratory complications
- Hypotonia

…motor neurons

neuropathies

- CNS manifestations

Image adapted from: Cupler EJ, et al. *Muscle Nerve*. 2012;45:319-33.
CNS, central nervous system; GAA, acid alfa-glucosidase; P, phosphate; UDP, uridine diphosphate.
1. Cupler EJ, et al. *Muscle Nerve*. 2012;45:319-33; 2. Peruzzo P, et al. *Ann Transl Med*. 2019;7:278; 3. Musumeci O, et al. *Eur J Neurol.* 2019;26:442–e35.

Classification of Pompe disease: A phenotypic spectrum

Infantile-onset[1-5]

- **GAA-activity <1%**
- **Presents within 1st year of infancy**
- **Severe and rapidly progressive phenotype:**

- Elevated CK and HEX_4
- Failure to thrive
- Cardiomyopathy: HCM, arrhythmia
- Respiratory insufficiency
- Muscular hypotonia + axial muscle weakness during 1st 6 months of life
- Death within 1st year of life if untreated

+ **CRIM**-positive	− **CRIM**-negative
Synthesize non-functional GAA	No native GAA synthesis

Late-onset[5,6]

- **Presents from 12 months of age to adulthood**
- **Chronic, slowly progressive phenotype characterized by limb-girdle presentation:**

- HyperCKemia; HEX_4 WNL
- CNS + PNS involvement
- Myalgia, exercise intolerance + fatigue
- Limb girdle + axial muscle weakness
- May progress to respiratory insufficiency
- May progress to significant motor disability

CK, creatinine kinase; CNS, central nervous system; CRIM, cross-reactive immunological material; GAA, acid alfa-glucosidase; HCM, hypertrophic cardiomyopathy; HEX_4, glucotetrasaccharide; PNS, peripheral nervous system; WNL, within normal limits.

1. Hahn A and Schänzer A. *Ann Transl Med*. 2019;7:283; 2. Kishnani PS, et al. *Pediatrics*. 2017;140(S1):e20160280B; 3. Meena NK, et al. *Mol Ther*. 2020;18:199; 4. Taverna S, et al. *Aging*. 2020;12:doi: 10.18632/aging.103794 [online ahead of print]; 5. Klug TL, et al. *Int J Neonatal Screen*. 2020;6:11; 6. Toscano A, et al. *Ann Transl Med*. 2019;7:284.

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IOPD: A progressive multisystem disease with profound impacts

Patient QoL and survival[1,2]

0 months

Progressive weakness, feeding + respiratory difficulties

12 months

Death if untreated

Voluntary functions

- Muscular hypotonia
- Axial muscle weakness
- PNS complications

Vital functions

- Cardiomyopathy
- CNS complications
- Respiratory failure

Family and caregivers[1,2]

- Frequent medical visits and hospital attendances
- Treatment and care delivery in the home
- Time needed for additional medical and care needs
- Financial impact of treatment and care costs
- Anxiety and emotional impact
- Access to additional support for child's academic and emotional development

CNS, central nervous system; IOPD, infantile-onset Pompe disease; PNS, peripheral nervous system; QoL, quality of life.

1. Hahn A and Schänzer A. *Ann Transl Med*. 2019;7:283; 2. Schoser B, et al. *PharmacoEcon Open*. 2019;3:479-93; 3. Kishnani PS, et al. *Pediatrics*. 2017;140:e20160280.

Clinical presentation usually permits diagnosis[1]

NBS programs are permitting earlier pre-symptomatic detection and diagnosis[2]

Symptoms and clinical findings[1,3]

- Cardiomegaly
- Congestive HF
- Arrhythmias
- Cardiomyopathy (HCM)

- Frequent infection
- Respiratory distress/insufficiency
- Nasal regurgitation/flaring

- Hypotonia
- Gross motor delay
- Delayed developmental milestones

- Failure to thrive/feeding difficulties
- Macroglossia
- Hepatomegaly

Clinical and laboratory tests[1–3]

- Chest X-ray (cardiomegaly)

- ECG, echo (cardiomyopathy)
- EP (myopathy)

- CK, HEX_4, AST, ALT, LDH
- Presence of GAA +/- confirmation
  - *GAA* mutations
  - GAA activity
    - detected by DBS at NBS
  - Lysosomal glycogen

ALT, alanine aminotransferase; AST, aspartate transaminase; CK, creatinine kinase; CNS, central nervous system; DBS, dried blood spot; ECG, electrocardiogram; echo, echocardiogram; EP, electrophysiology; GAA, acid alfa-glucosidase; HCM, hypertrophic cardiomyopathy; HEX_4, glucotetrasaccharide; HF, heart failure; LDH, lactate dehydrogenase; NBS, newborn screening.

1. Kishnani PS, et al. *Genet Med.* 2006;8:267; 2. Klug TL, et al. *Int J Neonatal Screen.* 2020;6:11; 3. Hahn A and Schänzer A. *Ann Transl Med*. 2019;7:283.

ERT and a patient-tailored multidisciplinary approach is needed[1,2]

Regular clinical assessments

- Monthly cardiac assessment
- Regular respiratory assessment and support if needed
- Monitor antibody titer consider immunomodulation if anti-rhGAA IgG elevated

Coordinated oversight of MDT care by experienced physician

ERT with rhGAA: the 'gold-standard'

Disease-specific

ERT restoration of GAA

rhGAA only approved therapy 20 mg/kg IV infusion[2–4]

Symptom-specific

Specialist management of multisystem manifestations

Individualized care of patient

Regular MDT monitoring and follow up

Adjust treatment regimen and clinical management schedule for individual patient needs

ERT, enzyme replacement therapy; GAA, acid alfa-glucosidase; Ig, immunoglobulin; IV, intravenous; MDT, multidisciplinary team; rhGAA, recombinant human GAA.

1. Kronn DF, et al. *Pediatrics*. 2017;140:e20160280; 2. Tarnopolsky M, et al. *Can J Neurol Sci.* 2016;43:472–85; 3. FDA. Alglucosidase alfa (lumizyme) PI. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/125291s151lbl.pdf (accessed September 2020); 4. EMA. Alglucosidase alfa (myozyme) SmPC. 2020. Available at: www.ema.europa.eu/en/documents/product-information/myozyme-epar-product-information_en.pdf (accessed September 2020).

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IOPD is a complex, multisystemic disease

Requires regular monitoring and vigilance for emergence of new signs and symptoms

From fatal disease in infancy...

- Timely management of cardiomyopathies and respiratory manifestations
- Whole-family support: Genetic counselling for new families
- Prompt intervention with ERT for better outcomes

- Physical therapy and support for progressive muscle weakening
- SLT for dysphagia speech difficulties
- Regular audiology assessment for hearing impairment

...to clinical management as a chronic progressive disorder?

Emerging patient voice: Patients with IOPD now surviving into adolescence and early adulthood, and are driving progress in future practice in IOPD

ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; SLT, speech and language therapy.

Kronn DF, et al. *Pediatrics*. 2017;140:e20160280.

Examining the expanding clinical manifestations of LOPD

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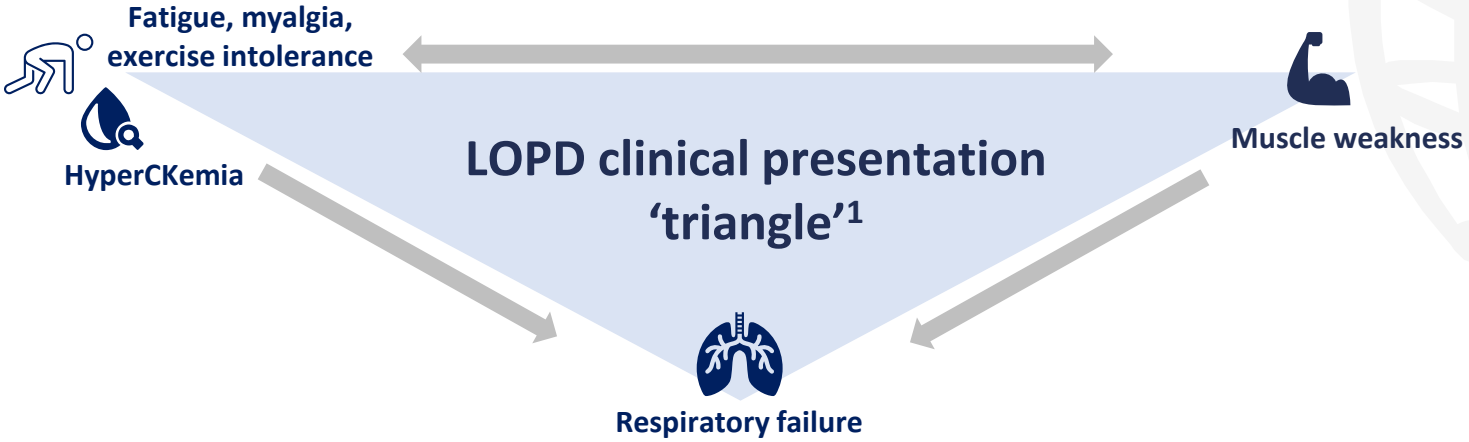
What is LOPD?

Late-onset Pompe disease is characterized by later age of presentation

~12 months of age to adulthood

Chronic course of disease that may progress to significant motor disability and respiratory insufficiency[1,2]



LOPD, late-onset Pompe disease.

1. Toscano A, et al. *Ann Transl Med.* 2019;7:284; 2. Musumeci O, Toscano, A. *Ann Transl Med.* 2019:7:286.

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How is LOPD diagnosed?

Diagnostic challenges due to:[1–3]

- Varying levels of residual GAA enzyme activity correspond to a wide spectrum of LOPD phenotypes
- Wide spectrum of symptoms and clinical presentation ranging in age of onset, severity and progression

Clinical presentation[1,3]

- Progressive limb girdle weakness
- Axial + proximal muscle weakness
- Scapular winging
- Respiratory insufficiency
- Exercise intolerance/fatigue

Laboratory findings[1,3]

- HyperCKemia
  may precede onset of symptoms
- Elevated ALT, AST, LDH
- Decreased GAA enzyme activity

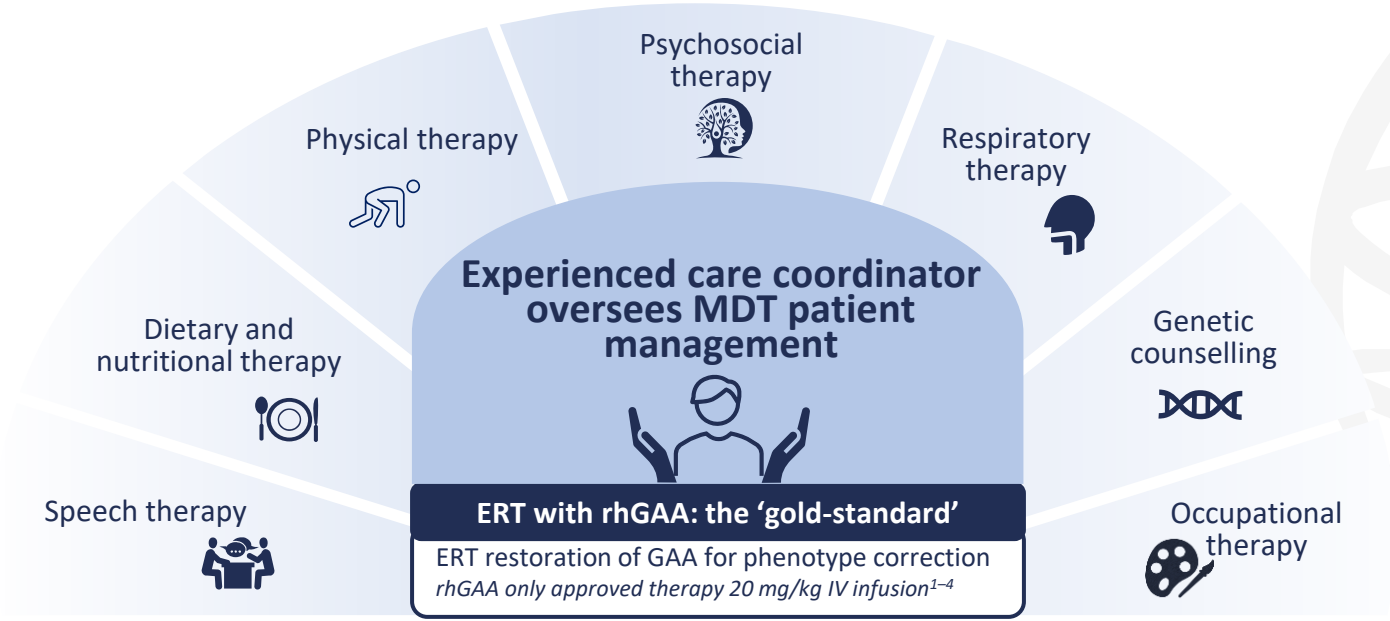
NBS programs are permitting earlier pre-symptomatic detection and diagnosis of LOPD[2]

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatinine kinase; GAA, acid alfa-glucosidase; LDH, lactate dehydrogenase; LOPD, late-onset Pompe disease; NBS, newborn screening.

1. Toscano A, et al. *Ann Transl Med.* 2019;7:284; 2. Musumeci O, Toscano, A. *Ann Transl Med.* 2019:7:286; 3. Klug TL, et al. *Int J Neonatal Screen*. 2020;6:11.

Patient-centered, multidisciplinary management is imperative[1,2]

Regular MDT monitoring and follow up encompassing all specialties to address multisystem manifestations



Adjust treatment regimen and clinical management schedule for individual patient needs

ERT, enzyme replacement therapy; GAA, acid alfa-glucosidase; IV, intravenous; MDT, multidisciplinary team; rhGAA, recombinant human GAA.

1. Cupler EJ, et al. *Muscle Nerve.* 2019;452:319–33; 2. Tarnopolsky M, et al. *Can J Neurol Sci.* 2016;43:472–85; 3. FDA. Product Information: Alglucosidase alfa (lumizyme) 2020; 4. EMA. Summary of Product Characteristics: Alglucosidase alfa (myozyme) 2020.

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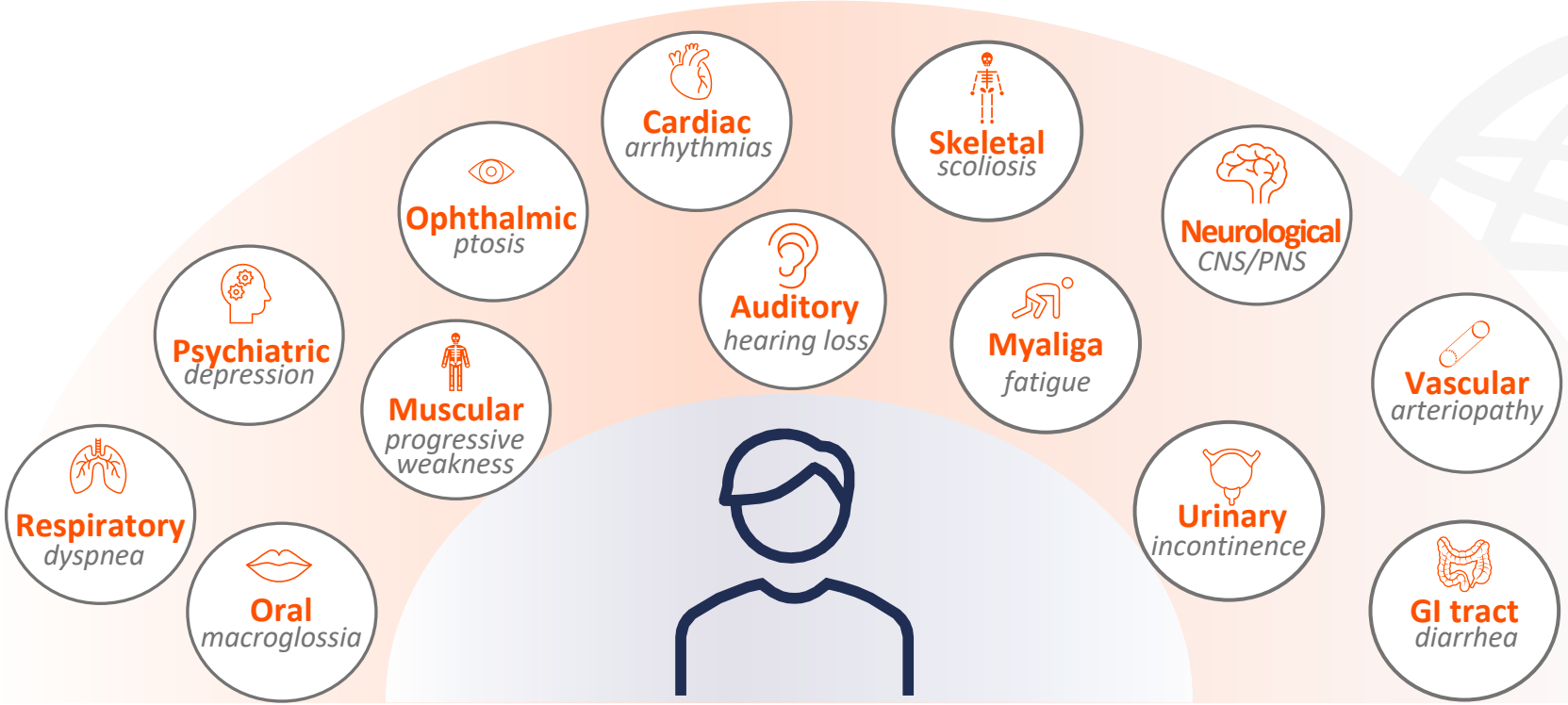
LOPD: A multisystem disorder with expanded phenotypic spectrum



New and emerging manifestations have expanded our understanding of LOPD phenotypes

NB: Illustrative examples given, but not a comprehensive list of all reported LOPD manifestations.
CNS, central nervous system; GI, gastrointestinal; LOPD, late-onset Pompe disease; PNS, peripheral nervous system.
Toscano A, et al. *Ann Transl Med.* 2019;7:284.

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Ongoing improvements in treatment and care offer hope

Optimized treatment and care for the LOPD patient and caregiver community is on the horizon

Gene therapy approaches are translating from preclinical to Phase I/II trials and may improve phenotype correction[1]

Second-generation rhGAA ERT designed to improve targeted delivery and uptake, and clinical efficacy[2]

Increased disease awareness and wider availability of testing are permitting earlier detection and overcoming diagnostic delays[3]

NBS permits early detection and diagnosis enabling swift treatment to prevent ongoing clinical deterioration[4]

ERT, enzyme replacement therapy; LOPD, late-onset Pompe disease; rhGAA, recombinant human GAA.

1. Clinical trial identifier NCT03533673. Available at: ClinicalTrials.gov (accessed September 2020).; 2. Do HV, et al. *Ann Transl Med.* 2019;7:291; 3. Musumeci O and Toscano A. *Ann Transl Med.* 2019:7:286; 4. Klug TL, et al. *Int J Neonatal Screen*. 2020;6:11.

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Improving skeletal muscle targeting with new approaches to ERT

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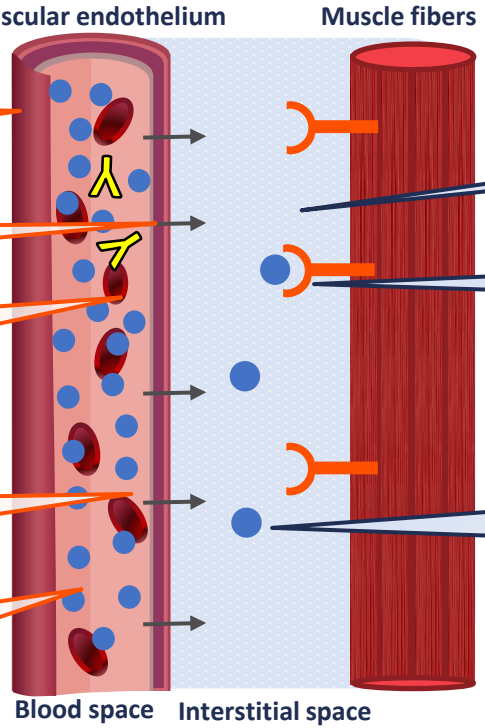
Exogenous rhGAA delivery and uptake remains challenging

Impaired delivery

- **limitations of inherent anatomy**
- **inefficient transcytosis** leads to poor ERT distribution in the interstitia
- nearly all patients with Pompe disease develop **anti-rhGAA antibodies** disrupting ERT efficacy
- **rhGAA unstable at neutral pH** leading to degradation and loss of ERT in circulation
- **'sink effect':** substantial rhGAA clearance from circulation by non-target muscle tissues e.g liver, spleen, lymphatic system, GI tract



Sub-optimal uptake

- cellular uptake of ERT is via **receptor-mediated endocytosis**
- **M6P required** for efficient cellular uptake
- **rhGAA poorly phosphorylated** limiting ERT uptake by target muscle cells

Anti-rhGAA antibody
rhGAA ERT
Receptor

ERT, enzyme replacement therapy; GAA, acid alfa-glucosidase; GI, gastrotintestinal; M6P, mannose-6-phosphate; rhGAA, recombinant human GAA.

Do HV, et al. *Ann Transl Med.* 2019;7:291.

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Second-generation ERTs: Optimized rhGAA delivery and uptake

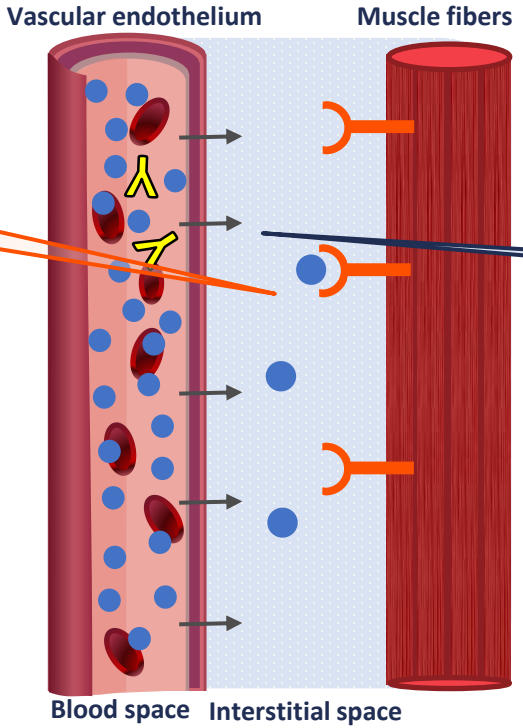
Overcoming impaired delivery

rhGAA unstable at neutral pH leading to degradation and loss of ERT in circulation[1]

AT-GAA
M6P-rich rhGAA co-administered with stabilizing chaperone molecule[1]

Limitations with ERT remain[3]

- Incomplete phenotype correction
- Lifelong treatment burden
- CNS penetration: rhGAA cannot pass BBB
- Immune responses to exogenous rhGAA



Overcoming sub-optimal uptake

VAL-1221
fusion protein potentiating M6P-independent uptake[1]

M6P required for efficient cellular uptake

neoGAA
synthetic oligosaccharide linker for improved M6P-mediated uptake[1,2]

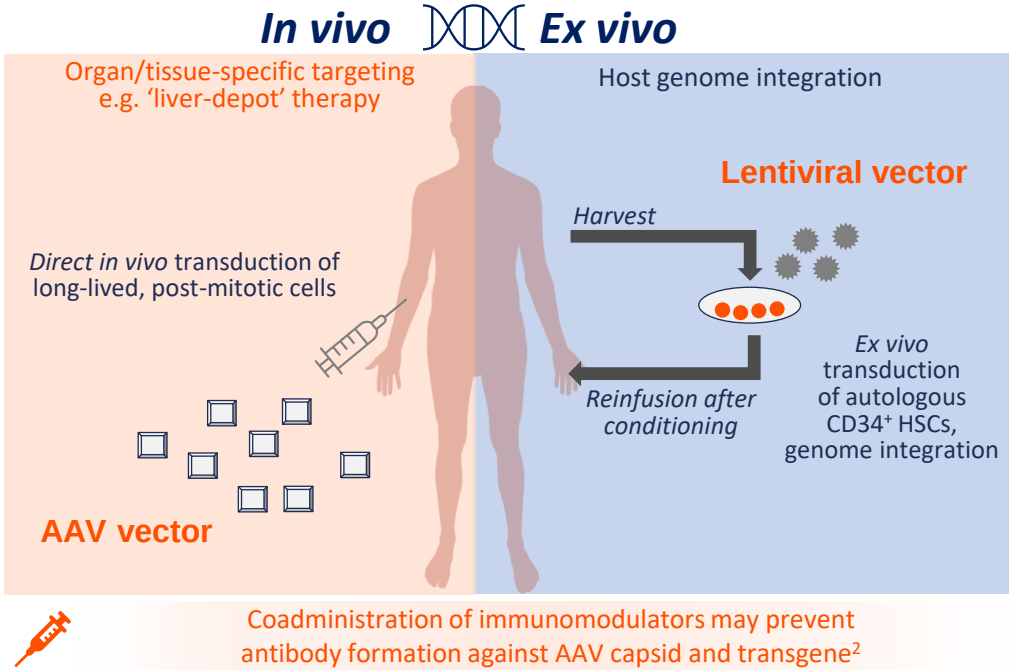
Anti-rhGAA antibody
rhGAA ERT
Receptor

BBB, blood–brain barrier; CNS, central nervous system; ERT, enzyme replacement therapy; GAA, acid alfa-glucosidase; M6P, mannose-6-phosphate; rhGAA, recombinant human GAA.

1. Do HV, et al. *Ann Transl Med.* 2019;7:291; 2. Pena LDM, et al. *Neuromusc Dis.* 2019;29:167–86; 3. Stok M, et al. *Mol Ther.* 2019;17:1014.

Gene therapy: A ‘one and done’ approach to treatment?

Gene therapy modalities using different viral vectors are being explored[1–4]



Aims of therapy[4]

- Long-term source of GAA
- Reduced GAA immunogenicity
- CNS penetration by GAA
- Improved ‘body-wide’ phenotype correction of a multisystem disorder

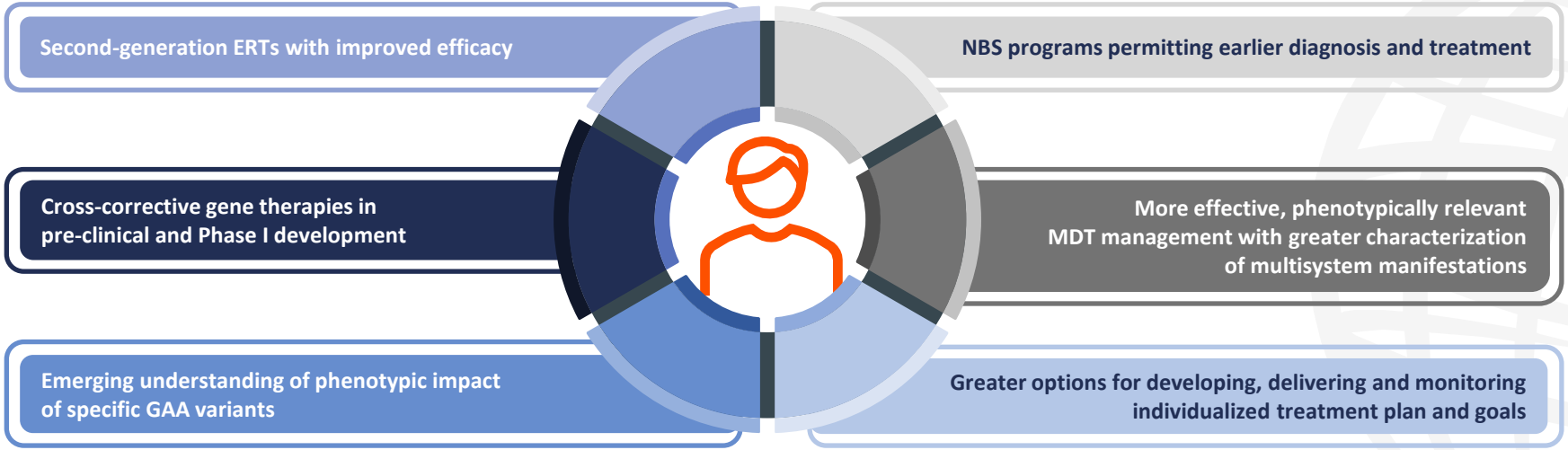
Possible concerns

- Immunogenicity of vector capsid and transgene[2]
- Inter-patient variability and individual complex genetic background[4]

Image adapted from Ronzitti G, et al. *Ann Transl Med.* 2019;7:287.
AAV, adeno-associated virus; CNS, central nervous system; ERT, enzyme replacement therapy; GAA, acid alfa-glucosidase; HSCs, hematopoietic stem cells; rhGAA, recombinant human GAA.
1. Do HV, et al. *Ann Transl Med.* 2019;7:291; 2. Byrne BJ, et al. *Ann Transl Med.* 2019;7:290; 3. Stok M, et al. *Mol Ther*. 2019;17:1014; 4 Ronzitti G, et al. *Ann Transl Med.* 2019;7:287.

A picture of individualized treatment and care emerges

Expanding patient and caregiver choice



Improving outcomes with individualized care

Improved management of individual phenotypes with clinical insights emerging in the era of prolonged survival will facilitate increasingly patient-centred treatment and care

ERT, enzyme replacement therapy; GAA, acid alfa-glucosidase; MDT, multidisciplinary team; NBS, newborn screening.