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Preclinical Development of New Therapy for Glycogen Storage Diseases

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Abstract

Glycogen storage disease (GSD) consists of more than 10 discrete conditions for which the biochemical and genetic bases have been determined, and new therapies have been under development for several of these conditions. Gene therapy research has generated proof-of-concept for GSD types I (von Gierke disease) and II (Pompe disease). Key features of these gene therapy strategies include the choice of vector and regulatory cassette, and recently adeno-associated virus (AAV) vectors containing tissue-specific promoters have achieved a high degree of efficacy. Efficacy of gene therapy for Pompe disease depend upon the induction of immune tolerance to the therapeutic enzyme. Efficacy of von Gierke disease is transient, waning gradually over the months following vector administration. Small molecule therapies have been evaluated with the goal of improving standard of care therapy or ameliorating the cellular abnormalities associated with specific GSDs. The receptor-mediated uptake of the therapeutic enzyme in Pompe disease was enhanced by administration of β2 agonists. Rapamycin reduced the liver fibrosis observed in GSD III. Further development of gene therapy could provide curative therapy for patients with GSD, if efficacy from preclinical research is observed in future clinical trials and these treatments become clinically available.

Keywords

glycogen storage disease; adeno-associated virus (AAV); Pompe disease; von Gierke disease

Introduction

Glycogen storage disease (GSD) is caused by the inherited deficiency of an enzyme involved in either the degradation or synthesis of glycogen. More than 10 such conditions have been characterized, and the features of the well characterized GSDs are listed in the Table [1]. Typically a GSD involves primarily liver, striated muscle, or both tissues. Liver GSDs, including type I, III, IV, VI, and IX, usually cause hepatomegaly and hypoglycemia during fasting, while muscle GSDs cause exercise intolerance, cramping, progressive

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weakness with variable heart involvement in the form of cardiomyopathy (Table). With the exception of GSD II (Pompe disease), for which an enzyme replacement therapy (ERT) has been developed, therapy is limited to dietary modification or organ transplantation [1]. Therefore, new therapies are under development to address the unmet need for treatment in the GSDs.

Experiments with gene therapy have demonstrated proof-of-concept in several GSDs in animal models. Animal models that mimic human GSDs have been described, and confirmed by biochemical and genetic evaluations (Table). These models have been used to develop gene therapy for GSD I, II, and V. The goal of gene therapy for a GSD has been to stably replace the pertinent enzyme in the affected tissues. All of the major classes of vectors have been employed to deliver a therapeutic transgene in a GSD (Table), including adeno-associated virus (AAV), adenovirus (Ad), retroviral in the form of lentiviral (LV), and non-viral plasmid vectors. The features of each of these vector systems have been summarized [2], and relevant characteristics are presented below in the context of preclinical studies in the animal models for each GSD.

Potential for clinical development of gene therapy in Pompe disease

The deficiency of acid α-glucosidase (GAA) causes Pompe disease. Pompe disease stands out among lysosomal storage disorders due to the lack of devastating central nervous system involvement, rendering it much more amenable to treatment even later in life. GAA normally functions as an acid hydrolase that metabolizes lysosomal glycogen, and GAA deficiency causes lysosomal glycogen accumulation in virtually all tissues [3]. However, Pompe disease affects the heart and skeletal muscle primarily, and untreated infants with Pompe disease develop profound weakness and hypotonia. Infantile-onset Pompe disease causes death early in childhood from cardiorespiratory failure related to an underlying hypertrophic cardiomyopathy, if enzyme replacement therapy (ERT) is delayed or the patient fails to respond sustainably to ERT [4, 5]. Late-onset Pompe disease features progressive weakness without significant cardiomyopathy, and patients typically survive until late adulthood.

Pompe disease was demonstrated in Lapphund dogs with megaesophagus, exercise intolerance, and recurrent emesis [6]. Glycogen accumulations consisting of membrane bound vacuoles were present in the heart, skeletal, and smooth muscle. The genetic basis was a c.2237G>A change corresponding to the nonsense mutation p.W746* in the acid α-glucosidase gene [7].

Need for immune tolerance to GAA in Pompe disease

ERT with GAA, like other lysosomal enzymes, depends upon mannose-6-phophate receptor mediated uptake in affected tissues [8]. The availability of ERT with recombinant human (rh) GAA has prolonged survival and ameliorates cardiomyopathy of infantile Pompe disease [9]. Documented limitations of ERT in Pompe disease include the requirement for frequent intravenous infusions of high levels of GAA to achieve efficacy, degree of pre-ERT muscle damage, and the possibility of humoral immunity [10]. The rhGAA doses are markedly higher than doses required for ERT in other lysosomal storage disorders, reflecting

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the high threshold for correction of GAA deficiency in the skeletal muscle of Pompe disease patients [11].

ERT has prolonged survival in the majority of patients with infantile Pompe disease, although many patients die or remain very weak despite compliance with ERT. Pompe disease patients who lack any residual GAA protein are deemed cross-reacting immune material negative (CRIM-negative). Among the poor responders, were many CRIM-negative patients who formed high, sustained anti-rhGAA antibody titers (HSAT). Patients with HSAT demonstrated greatly increased mortality, in comparison with patients who formed no or only low titer antibodies [12]. In the first pilot study of ERT in Pompe disease using Chinese hamster ovary cell-derived rhGAA, the two patients who were CRIM-negative produced higher titers of anti-rhGAA antibodies than the third patient who was CRIM-positive. This corresponded with a markedly reduced efficacy of the treatment in the CRIM-negative patients [8]. Furthermore, the ability to prevent antibody formation in patients at risk for HSAT with immunosuppression, which significantly prolonged survival, confirmed the clinical relevance of HSAT [13]. The relevance of antibody formation to efficacy of therapy in Pompe disease has been emphasized by the poor response of CRIM-negative patients to ERT, which correlated with the onset of HSAT [10, 12].

Gene therapy has been developed as an alternative approach to therapy in Pompe disease, which can also prevent immune responses to GAA [14]. The availability of novel AAV serotypes with increased tropism for target tissues has markedly advanced the field of gene therapy in the past 12 years [15, 16]. AAV vectors provide an optimized gene delivery vehicle, because AAV is a non-pathogenic virus and vectors derived from AAV contain no viral genes. Furthermore, vectors packaged with the novel AAV serotypes elicit a lower immune response than the original AAV2 capsid [17]. AAV serotype 8 has been developed to pseudotype AAV2 vector genomes as AAV2/8 vectors, which feature an extremely high tropism for liver [15]. AAV2/8 vectors transduce liver with higher efficiency due to rapid uncoating and delivery of the genome to the transduced cells' nuclei [18], and the entire liver can be transduced from an intravenous injection of an AAV2/8 vector [19]. Consequently, AAV2/8 vectors have been developed in preclinical models to effectively treat inherited metabolic diseases, such as Pompe disease. Importantly, AAV vectors have a favorable safety profile for clinical applications [16].

Multiple studies with AAV vectors encoding GAA have previously treated GAA-KO mice successfully [20–24]. However, antibody formation remains a major obstacle for GAA gene transfer approaches in which constitutive – vs. tissue-specific – expression of the therapeutic transgene is utilized to achieve disease correction [21, 22, 25]. A highly active muscle-specific regulatory cassette achieved wide-spread correction of GAA deficiency in striated muscles, and reduced accumulated glycogen in those muscles. However, AAV vectors containing muscle specific regulatory cassettes have required high numbers of vector particles (vp) to achieve biochemical correction, $>4\times10^{13}$ vp/body weight [26]. Furthermore, muscle-specific expression provoked anti-GAA antibodies with negative effects upon efficacy [27]. Recently, a new approach to immune suppression was shown to prevent anti-body formation in response to an immunogenic AAV vector. This strategy used coreceptor blockade with a non-depleting anti-C44 monoclonal antibody to block activation of helper T

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cells, which successfully prevented antibody formation and improved the efficacy from gene therapy [28].

Pompe disease can be effectively treated by converting the liver to a depot for secretion of GAA, accompanied by uptake of GAA in the heart and skeletal muscle [29, 30]. This concept was further developed with an AAV2/8 vector containing a liver-specific regulatory cassette to drive high-level GAA secretion from the liver [22]. This vector induced immune tolerance to prevent the anti-GAA antibody response in adult, immunocompetent *GAA* (−/−) mice. Preventing antibody formation in patients at risk for HSAT via immunosuppression has been demonstrated to significantly prolong survival [13]. AAV2/8-LSPhGAApA expressed hGAA exclusively in the liver and activated regulatory T (Treg) cells thereby preventing antibody formation [27]. Adaptive transfer of CD4+ T cells further confirmed the role of Tregs in achieving immune tolerance to GAA [31]. Immune tolerance to GAA from AAV2/8-LSPhGAApA might improve the response to ERT in patients at risk of HSAT [32], and in the long-term, at high enough doses, may even provide a curative therapy for Pompe disease. An intriguing variation on this theme was demonstrated by combining two vectors, one containing the liver-specific and one containing the constitutively active regulatory cassette, which suppressed antibody formation and achieved widespread correction of GAA deficiency [33]. AAV2/8-LSPhGAApA has undergone formal pharmacology-toxicology evaluation, and this vector was found to be safe and effective in the mouse model for Pompe disease [34].

Alternatively, an ex vivo approach to gene therapy was developed with, a lentiviral vector encoding human GAA that transduced cultured hematopoietic stem cells (HSCs), which were subsequently transplanted into a Pompe disease mouse model [35]. After mild conditioning to allow engraftment, transplantation of genetically engineered HSCs resulted in stable chimerism of approximately 35% hematopoietic cells that overexpressed acid alpha-glucosidase and in major clearance of glycogen in the heart, diaphragm, spleen, and liver. Despite the need for chemotherapy to deplete the patient's own HSCs that entails some toxicity, this approach to gene therapy was efficacious and presumably induced immune tolerance to introduced GAA.

Potential for AAV vector-mediated gene therapy to reverse neuromuscular involvement

Neuromuscular involvement remains an important aspect of Pompe disease. For instance, although ERT has prolonged survival and prevented the need for invasive ventilation in patients with infantile Pompe disease [9], neuromuscular involvement has been documented in children treated with ERT [36, 37]. The main goal of immunomodulatory gene therapy is to improve upon ERT by inducing immune tolerance to GAA, and by continuous secretion of GAA accompanied by receptor-mediated uptake in the heart, skeletal muscle, and other affected tissues. One strategy that has had an effect upon neuromuscular involvement consists of up-regulating the cation-independent mannose-6-phosphate receptor (CI-MPR). CI-MPR mediates the uptake of GAA and the trafficking of GAA to the lysosomes. The addition of a β2 agonist to increase CI-MPR expression during ERT increased the clearance of accumulated glycogen from skeletal muscles and the brain, and improved muscle function, in comparison with ERT alone [38, 39]. Similarly, adjunctive β2 agonist treatment

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following low dose AAV2/8-LSPhGAApA reduced the accumulated glycogen in muscle and the brain, and improved muscle function, in comparison with vector alone [40]. Furthermore, clenbuterol by itself was sufficient to significantly reduced muscle glycogen content in mice with Pompe disease through a mechanism independent of CI-MPR [41]. Finally, a pilot study of adjunctive albuterol with ERT in patients with Pompe disease increased 6MWT distance, and was well-tolerated [42]. If adjunctive therapy with β2 agonists proves to be safe and efficacious in on-going clinical trials, it will be available to enhance the efficacy of gene therapy in the future.

Clinical trial of gene therapy in Pompe disease

Gene therapy for Pompe disease has been evaluated in a clinical trial with an AAV2/1 vector encoding human GAA [43]. Direct injection of the vector into the diaphragm was evaluated in 5 pediatric patients with respiratory failure. No toxicity or T cell responses against the vector were detected, although antibody responses to both the AAV capsid proteins and to GAA were observed (the latter in a single participant). Modest improvements in volitional ventilatory performance measures were suggested. While invasive, this approach to gene therapy did target a muscle highly relevant to respiratory failure and further patient enrollment was proposed.

Alternative treatment approaches for Pompe disease

A novel approach in the form of substrate reduction therapy (by inhibiting glycogen synthesis) has been proposed as a potential adjuvant therapy for Pompe disease [44]. A phosphorodiamidate morpholino oligonucleotide (PMO) designed to invoke exon skipping and premature stop codon usage in the transcript for muscle specific glycogen synthase (Gys1) was conjugated to a cell penetrating peptide (GS-PPMO) to facilitate PMO delivery to muscle. GS-PPMO systemic administration to Pompe mice reduced glycogen synthase expression in the quadriceps, and the diaphragm, and to a lesser extent in the heart, but not the liver. These reductions correlated with significant decreases in lysosomal glycogen in the quadriceps, diaphragm, and heart of mice with Pompe disease. The lack of toxicity detected indicated that substrate reduction by GS-PPMO-mediated inhibition of muscle specific glycogen synthase might be useful in Pompe disease, and in other glycogen storage diseases involving muscle.

Progress and Challenges for Gene Therapy in GSD I

Liver and kidney involvement predominant in GSD Ia, which results from the deficiency of the catalytic subunit of glucose-6-phophosphatase-α (G6Pase) due to mutations in *G6PC* [45]. The importance of early diagnosis and treatment of GSD Ia is emphasized by the severe complications of untreated GSD Ia, including life threatening hypoglycemia, severe lactic acidosis, growth failure, renal Fanconi syndrome, and pancreatitis [1]. The acute complications of GSD Ia have responded favorably to dietary therapy that prevents hypoglycemia, including renal tubular dysfunction and growth failure, even though dietary therapy has significant limitations [46]. Long-term complications of GSD Ia frequently fail to respond to dietary therapy, including growth retardation, proteinuria occasionally progressing to renal failure, osteopenia, formation of hepatic adenomas and hepatocellular

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carcinoma, and rarely pancreatitis or pulmonary hypertension [47]. Dietary therapy consists of ingesting uncooked cornstarch at regular intervals around-the-clock, and requires constant vigilance to avoid acute metabolic decompensation accompanied by life-threatening hypoglycemia and lactic acidosis [48].

GSD Ia was reported in Maltese terriers that grew poorly in association with hypoglycemia, hepatomegaly, and nephromegaly [49]. Liver and kidney histology revealed glycogen storage, and G6Pase activity was reduced to nearly undetectable levels, confirming a diagnosis of GSD Ia. The genetic basis was a M121I missense mutation in the gene encoding G6PC [50].

Liver correction has efficacy in GSD Ia

The severe complications stemming from liver involvement in GSD Ia suggest that correction of hepatic abnormalities should be a primary goal for gene therapy [51]. As individuals with GSD Ia survive longer, complications such as increased size and number of liver adenomas and development of hepatocellular carcinoma have been observed [52]. Liver transplantation has been performed in patients with type I disease because multiple liver adenomas bear the risk of malignant transformation and/or inducing poor metabolic control. Hypoglycemia and other biochemical abnormalities were corrected after transplantation and height increased [53], confirming the efficacy of restoring G6Pase expression in the liver in GSD Ia. Glycogen breakdown was associated with increased glycolytic enzymes including glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in *G6Pase* (–/–) mouse liver [54]. GAPDH has been associated with non-enzymatic moonlighting activities including the induction of apoptosis [55], and apoptosis was increased in *G6pase* (–/–) mouse liver [54]. Hepatocellular abnormalities including increased apoptosis represent a challenge for liver-directed gene therapy in GSD Ia.

AAV vectors containing a G6Pase regulatory cassette / promoter have corrected G6Pase deficiency in the liver of animal models of GSD Ia, and these vectors contain sequence elements that regulate G6Pase expression appropriately [56, 57]. A double-stranded AAV2/8 vector containing a human G6Pase mini-gene demonstrated early efficacy in *G6pase* (–/–) mice and dogs with GSD Ia [57]. A single-stranded AAV vector containing a larger human G6Pase regulatory cassette also featured high efficacy in *G6pase* (–/–) mice, and the longer regulatory sequence featured greater activity than the G6Pase minimal promoter [58]. Other vectors that have been evaluated in the *G6pase* (–/–) mouse model have included helper-dependent adenovirus (Ad) vector encoding canine G6Pase [59, 60] and a lentiviral (LV) feline immunodeficiency virus vector encoding murine G6Pase that rescued neonatal *G6pase* (–/–) mice [61]. While both the Ad and LV vectors prolonged survival and prevented hypoglycemia in the majority of treated mice, each remains limited by significant concerns related to potential toxicity. Finally, complications of GSD Ib, caused by glucose-6-phosphate transporter deficiency, were incompletely reversed in experiments with an AAV vector, and longer-term surviving mice developed hepatocellular carcinoma related to inadequate correction [62].

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Efficacy from gene therapy gradually waned in GSD Ia

AAV vector-mediated gene therapy has effectively treated GSD Ia, due to relative long-term stability of episomal vector genomes in hepatocytes [56, 57, 63, 64]. Chromosomal integration of AAV vector genomes occurs very infrequently, and consequently AAV vector genomes are gradually lost from dividing cells [65, 66]. Gradual loss of AAV vector genomes requires the eventual readministration of AAV to maintain transgene expression in the liver. However, anti-AAV antibody formation dictates that any subsequent re-administration would require delivery by a new AAV serotype [67, 68]. Re-administration will be facilitated by the fact that a number of AAV serotypes are available, several of which transduce the liver with high efficiency. Several of these serotypes have reproducibly transduced the liver in both murine and canine GSD Ia, including AAV2/8 and AAV2/9 [57, 69].

The ability to re-administer AAV vectors will be limited by the number of AAV serotypes available for clinical use. The limited ability to re-administer an AAV vector of a particular serotype is a significant hurdle given studies that demonstrated transient expression from AAV vectors in the GSD Ia liver [64, 69, 70]. Mortality from uncorrected GSD Ia has required early treatment; however, AAV vector administration to young mice accomplished a high level of liver transduction followed by declining numbers of vector genomes over the ensuing months [56, 71]. For example, an AAV2/8 vector decreased from >2 copies per liver cell at 3 weeks of age to 0.3 copies per liver cell at 26 weeks of age in *G6pase* (−/−) mice [56]. Similarly, an AAV2/8 vector was administered to a GSD Ia puppy at one day of age, and prevented hypoglycemia for three hours at one month of age; however, by two months of age the dog became hypoglycemic after one hour of fasting [70]. Chou and colleagues also highlighted the transience of AAV vector-mediated expression by measuring a 12-fold decline in G6Pase expression in mice from age 2 to 6 weeks [72]. A later study revealed that hypoglycemia during fasting was corrected for >18 months, but G6Pase activity in the liver declined by >90% between ages 6 and 18 months [73]. The gradual loss of efficacy from AAV vectors underlies the failure to completely reverse growth failure associated with GSD Ia in animal models [74]. These studies showed that AAV vector genomes are gradually lost over the weeks following vector administration to young animals with GSD Ia, which presents a hurdle to gene therapy for genetic diseases in general. Very recently an integrating lentiviral vector prevented the formation of hepatocellular carcinoma in mice with a liver-specific knockout of G6Pase, as well as reversing biochemical abnormalities of GSDIa, indicating that an integrating vector might have unique advantages in this disorder [75].

Potential for Gene Therapy in Other GSDs

GSD III

Mutations in the AGL gene causes genetic deficiency of glycogen debranching enzyme (GDE), resulting in accumulation of non-membrane glycogen with short outer chains in liver and muscle. Most patients have involvement of both liver and muscle (type IIIa), although some patients (~15%) have only liver involvement (type IIIb) [76]. Liver symptoms occur early in childhood; liver cirrhosis and hepatocellular carcinoma (HCC) have been reported

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in some cases [77–79]. Progressive skeletal myopathy and cardiomyopathy are a major cause of morbidity in adults. Muscle weakness is present during childhood and becomes more predominant in the third or fourth decade of life. Sudden death caused by cardiac arrhythmias or cardiac failure has been reported [76, 80–82]. Currently there is no effective treatment for the disease. Dietary interventions include control of hypoglycemia by frequent meals high in carbohydrates with cornstarch supplements or nocturnal gastric drip feedings. High protein diet is recommended for patients with myopathy [76, 83, 84]. A case report showed that a combined treatment of synthetic ketone bodies, in conjunction with a ketogenic and high-protein diet, improved cardiomyopathy in a patient with GSD III [85]. A recent study indicated that a high-fat, high-protein, and low-carbohydrate diet could be a beneficial therapeutic choice for GSD III with cardiomyopathy [86].

Animal models of GSD III

GSD III was characterized in curly coated retrievers that presented with exercise intolerance and lethargy at >12 months of age [87]. Liver transaminases, alkaline phosphatase and creatine kinase were elevated in serum by 6 months of age. Accumulations of non-membrane bound glycogen with short outer chains of α1,4-linked glucose in liver and skeletal muscle were accompanied by absence of glycogen debranching enzyme. A deletion of an adenine in exon 32 of the canine *AGL* gene predicted a truncation of the debranching enzyme by 126 amino acid residues [87]. Furthermore, progressive age-related liver fibrosis leading to cirrhosis was described in the CCR up to 16 months of age [88], which mimicked liver involvement in the human disorder [89]. Skeletal muscle damage caused by progressive accumulation of glycogen was observed in the affected dogs after age of 12 months [88]. Taken together, the curly coated retriever dogs represent an accurate model of GSD IIIa for improving our understanding of the disease progression and developing therapy.

Two *Agl* knockout mouse models were reported recently by two different groups. The first model was generated by Liu *et al* [90] by removing the exons after exon 5 in the *Agl* gene. The GDE expression was undetectable in the liver, muscle, and heart of the homozygous affected mice, which was accompanied by massive glycogen accumulation in these tissues. Reduced motor activity and muscle weakness were observed after one year of age; hepatomegaly and progressive liver fibrosis were found in the affected mice. Hypoglycemia appeared only at a young age (3 weeks) but no hyperlipidemia was observed in this model [90]. More recently, a second GSD III mouse model was generated by deletion of the carboxyl end of the glucosidase domain and the glycogen-binding domain of the GDE protein [91]. In addition to the presentation of increased glycogen accumulation in the liver, skeletal and cardiac muscles, and brain, the affected mice showed a more severe phenotype than that of the first model by Liu et al., including the decreased survival rate and appearance of muscle weakness and exercise intolerance at young age [91]. In conclusion, both mouse models represent human GSD IIIa and will be useful for therapy development for GSD III.

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Challenges for gene therapy in GSD III

The human *AGL* gene is 85 kb in length and composed of 35 exons, encoding a 7.4-kb mRNA that includes a 4596-bp coding region and a 2371-bp 3′ untranslated sequence to express a 175 kDa GDE protein [92]. Thus, a minimum size of 5 kb GDE expression cassette (promoter + GDE coding sequence + polyA signal) needs to be packaged into a gene therapy vector for in vivo gene delivery. This >5 kb insert size exceeds the 4.7 kb AAV vector packaging limit [93] and would result in significant reduction in viral vector titer if packaged into lentiviral vectors [94]. Although the 36 kb genome of adenoviral vectors provides sufficient space for inserting large sequences, severe toxicity and strong immune responses induced by the viral vectors after systemic administration limit its application for treatment of patients with genetic diseases like GSD III [2]. Non-viral or DNA-based vectors offer no-size-limit advantage and are efficient systems for *in vitro* and *ex vivo* gene delivery, but there has been little success in achieving efficacious and safe *in vivo* gene transfer [2].

An AAV-based gene therapy approach that could be useful for GSD III is the hybrid-dual AAV (HD-AAV) system that was developed to expand AAV packaging capacity by splitting a large therapeutic gene into two independent vectors. High-level gene expression was achieved in mouse muscles upon systemic co-administration of the two vectors through the mechanisms of trans-splicing and homologous recombination (overlapping) [95, 96].

Alternative treatment approaches for GSD III

Enzyme replacement therapy (ERT) with GDE will not be effective for treatment of GSD III due to the lack of receptor-mediated enzyme uptake by the affected tissues. Recently we reported that recombinant human acid-alpha glucosidase (rhGAA, Alglucosidase alfa), an FDA approved therapy for Pompe disease, significantly reduced glycogen levels in primary muscles from patients with GSD IIIa [97]. Further study is needed to test the treatment efficacy of rhGAA in animal models of GSD III.

In another study daily administration of rapamycin, a specific inhibitor of mTOR, significantly reduced glycogen content in the liver and muscle, and effectively prevented liver fibrosis and muscle damage in the GSD IIIa dogs [98]. These data suggest that use of small molecule drugs like rapamycin to inhibit glycogen synthesis could be as an alternative approach for treatment of GSD III.

GSD IV

Mutations in the glycogen branching enzyme gene (GBE1) cause GSD IV which is characterized by the accumulation of amylopectin-like, poorly soluble polysaccharide deposits (polyglucosan bodies, PB) in multiple tissues including liver, skeletal and cardiac muscles, and the central nervous system (CNS). The typical presentation of hepatic form of GSD IV includes hepatomegaly and progressive liver cirrhosis that lead to death in early childhood. Four neuromuscular forms have been identified based on the age of disease onset and disease severity: perinatal form, congenital form, juvenile form, and adult form [76, 99]. Liver transplantation is the only treatment option for patients with liver cirrhosis. There are no other effective therapies available for this disease.

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Animal models of GSD IV

GSD IV was described in Norwegian forest cats presented with early demise, although surviving cats appeared normal until the onset of progressive neurological decline at 5 months of age [100]. Affected kittens developed hypoglycemia, and glucose administration in the neonatal period promoted the survival of affected kittens to adulthood. Glycogen accumulations in skeletal muscle and neurons prompted the analysis of glycogen branching activity in skeletal muscle, which was severely deficient. An underlying mutation in the *GBE1* gene was delineated, consisting of a 6.2 kb deletion and 332 bp insertion that altered splicing of the mRNA and decreased glycogen branching enzyme in liver and muscle [100].

The first GSD IV mouse model that recapitulated the clinical features of the severe fetal neuromuscular form of GSD-IV was reported by Lee et al [101]. The homozygous affected mice carry a stop codon mutation (E609X) in the *GBE1* gene resulted in GBE ablation that led to poor ventricular function in late gestation, and ultimately caused heart failure, fetal hydrops and embryonic lethality [101]. Soon after this report, Akman et al [102] reported another two mouse models of GSD IV. Homozygous deletion of exon 7 of the *Gbe1* gene in the $Gbe1^{-/-}$ mice completely eliminated GBE activity in tissues, leading to significant *in utero* PB accumulation and death at birth [102]. In contrast, the mice homozygous for the insertion of a phosphoglycerate kinase-Neomycin cassette within intron 7 of the *Gbe1* gene ($Gbe1^{neo/neo}$) exhibit a phenotype similar to juvenile neuromuscular form GSD IV, with reduced GBE enzyme activity and accumulation of PG in the liver, skeletal muscle, heart, and brain. The $Gbe1^{neo/neo}$ mice died between 3 to 9 months of age [102].

Therapeutic approaches for GSD IV

The formation of PB is the hallmark of GSD IV. The critical determinant of PB formation is an increase in the ratio of glycogen synthase (GS) to GBE, which leads to uncontrolled elongation of α-1,4-glycosidic glycogen chains without adequate α-1,6-glycosidic branching activity [103–105]. Thus, restoration of GBE activity or inhibition of GS expression will be two potential treatment approaches for correction of the abnormal GS/GBE ratio and prevention of PB formation in GSD IV. Increased expression of GBE could be achieved by traditional gene therapy approach by delivery of a GBE expression cassette. The 2.1-kb coding sequence of human *GBE1* gene could be easily packaged into an AAV vector. Widespread GBE expression could be achieved by systemic administration of an AAV2/9 vector, the most efficient AAV serotype for whole-body gene transfer, into GSD IV mice or cats, to test the treatment efficacy [102, 106–109]. Kakhlon et al demonstrated that inactivation of GS by rapamycin prevented PB formation in GBE-knocked down neurons derived from E18 rats [110]. Other approaches, such as antisense oligonucleotides, AAV-mediated shRNA, or screening of small molecule drugs, should be considered for inhibition of GS expression and prevent of PB formation in GSD IV. It should be noted that both treatment approaches, by increasing GBE expression and by inhibiting GS activity, are preventive therapies that require starting treatment at young age to achieve best outcomes. To clear the existing PB in the affected tissues at advanced stage of GSD IV disease, a glycogen-degrading enzyme will be needed.

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GSD V

GSD V, also known as McArdle disease, is frequently detected in the second to third decade of life by exercise intolerance with muscle cramping accompanied by elevated serum creatine kinase [1]. This is due to a mutation in the muscle phosphorylase gene (*PYGM*) most commonly associated with a change from an arginine to a stop codon in exon 1 (p.R50X) [111]. There is no effective treatment for this disease, but many patients are able to perform moderate, sustained exercise on a carbohydrate-rich diet with carbohydrate ingestion shortly before exercise [112].

Animal models of GSD V

There are currently 3 known GSD V animal models. The first was discovered in Charlois cattle with a C to T substitution in codon 489 leading to an arginine to tryptophan substitution in the myophosphorylase gene [113]. Affected cattle display signs of rhabdomyolysis including exercise intolerance and myoglobinuria [114]. A second large animal GSD V model was discovered in a flock of Merino sheep exhibiting exercise intolerance [115]. Affected sheep have a splice site mutation at the 3′ end of intron 19 of the myophosphorylase gene leading to disruption in the reading frame and premature truncation of the myophosphorylase protein. Upon biopsy, an increase of muscle glycogen and absence of muscle glycogen phosphorylase was discovered [115]. A mouse model was recently created using a knock-in for the common human mutation, p.*R50X* in the *PYGM* gene encoding for myophosphorylase. This mouse model demonstrates many features of GSD V including elevated creatine kinase serum concentrations, increased muscle glycogen, absence of myophosphorylase protein and activity in muscles and poor exercise performance [116].

Therapeutic approaches for GSD V

To date, only the ovine GSD V model has been used to test novel therapeutics using gene therapy and pharmaceuticals. Adenovirus 5 (Ad5) and AAV vectors expressing myophosphorylase were both used with some efficacy in sheep with GSD V. Different promoters were also utilized, namely, an Ad5 vector was evaluated containing either Rous Sarcoma virus (RSV) or Cytomegalovirus (CMV) promoters, and an AAV vector was evaluated containing a CMV promoter. All three vectors effectively transduced sheep muscle when injected intramuscularly in young sheep, but the Ad5 vector containing the CMV promoter featured the greatest sustained transduction. However, myophosphorylase activity waned over time in all cases (Howell et al 2008). The same study also demonstrated that damage to muscle fibers caused by injection with vectors, including a positive control vector expressing LacZ that caused re-expression of non-muscle isoforms of glycogen phosphorylase. Further studies have been performed using pharmaceuticals such as valproate and notexin to cause similar muscle damage and thus re-expression of non-muscle isoforms of myophosphorylase in the GSD V ovine model [117, 118].

GSD VII

GSD VII is inherited as an autosomal recessive trait characterized by a deficiency of the muscle isoenzyme of phosphofructokinase (PFKM). There are several mutations in the

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PFKM gene found on chromosome 12 that have been described to cause this disease in patients, but there have been no specific genotype-phenotype correlations found to date [119]. The typical clinical presentation of the classic form of GSD VII consists of muscle cramps, exercise intolerance, myoglobinuria, hyperuricemia and hemolytic anemia. The anemia occurs because erythrocytes express both PFKM and the liver isoenzyme of PFK (PFKL); PFKL accounts for about 50% of normal PFK activity in erythrocytes [1]. Other presentations of GSD VII include a severe infantile form leading to early death in childhood, a late onset form and a hemolytic form that lacks muscle symptoms [119]. There is no specific treatments for this disease, and therapy remains mainly palliative,

Animal models of GSD VII

An animal model for GSD VII was reported as an autosomal recessive trait demonstrated in three families of English Springer spaniels that had hemolytic crises and rhabdomyolysis during exercise in association with PFKM deficiency [120, 121]. The mutation in the *PFKM* gene was demonstrated as a nonsense mutation that caused premature termination [122]. Other dog breeds have been reported to have the same mutation including American Cocker spaniels and whippets. [123, 124]. More recently, PFK deficiency was described in Wachtelhunds exhibiting exercise intolerance, hemolytic anemia and pigmenturia, but apparently is not caused by the same mutation as that seen in other breeds [125]. These large animal models of PFK deficiency provide an opportunity to develop muscle-directed gene therapy for GSD VII, but have not been used in any specific therapeutic studies.

Two mouse models have been reported with PFKM deficiency, the first was developed by lexicon laboratories and has demonstrated an impairment in insulin secretion and decrease in fat stores [126] [127]. The second model is a *Pfkm*(−/−) and displays a severe cardiac and hematologic disorder accompanied by skeletal muscle symptoms similar to PFK human patients [128]. Neither has been developed for gene therapy models to the authors' knowledge.

Therapeutic approaches for GSD VII

Based on findings by Bruser et al 2012, pharmacologic agents that block the inhibitory allosteric binding site of muscle 6-phosphofructokinase to ADP may be therapeutic, but have yet to be tested in animal models [129].

Conclusion

Gene therapy can be efficacious in GSD, if the transgene stably expresses sufficient quantities of the therapeutic enzyme in involved tissues. Small molecule therapies show promise as both palliative and adjunctive therapies for specific GSDs. The development of new therapies will benefit affected human patients, if pharmacology-toxicology studies and clinical trials replicate these proof-of-principle experiments.

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Table 1

Features of the Classical Glycogen Storage Diseases

Type/Eponym	Enzyme Deficiency	Presenting Clinical Features	Primary Tissue Involvement	Animal Model	Vector Administered
I/von Gierke	Glucose-6-phosphatase	Growth retardation, hepatomegaly, hypoglycemia, lactic acidemia, hyperuricemia, and hyperlipidemia	Liver, kidney	Maltese dog, mouse	AAV, Ad, LV, plasmid
II/Pompe	Acid alpha-glucosidase	Cardiomyopathy, myopathy, respiratory failure	Heart, skeletal muscle, nerves	Lapphund dog, mouse	AAV, Ad, LV
III/Cori, Forbes	Debrancher	hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation	Liver, heart, skeletal muscles	Curly coated retriever dog, mouse	None
IV/Anderson	Branching	Hepatosplenomegaly, failure to thrive	Liver, heart, nerves	Norwegian forest cat, mouse	None
V/McArdle	Muscle phosphorylase	Exercise intolerance, muscle cramps	Skeletal muscle	Charlois cattle, sheep, mouse	AAV, Ad
VII/Tarui	Phosphofructokinase	Exercise intolerance, muscle cramps, hemolytic anemia	Skeletal muscle, erythrocytes	English Springer spaniel dog, mouse	None