Evolution of Pompe Disease Therapy

Subjects: Medicine, Research & Experimental

Contributor: Naresh K. Meena , Nina Raben

Pompe disease, also known as glycogen storage disease type II, is caused by the lack or deficiency of a single enzyme, lysosomal acid alpha-glucosidase, leading to severe cardiac and skeletal muscle myopathy due to progressive accumulation of glycogen. The discovery that acid alpha-glucosidase resides in the lysosome gave rise to the concept of lysosomal storage diseases, and Pompe disease became the first among many monogenic diseases caused by loss of lysosomal enzyme activities.

Pompe disease lysosome lysosomal targeting autophagy

1. Next-Generation ERT

Notably, the less than optimal intrinsic quality of alglucosidase alfa was understood years ago, as indicated by the efforts in the early 2000s to enhance the delivery of the therapeutic enzyme to the affected muscle by carbohydrate remodeling of the original enzyme to increase the amount of M6P [1]. This early work and an extended follow-up study [2] led to the development of a modified glycoengineered enzyme with a synthetic oligosaccharide harboring mannose 6-phosphate (M6P) residues. This new recombinant human GAA, called neo-GAA, with much improved affinity for the CI-MPR and uptake by muscle cells, showed more efficient glycogen clearance in immunotolerized KO mice compared to the unmodified enzyme, particularly in younger mice. Muscle glycogen reduction was also achieved in older symptomatic KO mice, but the improvement in motor function was only marginal [2].

Neo-GAA (Avalglucosidase alfa; Sanofi Genzyme, Cambridge, MA, USA), a second-generation glycoengineered recombinant GAA with increased bis-M6P levels, was first evaluated for safety and tolerability in a now completed clinical trial (NCT01898364). The results of this Phase 1/2 open-labeled, ascending-dose (5, 10, and 20 mg/kg biweekly over the course of 24 weeks) study in previously ERT-treated (switch group) and -untreated (naïve group) LOPD patients was recently published [3]. Neo-GAA was overall well-tolerated and safe; only two of the 24 enrolled patients discontinued because of the drug-related serious adverse events. Based on the glycogen levels in baseline quadriceps biopsies (~6% of tissue area), patients from both groups were considered to be mildly affected. Although the assessment of efficacy was not a part of the protocol, exploratory efficacy parameters showed a slight improvement in pulmonary function in ERT-naïve and no decline in ERT-switch patients. A Phase 3 study to compare the safety and efficacy of neo-GAA and alglucosidase alfa in previously untreated LOPD was initiated in 2016 and is ongoing (COMET; NCT02782741). In the randomized, double-blind portion of the study, patients received either neo-GAA or alglucosidase alfa (standard of care) for 49 weeks; thereafter, all patients participated in ongoing open-label treatment with neo-GAA. In addition, the company's clinical development program includes several other exploratory efficacy studies with neo-GAA in LOPD and IOPD patients.

Another new investigational drug, AT-GAA (Amicus Therapeutics, Cranbury, NJ, USA) is the combination of a novel non-modified rhGAA bearing high bis-M6P (Amicus proprietary cell line) with a pharmacological chaperone (AT2221; N-butyldeoxynojirimycin; NB-DNJ, miglustat) for stabilizing the enzyme in the circulation (reviewed in [4]). Both preclinical and clinical studies in Pompe disease patients demonstrated that small molecules chaperones increased the stability and bioavailability of the therapeutic enzyme [5][6][7][8].

In a large preclinical study in KO mice, AT-GAA was shown to significantly outperform alglucosidase alfa in all measured outcomes: GAA uptake and activity, muscle strength, reduction in lysosomal size and glycogen levels, and mitigation of autophagic defect [9]. Furthermore, long-term treatment of KO with AT-GAA completely reversed muscle lysosomal glycogen accumulation, eliminated autophagic buildup in >80% of muscle fibers, and to a large degree restored AMPK/mTORC1 signaling, muscle proteostasis, and metabolic abnormalities [10]. This outcome is in striking contrast with the limited effect of a long-term treatment of KO mice with alglucosidase alfa at a similar dose of 20 mg/kg [11].

AT-GAA was evaluated in Phase 1/2 clinical trial in ERT-switch and naïve non-ambulatory LOPD patients; the drug was well-tolerated with a low number of infusion-associated reactions and showed promising results, as evidenced by improvement in muscle function, increase in upper-body muscle strength, and patient-reported outcomes (reviewed in [4]). Two Phase 3 studies, one comparing AT- GAA with alglucosidase alfa/placebo (PROPEL Study; NCT03729362; active, not recruiting), and the second one (ZIP Study: NCT03911505; recruiting) evaluating the pharmacokinetics, safety, efficacy, and pharmacodynamic of AT-GAA in LOPD patients were initiated in 2018 and 2019 respectively.

An attempt was made to target both lysosomal and extra-lysosomal glycogen accumulation in the affected muscle. VAL-1221 (Valerion Therapeutics, Concord, MA, USA) is a CHO-produced fusion protein containing the 110 kDa human GAA precursor and the Fab fragment of a murine lupus anti-DNA antibody, 3E10. This monoclonal anti-DNA antibody were shown to penetrate living cells and move to the nucleus through the equilibrative nucleoside transporter 2 (ENT2) [12][13][14]. Experiments in cultured L6 myoblasts and fibroblasts derived from Pompe disease patients as well as in vivo studies in KO mice suggested a potential benefit of this fusion protein [15]. However, VAL-1221 in KO mice did not show any improvement in muscle glycogen content (unpublished data). A Phase 1/2 dose-escalation clinical trial (NCT02898753) of VAL-1221 in previously treated LOPD patients was initiated in 2017 [16], but the results of this study were not validated by peer review. As of June 2020, the company terminated this trial in the US and UK.

Finally, a combination of alglucosidase alfa with β2 agonists, clenbuterol, or albuterol, was shown to enhance the efficacy of the therapeutic enzyme owing to the increased expression of CI-MPR in skeletal muscle [17][18]. A pilot study of albuterol plus ERT in LOPD patients who were not improving further following more than two years on ERT alone showed the benefit of this approach [19]. A phase 1/2 double-blind, randomized, placebo-controlled 52-week study (NCT01942590) of clenbuterol in LOPD patients treated with ERT provided evidence for safety and showed a modest improvement in motor function [20]. This study (initiated in 2013) is now completed. **Table 1** summarizes the above-mentioned clinical trials.

Table 1. Next generation therapies for Pompe disease.

Intervention/Treatment	Characteristics/Delivery Method	Company/Institution	Clinical Trial Phase/Identifier	References
ERT				
neo-GAA	Glycoengineered recombinant GAA with increased bis-M6P levels (avalglucosidase alfa)	Genzyme, a Sanofi Company	Completed/NCT01898364 Phase 3/NCT02782741	Zhu et al. [2] Pena et al. [3]
AT-GAA (ATB200/AT2221)	rhGAA bearing high bis-M6P with a pharmacological chaperone (miglustat)	Amicus Therapeutics	Phase 3/NCT03729362 Phase 3/NCT03911505	Khanna et al. [7] Xu et al. [9] Meena et al. [10]
VAL-1221	Fusion protein containing antibody 3E10 and rhGAA	Valerion Therapeutics	Terminated/NCT02898753	Weisbart et al. [13] [14] Yi et al. [15] Kishnani et al. [16]
ERT + Clenbuterol	Alglucosidase alfa with β2-adrenergic agonist clenbuterol	Duke University	Completed/NCT01942590	Koeberl et al. [17][18] [19][20]
Gene Therapy				
rAAV2/1-CMV-hGAA	Intramuscular injection into the diaphragm	University of Florida	Completed/NCT00976352	Smith et al. [21] Byrne et al. [22] Corti et al. [23]
rAAV9-DES-hGAA	Intramuscular re-administration	Lacerta Therapeutics/University of Florida	Phase 1/2/NCT02240407	Salabarria et al. [24]
AAV2/8-LSPhGAA	Screening for eligibility Ascending dose intravenous administration	Duke University Asklepios Biopharmaceutical/Duke University	Completed/NCT03285126 Phase 1/2/ NCT03533673	Kishnani et al. [25] Han et al. [26]
SPK-3006 (AAV liver directed secretable GAA)	Intravenous administration	Spark Therapeutics	Phase 1/2/ NCT04093349	Puzzo et al. [27]

2. Gene Therapy

Intervention/Treatment	Characteristics/Delivery Method	Company/Institution	Clinical Trial Phase/Identifier	References
				Cagin et al. [28]

ses, and
ment for
oment of

gene therapy for Pompe disease an attractive option. Over the past years, the field has witnessed the explosion of gene therapy studies testing different AAV serotypes, vector designs, and routes of delivery in preclinical settings. These studies are discussed in several recent reviews [24][29][30][31][32].

ERT: therapy replacement therapy; M6P: mannose-6-phosphate; clinicaltrials.gov is the database of registered clinical trials.

Based on the results of the early preclinical studies evaluating the effect of systemic or intramuscular administration of AAV vectors in KO mice [33][34][35], the first-in-human trial of gene therapy for Pompe disease began in 2006, thus marking a milestone in the field. This was an open label, Phase 1/2 trial (NCT00976352) using direct injection of rAAV2/1-CMV-hGAA into the diaphragm of a small group of children who required assisted ventilation despite ERT. The study confirmed safety and showed a tendency to improve respiratory function in some patients [21][22][23].

Phase 1/2 clinical trial evaluating the feasibility of two successive intramuscular (into tibialis anterior muscle) administration of an AAV9 vector expressing GAA is ongoing and is recruiting patients with LOPD (NCT02240407). The recombinant AAV carries the codon-optimized acid alpha-glucosidase under the control of human desmin enhancer/promoter (rAAV9-DES-hGAA). The immune modulation strategy using Rituximab and Sirolimus prior and after the first administration of the vector is designed to prevent the immune response against the AAV capsid and the transgene, thus allowing for the second vector administration. The same group of researchers from University of Florida are planning to initiate a new Phase 1/2 clinical trial of systemic injection of rAAV9-DES-GAA in 3–5-year-old IOPD patients.

Another approach-hepatic gene transfer-relies on a remarkable ability of hepatocytes to produce and secrete the expressed protein into the bloodstream, thus providing a steady supply of the therapeutic enzyme for the uptake by other tissues. Early studies on KO mice demonstrated that a single i.v. administration of a modified adenovirus (AV) vector encoding human GAA resulted in efficient liver transduction, secretion of the GAA precursor, and clearance of lysosomal glycogen accumulation in skeletal and cardiac muscles [36]. These results along with the follow-up studies [37][38] provided a solid foundation for using what is now called “liver depot gene therapy” in Pompe disease. However, the use of AAV vectors is now highly preferred for achieving a long-term persistent therapeutic gene transfer.

The unique immunologic properties of the liver allow for the induction of immune tolerance to foreign antigens through a regulatory T-cell mediated mechanism (reviewed in [39]). Indeed, AAV-mediated liver-specific expression of human GAA in KO mice was shown to prevent the formation of anti-GAA antibody when the vector was administered prior to the start of ERT, thus improving ERT efficacy [40][41][42]. The concept of induction of tolerance to the therapeutic enzyme delivered during ERT by low-dose AAV vector administration is termed “immunomodulatory gene therapy” [43]. Multiple preclinical studies have explored the impact of different AAV serotypes and promoters, vector dosages, and modifications of the GAA sequence, such as the signal peptide and

codon optimization, to enhance GAA secretion into the bloodstream and to better control humoral immune responses (reviewed in [25][31][32]). These studies have culminated in the first liver gene therapy clinical trials for Pompe disease.

A Phase 1 clinical trial (NCT03533673) of liver depot gene therapy in adult patients is designed to evaluate an rAAV serotype 8 vector carrying the human GAA under the control of liver-specific promoter (AAV2/8-LSPhGAA). This is an ongoing open label, randomized study (currently recruiting). A careful consideration of the vector dosage for this trial was based on the preclinical data showing effective biochemical correction of skeletal muscle at a dose of 2×10^{12} vg/kg, and induction of immune tolerance to the ERT delivered rhGAA (with only partial correction of the muscle defect) at a minimum effective dose of 2×10^{11} vg/kg [26]. These data justified a starting dose of 1.6×10^{12} vg/kg for Phase 1 clinical trial [25]. This clinical trial was preceded by a Pompe gene therapy trial (NCT03285126; completed), designed to determine eligibility for the forthcoming trial in adults with LOPD.

Another Phase 1/2 liver transfer gene therapy clinical trial (NCT04093349; RESOLUTE), initiated by Spark Therapeutics is recruiting patients with LOPD receiving ERT. The study is designed to evaluate the safety, tolerability, and efficacy of investigational liver-directed AAV gene therapy of the secretable GAA (SPK-3006) in adults, treated in sequential dose-level cohorts. Preclinical studies using this AAV8-mediated liver gene transfer of an engineered secretable GAA (secGAA) resulted in high and stable levels of GAA in the circulation and rescued muscle and CNS pathology in adult and severely affected older KO mice without development of humoral immune responses to the enzyme [27][28].

An inherent limitation of hepatic gene transfer is that AAV episomal vectors will be diluted over time in the developing and growing liver, eventually leading to the loss of vector genomes and transgene expression. This creates a major problem for treatment of pediatric patients with the disease, who are likely to require a second round of vector administration and immunosuppression to prevent the formation of neutralizing antibodies. In general, the success of liver-directed gene therapy for Pompe disease relies on both secretion of large amount of precursor GAA and its efficient CI-MPR-mediated uptake and lysosomal trafficking in distant organs. As with traditional ERT, the same requirement for high M6P content and affinity for the CI-MPR applies to the liver-produced secreted GAA to achieve efficient targeting and correction of muscle defect. This raises a possibility of generating an “ideal” transgene expression cassette to allow for the maximally reduced dose of vector. Although challenging, the era of gene therapy for Pompe disease has arrived, and the therapy has the potential to one day become a lifelong cure.

References

1. Zhu, Y.; Li, X.; McVie-Wylie, A.; Jiang, C.; Thurberg, B.L.; Raben, N.; Mattaliano, R.J.; Cheng, S.H. Carbohydrate-remodelled acid α-glucosidase with higher affinity for the cation-independent mannose 6-phosphate receptor demonstrates improved delivery to muscles of Pompe mice. Biochem. J. 2005, 389, 619–628.

2. Zhu, Y.; Jiang, J.-L.; Gumlaw, N.K.; Zhang, J.; Bercury, S.D.; Ziegler, R.J.; Lee, K.; Kudo, M.; Canfield, W.M.; Edmunds, T.; et al. Glycoengineered Acid α-Glucosidase with Improved Efficacy at Correcting the Metabolic Aberrations and Motor Function Deficits in a Mouse Model of Pompe Disease. Mol. Ther. 2009, 17, 954–963.
3. Pena, L.D.M.; Barohn, R.J.; Byrne, B.J.; Desnuelle, C.; Goker-Alpan, O.; Ladha, S.; Laforêt, P.; Mengel, K.E.; Pestronk, A.; Pouget, J.; et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. Neuromuscul. Disord. 2019, 29, 167–186.
4. Do, H.V.; Khanna, R.; Gotschall, R. Challenges in treating Pompe disease: An industry perspective. Ann. Transl. Med. 2019, 7, 291.
5. Parenti, G.; Andria, G.; Valenzano, K.J. Pharmacological Chaperone Therapy: Preclinical Development, Clinical Translation, and Prospects for the Treatment of Lysosomal Storage Disorders. Mol. Ther. 2015, 23, 1138–1148.
6. Porto, C.; Cardone, M.; Fontana, F.; Rossi, B.; Tuzzi, M.R.; Tarallo, A.; Barone, M.V.; Andria, G.; Parenti, G. The Pharmacological Chaperone N-butyldeoxynojirimycin Enhances Enzyme Replacement Therapy in Pompe Disease Fibroblasts. Mol. Ther. 2009, 17, 964–971.
7. Khanna, R.; Flanagan, J.J.; Feng, J.; Soska, R.; Frascella, M.; Pellegrino, L.J.; Lun, Y.; Guillen, D.; Lockhart, D.J.; Valenzano, K.J. The Pharmacological Chaperone AT2220 Increases Recombinant Human Acid α-Glucosidase Uptake and Glycogen Reduction in a Mouse Model of Pompe Disease. PLoS ONE 2012, 7, e40776.
8. Parenti, G.; Fecarotta, S.; La Marca, G.; Rossi, B.; Ascione, S.; Donati, M.A.; Morandi, L.O.; Ravaglia, S.; Pichiecchio, A.; Ombrone, D.; et al. A Chaperone Enhances Blood α-Glucosidase Activity in Pompe Disease Patients Treated with Enzyme Replacement Therapy. Mol. Ther. 2014, 22, 2004–2012.
9. Xu, S.; Lun, Y.; Frascella, M.; Garcia, A.; Soska, R.; Nair, A.; Ponery, A.S.; Schilling, A.; Feng, J.; Tuske, S.; et al. Improved efficacy of a next-generation ERT in murine Pompe disease. JCI Insight 2019, 4, 125358.
10. Meena, N.K.; Ralston, E.; Raben, N.; Puertollano, R. Enzyme Replacement Therapy Can Reverse Pathogenic Cascade in Pompe Disease. Mol. Ther. Methods Clin. Dev. 2020, 18, 199–214.
11. Raben, N.; Danon, M.; Gilbert, A.; Dwivedi, S.; Collins, B.; Thurberg, B.; Mattaliano, R.; Nagaraju, K.; Plotz, P. Enzyme replacement therapy in the mouse model of Pompe disease. Mol. Genet. Metab. 2003, 80, 159–169.

12. Hansen, J.E.; Tse, C.-M.; Chan, G.; Heinze, E.R.; Nishimura, R.N.; Weisbart, R.H. Intranuclear Protein Transduction through a Nucleoside Salvage Pathway. J. Boil. Chem. 2007, 282, 20790–20793.
13. Weisbart, R.H.; Gera, J.; Chan, G.; Hansen, J.E.; Li, E.; Cloninger, C.; Levine, A.J.; Nishimura, R.N. A Cell-Penetrating Bispecific Antibody for Therapeutic Regulation of Intracellular Targets. Mol. Cancer Ther. 2012, 11, 2169–2173.
14. Weisbart, R.H.; Chan, G.; Jordaan, G.; Noble, P.W.; Liu, Y.; Glazer, P.M.; Nishimura, R.N.; Hansen, J.E. DNA-dependent targeting of cell nuclei by a lupus autoantibody. Sci. Rep. 2015, 5, 12022.
15. Yi, H.; Sun, T.; Armstrong, D.; Borneman, S.; Yang, C.; Austin, S.; Kishnani, P.S.; Sun, B. Antibody-mediated enzyme replacement therapy targeting both lysosomal and cytoplasmic glycogen in Pompe disease. J. Mol. Med. 2017, 95, 513–521.
16. Kishnani, P.; Lachmann, R.; Mozaffar, T.; Walters, C.; Case, L.; Appleby, M.; Libri, V.; Kak, M.; Wencel, M.; Landy, H. Safety and efficacy of VAL-1221, a novel fusion protein targeting cytoplasmic glycogen, in patients with late-onset Pompe disease. Mol. Genet. Metab. 2019, 126, S85–S86.
17. Koeberl, D.; Luo, X.; Sun, B.; McVie-Wylie, A.; Dai, J.; Li, S.; Banugaria, S.G.; Chen, Y.-T.; Bali, D.S. Enhanced efficacy of enzyme replacement therapy in Pompe disease through mannose-6-phosphate receptor expression in skeletal muscle. Mol. Genet. Metab. 2011, 103, 107–112.
18. Koeberl, D.D.; Li, S.; Dai, J.; Thurberg, B.L.; Bali, D.; Kishnani, P.S. Beta2 Agonists enhance the efficacy of simultaneous enzyme replacement therapy in murine Pompe disease. Mol. Genet. Metab. 2012, 105, 221–227.
19. Koeberl, D.; Austin, S.; E Case, L.; Smith, E.C.; Buckley, A.F.; Young, S.P.; Bali, D.; Kishnani, P.S. Adjunctive albuterol enhances the response to enzyme replacement therapy in late-onset Pompe disease. FASEB J. 2014, 28, 2171–2176.
20. Koeberl, D.; E Case, L.; Smith, E.C.; Walters, C.; Han, S.-O.; Li, Y.; Chen, W.; Hornik, C.P.; Huffman, K.M.; Kraus, W.E.; et al. Correction of Biochemical Abnormalities and Improved Muscle Function in a Phase I/II Clinical Trial of Clenbuterol in Pompe Disease. Mol. Ther. 2018, 26, 2304–2314.
21. Smith, B.K.; Collins, S.W.; Conlon, T.J.; Mah, C.S.; Lawson, L.A.; Martin, A.D.; Fuller, D.D.; Cleaver, B.D.; Clement, N.; Phillips, D.; et al. Phase I/II Trial of Adeno-Associated Virus–Mediated Alpha-Glucosidase Gene Therapy to the Diaphragm for Chronic Respiratory Failure in Pompe Disease: Initial Safety and Ventilatory Outcomes. Hum. Gene Ther. 2013, 24, 630–640.
22. Byrne, P.I.; Collins, S.; Mah, C.C.; Smith, B.; Conlon, T.; Martin, S.D. Phase I/II trial of diaphragm delivery of recombinant adeno-associated virus acid alpha-glucosidase (rAAaV1-CMV-GAA) gene

vector in patients with Pompe disease. Hum. Gene Ther. Clin. Dev. 2014, 25, 134–163.

23. Corti, M.; Liberati, C.; Smith, B.K.; Lawson, L.A.; Tuna, I.S.; Conlon, T.J.; Coleman, K.E.; Islam, S.; Herzog, R.W.; Fuller, D.D.; et al. Safety of Intradiaphragmatic Delivery of Adeno-Associated Virus-Mediated Alpha-Glucosidase (rAAV1-CMV-hGAA) Gene Therapy in Children Affected by Pompe Disease. Hum. Gene Ther. Clin. Dev. 2017, 28, 208–218.
24. Salabarria, S.; Nair, J.; Clement, N.; Smith, B.; Raben, N.; Fuller, D.; Byrne, B.J.; Corti, M. Advancements in AAV-mediated Gene Therapy for Pompe Disease. J. Neuromuscul. Dis. 2020, 7, 15–31.
25. Kishnani, P.S.; Koeberl, D. Liver depot gene therapy for Pompe disease. Ann. Transl. Med. 2019, 7, 288.
26. Han, S.-O.; Ronzitti, G.; Arnson, B.; Leborgne, C.; Li, S.; Mingozzi, F.; Koeberl, D. Low-Dose Liver-Targeted Gene Therapy for Pompe Disease Enhances Therapeutic Efficacy of ERT via Immune Tolerance Induction. Mol. Ther. Methods Clin. Dev. 2017, 4, 126–136.
27. Puzzo, F.; Colella, P.; Biferi, M.G.; Bali, D.; Paulk, N.K.; Vidal, P.; Collaud, F.; Simon-Sola, M.; Charles, S.; Hardet, R.; et al. Rescue of Pompe disease in mice by AAV-mediated liver delivery of secretable acid α-glucosidase. Sci. Transl. Med. 2017, 9, eaam6375.
28. Cagin, U.; Puzzo, F.; Gomez, M.J.; Moya-Nilges, M.; Sellier, P.; Abad, C.; Van Wittenberghe, L.; Daniele, N.; Guerchet, N.; Gjata, B.; et al. Rescue of Advanced Pompe Disease in Mice with Hepatic Expression of Secretable Acid α-Glucosidase. Mol. Ther. 2020, 28.
29. Kohler, L.; Puertollano, R.; Raben, N. Pompe Disease: From Basic Science to Therapy. Neurotherapeutics 2018, 15, 928–942.
30. Doerfler, P.A.; Nayak, S.; Corti, M.; Morel, L.; Herzog, R.W.; Byrne, B.J. Targeted approaches to induce immune tolerance for Pompe disease therapy. Mol. Ther. Methods Clin. Dev. 2016, 3, 15053.
31. Ronzitti, G.; Collaud, F.; Laforet, P.; Mingozzi, F. Progress and challenges of gene therapy for Pompe disease. Ann. Transl. Med. 2019, 7, 287.
32. Byrne, B.J.; Fuller, D.D.; Smith, B.K.; Clement, N.; Coleman, K.; Cleaver, B.; Vaught, L.; Falk, D.J.; McCall, A.; Corti, M. Pompe disease gene therapy: Neural manifestations require consideration of CNS directed therapy. Ann. Transl. Med. 2019, 7, 290.
33. Mah, C.S.; Pacak, C.A.; Cresawn, K.O.; DeRuisseau, L.R.; Germain, S.; Lewis, M.A.; Cloutier, D.A.; Fuller, D.D.; Byrne, B.J. Physiological Correction of Pompe Disease by Systemic Delivery of Adeno-associated Virus Serotype 1 Vectors. Mol. Ther. 2007, 15, 501–507.
34. Mah, C.S.; Falk, D.J.; Germain, S.A.; Kelley, J.S.; Lewis, M.A.; A Cloutier, D.; DeRuisseau, L.R.; Conlon, T.J.; Cresawn, K.O.; Fraites, T.J., Jr.; et al. Gel-mediated Delivery of AAV1 Vectors

Corrects Ventilatory Function in Pompe Mice with Established Disease. Mol. Ther. 2010, 18, 502–510.

35. Elmallah, M.K.; Falk, D.J.; Nayak, S.; Federico, R.A.; Sandhu, M.S.; Poirier, A.; Byrne, B.J.; Fuller, D.D. Sustained Correction of Motoneuron Histopathology Following Intramuscular Delivery of AAV in Pompe Mice. Mol. Ther. 2014, 22, 702–712.
36. Amalfitano, A.; McVie-Wylie, A.J.; Hu, H.; Dawson, T.L.; Raben, N.; Plotz, P.; Chen, Y.T. Systemic correction of the muscle disorder glycogen storage disease type II after hepatic targeting of a modified adenovirus vector encoding human acid-α-glucosidase. Proc. Natl. Acad. Sci. USA 1999, 96, 8861–8866.
37. Kiang, A.; Hartman, Z.C.; Liao, S.; Xu, F.; Serra, D.; Palmer, D.J.; Ng, P.; Amalfitano, A.; Kiang, Z.C.H.A. Fully Deleted Adenovirus Persistently Expressing GAA Accomplishes Long-Term Skeletal Muscle Glycogen Correction in Tolerant and Nontolerant GSD-II Mice. Mol. Ther. 2006, 13, 127–134.
38. Rastall, D.P.W.; Seregin, S.S.; Aldhamen, Y.A.; Kaiser, L.; Mullins, C.; Liou, A.; Ing, F.; Pereria-Hicks, C.; Godbehere-Roosa, S.; Palmer, D.; et al. Long-term, high-level hepatic secretion of acid α-glucosidase for Pompe disease achieved in non-human primates using helper-dependent adenovirus. Gene Ther. 2016, 23, 743–752.
39. Mingozzi, F.; High, K.A. Therapeutic in vivo gene transfer for genetic disease using AAV: Progress and challenges. Nat. Rev. Genet. 2011, 12, 341–355.
40. Franco, L.M.; Sun, B.; Yang, X.; Bird, A.; Zhang, H.; Schneider, A.; Brown, T.; Young, S.P.; Clay, T.M.; Amalfitano, A.; et al. Evasion of Immune Responses to Introduced Human Acid α-Glucosidase by Liver-Restricted Expression in Glycogen Storage Disease Type II. Mol. Ther. 2005, 12, 876–884.
41. Sun, B.; Bird, A.; Young, S.P.; Kishnani, P.S.; Chen, Y.-T.; Koeberl, D. Enhanced Response to Enzyme Replacement Therapy in Pompe Disease after the Induction of Immune Tolerance. Am. J. Hum. Genet. 2007, 81, 1042–1049.
42. Sun, B.; Kulis, M.D.; Young, S.P.; Hobeika, A.C.; Li, S.; Bird, A.; Zhang, H.; Li, Y.; Clay, T.M.; Burks, W.; et al. Immunomodulatory Gene Therapy Prevents Antibody Formation and Lethal Hypersensitivity Reactions in Murine Pompe Disease. Mol. Ther. 2010, 18, 353–360.
43. Bond, J.; Kishnani, P.; Koeberl, D. Immunomodulatory, liver depot gene therapy for Pompe disease. Cell. Immunol. 2019, 342, 103737.