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REVIEW ARTICLE

Replacement Therapies in Metabolic Disease

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Abstract: ***Background***: Replacement therapies have revolutionized treatment paradigms in metabolic diseases by restoring defective enzymes and supplementing missing downstream metabolites. Through most of the 20th century, no targeted therapies existed for these conditions, the only treatment options available focusing on symptoms rather than the underlying disorders. Improved understanding of the molecular pathways underlying metabolic disease has allowed not only supplementation of missing metabolites and reduction of upstream substrates, but replacement of defective or missing enzymes.

Objective: Modern genetic technologies have facilitated steady progress in recombinant enzyme innovation, providing treatments that replicate not only endogenous enzymes, but also their post-translational modifications to optimize their delivery and function. The advent of the gene therapy revolution brings a possibility of new therapeutic opportunities in which the enzymes at the core of metabolic diseases may not only be added back, but genetically replaced.

Conclusion: With the next generation of treatments approaching, this review examines the recent decades of replacement therapy innovation in metabolic disease and discusses the challenges and opportunities for the next generation of treatments.

Keywords: Rare diseases, metabolic disease, lysosomal storage disorder, gene therapy, recombinant enzymes, enzyme replacement therapy.

1. INTRODUCTION

Many metabolic disorders are driven by genetic mutations that cause deficiencies in key metabolic enzymes. In contrast to the use of pharmacologic approaches that seek designer molecules as solutions to treat a wide array of disease states, some metabolic disorders can be treated by simply replacing what nature would normally provide. A missing or defective enzyme might be treated with a recombinant wild-type copy of the protein [1], or an interrupted metabolic pathway might be addressed *via* supplementation of the missing downstream metabolite paired with avoidance of the molecule that accumulates upstream (*e.g.*, Fig. **1**).

This review explores the advances over recent decades in enzyme replacement therapy (ERT) for metabolic diseases, contrasting these examples against similar diseases that remain untreated as well as metabolic diseases that are treated with dietary management of the biomolecules of which metabolism is affected. We also discuss briefly the future therapeutic possibilities for these diseases that could result from modern genetic solutions.

2. ENZYME REPLACEMENT THERAPY IN LYSOSOMAL STORAGE DISORDERS

Lysosomal storage disorders (LSDs) are a family of metabolic disorders that result from genetic mutations to enzymes that support lysosomal processes, leading to defective enzymatic function and harmful accumulation of the biomolecules that they fail to metabolize. Individual LSDs are somewhat rare, but collectively, LSDs are somewhat prevalent and result in diverse clinical outcomes [1]. Over the past half-century, the discovery of molecular processes underlying many LSDs and identification of the cellular mechanisms facilitating the uptake of exogenous enzymes have provided a foundation for the development of the first ERTs for metabolic diseases [2]. A handful of the nearly 50

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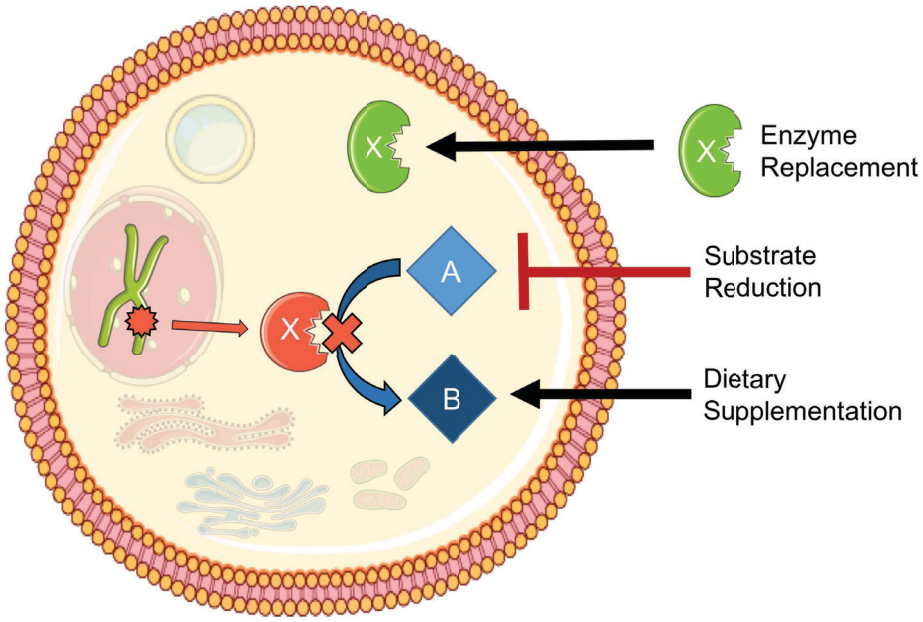

Fig. (1). Genetic mutations creating defective enzymes (X) can cause severe metabolic diseases as biomolecules are not metabolized appropriately. Enzyme replacement therapies treat patients with an exogenous form of the defective enzyme to restore the missing enzymatic activity. Alternatively, substrate reduction therapies seek to prevent buildup of problematic biomolecules (A), while dietary supplementation augments the availability of missing downstream metabolites (B)".

lysosomal storage diseases now have FDA-approved ERT treatment options (Table **1**). We also discuss additional opportunities for future therapeutic development.

2.1. Gaucher Disease

Gaucher Disease (GD) is the most common LSD [3-5] and the first for which an ERT was licensed [2]. GD is characterized by a glucocerebrosidase deficiency [6-9] caused by any of a number of individual mutations [10, 11], leading to lysosomal accumulation of glucocerebroside in macrophages [12]. Patients suffer from a variety of hematologic [13], splenic [13, 14], skeletal [13, 15, 16], and other [17-20], symptoms; further classification is based on the presence or absence of neuropathic symptoms [21].

In the mid-1960s, treatment for GD was envisioned *via* "the replacing or supplementing of these deficiencies by exogenous administration of the respective enzymes" [22], and in a 1974 study, injections of isolated placental glucocerebrosidase were successful in decreasing glucocerebroside levels in the blood and liver of patients [23]. Subsequent research identified the importance of glycosylation to macrophage uptake [24-26] and glucocerebroside distribution [27], facilitating synthetic pharmacokinetic optimization of β-glucocerebrosidase glycosylation [28]. In a 1991 trial of 12 GD patients, ongoing replacement therapy with macrophage-targeted human placental glucocerebrosidase infusions every other week yielded hematologic, biochemical, and visceral improvements in disease state within six months [29]. Other clinical trials quickly corroborated the efficacy of this approach [30, 31].

Following designation as the first orphan drug in 1985 [32], macrophage-targeted glucocerebrosidase extracted from human placentae received FDA approval in 1991 and was produced by Genzyme as alglucerase (Ceredase®) [21], the first commercially available ERT [2]. However, this groundbreaking therapy was complicated by the logistical challenge of harvesting and processing millions of placentas for enzyme extraction and the risk of transmitting infection from placental tissue. The record-breaking cost of the resulting treatment [21] spurred an immediate discussion of cost-effective treatment regimens [33, 34] and a search for alternative means of enzyme production.

Soon after the introduction of alglucerase, Genzyme developed a recombinant alternative using a Chinese Hamster Ovary (CHO) cell production system and further modification of the glucocerebrosidase glycosylation pattern. The recombinant ERT was shown to be therapeutically similar and less prone to antibody response [35], and was brought to market as imiglucerase (Cerezyme®) following rapid FDA approval in 1994. Two biosimilars have since been brought to market. Velaglucerase alfa [36-38], marketed by Shire as VPRIV®, is produced in a human fibrosarcoma cell line and contains minor amino acid and glycosylation distinctions from imiglucerase [39], while taliglucerase alfa [40, 41], marketed by Protalix and Pfizer as Elelyso®, is produced in a carrot root cell expression system and avoids the need for post-production glycosidic modifications [42]. Research continues to understand better the benefits of the ERT options [43, 44] and optimal dosing strategies [45]. The early success of ERT in GD has also led to similar treatment approaches in other LSDs [2, 32, 46].

2.2. Fabry Disease

Fabry Disease (FD) is a rare [4, 5], recessive, X-linked lipidosis in which α-galactosidase A (α-gal A, also referred to as ceramide trihexosidase) deficiency creates an LSD [47].

Table 1. Enzyme replacement therapies for lysosomal storage disorders.

Disease	Enzyme Replacement Therapy	Method of Production	Manufacturer	Year of FDA Approval	Notes
Gaucher Disease	Alglucerase (Ceredase)	Human placental tissue	Genzyme	1991	Discontinued
Gaucher Disease	Imiglucerase (Cerezyme)	Chinese hamster ovary cells	Genzyme	1994	
Gaucher Disease	Velaglucerase alfa (VPRIV)	Human fibrosarcoma cells	Shire	2010	Biosimilar
Gaucher Disease	Taliglucerase Alfa (Elelyso)	Carrot root cells	Protalix and Pfizer	2012	Biosimilar
Fabry Disease	Agalsidase beta (Fabrazyme)	Chinese hamster ovary cells	Genzyme	2003	
Fabry Disease	Agalsidase alfa (Replagal)	Human HT-1080 fibro-sarcoma cells	Shire	Approved by EMA but not FDA	
Pompe Disease	Algucosidase alfa (Myozyme)	Chinese hamster ovary cells	Genzyme	2006	
Pompe Disease	Algucosidase alfa (Lumizyme)	Chinese hamster ovary cells	Genzyme	2014	Scaled-up version of Myozyme that re-quired separate FDA approval [116]
Lysosomal Acid Lipase Deficiency	Sebelipase alfa (Kanuma)	Chicken eggs	Alexion	2015	
MPS Type I (Hurler Syndrome)	Alpha-L-iduronidase (Aldurazyme)	Chinese hamster ovary cells	BioMarin and Genzyme	2003	Manufactured by BioMarin; marketed by Genzyme
MPS Type II (Hunter Syndrome)	Idursulfase (Elaprase)	Human cell line HT-1080	Shire	2006	
MPS Type IV (Mor-quio Syndrome)	Elosulfase Alfa (Vimizim)	Chinese hamster ovary cells	BioMarin	2014	
MPS Type VI (Ma-roteaux-Lamy Syn-drome)	Galsulfase (Naglazyme)	Chinese hamster ovary cells	BioMarin	2005	

The resulting accumulation of globotriaosylceramide and other glycosphingolipids, especially that in the cardiovascular system, leads to a broad range of clinical manifestations including angiokeratomas, pain crises, vascular occlusion, cardiomyopathy, renal failure, and ischemia and infarction in the brain, heart, and kidney [47-51].

The defective lipid metabolism underlying FD has been studied for over half a century [52, 53], and broad medical improvements have allowed treatment of individual symptoms such as pain, hypertension, renal failure, and valvular disease [47]. However, replacement of the deficient α-gal A enzyme is necessary to reverse the metabolic dysfunction underlying the disease. The concept of ERT to treat FD was piloted in a small clinical trial in 1970, achieving both enzymatic activity and reduction of the substrate *via* intravenous (IV) infusion of healthy plasma [54]. Subsequent clinical trials refined this ERT approach *via* IV administration of α-gal A purified from human placental tissue, [55] then a comparison of the performance of splenic versus plasma α-gal A isozymes that suggested the importance of posttranslational modifications [56].

Following placebo-controlled, double-blind clinical trials at Mount Sinai Hospital and the NIH [57], two α-gal A replacement therapies (agalsidase beta, marketed by Genzyme as Fabrazyme®, and agalsidase alfa, marketed by Shire as Replagal®) were approved for use in Europe, while only agalsidase beta has been approved for use in the USA. In the Mount Sinai study, the agalsidase beta preparation successfully cleared microvascular endothelial accumulation of globotriaosylceramide [58], while in the NIH study, the agalsidase alfa preparation met neuropathic pain and renal performance outcome measures [59]. Numerous subsequent studies have since compared the clinical results of the two treatments [60] using various endpoints [61-73], evaluated their dosing [74], pharmacokinetic/pharmacodynamics properties [75, 76], and studied FD progression [77, 78]. While

the different production methods of agalsidase alfa [79] and beta [80] render the two preparations biologically distinct, during an agalsidase beta shortage treatment was switched to agalsidase alfa without a change in disease stability [80].

2.3. Pompe Disease

Pompe Disease (PD), also known as glycogen storage disease type II or acid maltase deficiency, is a rare [4, 81, 82] LSD resulting from any of hundreds of individual mutations [83-91] that cause a deficiency of acid α-glucosidase (AAG), the enzyme [92, 93] responsible for the lysosomal metabolism of glycogen [94]. Widespread lysosomal glycogen storage results, and depending on the severity of AAG deficiency, presents during infancy in the fatal infantile form, or later in life in other forms, with a variety of muscular, respiratory, and cardiac deficits [95, 96].

The first attempts at ERT for PD were made in the 1960s; however, these efforts were unsuccessful until cell surface receptor-mediated uptake of AAG was better understood [97, 98] and the necessity of recognition markers clarified [99]. Cloning of the AAG gene allowed for production of recombinant human AAG [100] (rhAAG), scale-up of production [101], and further refinement of glycosylation patterns to optimize rhAAG for use in ERT [102, 103]. Early clinical trials using rhAAG produced in rabbit milk found mixed therapeutic outcomes, based largely on disease progression in the patient at the initiation of treatment [104-107]. Around the same time, a Phase I/II clinical trial using CHO-derived rhAAG showed improvement in cardiac and muscular function in infantile-onset PD patients [108], after which a subsequent cohort treated with CHO-derived rhAAG solidified these findings [109] and provided more thorough analysis of post-treatment pathology [110]. A larger dose-comparison study of 18 infantile-onset patients [111] led to FDA approval of recombinant human alglucosidase alfa (Myozyme®, marketed by Genzyme Corp) for infantile-onset PD, after which an extension of the study confirmed longer-term effects of survival, pulmonary performance, and improved cardiomyopathy following prolonged treatment [112].

Treatment of late-onset PD patients with rhAAG yielded improved mobility and pulmonary function [113], broadening the potential clinical application of Myozyme®. Industrial scale-up of rhAAG production to larger bioreactors initially encountered difficulties with the FDA based on biosimilarity issues [114], but received clearance from European regulators [115] and ultimately was also approved in the US for use in late-onset PD patients, marketed as Lumizyme®. The therapeutic importance of post-translational modification details in ERT is underscored by the fact that the FDA considers Myozyme® and Lumizyme®, two forms of rhAAG produced by the same company with separate manufacturing processes, to be biologically distinct drugs [116]. Lumizyme® approval has since been expanded by the FDA to include infantile-onset PD patients.

2.4. Lysosomal Acid Lipase Deficiency

Lysosomal acid lipase deficiency (LALD) is a rare, autosomal recessive LSD that results from mutations [117] to the *LIPA* gene encoding lysosomal acid lipase. The most severe *LIPA* mutations with minimal or no LAL activity cause Wolman disease [118, 119] (WD), while mutations leaving greater residual LAL activity cause a later-onset sub-type of LALD called cholesteryl ester storage disease (CESD) [120].

First identified as xanthomatosis with calcification of the adrenal gland [118, 119, 121], WD presents during infancy with acute gastrointestinal symptoms, growth failure, hepatosplenomegaly, and rapid liver failure, generally leading to death within six months of birth [122]. The less severe CESD typically presents during childhood with clinical manifestations including hepatomegaly, steatosis, and fibrosis; splenomegaly; elevated total serum cholesterol (including elevated LDL-cholesterol and low HDL-cholesterol); and a range of cardiovascular, hepatic, and gastro-intestinal problems [117].

In the early 1980s, purification of lysosomal LAL from human liver tissue [123] and confirmation of a mannose 6-phosphate-dependent cellular mechanism of LAL uptake [124] facilitated early *in vitro* replacement of LAL from enriched media into CESD fibroblasts [124, 125]. Further *in vitro* experiments conjugated LAL to insulin or apolipoprotein-B to demonstrate insulin receptor and apolipoprotein B receptor-mediated LAL uptake and cholesteryl ester clearance in CESD fibroblasts [126]. Cloning of the human LAL gene [127] enabled its recombinant expression. Treatment of an LAL-deficient mouse model was demonstrated with recombinant mannose-terminated human LAL (rhLAL) expressed in *Pichia pastoris* yeast [128], CHO cells [129], and *Nicotiana benthamiana* plants [130], establishing the possibility of human ERT for LALD. Beginning in 2011, a phase 1/2 clinical trial (LAL-CL01; NCT01307098) treated nine CESD patients with sebelipase alfa, a rhLAL expressed in hen oviduct cells and secreted into egg whites, demonstrating safety while ameliorating serum lipid profiles [131]. Its extension study (LAL-CL04; NCT01488097) showed consistent results through a year of treatment, including improvements in various markers of liver damage and lipid levels [132]. A phase 3 double-blind, placebo-controlled clinical trial (NCT01757184) subsequently demonstrated improvements in similar disease-related endpoints in a larger study of 66 CESD patients [133]. Granted orphan drug status, Alexion Pharmaceuticals received approval for sebelipase alfa (marketed as Kanuma®) from the European Medicines Agency [134] and the US FDA [135] in 2015. The long-term safety and efficacy of sebelipase alfa are still being examined in multiple ongoing studies [136, 137].

2.5. Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a group of seven metabolic disorders (MPS I, MPSII, MPS III, MPS IV, MPS VI, MPS VII, and MPS IX) caused by genetic mutations to key lysosomal enzymes that are required for the breakdown and recycling of long-chain carbohydrates called glycosaminoglycans (GAGs) [138]. Reduced function of these enzymes leads to lysosomal accumulation of GAGs, cell enlargement, and multi-organ dysfunction [139]. MPS patients suffer from a continuum of symptoms including enlarged head, lips, cheeks, tongues, vocal cords, and nose; frequent upper respiratory infections; hydrocephalus; hepatosplenomegaly; loss of hearing and vision; joint and bone de-

formities; carpal tunnel syndrome; heart valve abnormalities; neurological and developmental delays in severely affected individuals, and shortened lifespan [140].

MPS are genetically inherited disorders that follow either autosomal recessive (*e.g*. MPS I, MPS IV, Hurler Syndrome) or x-linked recessive (*e.g*. MPS II, Hunter Syndrome) inheritance patterns [141]. Although no cure for MPS yet exists, early-age symptom management strategies have been shown to improve lifespan; however, these management strategies require multidisciplinary and long-term health care (physical therapy, surgery, and dietary restrictions) [140]. Both ERT and hematopoietic stem cell transplantation (HSCT) to correct mutations in lysosomal enzyme genes have emerged as possibilities for MPS treatment. While the focus of this review is on ERT, a comprehensive review of HSCT can be found here [142].

The prospect of ERT for MPS followed the discovery that the accumulation of GAGs in MPS I and MPS II fibroblasts could be corrected by mixing the two cell types or growing each in media conditioned by the other [143]. Discovery of receptor-mediated uptake of lysosomal enzymes [144] further clarified the mechanism of rescued lysosomal functionality. The understanding that unique lysosomal enzyme deficiencies are responsible for causing MPS I and II, as well as the advent of recombinant protein biology, made it possible to identify and develop corrective factors (enzymes) to treat MPS.

MPS I is caused by mutations in the *IDUA* gene, which encodes the lysosomal enzyme α-L-iduronidase that is responsible for breaking down heparin sulfate and dermatan sulfate [145, 146]. BioMarin and Genzyme partnered in 2000 to develop and test a recombinant form of the human α-L-iduronidase enzyme (now marketed as Aldurazyme®) for treatment of MPS I. A randomized, double-blinded, placebo-controlled clinical trial found improvements in forced vital capacity and six-minute walking test distance, reduced hepatomegaly, and reduced urinary GAG levels after 26 weeks of weekly recombinant α-L-iduronidase injections (NCT00912925) [147]. An extension trial was conducted to determine long-term safety (NCT00146770) [148], and further trials were pursued to determine dosing levels (NCT00144781) [149] and safety and efficacy of Aldurazyme® in patients under 5 years old (NCT00146757) [150]. These observations have since been confirmed more broadly *via* a recent meta-analysis [151].

ERT has also been developed to treat MPS II, MPS IV, and MPS VI. MPS II is caused by mutations in the *IDS* gene that produces the iduronate sulfatase enzyme [152]. Idursulfase, a human recombinant form of the iduronate sulfatase enzyme, was developed by Shire Pharmaceuticals and is marketed as Elaprase®. Similar to the mechanism of MPS I, iduronate sulfatase is required to process heparan sulfate and dermatan sulfate, which otherwise accumulate in the lysosomal compartment. In a pivotal Phase I/II clinical trial, Elaprase® was found to reduce urinary GAG levels and improve 6-minute walking distance after 24 weeks [153]. The success of this study led to further trials to investigate the appropriate dosage of Elaprase® (NCT00920647) [154], as well as its efficacy in treating the neurological degeneration found in MPS patients (NCT00929647) [155].

MPS IV (Morquio Syndrome) results from mutations that cause a deficiency in either the N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme (MPS IVA) [156, 157] or in the less severe MPS IVB form, deficiencies in the β-galactosidase enzyme [158, 159]). Resulting inability to metabolize keratin sulfate (KS) leads to its excessive urinary excretion [160] and causes symptoms such as skeletal deformities, short stature, osteoarthritis, restricted motion, and discomfort, among other symptoms [161]. Recombinant human GALNS (elosulfase alfa) was developed as a treatment for MPS IVA with the goal of increasing KS metabolism and preventing its accumulation [162]. Following a phase I/II trial of 20 MPS IVA patients (NCT00884949, extended *via* NCT01242111) [163,164], a Phase III randomized, placebo-controlled trial (NCT01275066) demonstrated a significant improvement in 6-minute walk distance in response to weekly elosulfase alfa treatment [165], a roughly 40% reduction in urinary KS excretion [165], and modest improvements in additional tertiary endpoints [162]. Elosulfase alfa received FDA and EMA approval in 2014 for use in MPS IVA patients [166] and is marketed by BioMarin as Vimizim®.

The rare MPS VI (Maroteaux-Lamy Syndrome) results from mutations that lead to a deficiency in N-acetylgalactosamine-4-sulfatase (arylsulfatase B, ARSB) function [167], leading to a similar result of GAG buildup and causing cardiac [168], pulmonary [169], and skeletal [170] defects, among other morbidities [167, 171]. In early clinical trials, treatment with recombinant human ARSB (galsulfase) improved 6- and 12-minute walking distance, 3-minute stair climb, shoulder range of motion, and joint pain, and reduced urinary excretion of GAG [172-174]. Galsulfase received FDA approval in 2005 for use in MPS VI patients [175], and is marketed by BioMarin as Naglazyme®. A recent 10-year follow-up study (NCT01387854) demonstrated long-term improvement in cardiopulmonary function, exercise capacity, and survival ERT patients [176]. HSCT treatment for MPS VI also exists but is subject to transplant-related risks [177, 178]. Neither of these existing options are able to address certain cardiac and skeletal morbidities of MPS VI, leaving significant room for improvement in future treatments [179].

Additional ERT candidates are currently under development to improve the treatment of the neurological complications found in patients with MPS. A drug candidate from ArmaGen named AGT-181 has received Fast Track designation from the FDA and is currently in clinical development for MPS I [180, 181]. ArmaGen is also developing AGT-182 [182], a fusion protein of iduronate-2-sulfatase (IDS) engineered to cross the blood-brain barrier in MPS II patients; AGT-184 [183], a fusion protein for the treatment of Sanfilippo A syndrome, a subtype of MPS III caused by heparin sulfamidase mutations; and AGT-187 [184], a fusion protein for the treatment of Sanfilippo B syndrome, a subtype of MPS III caused by mutations to N-acetylglucosaminidase. Substrate reduction *via* inhibition of GAG synthesis has also been explored in MPS III *via* clinical trials of genistein [185-187] and murine testing of rhodamine B [188-190].

2.6. Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is an extremely rare but fatal autosomal-recessive LSD [191], with an overall incidence estimated between 1.1 and 1.9 cases per 100,000 people [5]. MLD is most commonly caused by genetic mutations that cause arylsulfatase A (ARSA) deficiency, preventing metabolism of sulfatides and allowing them to accumulate in lysosomal storage deposits across the nervous system. Subsequent demyelination of neurons and atrophy across the central and peripheral nervous system leads to neurological problems and ultimately death [192].

Two hundred ARSA alleles have been identified [193], either completely lacking enzymatic activity or retaining partial enzymatic activity. Only 10-15% of normal enzyme activity is necessary to provide sufficient hydrolysis of sulfatides to avoid disease symptoms. Three clinical subtypes of the disorder exist, based on the extent of ARSA enzymatic dysfunction. Late-infantile MLD results from a complete lack of functional ARSA, arises before 30 months, and progresses quickly to death within childhood. Small amounts of functional ARSA lead to the juvenile or adult variants of MLD, but these too are fatal within decades [192]. Diagnosis and progression of MLD can be determined *via* an MRI scoring system, as all three forms of the disease present similar patterns [194].

MLD treatments with functional ARSA enzyme or its gene have both been explored. ERT for lysosomal storage diseases is theoretically possible, as cellular uptake of extracellular lysosomal enzymes could facilitate delivery of replacement enzymes to the lysosome [192]. However, ERT for MLD is greatly complicated by the difficulty of delivering therapeutic proteins across the blood-brain barrier (BBB) to the central nervous system, making effective treatment unlikely unless the direct administration is achieved [191]. Matzner *et al.*'s early study of ERT in a mouse model of MLD encountered this challenge, as an intravenous injection of recombinant human ARSA (rhARSA) yielded moderate uptake into the PNS but minimal uptake into the central nervous system (CNS), resulting in a significant decline of excess sulfatide in the peripheral nervous system (PNS) but not CNS, although repeated IV dosing improved sulfatide clearance from the CNS [195]. In contrast, a subsequent study revealed that infusion of a much lower concentration of rhARSA directly into the cerebrospinal fluid resulted in the reversal of sulfatide storage across the CNS in a distance-dependent manner, as well as the resolution of ataxia [196]. Both of these studies revealed a short half-life of rhARSA in MLD mouse models, complicating the difficulty of achieving sustained enzyme concentrations *via* ERT. In a more aggressive mouse model of MLD, therapeutic benefit was lost if treatment was initiated after the onset of motor deterioration [197], suggesting that timing of treatment is also critical.

Given the difficulty of maintaining ARSA concentrations with ERT, gene therapy approaches to MLD have instead taken prevalence in the clinic. In a Phase I/II trial (NCT01560182, ongoing), lentiviral-transduced HSCs infused into presymptomatic late-infantile and early-juvenile MLD patients reconstituted ARSA enzymatic activity to above normal levels in CSF and prevented disease progression [198, 199]. Since CNS engraftment of infused cells provides a long-lasting source of ARSA enzyme to circulate through both the CNS and PNS, administration of HSCs avoids both major challenges facing ERT administration of therapeutic proteins: crossing the BBB and overcoming a short half-life. While another clinical trial for the treatment of MLD with rhARSA was also recently completed (NCT01510028, results unpublished), the HSC-gene therapy approach appears to have greater potential as a treatment for MLD.

3. SUBSTRATE REDUCTION AND METABOLITE SUPPLEMENTATION IN METABOLIC DISEASES

Whereas many LSDs can be treated through the administration of exogenous wild-type recombinant enzymes, treatment of other metabolic disorders depends upon avoidance of the biomolecules upstream of the defective process and/or supplementation of deficient metabolites. For these disorders, substrate reduction or metabolite supplementation constitutes the central treatment, leaving significant unmet medical need in many cases.

3.1. Phosphofructokinase Deficiency

Phosphofructokinase (PFK) deficiency, also known as glycogen storage disease type VII (GSD VII) or Tarui's disease [200], is an extremely rare [201] autosomal recessive metabolic disorder [202]. PFK is a tetrameric allosteric enzyme made up of tissue-specific subunits for muscle (PFKM), platelet (PFKP), and liver (PFKL) [203-205]; human skeletal muscle only expresses homotetramers made up of the PFKM subunits [206]. PFK deficiency (PFKD) can be caused by numerous genetic mutations in the PFKM gene [204, 207]. PFK is a rate-limiting enzyme in the glycolysis pathway, converting fructose-6-phosphate to fructose 1,6-bisphosphate and ADP [203]. Muscle cells in PFKD patients cannot break down glycogen to regenerate ATP, resulting in exercise intolerance and buildup of excess glycogen in the muscle [207].

Variants of PFKD are categorized by their medical severity, including a classical form, severe infantile form, late-onset form, and hemolytic form [206]. The severe infantile form of PFKD is associated with hypotonia, commonly known as a floppy baby syndrome, myopathy including cardiomyopathy, heart disease, arthrogryposis, and respiratory failure that typically results in early death [206-208]. Classical PFKD, the most common form, typically presents in childhood with exercise intolerance, muscle weakness, muscle stiffness, myalgias, and myoglobinuria. It may also present with nausea and vomiting after strenuous exercise, jaundice due to elevated creatine kinase (CK), high uric acid in the blood, reticulocytosis, and increased serum bilirubin [208]. Late-onset PFKD affects adults with muscle cramps, weakness, and pain, but often coincides with a history of low exercise ability in childhood. The hemolytic form presents as non-spherocytic hemolytic anemia, causing premature destruction of red blood cells, increased reticulocyte counts, and hyperplasia of bone marrow; however, it may exhibit none of the muscular symptoms seen in other forms of PFKD [208, 209].

Although PFKD was described as early as 1965, no treatments are available, in part because the disease is so rare. Swoboda *et al*. described a case [207] in which a patient diagnosed with severe infantile PFKD was treated with a ketogenic diet from four months of age. This approach was intended to promote metabolism of fatty acids and ketones while bypassing glycogen as a cellular energy source in order to avoid the effects of PFKD. After two months on the high fat, ketogenic diet, the patient showed remarkable improvement in muscle strength, and by 9 months old gained full hand function, speech, and the ability to sit up. His motor responses were improved but still below the normal range. Unfortunately, the patient died at 35 months of age from complications due to pneumonia. Still, this represents an extension of nearly two years beyond average survival of severe infantile PFKD patients. Swodoba *et al*. recommended additional research into diet therapy for PFKD patients, though the rarity of the disorder is prohibitive for broader clinical studies.

In contrast to other metabolic diseases, restoration of PFK function may not require replacement of the entire defective enzyme. Study of the crystal structure of eukaryotic PFK has identified opportunities to modulate its allosteric binding sites for adenine [203] in order to regulate PFK activity. Using the known human PFKD mutation D543A, Bruser *et al*. demonstrated that mutation of the adenosine monophosphate (AMP) and adenosine diphosphate (ADP) binding site of PFK results in increased adenosine triphosphate (ATP) inhibition of the enzyme [204]. On this basis, the ATP inhibitory site is a potential therapeutic target to rescue activity in mutated PFK.

3.2. Organic Acidemias

Deficiencies of substrates for energy production and the tricarboxylic acid cycle have been an area of particular success for treatment *via* substrate reduction or supplementation. Organic acidemias are metabolic disorders in which defective metabolic pathways lead to accumulation of acidic intermediate compounds. The metabolism of fatty acids, cholesterol, and amino acids such as methionine, threonine, isoleucine, and valine provides substrates for gluconeogenesis. Enzymes such as propionyl CoA carboxylase and methylmalonyl CoA mutase facilitate crucial steps of these metabolic pathways to ensure the availability of tricarboxylic acid (TCA) cycle precursors. The broad therapeutic strategy for most organic acidemias is to reduce protein intake in order to prevent the buildup of cytotoxic TCA substrates, in some cases paired with supplementation of vitamins that facilitate the defective metabolic pathways. This approach can be accomplished with medical formula for infants and a closely monitored diet for adults [210].

3.3. Propionic Acidemia

Propionyl Coenzyme A (propionyl CoA) is produced from odd-chain fatty acids and the essential amino acids valine, methionine, isoleucine, and threonine, all of which must be obtained from the diet. These amino acid substrates are broken down into propionic acid, which is added to the hydrocarbon tail of coenzyme A, itself the product of fatty acid and cholesterol breakdown pathways, to form propionyl CoA [211]. Transformation of propionyl CoA into methylmalonyl CoA occurs *via* propionyl CoA carboxylase, a biotin-dependent, 6-α, 6-β, dodecameric enzyme encoded by the genes *PCCA* and *PCCB*. Rare autosomal recessive mutations that render either subunit defective [212-214] result in accumulation of propionyl CoA, inhibiting the TCA cycle and causing severe, systemic pathologies including poor feeding, muscle wasting, vomiting, and lethargy.

When propionic acidemia was first described by Childs *et al.* in 1961 [215], it was observed that administration of branched-chain amino acids, including leucine, isoleucine, threonine, and valine led to increased symptoms. Pathologies correlated with protein intake in the diet of the child, suggesting that a low protein diet might be beneficial for the management of this disease. Later studies identified this disease described by Childs as propionic acidemia, and that a low-protein diet facilitates normalization of growth and intellectual development [216, 217]. Additionally, a subset of propionic acidemias resulting from certain mutations are responsive to biotin administration [218]. Given the range of genetic defects that can cause propionic acidemia, the relevant mutation must be identified to inform the most effective treatment.

3.4. Methylmalonic Acidemia

Downstream of propionyl CoA in the same metabolic pathway, methylmalonyl CoA is converted to succinyl CoA by two enzymes: methylmalonyl CoA mutase and methylmalonyl CoA epimerase. Deficiencies in the activity of either of these enzymes can lead to methylmalonic acidemia [219]. Methylmalonyl CoA mutase depends on adenosylcobalamin (vitamin B12) as a cofactor for enzymatic action; thus, genetic mutations that result in decreased levels of active vitamin B12 may also cause methylmalonic acidemia. Indeed, early descriptions of methylmalonic acidemia described cobalamin-responsive and -unresponsive diseases [220]. The existence of two genetic causes of this disease [219] leads to two possible cases for its treatment. As in propionic acidemia, a low-protein diet facilitates normal development and management of symptoms by reducing toxic byproducts of branched-chain amino acid metabolism. Patients with strict dietary monitoring may live a normal life, and in one documented case, deliver offspring without an acidemic phenotype [221]. For patients who respond to cobalamin, oral administration of cobalamin has debatable therapeutic value, but an analog, hydroxocobalamin, has been documented to have positive effects [222]. However, in one case of fetal methylmalonic acidemia, oral cyanocobalamin supplementation during gestation and intramuscular injections after birth, combined with a low protein diet, yielded positive effects [223].

3.5. Isovaleric Acidemia

Isovaleric acidemia is caused by an excess of isovaleric acid, a neurotoxic precursor to the amino acid leucine. Mutations in the enzyme responsible for its metabolism, isovaleryl-CoA dehydrogenase, can cause ketoacidosis. Two etiologies of this disease have been identified, one a severe form that causes neonatal death [224] and the other a less-severe, intermittent acidosis that can be managed throughout

life [225]. A common feature of severe isovaleric acidemia is a urine odor described as "sweaty feet", which is attributed to the excretion of isovaleric acid [226]. Isovaleric acid accumulation causes developmental defects, motor defects, convulsions, and lethargy [227]. For both neonatal and intermittent onset disease types, administration of glycine has been shown to be effective for symptomatic relief [228, 229], as conjugation of glycine to isovaleric acid facilitates its excretion. A low-protein diet may also be required to reduce toxicity from metabolic products to reduce ketoacidosis [229].

3.6. Maple Syrup Urine Disease

Branched chain ketoacidosis, or Maple Syrup Urine Disease (MSUD) is a disorder resulting from mutations to any of three subunits of the large protein complex responsible for decarboxylation of short, branched-chain amino acids [230]. The resulting inability to process branched-chain amino acids leads to toxic buildup of these amino acids and their metabolites. MSUD is easily recognizable by its urinary odor, described as maple syrup- or fenugreek-like [230]. The disease has five subtypes with varying levels of enzymatic activity and responsiveness to therapeutic agents [231]. Among the negative effects, mental and physical defects are observed, usually quickly after birth. "Severe" and "intermediate" varieties of MSUD are differentiated by the extent of residual enzyme activity resulting from different mutations, with minimal enzymatic activity yielding a more severe phenotype [232-234]. "Intermittent" MSUD has been described in a few patients, though the etiology of delays between disease periods has not been fully elucidated. A fourth form, thiamine-responsive MSUD, is manageable by administration of thiamine [235]. Thiamine is a required substrate for the first reaction of the branched-chain ketoacid dehydrogenase complex. Thus, mutations that decrease affinity for thiamine in the E1 subunit of the subunit can be overcome with increased substrate concentration [235-237]. Because thiamine has been therapeutically effective in cases with no observed E1 mutation, subunit E2 has been hypothesized to play a role in thiamine utilization as well [238]. Although not directly observed, this function is attributed to cooperative binding between subunits. A fifth subset of MSUD patients present with a deficiency in the E3 enzyme as part of the total branched-chain ketoacid dehydrogenase complex. As the E3 subunit is common to a few protein complexes, its dysfunction causes multiple biochemical issues [239]. Apart from thiamine responsive MSUD cases, the major treatment strategy is to reduce dietary protein intake and stringently monitor buildup of toxic byproducts. Neonatal monitoring and treatment by reducing dietary protein breakdown and normalizing blood osmolarity has been described recently as an effective option to allow persons harboring MSUD-causing mutations to develop normally [240].

3.7. Citrullinemia

Citrullinemia is caused by mutations to arginosuccinate synthetase (ASS), resulting in an inability to break down citrulline in the arginine synthesis pathway. Citrulline is a byproduct of nitric oxide synthesis, which depends on arginine as a substrate. Thus, a pathway to recycle citrulline to arginine is necessary for maintenance of arginine concentrations in the body. As the first enzyme in the recycling pathway, ASS is of vital importance. The urea cycling function of the liver also requires citrulline conversion to arginosuccinate to prevent urea toxicity.

Mutations to ASS [241] may prevent proper transcription (deletions of exons 7 or 12 [242, 243] reduce affinity of the enzyme for its substrate citrulline [244]) or prevent enzyme activity [244]. In mutations with decreased affinity, some activity of the enzyme can be rescued by increased substrate concentrations. Clinically, citrullinemia leads to hyperammonemia and ammonia intoxication, resulting in developmental and hepatic defects [245, 246]. To manage this disease, a low protein diet helps to prevent buildup of citrulline and urea products. More severe hyperammonemia is usually treated with dialysis or with drugs to decrease plasma ammonia [247].

3.8. Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder caused by mutations to the phenylalanine hydroxylase (PAH) gene [248] that lead to a deficiency for the enzyme, preventing the metabolism of phenylalanine (Phe) to tyrosine [248, 249]. With an incidence of 1 in 10,000 live births in Europe and 1 in 15,000 in the United States, PKU is the most prevalent inherited disorder of amino acid metabolism [249], as well as the first metabolic disorder found to affect the mind and the first for which an effective treatment was developed [250]. In addition to PAH deficiency, the metabolic phenotype of PKU is attributable to dietary consumption of phenylalanine (Phe), and both aspects must be present in order for the classic PKU phenotype to result [251]. PKU results in toxic buildup of Phe in the blood and brain [249], and is characterized by severe neurological deficits as well as epilepsy, microcephaly, behavioral and motor problems, and skin abnormalities [252, 253].

Due to the impact of dietary intake on blood Phe levels, PKU may be successfully treated using a low-Phe diet to normalize blood levels of Phe. Before this substrate reduction treatment was developed in the 1950's, untreated individuals with PKU suffered from severe intellectual disability, microcephaly, and an array of behavioral impairments [254]. Although normalizing Phe levels stabilizes development, some studies suggest that children with PKU may still suffer a mild degree of neurological impairment due to delays in treatment after birth. A clinical cohort study following 808 children from 1964-1980 found that IQ decreased by an average of 4 IQ points for each month after birth that treatment is delayed, demonstrating the importance of early identification and strict treatment regulation [255]. Neonatal screening for PKU is now widespread in order to facilitate timely diagnosis and immediate initiation of treatment [256].

3.9. Multiple Carboxylase Deficiency

Multiple carboxylase deficiency (MCD) is a metabolic disorder deriving from a lack of biotin-dependent carboxylase activity. Its two main forms are neonatal (early-onset) MCD, characterized by a deficiency in biotin holocarboxylase synthetase activity, and juvenile (late-onset) MCD, characterized by a deficiency in biotinidase activity [257].

A prominent late-onset form of MCD, biotinidase deficiency (BD) is an autosomal recessive inherited metabolic disease deriving from any of over 150 mutations to the biotinidase gene [258-260], with an estimated incidence of 1 in 60,000 births worldwide [261]. The primary enzymatic defect in late-onset MCD, it is caused by a lack of biotinidase activity and failure to recycle and process the vitamin biotin [257], impairing the activities of biotin-dependent carboxylase enzymes [262]. Symptoms include skin rashes, ataxia, candidiasis, developmental delay, and alopecia [262]. More severe, early-onset forms of MCD are caused by other mutations, such as those to holocarboxylase synthetase (HCS), the enzyme that facilitates biotin binding to activate holocarboxylases [263].

Lacking the biotin salvage pathway, BD patients excrete biotin and biocytin rapidly [264], and are heavily dependent on exogenous forms of biotin [257]. BD can be treated with pharmacologic doses of biotin supplements, leaving affected individuals asymptomatic or significantly improving their symptoms [265]. HCS-deficient patients may also be responsive to biotin supplementation [266], depending on the mutation causing their condition. Disorders resulting from mutations to the putative biotin-binding domain of HCS, reducing the affinity of the enzyme for biotin, are responsive to biotin supplementation, while mutations outside this domain are less responsive, perhaps due to saturation of the HCS enzyme [267].

Biotin supplementation has been clinically effective in treating deficient patients and newborns screened for the disorder will be asymptomatic as long as they are continuously taking biotin supplements. However, ceasing biotin therapy will result in the development of symptoms in as little as several weeks [268]. Since some of the symptoms associated with Biotinidase deficiency such as, hearing loss or developmental delay, are irreversible, neonatal screening processes have been developed [257]. As such, many different parts of the world, including most states in the United States, screen their newborns for biotinidase deficiency [269] similarly to PKU screening [257].

3.10. MELAS Syndrome

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a maternally inherited mitochondrial disease [270]. While MELAS can arise from multiple mutations in mitochondrial DNA, the most common is an A3243G mutation to the MT-TL1 gene that encodes a mitochondrial transfer RNA [271]. Impaired mitochondrial translation of proteins leads to insufficient cellular energy production, nitric oxide (NO) deficiency, and microvascular angiopathy that results in circulation problems. Combined, these problems cause multi-organ dysfunction with a wide variety of specific phenotypes [270]. MELAS typically presents before the age of 20. Stroke-like episodes are a defining characteristic of the disease [272], along with encephalopathy and mitochondrial myopathy [273].

With no cure available for MELAS, supplement use seeks to bypass deficient processes biochemically and manage complications, although there is little clinical evidence to support these approaches [274]. L-arginine, a substrate for enzymatic NO production, may be administered to support NO production with the goal of preventing and treating stroke-like episodes [275-280]; L-citrulline, a byproduct of NO production that can be converted into L-arginine, has been proposed for the same purpose [278-280]. To support the electron transport chain, supplementation of coenzyme Q10 has also been proposed, but beyond minor exercise benefits [281] was not found to improve clinically relevant variables at rest [282]. Idebenone, a synthetic analog of coenzyme Q10, has been tested, individually [283] or in combination with other supplements such as riboflavin [284], with some success [283, 284]. However, IV and oral L-arginine supplementation, for acute and chronic treatment, respectively, remain the consensus recommendations for supplemental approaches for MELAS [285].

CONCLUSION

From the treatment approaches described above for metabolic diseases lacking approved ERTs, it is evident that attempting to bypass defective metabolic processes *via* dietary restriction or supplementation is helpful, but in most cases a far from perfect solution. Development of ERTs in recent decades has revolutionized the treatment paradigm for deadly metabolic disorders by allowing defective or missing enzymes to be replaced [139, 286], thereby addressing disease at its root cause. The improvement in patient care for those diseases that now have ERTs available has been varied but broadly positive [1]. Future progress in ERT may depend on surmounting remaining challenges such as accessing the CNS with a recombinant enzyme across the BBB [191].

The next revolution in the treatment of these metabolic diseases appears likely to be gene therapy. ERT requires ongoing administration of exogenous recombinant wild-type enzyme, which is both demanding on the patient and expensive. An ideal genetic solution would require a single administration to provide ongoing production of functional enzyme, providing a solution to cure the disorder rather than continually treat it. Genetic approaches are well-suited to metabolic diseases such as LSDs, as these conditions can be traced to a specific genetic mutation and modest levels of replacement enzyme activity are frequently sufficient to ameliorate disease progression [287]. As discussed above, lentiviral-transduced hematopoietic stem cells have been used to reconstitute ARSA enzymatic activity in CSF in MLD clinical trials [198-199] demonstrating early-stage safety and the potential to inhibit disease progression. Gene therapy approaches using lentiviral or adeno-associated viral BBB-crossing vectors for direct delivery have also been proposed for MPS [288]. As viral-transduced hematopoietic stem cells and direct viral delivery techniques are refined for the next generation of treatments [289], increasing attention is being focused on these possibilities [290-292]. Ongoing and future clinical trials will inform the potential for gene therapy approaches to provide single-dose treatments or cures for metabolic diseases with remaining unmet need [293-298].

LIST OF ABBREVIATIONS

α-gal A = α-galactosidase A

AAG = Acid α-glucosidase

ADP = Adenosine Diphosphate
AMP = Adenosine Monophosphate
ARSA = Arylsulfatase A
ASS = Arginosuccinate Synthetase
ATP = Adenosine Triphosphate
BBB = Blood-brain Barrier
BD = Biotinidase Deficiency
CESD = Cholesteryl Ester Storage Disease
CK = Creatine Kinase
CoA = Coenzyme A
CNS = Central Nervous System
EMA = European Medicines Agency
ERT = Enzyme Replacement Therapy
FD = Fabry Disease
FDA = Food & Drug Administration
GAG = Glycosaminoglycans
GD = Gaucher Disease
CHO = Chinese Hamster Ovary
GALNS = N-acetylgalactosamine-6-sulfate sulfatase
GSD = Glycogen Storage Disease
HCS = Holocarboxylase synthetase
HDL = High-Density Lipoprotein
HSCT = Hematopoietic Stem Cell Transplantation
IQ = Intelligence Quotient
KS = Keratin Sulfate
LALD = Lysosomal Acid Lipase Deficiency
LDL = Low-Density Lipoprotein
LSD = Lysosomal Storage Disorder
MCD = Multiple Carboxylase Deficiency
MELAS = Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes
NO = Nitric Oxide
MLD = Metachromatic Leukodystrophy
MPS = Mucopolysaccharidosis
MSUD = Maple Syrup Urine Disease
PD = Pompe Disease
PFKD = Phosphofructokinase Deficiency
Phe = Phenylalanine
PKU = Phenylketonuria
PNS = Peripheral Nervous System
rhAAG = Recombinant Human AAG
TCA = Tricarboxylic Acid
WD = Wolman Disease

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Parenti, G.; Pignata, C.; Vajro, P.; Salerno, M. New strategies for the treatment of lysosomal storage diseases (review). *Int. J. Mol. Med.,* **2013**, *31*(1), 11-20.
[2] Lachmann, R.H. Enzyme replacement therapy for lysosomal storage diseases. *Curr. Opin. Pediatr.,* **2011**, *23*(6), 588-593.
[3] Grabowski, G.A. Gaucher disease: Gene frequencies and genotype/phenotype correlations. *Genet Test.,* **1997**, *1*(1), 5-12.
[4] Meikle, P.J.; Hopwood, J.J.; Clague, A.E.; Carey, W.F. Prevalence of lysosomal storage disorders. *JAMA*, **1999**, *281*, 249-254.
[5] Pinto, R.; Caseiro, C.; Lemos, M.; Lopes, L.; Fontes, A.; Ribeiro, H.; Pinto, E.; Silva, E.; Rocha, S.; Marcao, A.; Ribeiro, I.; Lacerda, L.; Ribeiro, G.; Amaral, O.; Sa Miranda, M.C. Prevalence of lysosomal storage diseases in Portugal. *Eur. J. Hum. Genet.*, **2004**, *12*, 87-92.
[6] Patrick, A.D. A deficiency of glucocerebrosidase in Gaucher's Disease. *Biochem. J.,* **1965**, *97*(2), 17C.
[7] Brady, R.O.; Kanfer, J.N.; Bradley, R.M.; Shapiro, D. Demonstration of a deficiency of glucocerebroside-cleaving enzyme in Gaucher's disease. *J. Clin. Invest.* **1966**, *45*(7), 1112-1115.
[8] Kampine, J.P.; Bardy, R.O.; Kanfer, J.N.; Feld, M.; Shapiro, D. Diagnosis of Gaucher's Disease and Niemann-Pick Disease with small samples of venous blood. *Science,* **1967**, *155*(3758), 86.
[9] Ho, M.W.; O'Brien, J.S. Gaucher's Disease: Deficiency of "cid"β-glucosidase and reconstitution of enzyme activity *in vitro*. *Proc. Natl. Acad. Sci.,* **1971**, *68*(11), 2810-2813.
[10] Tsuji, S.; Choudary, P.V.; Martin, B.M.; Stubblefield, B.K.; Mayor, J.A.; Barranger, J.A.; Ginns, E.I. A Mutation in the human glucocerebrosidase gene in neuronopathic Gaucher's Disease. *N. Engl. J. Med.,* **1987**, *316*(10), 570-575.
[11] Latham, T.E.; Theophilus, B.D.; Grabowski, G.A.; Smith, F.I. Heterogeneity of mutations in the acid beta-glucosidase gene of Gaucher disease patients. *DNA Cell Biol.,* **1991**, *10*(1), 15-21.
[12] Parkin, J.L.; Brunning, R.D. Pathology of the Gaucher cell. *Prog. Clin. Biol. Res.,* **1982**, *95*, 151-175.
[13] Charrow, J.; Andersson, H.C.; Kaplan, P.; Kolodny, E.H.; Mistry, P.; Pastores, G.; Rosenbloom, B.E.; Scott, C.R.; Wappner, R.S.; Weinreb, N.J.; Zimran, A. The gaucher registry: Demographics and disease characteristics of 1698 patients with gaucher disease. *Archiv. Intern. Med.,* **2000**, *160*(18), 2835-2843.
[14] Evans, F.A. Gaucher splenomegaly in a child. *Proc. NY. Pathologic Soc.,* **1916**, *16*(5), 114.
[15] Stowens, D.W.; Teitelbaum, S.L.; Kahn, A.J.; Barranger, J.A. Skeletal complications of Gaucher disease. *Medicine, (Baltimore)* **1985**, *64*(5), 310-322.
[16] Wenstrup, R.J.; Roca-Espiau, M.; Weinreb, N.J.; Bembi, B. Skeletal aspects of Gaucher disease: A review. *Brit. J. Radiol.,* **2002**, *75*(Suppl 1), A2-A12.
[17] Schneider, E.L.; Epstein, C.J.; Kaback, M.J.; Brandes, D. Severe pulmonary involvement in adult Gaucher's disease. Report of three cases and review of the literature. *Am. J. Med.*, **1977**, *63*, 475-480.
[18] Shiran, A.; Brenner, B.; Laor, A.; Tatarsky, I. Increased risk of cancer in patients with gaucher disease. *Cancer,* **1993**, *72*(1), 219-224.
[19] Kauli, R.; Zaizov, R.; Lazar, L.; Pertzelan, A.; Laron, Z.; Galatzer, A.; Phillip, M.; Yaniv, Y.; Cohen, I.J. Delayed growth and puberty in patients with Gaucher disease type 1: Natural history and effect of splenectomy and/or enzyme replacement therapy. *Isr. Med. Assoc. J.,* **2000**, *2*(2), 158-163.

[20] Lachmann, R.H.; Wight, D.G.; Lomas, D.J.; Fisher, N.C.; Schofield, J.P.; Elias, E.; Cox, T.M. Massive hepatic fibrosis in Gaucher's disease: Clinico-pathological and radiological features. *QJM,* **2000**, *93*(4), 237-244.

[21] Deegan, P.B.; Cox, T.M. Imiglucerase in the treatment of Gaucher disease: A history and perspective. *Drug Design Devel. Therapy,* **2012**, *6*, 81-106.

[22] Brady, R.O. The sphingolipidoses. *N. Engl. J. Med.,* **1966**, *275*(6), 312-318.

[23] Brady, R.O.; Pentchev, P.G.; Gal, A.E.; Hibbert, S.R.; Dekaban, A. S. Replacement therapy for inherited enzyme deficiency. *N. Engl. J. Med.,* **1974**, *291*(19), 989-993.

[24] Stahl, P.D.; Rodman, J.S.; Miller, M.J.; Schlesinger, P.H. Evidence for receptor-mediated binding of glycoproteins, glycoconjugates, and lysosomal glycosidases by alveolar macrophages. *Proc. Natl. Acad. Sci. USA,* **1978**, *75*(3), 1399-1403.

[25] Stahl, P.; Schlesinger, P.H.; Sigardson, E.; Rodman, J.S.; Lee, Y.C. Receptor-mediated pinocytosis of mannose glycoconjugates by macrophages: Characterization and evidence for receptor recycling. *Cell*, **1980**, *19*, 207-215.

[26] Shepherd, V.L.; Lee, Y.C.; Schlesinger, P.H.; Stahl, P.D. L-Fucose-terminated glycoconjugates are recognized by pinocytosis receptors on macrophages. *Proc. Natl. Acad. Sci. USA,* **1981**, *78*(2), 1019-1022.

[27] Furbish, F.S.; Steer, C.J.; Krett, N.L.; Barranger, J.A. Uptake and distribution of placental glucocerebrosidase in rat hepatic cells and effects of sequential deglycosylation. *Biochim. Biophys. Acta,* **1981**, *673*(4), 425-434.

[28] Doebber, T.W.; Wu, M.S.; Bugianesi, R.L.; Ponpipom, M.M.; Furbish, F.S.; Barranger, J.A.; Brady, R.O.; Shen, T.Y. Enhanced macrophage uptake of synthetically glycosylated human placental beta-glucocerebrosidase. *J. Biol. Chem.,* **1982**, *257*(5), 2193-2199.

[29] Barton, N.W.; Brady, R.O.; Dambrosia, J.M.; Di Bisceglie, A.M.; Doppelt, S.H.; Hill, S.C.; Mankin, H.J.; Murray, G.J.; Parker, R.I.; Argoff, C.E.; Grewal, R.P.; Yu, K.-T. Replacement therapy for inherited enzyme deficiency - macrophage-targeted glucocerebrosidase for Gaucher's Disease. *N. Engl. J. Med.,* **1991**, *324*(21), 1464-1470.

[30] Fallet, S.; Grace, M.E.; Sibille, A.; Mendelson, D.S.; Shapiro, R. S.; Hermann, G.; Grabowski, G.A. Enzyme augmentation in moderate to life-threatening Gaucher disease. *Pediatr. Res.,* **1992**, *31*(5), 496-502.

[31] Mistry, P.K.; Davies, S.; Corfield, A.; Dixon, A.K.; Cox, T.M. Successful treatment of bone marrow failure in Gaucher's disease with low-dose modified glucocerebrosidase. *Q.J. Med.,* **1992**, *83*(303), 541-546.

[32] Mechler, K.; Mountford, W.K.; Hoffmann, G.F.; Ries, M. Pressure for drug development in lysosomal storage disorders - a quantitative analysis thirty years beyond the US orphan drug act. *Orphanet J. Rare Dis.,* **2015**, *10*, 46.

[33] Beutler, E.; Kay, A.; Saven, A.; Garver, P.; Thurston, D.; Dawson, A.; Rosenbloom, B. Enzyme replacement therapy for Gaucher disease. *Blood,* **1991**, *78*(5), 1183-1189.

[34] Figueroa, M.L.; Rosenbloom, B.E.; Kay, A.C.; Garver, P.; Thurston, D.W.; Koziol, J.A.; Gelbart, T.; Beutler, E. A less costly regimen of alglucerase to treat Gaucher's Disease. *N. Engl. J. Med.,* **1992**, *327*(23), 1632-1636.

[35] Grabowski, G.A.; Barton, N.W.; Pastores, G.; Dambrosia, J.M.; Banerjee, T.K.; McKee, M.A.; Parker, C.; Schiffmann, R.; Hill, S.C.; Brady, R.O. Enzyme therapy in type 1 Gaucher disease: Comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. *Ann. Intern Med.,* **1995**, *122*(1), 33-39.

[36] Zimran, A.; Altarescu, G.; Philips, M.; Attias, D.; Jmoudiak, M.; Deeb, M.; Wang, N.; Bhirangi, K.; Cohn, G.M.; Elstein, D. Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience. *Blood*, **2010**, *115*, 4651-4656.

[37] Elstein, D.; Cohn, G.M.; Wang, N.; Djordjevic, M.; Brutaru, C.; Zimran, A. Early achievement and maintenance of the therapeutic goals using velaglucerase alfa in type 1 Gaucher disease. *Blood Cells Mol. Dis.*, **2011**, *46*, 119-123.

[38] Smith, L.; Rhead, W.; Charrow, J.; Shankar, S.P.; Bavdekar, A.; Longo, N.; Mardach, R.; Harmatz, P.; Hangartner, T.; Lee, H.-M.; Crombez, E.; Pastores, G. M. Long-term velaglucerase alfa treatment in children with Gaucher disease type 1 naïve to enzyme replacement therapy or previously treated with imiglucerase. *Mol. Genet. Metab.,* **2016**, *117*(2), 164-171.

[39] Burrow, T.A.; Grabowski, G.A. Velaglucerase alfa in the treatment of Gaucher disease type 1. *J. Clin. Invest.,* **2011**, *1*(2), 285-293.

[40] Zimran, A.; Brill-Almon, E.; Chertkoff, R.; Petakov, M.; Blanco-Favela, F.; Munoz, E.T.; Solorio-Meza, S.E.; Amato, D.; Duran, G.; Giona, F.; Heitner, R.; Rosenbaum, H.; Giraldo, P.; Mehta, A.; Park, G.; Phillips, M.; Elstein, D.; Altarescu, G.; Szleifer, M.; Hashmueli, S.; Aviezer, D. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease. *Blood*, **2011**, *118*, 5767-5773.

[41] Pastores, G.M.; Shankar, S.P.; Petakov, M.; Giraldo, P.; Rosenbaum, H.; Amato, D.J.; Szer, J.; Chertkoff, R.; Brill-Almon, E.; Zimran, A. Enzyme replacement therapy with taliglucerase alfa: 36-month safety and efficacy results in adult patients with Gaucher disease previously treated with imiglucerase. *Am. J. Hematol.,* **2016**, *91*(7), 661-665.

[42] Grabowski, G.A.; Golembo, M.; Shaaltiel, Y. Taliglucerase alfa: An enzyme replacement therapy using plant cell expression technology. *Mol. Genet. Metab.*, **2014**, *112*, 1-8.

[43] Ceron-Rodriguez, M.; Barajas-Colon, E.; Ramirez-Devars, L.; Gutierrez-Camacho, C.; Salgado-Loza, J.L. Improvement of life quality measured by Lansky Score after enzymatic replacement therapy in children with Gaucher disease type 1. *Mol. Genet. Genomic Med.,* **2018**, *6*(1), 27-34.

[44] Gras-Colomer, E.; Martinez-Gomez, M.A.; Climente-Marti, M.; Fernandez-Zarzoso, M.; Almela-Tejedo, M.; Giner-Galvan, V.; Marcos-Rodriguez, J.A.; Rodriguez-Fernandez, A.; Torralba-Cabeza, M.A.; Merino-Sanjuan, M. Relationship between glucocerebrosidase activity and clinical response to enzyme replacement therapy in patients with Gaucher Disease type I. *Basic Clin. Pharmacol. Toxicol.,* **2018**, *123*(1), 65-71.

[45] Zimran, A.; Wajnrajch, M.; Hernandez, B.; Pastores, G.M. Taliglucerase alfa: Safety and efficacy across 6 clinical studies in adults and children with Gaucher disease. *Orphanet J. Rare Dis.*, **2018**, *13*, 36.

[46] Ries, M. Enzyme replacement therapy and beyond - in memoriam Roscoe O. Brady, M.D. (1923-2016). *J. Inherit. Metab. Dis.*, **2017**, *40*, 343-356.

[47] Desnick, R.J.; Brady, R.; Barranger, J.; Collins, A.J.; Germain, D.P.; Goldman, M.; Grabowski, G.; Packman, S.; Wilcox, W.R. Fabry disease, an under-recognized multisystemic disorder: Expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann. Intern. Med.*, **2003**, *138*, 338-346.

[48] MacDermot, K.D.; Holmes, A.; Miners, A.H. Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J. Med. Genet.,* **2001**, *38*(11), 750-760.

[49] Mehta, A.; Ricci, R.; Widmer, U.; Dehout, F.; Garcia de Lorenzo, A.; Kampmann, C.; Linhart, A.; Sunder-Plassmann, G.; Ries, M.; Beck, M. Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur. J. Clin. Invest.*, **2004**, *34*, 236-242.

[50] Mehta, A.; Beck, M.; Eyskens, F.; Feliciani, C.; Kantola, I.; Ramaswami, U.; Rolfs, A.; Rivera, A.; Waldek, S.; Germain, D.P. Fabry disease: A review of current management strategies. *QJM,* **2010**, *103*(9), 641-659.

[51] Mahmud, H.M. Fabry's disease – a comprehensive review on pathogenesis, diagnosis and treatment. *J. Pak. Med. Assoc.*, **2014**, *64*, 189-194.

[52] Sweeley, C.C.; Klionsky, B. Fabry's disease: Classification as a sphingolipidosis and partial characterization of a novel glycolipid. *J. Biol. Chem.,* **1963**, *238*, 3148-3150.

[53] Brady, R.O.; Gal, A.E.; Bradley, R.M.; Martensson, E.; Warshaw, A.L.; Laster, L. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. *N. Engl. J. Med.,* **1967**, *276*(21), 1163-1167.

[54] Mapes, C.A.; Anderson, R.L.; Sweeley, C.C.; Desnick, R.J.; Krivit, W. Enzyme replacement in Fabry's disease, an inborn error of metabolism. *Science,* **1970**, *169*(3949), 987-989.

[55] Brady, R.O.; Tallman, J.F.; Johnson, W.G.; Gal, A.E.; Leahy, W.R.; Quirk, J.M.; Dekaban, A.S. Replacement therapy for inherited enzyme deficiency. *N. Engl. J. Med.,* **1973**, *289*(1), 9-14.

[56] Desnick, R.J.; Dean, K.J.; Grabowski, G.; Bishop, D.F.; Sweeley, C.C. Enzyme therapy in Fabry disease: Differential *in vivo* plasma clearance and metabolic effectiveness of plasma and splenic alpha-

galactosidase an isozyme. *Proc. Natl. Acad. Sci. USA,* **1979**, *76*(10), 5326-5330.

[57] Pastores, G.M.; Thadhani, R. Enzyme-replacement therapy for Anderson-Fabry disease. *Lancet,* **2001**, *358*(9282), 601-603.

[58] Eng, C.M.; Guffon, N.; Wilcox, W.R.; Germain, D.P.; Lee, P.; Waldek, S.; Caplan, L.; Linthorst, G.E.; Desnick, R.J. Safety and efficacy of recombinant human α-galactosidase, a replacement therapy in Fabry's disease. *N. Engl. J. Med.,* **2001**, *345*(1), 9-16.

[59] Schiffmann, R.; Kopp, J.B.; Austin, H.A., 3rd; Sabnis, S.; Moore, D.F.; Weibel, T.; Balow, J.E.; Brady, R.O. Enzyme replacement therapy in Fabry disease: A randomized controlled trial. *JAMA*, **2001**, *285*, 2743-9.

[60] Arends, M.; Biegstraaten, M.; Wanner, C.; Sirrs, S.; Mehta, A.; Elliott, P.M.; Oder, D.; Watkinson, O.T.; Bichet, D.G.; Khan, A.; Iwanochko, M.; Vaz, F.M.; van Kuilenburg, A.B.P.; West, M.L.; Hughes, D.A.; Hollak, C.E.M. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: An international cohort study. *J. Med. Genet.*, **2018**, *55*(5), 351-358.

[61] Baehner, F.; Kampmann, C.; Whybra, C.; Miebach, E.; Wiethoff, C.M.; Beck, M. Enzyme replacement therapy in heterozygous females with Fabry disease: Results of a phase IIIB study. *J. Inherit. Metab. Dis.*, **2003**, *26*, 617-627.

[62] Schiffmann, R.; Floeter, M.K.; Dambrosia, J.M.; Gupta, S.; Moore, D.F.; Sharabi, Y.; Khurana, R.K.; Brady, R.O. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. *Muscle Nerve,* **2003**, *28*(6), 703-710.

[63] Weidemann, F.; Breunig, F.; Beer, M.; Sandstede, J.; Turschner, O.; Voelker, W.; Ertl, G.; Knoll, A.; Wanner, C.; Strotmann, J.M. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: A prospective strain rate imaging study. *Circulation*, **2003**, *108*, 1299-1301.

[64] Hilz, M.J.; Brys, M.; Marthol, H.; Stemper, B.; Dutsch, M. Enzyme replacement therapy improves function of C-, Adelta-, and Abeta-nerve fibers in Fabry neuropathy. *Neurology,* **2004**, *62*(7), 1066-1072.

[65] Jardim, L.; Vedolin, L.; Schwartz, I.V.D.; Burin, M.G.; Cecchin, C.; Kalakun, L.; Matte, U.; Aesse, F.; Pitta-Pinheiro, C.; Marconato, J.; Giugliani, R. CNS involvement in Fabry disease: Clinical and imaging studies before and after 12 months of enzyme replacement therapy. *J. Inherit. Metab. Dis.,* **2004**, *27*(2), 229-240.

[66] Spinelli, L.; Pisani, A.; Sabbatini, M.; Petretta, M.; Andreucci, M. V.; Procaccini, D.; Lo Surdo, N.; Federico, S.; Cianciaruso, B. Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. *Clin. Genet.*, **2004**, *66*, 158-165.

[67] Breunig, F.; Weidemann, F.; Strotmann, J.; Knoll, A.; Wanner, C. Clinical benefit of enzyme replacement therapy in Fabry disease. *Kidney Int.*, **2006**, *69*, 1216-1221.

[68] Schiffmann, R.; Ries, M.; Timmons, M.; Flaherty, J.T.; Brady, R.O. Long-term therapy with agalsidase alfa for Fabry disease: Safety and effects on renal function in a home infusion setting. *Nephrol. Dial. Transplant.*, **2006**, *21*, 345-354.

[69] Lidove, O.; Joly, D.; Barbey, F.; Bekri, S.; Alexandra, J.F.; Peigne, V.; Jaussaud, R.; Papo, T. Clinical results of enzyme replacement therapy in Fabry disease: A comprehensive review of literature. *Int. J. Clin. Pract.*, **2007**, *61*, 293-302.

[70] Ramaswami, U.; Wendt, S.; Pintos-Morell, G.; Parini, R.; Whybra, C.; Leon Leal, J.A.; Santus, F.; Beck, M. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease. *Acta. Paediatr*. Norway, **2007**, *96*, 122-127.

[71] Vedder, A.C.; Linthorst, G.E.; Houge, G.; Groener, J.E.M.; Ormel, E.E.; Bouma, B.J.; Aerts, J.; Hirth, A.; Hollak, C.E.M. Treatment of Fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. *PLoS One,* **2007**, *2*(7), e598.

[72] Fervenza, F.C.; Torra, R.; Warnock, D.G. Safety and efficacy of enzyme replacement therapy in the nephropathy of Fabry disease. *Biologics,* **2008**, *2*(4), 823-843.

[73] Warnock, D.G.; Ortiz, A.; Mauer, M.; Linthorst, G.E.; Oliveira, J.P.; Serra, A.L.; Marodi, L.; Mignani, R.; Vujkovac, B.; Beitner-Johnson, D.; Lemay, R.; Cole, J.A.; Svarstad, E.; Waldek, S.; Germain, D.P.; Wanner, C. Renal outcomes of agalsidase beta treatment for Fabry disease: Role of proteinuria and timing of treatment initiation. *Nephrol. Dial. Transplant.,* **2012**, *27*(3), 1042-1049.

[74] Pisani, A.; Riccio, E.; Sabbatini, M. Agalsidase alfa and agalsidase beta in the treatment of Fabry disease: Does the dose really matter? *Genet. Med.,* **2015**, *17*(1), 21-23.

[75] Pastores, G.M.; Boyd, E.; Crandall, K.; Whelan, A.; Piersall, L.; Barnett, N., Safety and pharmacokinetics of agalsidase alfa in patients with Fabry disease and end-stage renal disease. *Nephrol. Dial. Transplant.*, **2007**, *22*, 1920-1925.

[76] Ries, M.; Clarke, J.T.; Whybra, C.; Mehta, A.; Loveday, K.S.; Brady, R.O.; Beck, M.; Schiffmann, R. Enzyme replacement in Fabry Disease: Pharmacokinetics and pharmacodynamics of agalsidase alfa in children and adolescents. *J. Clin. Pharmacol.,* **2007**, *47*(10), 1222-1230.

[77] Waldek, S.; Patel, M.R.; Banikazemi, M.; Lemay, R.; Lee, P. Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry. *Genet. Med.,* **2009**, *11*(11), 790-796.

[78] Marchesoni, C.L.; Roa, N.; Pardal, A.M.; Neumann, P.; Caceres, G.; Martinez, P.; Kisinovsky, I.; Bianchi, S.; Tarabuso, A.L.; Reisin, R.C. Misdiagnosis in Fabry disease. *J. Pediatr.*, **2010**, *156*, 828-831.

[79] Pastores, G.M. Agalsidase alfa (Replagal) in the treatment of Anderson-Fabry disease. *Biologics,* **2007**, *1*(3), 291-300.

[80] Tsuboi, K.; Yamamoto, H. Clinical observation of patients with Fabry disease after switching from agalsidase beta (Fabrazyme) to agalsidase alfa (Replagal). *Genet. Med.,* **2012**, *14*(9), 779-786.

[81] Martiniuk, F.; Chen, A.; Mack, A.; Arvanitopoulos, E.; Chen, Y.; Rom, W.N.; Codd, W.J.; Hanna, B.; Alcabes, P.; Raben, N.; Plotz, P. Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. *Am. J. Med. Genet.*, **1998**, *79*, 69-72.

[82] Ausems, M.G.; Verbiest, J.; Hermans, M.P.; Kroos, M.A.; Beemer, F.A.; Wokke, J.H.; Sandkuijl, L.A.; Reuser, A.J.; van der Ploeg, A.T. Frequency of glycogen storage disease type II in The Netherlands: Implications for diagnosis and genetic counselling. *Eur. J. Hum. Genet.,* **1999**, *7*(6), 713-716.

[83] Hermans, M.M.; De Graaff, E.; Kroos, M.A.; Mohkamsing, S.; Eussen, B.J.; Joosse, M.; Willemsen, R.; Kleijer, W.J.; Oostra, B.A.; Reuser, A.J. The effect of a single base pair deletion (delta T525) and a C1634T missense mutation (pro545leu) on the expression of lysosomal alpha-glucosidase in patients with glycogen storage disease type II. *Hum. Mol. Genet.,* **1994**, *3*(12), 2213-2218.

[84] Huie, M.L.; Chen, A.S.; Tsujino, S.; Shanske, S.; DiMauro, S.; Engel, A.G.; Hirschhorn, R. Aberrant splicing in adult onset glycogen storage disease type II (GSDII): Molecular identification of an IVS1 (-13T-->G) mutation in a majority of patients and a novel IVS10 (+1GT-->CT) mutation. *Hum. Mol. Genet.,* **1994**, *3*(12), 2231-2236.

[85] Raben, N.; Nichols, R.C.; Boerkoel, C.; Plotz, P. Genetic defects in patients with glycogenosis type II (acid maltase deficiency). *Muscle Nerve,* **1995**, *18*(S14), S70-S74.

[86] Lin, C.Y.; Shieh, J.J. Identification of a *de novo* point mutation resulting in infantile form of Pompe's disease. *Biochem. Biophys. Res. Commun.*, **1995**, *208*, 886-893.

[87] Adams, E.M.; Becker, J.A.; Griffith, L.; Segal, A.; Plotz, P.H.; Raben, N. Glycogenosis type II: A juvenile-specific mutation with an unusual splicing pattern and a shared mutation in African Americans. *Hum. Mutat.*, **1997**, *10*, 128-134.

[88] Shieh, J.J.; Lin, C.Y. Frequent mutation in Chinese patients with infantile type of GSD II in Taiwan: Evidence for a founder effect. *Hum. Mutat.*, **1998**, *11*, 306-312.

[89] Hermans, M.M.; van Leenen, D.; Kroos, M.A.; Beesley, C.E.; Van Der Ploeg, A.T.; Sakuraba, H.; Wevers, R.; Kleijer, W.; Michelakakis, H.; Kirk, E.P.; Fletcher, J.; Bosshard, N.; Basel-Vanagaite, L.; Besley, G.; Reuser, A.J. Twenty-two novel mutations in the lysosomal alpha-glucosidase gene (GAA) underscore the genotype-phenotype correlation in glycogen storage disease type II. *Hum. Mutat.,* **2004**, *23*(1), 47-56.

[90] Bekircan-Kurt, C.E.; Gunes, H.N.; Yildiz, F.G.; Saka, E.; Tan, E.; Erdem-Ozdamar, S. New mutations and genotype-phenotype correlation in late-onset Pompe patients. *Acta Neurol. Belg.*, **2017**, *117*, 269-275.

[91] Ebrahimi, M.; Behnam, M.; Behranvand-jazi, N.; Yari, L.; Sheikh-kanlomilan, S.; Salehi, M.; Tahmasebi, P.; Amini, M.; Behjati, M.; Hosseini, N. Identification a novel mononucleotide deletion mutation in GAA in pompe disease patients. *J. Res. Med. Sci.,* **2017**, *22*, 100.

[92] Martiniuk, F.; Mehler, M.; Pellicer, A.; Tzall, S.; La Badie, G.; Hobart, C.; Ellenbogen, A.; Hirschhorn, R. Isolation of a cDNA for human acid alpha-glucosidase and detection of genetic heterogene-

ity for mRNA in three alpha-glucosidase-deficient patients. *Proc. Natl. Acad. Sci. USA,* **1986**, *83*(24), 9641-9644.

[93] Hoefsloot, L.H.; Hoogeveen-Westerveld, M.; Kroos, M.A.; van Beeumen, J.; Reuser, A.J.; Oostra, B.A. Primary structure and processing of lysosomal alpha-glucosidase; homology with the intestinal sucrase-isomaltase complex. *EMBO J.,* **1988**, *7*(6), 1697-1704.

[94] Hers, H.G. α-Glucosidase deficiency in generalized glycogen-storage disease (Pompe's disease). *Biochem. J.,* **1963**, *86*(1), 11-16.

[95] van der Ploeg, A.T.; Reuser, A.J.J. Pompe's disease. *Lancet,* **2008**, *372*(9646), 1342-1353.

[96] Winkel, L.P.F.; Hagemans, M.L.C.; van Doorn, P.A.; Loonen, M.C.B.; Hop, W.J.C.; Reuser, A.J.J.; Van der Ploeg, A.T. The natural course of non-classic Pompe's disease; a review of 225 published cases. *J. Neurol.,* **2005**, *252*(8), 875-884.

[97] Reuser, A.J.; Kroos, M.A.; Ponne, N.J.; Wolterman, R.A.; Loonen, M.C.; Busch, H.F.; Visser, W.J.; Bolhuis, P.A. Uptake and stability of human and bovine acid alpha-glucosidase in cultured fibroblasts and skeletal muscle cells from glycogenosis type II patients. *Exp. Cell. Res.*, **1984**, *155*, 178-189.

[98] Van der Ploeg, A.T.; Loonen, M.C.; Bolhuis, P.A.; Busch, H.M.; Reuser, A.J.; Galjaard, H. Receptor-mediated uptake of acid alpha-glucosidase corrects lysosomal glycogen storage in cultured skeletal muscle. *Pediatr. Res.,* **1988**, *24*(1), 90-94.

[99] van der Ploeg, A.T.; van der Kraaij, A.M.; Willemsen, R.; Kroos, M.A.; Loonen, M.C.; Koster, J.F.; Reuser, A.J. Rat heart perfusion as model system for enzyme replacement therapy in glycogenosis type II. *Pediatr. Res.,* **1990**, *28*(4), 344-347.

[100] Bijvoet, A.G.; Kroos, M.A.; Pieper, F.R.; Van der Vliet, M.; De Boer, H.A.; Van der Ploeg, A.T.; Verbeet, M.P.; Reuser, A.J. Recombinant human acid alpha-glucosidase: High level production in mouse milk, biochemical characteristics, correction of enzyme deficiency in GSDII KO mice. *Hum. Mol. Genet.*, **1998**, *7*, 1815-1824.

[101] Van Hove, J.L.; Yang, H.W.; Wu, J.Y.; Brady, R.O.; Chen, Y.T. High-level production of recombinant human lysosomal acid alpha-glucosidase in Chinese hamster ovary cells which targets to heart muscle and corrects glycogen accumulation in fibroblasts from patients with Pompe disease. *Proc. Natl. Acad. Sci. USA,* **1996**, *93*(1), 65-70.

[102] Zhu, Y.; Li, X.; Kyazike, J.; Zhou, Q.; Thurberg, B.L.; Raben, N.; Mattaliano, R.J.; Cheng, S.H. Conjugation of mannose 6-phosphate-containing oligosaccharides to acid alpha-glucosidase improves the clearance of glycogen in pompe mice. *J. Biol. Chem.*, **2004**, *279*, 50336-50341.

[103] Zhu, Y.; Li, X.; McVie-Wylie, A.; Jiang, C.; Thurberg, B.L.; Raben, N.; Mattaliano, R.J.; Cheng, S.H. Carbohydrate-remodelled acid alpha-glucosidase with higher affinity for the cation-independent mannose 6-phosphate receptor demonstrates improved delivery to muscles of Pompe mice. *Biochem. J.,* **2005**, *389*(3), 619-628.

[104] Van den Hout, H.; Reuser, A.J.; Vulto, A.G.; Loonen, M.C.; Cromme-Dijkhuis, A.; Van der Ploeg, A.T. Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. *Lancet*, **2000**, *356*, 397-398.

[105] Winkel, L.P.; Kamphoven, J.H.; van den Hout, H.J.; Severijnen, L.A.; van Doorn, P.A.; Reuser, A.J.; van der Ploeg, A.T. Morphological changes in muscle tissue of patients with infantile Pompe's disease receiving enzyme replacement therapy. *Muscle Nerve,* **2003**, *27*(6), 743-751.

[106] Winkel, L.P.; Van den Hout, J.M.; Kamphoven, J.H.; Disseldorp, J.A.; Remmerswaal, M.; Arts, W.F.; Loonen, M.C.; Vulto, A.G.; Van Doorn, P.A.; De Jong, G.; Hop, W.; Smit, G.P.; Shapira, S.K.; Boer, M.A.; van Diggelen, O.P.; Reuser, A.J.; Van der Ploeg, A.T. Enzyme replacement therapy in late-onset Pompe's disease: A three-year follow-up. *Ann. Neurol.,* **2004**, *55*(4), 495-502.

[107] Van den Hout, J.M.; Kamphoven, J.H.; Winkel, L.P.; Arts, W.F.; De Klerk, J.B.; Loonen, M.C.; Vulto, A.G.; Cromme-Dijkhuis, A.; Weisglas-Kuperus, N.; Hop, W.; Van Hirtum, H.; Van Diggelen, O.P.; Boer, M.; Kroos, M.A.; Van Doorn, P.A.; Van der Voort, E.; Sibbles, B.; Van Corven, E.J.; Brakenhoff, J.P.; Van Hove, J.; Smeitink, J.A.; de Jong, G.; Reuser, A.J.; Van der Ploeg, A.T. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. *Pediatrics,* **2004**, *113*(5), 448-457.

[108] Amalfitano, A.; Bengur, A.R.; Morse, R.P.; Majure, J.M.; Case, L.E.; Veerling, D.L.; Mackey, J.; Kishnani, P.; Smith, W.; McVie-Wylie, A.; Sullivan, J.A.; Hoganson, G.E.; Phillips, J.A., 3rd; Schaefer, G.B.; Charrow, J.; Ware, R.E.; Bossen, E.H.; Chen, Y.T. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: Results of a phase I/II clinical trial. *Genet. Med.,* **2001**, *3*(2), 132-138.

[109] Kishnani, P.S.; Nicolino, M.; Voit, T.; Rogers, R.C.; Tsai, A.C.-H.; Waterson, J.; Herman, G.E.; Amalfitano, A.; Thurberg, B.L.; Richards, S.; Davison, M.; Corzo, D.; Chen, Y.T. Chinese hamster ovary cell-derived recombinant human acid α-glucosidase in infantile-onset Pompe disease. *J. Pediatr.,* **2006**, *149*(1), 89-97.

[110] Thurberg, B.L.; Lynch Maloney, C.; Vaccaro, C.; Afonso, K.; Tsai, A.C.; Bossen, E.; Kishnani, P.S.; O'Callaghan, M. Characterization of pre- and post-treatment pathology after enzyme replacement therapy for Pompe disease. *Lab. Invest.*, **2006**; *86*, 1208-1220.

[111] Kishnani, P.S.; Corzo, D.; Nicolino, M.; Byrne, B.; Mandel, H.; Hwu, W.L.; Leslie, N.; Levine, J.; Spencer, C.; McDonald, M.; Li, J.; Dumontier, J.; Halberthal, M.; Chien, Y.H.; Hopkin, R.; Vijayaraghavan, S.; Gruskin, D.; Bartholomew, D.; van der Ploeg, A.; Clancy, J.P.; Parini, R.; Morin, G.; Beck, M.; De la Gastine, G.S.; Jokic, M.; Thurberg, B.; Richards, S.; Bali, D.; Davison, M.; Worden, M.A.; Chen, Y.T.; Wraith, J.E. Recombinant human acid [alpha]-glucosidase: Major clinical benefits in infantile-onset Pompe disease. *Neurology*, **2007**, *68*, 99-109.

[112] Kishnani, P.S.; Corzo, D.; Leslie, N.D.; Gruskin, D.; Van der Ploeg, A.; Clancy, J.P.; Parini, R.; Morin, G.; Beck, M.; Bauer, M. S.; Jokic, M.; Tsai, C.E.; Tsai, B.W.; Morgan, C.; O'Meara, T.; Richards, S.; Tsao, E.C.; Mandel, H. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. *Pediatr. Res.,* **2009**, *66*(3), 329-335.

[113] van der Ploeg, A.T.; Clemens, P.R.; Corzo, D.; Escolar, D.M.; Florence, J.; Groeneveld, G.J.; Herson, S.; Kishnani, P.S.; Laforet, P.; Lake, S.L.; Lange, D.J.; Leshner, R.T.; Mayhew, J.E.; Morgan, C.; Nozaki, K.; Park, D.J.; Pestronk, A.; Rosenbloom, B.; Skrinar, A.; van Capelle, C.I.; van der Beek, N.A.; Wasserstein, M.; Zivkovic, S.A. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N. Engl. J. Med.*, **2010**, *362*, 1396-1406.

[114] Mack, G. FDA balks at Myozyme scale-up. *Nat. Biotechnol.*, **2008**, *26*, 592.

[115] Ratner, M. Genzyme's Lumizyme clears bioequivalence hurdles. *Nat. Biotechnol.,* **2009**, *27*, 685.

[116] Guo, J.; Kelton, C.M.; Guo, J.J. Recent developments, utilization, and spending trends for pompe disease therapies. *Am. Health Drug Benefits,* **2012**, *5*(3), 182-189.

[117] Bernstein, D.L.; Hulkova, H.; Bialer, M.G.; Desnick, R.J. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. *J. Hepatol.*, **2013**, *58*, 1230-1243.

[118] Wolman, M.; Sterk, V.V.; Gatt, S.; Frenkel, M. Primary familial xanthomatosis with involvement and calcification of the adrenals. Report of two more cases in siblings of a previously described infant. *Pediatrics,* **1961**, *28*, 742-757.

[119] Marshall, W.C.; Ockenden, B.G.; Fosbrooke, A.S.; Cumings, J.N. Wolman's disease. A rare lipidosis with adrenal calcification. *Arch. Dis. Child.,* **1969**, *44*(235), 331-341.

[120] Scott, S.A.; Liu, B.; Nazarenko, I.; Martis, S.; Kozlitina, J.; Yang, Y.; Ramirez, C.; Kasai, Y.; Hyatt, T.; Peter, I.; Desnick, R.J. Frequency of the cholesteryl ester storage disease common LIPA E8SJM mutation (c.894G>A) in various racial and ethnic Groups. *Hepatology,* **2013**, *58*(3), 958-965.

[121] Ireland, R.M. Morphology of Wolman cholesteryl ester storage disease. *Blood*, **2017**, *129*, 803.

[122] Reiner, Ž.; Guardamagna, O.; Nair, D.; Soran, H.; Hovingh, K.; Bertolini, S.; Jones, S.; Ćorić, M.; Calandra, S.; Hamilton, J.; Eagleton, T.; Ros, E. Lysosomal acid lipase deficiency - An under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis,* **2014**, *235*(1), 21-30.

[123] Warner, T.G.; Dambach, L.M.; Shin, J.H.; O'Brien, J.S. Purification of the lysosomal acid lipase from human liver and its role in lysosomal lipid hydrolysis. *J. Biol. Chem.,* **1981**, *256*(6), 2952-2957.

[124] Sando, G.N.; Henke, V.L. Recognition and receptor-mediated endocytosis of the lysosomal acid lipase secreted by cultured human fibroblasts. *J. Lipid Res.,* **1982**, *23*(1), 114-123.

[125] Hoeg, J.M.; Demosky, S.J.; Pescovitz, O.H.; Brewer, H.B. Cholesteryl ester storage disease and Wolman disease: Phenotypic variants of lysosomal acid cholesteryl ester hydrolase deficiency. *Am. J. Hum. Genet.,* **1984**, *36*(6), 1190-1203.

[126] Poznansky, M.J.; Hutchison, S.K.; Davis, P.J. Enzyme replacement therapy in fibroblasts from a patient with cholesteryl ester storage disease. *FASEB J.,* **1989**, *3*(2), 152-156.

[127] Anderson, R.A.; Sando, G.N. Cloning and expression of cDNA encoding human lysosomal acid lipase/cholesterol ester hydrolase. *J. Biol. Chem.,* **1991**, *266*(33), 22479-22484.

[128] Du, H.; Schiavi, S.; Levine, M.; Mishra, J.; Heur, M.; Grabowski, G.A. Enzyme therapy for lysosomal acid lipase deficiency in the mouse. *Hum. Mol. Genet.,* **2001**, *10*(16), 1639-1648.

[129] Du, H.; Levine, M.; Ganesa, C.; Witte, D.P.; Cole, E.S.; Grabowski, G.A. The role of mannosylated enzyme and the mannose receptor in enzyme replacement therapy. *Am. J. Hum. Genet.,* **2005**, *77*(6), 1061-1074.

[130] Du, H.; Cameron, T.L.; Garger, S.J.; Pogue, G.P.; Hamm, L.A.; White, E.; Hanley, K.M.; Grabowski, G.A. Wolman disease/cholesteryl ester storage disease: Efficacy of plant-produced human lysosomal acid lipase in mice. *J. Lipid Res.,* **2008**, *49*(8), 1646-1657.

[131] Balwani, M.; Breen, C.; Enns, G.M.; Deegan, P.B.; Honzik, T.; Jones, S.; Kane, J.P.; Malinova, V.; Sharma, R.; Stock, E.O.; Valayannopoulos, V.; Wraith, J.E.; Burg, J.; Eckert, S.; Schneider, E.; Quinn, A.G. Clinical effect and safety profile of recombinant human lysosomal acid lipase in patients with cholesteryl ester storage disease. *Hepatology,* **2013**, *58*(3), 950-957.

[132] Valayannopoulos, V.; Malinova, V.; Honzík, T.; Balwani, M.; Breen, C.; Deegan, P.B.; Enns, G.M.; Jones, S.A.; Kane, J.P.; Stock, E.O.; Tripuraneni, R.; Eckert, S.; Schneider, E.; Hamilton, G.; Middleton, M.S.; Sirlin, C.; Kessler, B.; Bourdon, C.; Boyadjiev, S.A.; Sharma, R.; Twelves, C.; Whitley, C.B.; Quinn, A.G. Sebelipase alfa over 52weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. *J. Hepatol.,* **2014**, *61*(5), 1135-1142.

[133] Burton, B.K.; Balwani, M.; Feillet, F.; Barić, I.; Burrow, T.A.; Camarena Grande, C.; Coker, M.; Consuelo-Sánchez, A.; Deegan, P.; Di Rocco, M.; Enns, G.M.; Erbe, R.; Ezgu, F.; Ficicioglu, C.; Furuya, K.N.; Kane, J.; Laukaitis, C.; Mengel, E.; Neilan, E.G.; Nightingale, S.; Peters, H.; Scarpa, M.; Schwab, K.O.; Smolka, V.; Valayannopoulos, V.; Wood, M.; Goodman, Z.; Yang, Y.; Eckert, S.; Rojas-Caro, S.; Quinn, A.G. A phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency. *N. Engl. J. Med.,* **2015**, *373*(11), 1010-1020.

[134] Shirley, M. Sebelipase alfa: First global approval. *Drugs,* **2015**, *75*(16), 1935-1940.

[135] Sheridan, C. FDA approves 'farmaceutical' drug from transgenic chickens. *Nat. Biotechnol.*, **2016**, *34*, 117-119.

[136] Frampton, J.E. Sebelipase alfa: A review in lysosomal acid lipase deficiency. *Am. J. Cardiovasc. Drugs,* **2016**, *16*(6), 461-468.

[137] Su, K.; Donaldson, E.; Sharma, R. Novel treatment options for lysosomal acid lipase deficiency: Critical appraisal of sebelipase alfa. *App. Clin. Genet.,* **2016**, *9*, 157-167.

[138] Muenzer, J. The mucopolysaccharidoses: A heterogeneous group of disorders with variable pediatric presentations. *J. Pediatr.*, **2004**, *144*, S27-34.

[139] Clarke, L.A. The mucopolysaccharidoses: A success of molecular medicine. *Expert Rev. Mol. Med.*, **2008**, *10*, e1.

[140] Moore, D.; Connock, M.J.; Wraith, E.; Lavery, C. The prevalence of and survival in Mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. *Orphanet J. Rare Dis.,* **2008**, *3*, 24.

[141] Campos, D.; Monaga, M. Mucopolysaccharidosis type I: Current knowledge on its pathophysiological mechanisms. *Metab. Brain Dis.,* **2012**, *27*(2), 121-129.

[142] Lum, S.H.; Miller, W.; Poulton, K.; Ghosh, A.; Webster, H.; Mercer, J.; Bonney, D.; Jones, S.; Orchard, P.J.; Wynn, R. A 20-year review of the changing pattern of graft failure in cord blood transplant for Hurler syndrome. *Mol. Genet. Metab.,* **2016**, *120*(1), S88.

[143] Fratantoni, J.C.; Hall, C.W.; Neufeld, E.F. Hurler and Hunter syndromes: Mutual correction of the defect in cultured fibroblasts. *Science,* **1968**, *162* 3853), 570-572.

[144] Sando, G.N.; Neufeld, E.F. Recognition and receptor-mediated uptake of a lysosomal enzyme, alpha-l-iduronidase, by cultured human fibroblasts. *Cell*, **1977**, *12*, 619-627.

[145] Bach, G.; Friedman, R.; Weissmann, B.; Neufeld, E.F. The defect in the Hurler and Scheie syndromes: Deficiency of -L-iduronidase. *Proc. Natl. Acad. Sci. USA,* **1972**, *69*(8), 2048-2051.

[146] Bach, G.; Eisenberg, F., Jr.; Cantz, M.; Neufeld, E.F. The defect in the Hunter syndrome: Deficiency of sulfoiduronate sulfatase. *Proc. Natl. Acad. Sci. USA,* **1973**, *70*(7), 2134-2138.

[147] Wraith, J.E.; Clarke, L.A.; Beck, M.; Kolodny, E.H.; Pastores, G.M.; Muenzer, J.; Rapoport, D.M.; Berger, K.I.; Swiedler, S.J.; Kakkis, E.D.; Braakman, T.; Chadbourne, E.; Walton-Bowen, K.; Cox, G.F. Enzyme replacement therapy for mucopolysaccharidosis I: A randomized, double-blinded, placebo-controlled, multinational study of recombinant human α-L-iduronidase (laronidase). *J. Pediatr.,* **2004**, *144*(5), 581-588.

[148] Clarke, L.A.; Wraith, J.E.; Beck, M.; Kolodny, E.H.; Pastores, G.M.; Muenzer, J.; Rapoport, D.M.; Berger, K.I.; Sidman, M.; Kakkis, E.D.; Cox, G.F. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. *Pediatrics*, **2009**, *123*, 229-240.

[149] Giugliani, R.; Rojas, V.M.; Martins, A.M.; Valadares, E.R.; Clarke, J.T.R.; Góes, J.E.C.; Kakkis, E.D.; Worden, M.A.; Sidman, M.; Cox, G.F. A dose-optimization trial of laronidase (Aldurazyme®) in patients with mucopolysaccharidosis I. *Mol. Genet. Metab.,* **2009**, *96*(1), 13-19.

[150] Wraith, J.E.; Beck, M.; Lane, R.; van der Ploeg, A.; Shapiro, E.; Xue, Y.; Kakkis, E.D.; Guffon, N. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: Results of a multinational study of recombinant human alpha-L-iduronidase (laronidase). *Pediatrics*, **2007**, *120*, e37-46.

[151] Perez-Lopez, J.; Morales-Conejo, M.; Lopez-Rodriguez, M.; Hermida-Ameijeiras, A.; Molto-Abad, M. Efficacy of laronidase therapy in patients with mucopolysaccharidosis type I who initiated enzyme replacement therapy in adult age. A systematic review and meta-analysis. *Mol. Genet. Metab.*, **2017**, *121*, 138-149.

[152] Vairo, F.; Federhen, A.; Baldo, G.; Riegel, M.; Burin, M.; Leistner-Segal, S.; Giugliani, R. Diagnostic and treatment strategies in mucopolysaccharidosis VI. *Appl. Clin. Genet.,* **2015**, *8*, 245-55.

[153] Sohn, Y.B.; Cho, S.Y.; Park, S.W.; Kim, S.J.; Ko, A.R.; Kwon, E.K.; Han, S.J.; Jin, D.K. Phase I/II clinical trial of enzyme replacement therapy with idursulfase beta in patients with mucopolysaccharidosis II (Hunter syndrome). *Orphanet J. Rare Dis.,* **2013**, *8*, 42.

[154] Muenzer, J.; Hendriksz, C.J.; Fan, Z.; Vijayaraghavan, S.; Perry, V.; Santra, S.; Solanki, G.A.; Mascelli, M.A.; Pan, L.; Wang, N.; Sciarappa, K.; Barbier, A.J. A phase I/II study of intrathecal idursulfase-IT in children with severe mucopolysaccharidosis II. *Genet. Med.*, **2016**, *18*, 73-81.

[155] Chiong, M.A.D.; Canson, D.M.; Abacan, M.A.R.; Baluyot, M.M.P.; Cordero, C.P.; Silao, C.L.T. Clinical, biochemical and molecular characteristics of Filipino patients with mucopolysaccharidosis type II - Hunter syndrome. *Orphanet J. Rare Dis.,* **2017**, *12*.

[156] Matalon, R.; Arbogast, B.; Justice, P.; Brandt, I.K.; Dorfman, A. Morquio's syndrome: Deficiency of a chondroitin sulfate N-acetylhexosamine sulfate sulfatase. *Biochem. Biophys. Res. Comm.,* **1974**, *61*(2), 759-765.

[157] Hecht, J.T.; Scott, C.I., Jr.; Smith, T.K.; Williams, J.C. Mild manifestations of the Morquio syndrome. *Am. J. Med. Genet.,* **1984**, *18*(2), 369-371.

[158] Groebe, H.; Krins, M.; Schmidberger, H.; von Figura, K.; Harzer, K.; Kresse, H.; Paschke, E.; Sewell, A.; Ullrich, K. Morquio syndrome (mucopolysaccharidosis IV B) associated with beta-galactosidase deficiency. Report of two cases. *Am. J. Hum. Genet.,* **1980**, *32*(2), 258-272.

[159] Ishii, N.; Oohira, T.; Oshima, A.; Sakuraba, H.; Endo, F.; Matsuda, I.; Sukegawa, K.; Orii, T.; Suzuki, Y. Clinical and molecular analysis of a Japanese boy with Morquio B disease. *Clin. Genet.,* **1995**, *48*(2), 103-108.

[160] Kaplan, D.; McKusick, V.; Trebach, S.; Lazarus, R. Keratosulfate-chondroitin sulfate peptide from normal urine and from urine of patients with Morquio syndrome (mucopolysaccharidosis IV). *J. Lab. Clin. Med.*, **1968**, *71*, 48-55.

[161] Prat, C.; Lemaire, O.; Bret, J.; Zabraniecki, L.; Fournié, B. Morquio syndrome: Diagnosis in an adult. *Joint Bone Spine,* **2008**, *75*(4), 495-498.

[162] Hendriksz, C.J.; Giugliani, R.; Harmatz, P.; Mengel, E.; Guffon, N.; Valayannopoulos, V.; Parini, R.; Hughes, D.; Pastores, G.M.; Lau, H.A.; Al-Sayed, M.D.; Raiman, J.; Yang, K.; Mealiffe, M.;

Haller, C. Multi-domain impact of elosulfase alfa in Morquio A syndrome in the pivotal phase III trial. *Mol. Genet. Metab.,* **2015**, *114*(2), 178-185.

[163] Hendriksz, C.; Vellodi, A.; Jones, S.; Takkele, H.; Lee, S.; Chesler, S.; Decker, C. Long term outcomes of a phase 1/2, multicenter, open-label, dose-escalation study to evaluate the safety, tolerability, and efficacy of bmn 110 in patients with mucopolysaccharidosis iva (morquio a syndrome). *Mol. Genet. Metab.,* **2012**, *105*(2), S35.

[164] Hendriksz, C.; Santra, S.; Jones, S.A.; Geberhiwot, T.; Jesaitis, L.; Long, B.; Qi, Y.; Hawley, S.M.; Decker, C. Safety, immunogenicity, and clinical outcomes in patients with Morquio A syndrome participating in 2 sequential open-label studies of elosulfase alfa enzyme replacement therapy (MOR-002/MOR-100), representing 5years of treatment. *Mol. Genet. Metab.*, **2018**, *123*, 479-487.

[165] Hendriksz, C.J.; Burton, B.; Fleming, T.R.; Harmatz, P.; Hughes, D.; Jones, S.A.; Lin, S.P.; Mengel, E.; Scarpa, M.; Valayannopoulos, V.; Giugliani, R.; Slasor, P.; Lounsbury, D.; Dummer, W. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): A phase 3 randomised placebo-controlled study. *J. Inherit. Metab. Dis.,* **2014**, *37*(6), 979-990.

[166] Sanford, M.; Lo, J.H. *Elosulfase alfa*: First global approval. *Drugs,* **2014**, *74*(6), 713-718.

[167] Kantaputra, P.N.; Kayserili, H.; Guven, Y.; Kantaputra, W.; Balci, M.C.; Tanpaiboon, P.; Tananuvat, N.; Uttarilli, A.; Dalal, A. Clinical manifestations of 17 patients affected with mucopolysaccharidosis type VI and eight novel ARSB mutations. *Am. J. Med. Genet.,* **2014**, *164A*(6), 1443-1453.

[168] Jurecka, A.; Golda, A.; Opoka-Winiarska, V.; Piotrowska, E.; Tylki-Szymanska, A., Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) with a predominantly cardiac phenotype. *Mol. Genet. Metab.*, **2011**, *104*, 695-699.

[169] Lin, S.P.; Shih, S.C.; Chuang, C.K.; Lee, K.S.; Chen, M.R.; Niu, D.M.; Chiu, P.C.; Lin, S.J.; Lin, H.Y. Characterization of pulmonary function impairments in patients with mucopolysaccharidoses--changes with age and treatment. *Pediatr. Pulmonol.,* **2014**, *49*(3), 277-284.

[170] Modi, M.; Singla, V.; Khandelwal, N.; Prabhakar, S.; Duberkar, D. Maroteaux-Lamy syndrome (mucopolysaccharidosis VI) presenting as familial myelopathy. *Int. J. Neurosci.,* **2011**, *121*(6), 337-340.

[171] Azevedo, A.; Schwartz, I.V.; Kalakun, L.; Brustolin, S.; Burin, M.G.; Beheregaray, A.P.C.; Leistner, S.; Giugliani, C.; Rosa, M.; Barrios, P.; Marinho, D.; Esteves, P.; Valadares, E.; Boy, R.; Horovitz, D.; Mabe, P.; Da Silva, L.C.S.; De Souza, I.C.N.; Ribeiro, M.; Martins, A.M.; Palhares, D.; Kim, C.A.; Giugliani, R. Clinical and biochemical study of 28 patients with mucopolysaccharidosis type VI. *Clin. Genet.,* **2004**, *66*(3), 208-213.

[172] Harmatz, P.; Whitley, C.B.; Waber, L.; Pais, R.; Steiner, R.; Plecko, B.; Kaplan, P.; Simon, J.; Butensky, E.; Hopwood, J.J. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *J. Pediatr.*, **2004**, *144*, 574-80.

[173] Harmatz, P.; Ketteridge, D.; Giugliani, R.; Guffon, N.; Teles, E.L.; Miranda, M.C.; Yu, Z.F.; Swiedler, S.J.; Hopwood, J.J. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): Results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. *Pediatrics*, 2**005**, *115*, e681-9.

[174] Harmatz, P.; Giugliani, R.; Schwartz, I.; Guffon, N.; Teles, E.L.; Miranda, M.C.; Wraith, J.E.; Beck, M.; Arash, L.; Scarpa, M.; Yu, Z.F.; Wittes, J.; Berger, K.I.; Newman, M.S.; Lowe, A.M.; Kakkis, E.; Swiedler, S.J. Enzyme replacement therapy for mucopolysaccharidosis VI: A phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J. Pediatr.*, **2006**, *148*, 533-539.

[175] Weiss, K.D. Approval package for Application Number BLA 125117/0. United States Food and Drug Administration: Rockville, MD, **2005**.

[176] Giugliani, R.; Lampe, C.; Guffon, N.; Ketteridge, D.; Leao-Teles, E.; Wraith, J.E.; Jones, S.A.; Piscia-Nichols, C.; Lin, P.; Quartel, A.; Harmatz, P. Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)--10-year follow-up of patients who previously participated in an MPS VI Survey Study. *Am. J. Med. Genet.,* **2014**, *164A*(8), 1953-1964.

[177] Turbeville, S.; Nicely, H.; Rizzo, J.D.; Pedersen, T.L.; Orchard, P.J.; Horwitz, M.E.; Horwitz, E.M.; Veys, P.; Bonfim, C.; Al-Seraihy, A. Clinical outcomes following hematopoietic stem cell transplantation for the treatment of mucopolysaccharidosis VI. *Mol. Genet. Metab.,* **2011**, *102*(2), 111-115.

[178] Jester, S.; Larsson, J.; Eklund, E.A.; Papadopoulou, D.; Mansson, J.E.; Bekassy, A.N.; Turkiewicz, D.; Toporski, J.; Ora, I. Haploidentical stem cell transplantation in two children with mucopolysaccharidosis VI: Clinical and biochemical outcome. *Orphanet J. Rare Dis.,* **2013**, *8*, 134.

[179] Giugliani, R.; Herber, S.; Lapagesse, L.; de Pinto, C.; Baldo, G. Therapy for mucopolysaccharidosis VI: (Maroteaux-Lamy syndrome) present status and prospects. *Pediatr. Endocrinol. Rev.,* **2014**, *12*(Suppl 1), 152-158.

[180] Boado, R.J.; Zhang, Y.; Xia, C.F.; Wang, Y.; Pardridge, W.M. Genetic engineering of a lysosomal enzyme fusion protein for targeted delivery across the human blood-brain barrier. *Biotechnol. Bioeng.,* **2008**, *99*(2), 475-484.

[181] Boado, R.J.; Pardridge, W.M. Brain and organ uptake in the rhesus monkey *in vivo* of recombinant iduronidase compared to an insulin receptor antibody-iduronidase fusion protein. *Mol. Pharm.,* **2017**, *14*(4), 1271-1277.

[182] Boado, R.J.; Hui, E.K.; Lu, J.Z.; Sumbria, R.K.; Pardridge, W.M. Blood-brain barrier molecular trojan horse enables imaging of brain uptake of radioiodinated recombinant protein in the rhesus monkey. *Bioconjug. Chem.,* **2013**, *24*(10), 1741-1749.

[183] Boado, R.J.; Lu, J.Z.; Hui, E.K.-W.; Pardridge, W.M. Insulin receptor antibody-sulfamidase fusion protein penetrates the primate blood-brain barrier and reduces glycosoaminoglycans in Sanfilippo type A cells. *Mol. Pharm.,* **2014**, *11*(8), 2928-2934.

[184] Boado, R.J.; Lu, J.Z.; Hui, E.K.-W.; Lin, H.; Pardridge, W.M. Insulin receptor antibody-α-N-acetylglucosaminidase fusion protein penetrates the primate blood-brain barrier and reduces glycosoaminoglycans in sanfilippo type B fibroblasts. *Mol. Pharm.,* **2016**, *13*(4), 1385-1392.

[185] Ghosh, A.; Rust, S.; Weisberg, D.; Canal, M.; Wijburg, F.A.; Vaz, F.M.; Tylee, K.L.; Church, H.J.; Hepburn, M.; Bigger, B.W.; Jones, S.A. High dose genistein aglycone in Sanfilippo syndrome: Results of a randomised, double-blinded, placebo controlled clinical trial. *Mol. Genet. Metab.* **2018**, *123*(2), S51-S52.

[186] de Ruijter, J.; Valstar, M.J.; Narajczyk, M.; Wegrzyn, G.; Kulik, W.; Ijlst, L.; Wagemans, T.; van der Wal, W.M.; Wijburg, F.A. Genistein in Sanfilippo disease: A randomized controlled crossover trial. *Ann. Neurol.,* **2012**, *71*(1), 110-120.

[187] Piotrowska, E.; Jakóbkiewicz-Banecka, J.; Tylki-Szymanska, A.; Liberek, A.; Maryniak, A.; Malinowska, M.; Czartoryska, B.; Puk, E.; Kloska, A.; Liberek, T.; Baranska, S.; Wegrzyn, A.; Wegrzyn, G. Genistin-rich soy isoflavone extract in substrate reduction therapy for Sanfilippo syndrome: An open-label, pilot study in 10 pediatric patients. *Curr. Ther. Res. Clin. E,* **2008**, *69*(2), 166-179.

[188] Roberts, A.L.; Thomas, B.J.; Wilkinson, A.S.; Fletcher, J.M.; Byers, S. Inhibition of glycosaminoglycan synthesis using rhodamine B in a mouse model of mucopolysaccharidosis type IIIA. *Pediatr. Res.*, **2006**, *60*, 309-314.

[189] Roberts, A.L.; Rees, M.H.; Klebe, S.; Fletcher, J.M.; Byers, S. Improvement in behaviour after substrate deprivation therapy with rhodamine B in a mouse model of MPS IIIA. *Mol. Genet. Metab.*, **2007**, *92*, 115-121.

[190] Roberts, A.L.; Fletcher, J.M.; Moore, L.; Byers, S. Transgenerational exposure to low levels of rhodamine B does not adversely affect litter size or liver function in murine mucopolysaccharidosis type IIIA. *Mol. Genet. Metab.*, **2010**, *101*, 208-213.

[191] Biffi, A.; Lucchini, G.; Rovelli, A.; Sessa, M. Metachromatic leukodystrophy: An overview of current and prospective treatments. *Bone Marrow Transplant.*, **2008**, *42*(Suppl 2), S2-6.

[192] van Rappard, D.F.; Boelens, J.J.; Wolf, N.I. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. *Best Pract. Res. Clin. En. Metab.,* **2015**, *29*(2), 261-273.

[193] Cesani, M.; Lorioli, L.; Grossi, S.; Amico, G.; Fumagalli, F.; Spiga, I.; Filocamo, M.; Biffi, A. Mutation Update of ARSA and PSAP genes causing metachromatic leukodystrophy. *Hum. Mutat.,* **2016**, *37*(1), 16-27.

[194] Eichler, F.; Grodd, W.; Grant, E.; Sessa, M.; Biffi, A.; Bley, A.; Kohlschuetter, A.; Loes, D.J.; Kraegeloh-Mann, I. Metachromatic leukodystrophy: A scoring system for brain MR imaging observations. *Am. J. Neuroradiol.*, **2009**, *30,* 1893-1897.

[195] Matzner, U.; Herbst, E.; Hedayati, K.K.; Lullmann-Rauch, R.; Wessig, C.; Schroder, S.; Eistrup, C.; Moller, C.; Fogh, J.; Gieselmann, V. Enzyme replacement improves nervous system pathology and function in a mouse model for metachromatic leukodystrophy. *Hum. Mol. Genet.*, **2005**, *14*, 1139-1152.

[196] Stroobants, S.; Gerlach, D.; Matthes, F.; Hartmann, D.; Fogh, J.; Gieselmann, V.; D'Hooge, R.; Matzner, U. Intracerebroventricular enzyme infusion corrects central nervous system pathology and dysfunction in a mouse model of metachromatic leukodystrophy. *Hum. Mol. Genet.*, **2011**, *20*, 2760-2769.

[197] Matthes, F.; Stroobants, S.; Gerlach, D.; Wohlenberg, C.; Wessig, C.; Fogh, J.; Gieselmann, V.; Eckhardt, M.; D'Hooge, R.; Matzner, U. Efficacy of enzyme replacement therapy in an aggravated mouse model of metachromatic leukodystrophy declines with age. *Hum. Mol. Genet.*, **2012**, *21*, 2599-2609.

[198] Biffi, A.; Montini, E.; Lorioli, L.; Cesani, M.; Fumagalli, F.; Plati, T.; Baldoli, C.; Martino, S.; Calabria, A.; Canale, S.; Benedicenti, F.; Vallanti, G.; Biasco, L.; Leo, S.; Kabbara, N.; Zanetti, G.; Rizzo, W.B.; Mehta, N.A.L.; Cicalese, M.P.; Casiraghi, M.; Boelens, J.J.; Del Carro, U.; Dow, D.J.; Schmidt, M.; Assanelli, A.; Neduva, V.; Di Serio, C.; Stupka, E.; Gardner, J.; von Kalle, C.; Bordignon, C.; Ciceri, F.; Rovelli, A.; Roncarolo, M.G.; Aiuti, A.; Sessa, M.; Naldini, L. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. *Science,* **2013**, *341*(6148), 1233158.

[199] Sessa, M.; Lorioli, L.; Fumagalli, F.; Acquati, S.; Redaelli, D.; Baldoli, C.; Canale, S.; Lopez, I.D.; Morena, F.; Calabria, A.; Fiori, R.; Silvani, P.; Rancoita, P.M.V.; Gabaldo, M.; Benedicenti, F.; Antonioli, G.; Assanelli, A.; Cicalese, M.P.; del Carro, U.; Sora, M.G.N.; Martino, S.; Quattrini, A.; Montini, E.; Di Serio, C.; Ciceri, F.; Roncarolo, M.G.; Aiuti, A.; Naldini, L.; Biffi, A. Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: An ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. *Lancet,* **2016**, *388*(10043), 476-487.

[200] Tarui, S.; Okuno, G.; Ikura, Y.; Tanaka, T.; Suda, M.; Nishikawa, M. Phosphofructokinase deficiency in skeletal muscle. a new type of glycogenosis. *Biochem. Biophys. Res. Commun.*, **1965**, *19*, 517-523.

[201] Vissing, J.; Di Donato, S.; Taroni, F.; Karpati, G. Metabolic Myopathies. In: *Disorders of voluntary muscles*; Hilton-Jones, D.; Bushby, K.; Griggs, R.C.; Eds. Cambridge University Press: Cambridge, **2001**.

[202] Raben, N.; Sherman, J.B. Mutations in muscle phosphofructokinase gene. *Hum. Mutat.,* **1995**, *6*(1), 1-6.

[203] Banaszak, K.; Mechin, I.; Obmolova, G.; Oldham, M.; Chang, S.H.; Ruiz, T.; Radermacher, M.; Kopperschlager, G.; Rypniewski, W. The crystal structures of eukaryotic phosphofructokinases from baker's yeast and rabbit skeletal muscle. *J. Mol. Biol.*, **2011**, *407*, 284-297.

[204] Bruser, A.; Kirchberger, J.; Schoneberg, T. Altered allosteric regulation of muscle 6-phosphofructokinase causes Tarui disease. *Biochem. Biophys. Res. Commun.*, **2012**, *427*, 133-137.

[205] Malfatti, E.; Birouk, N.; Romero, N.B.; Piraud, M.; Petit, F.M.; Hogrel, J.Y.; Laforet, P. Juvenile-onset permanent weakness in muscle phosphofructokinase deficiency. *J. Neurol. Sci.*, **2012**, *316*, 173-177.

[206] Musumeci, O.; Bruno, C.; Mongini, T.; Rodolico, C.; Aguennouz, M.; Barca, E.; Amati, A.; Cassandrini, D.; Serlenga, L.; Vita, G.; Toscano, A. Clinical features and new molecular findings in muscle phosphofructokinase deficiency (GSD type VII). *Neuromuscul. Disord.*, **2012**, *22*, 325-330.

[207] Swoboda, K.J.; Specht, L.; Jones, H.R.; Shapiro, F.; DiMauro, S.; Korson, M. Infantile phosphofructokinase deficiency with arthrogryposis: Clinical benefit of a ketogenic diet. *J. Pediatr.*, **1997**, *131*, 932-924.

[208] Toscano, A.; Musumeci, O. Tarui disease and distal glycogenoses: Clinical and genetic update. *Acta. Myol.,* **2007**, *26*(2), 105-107.

[209] Tarui, S.; Kono, N.; Nasu, T.; Nishikawa, M. Enzymatic basis for the coexistence of myopathy and hemolytic disease in inherited muscle phosphofructokinase deficiency. *Biochem. Biophys. Res. Commun.*, **1969**, *34*, 77-83.

[210] Manoli, I.; Myles, J.G.; Sloan, J.L.; Shchelochkov, O.A.; Venditti, C.P. A critical reappraisal of dietary practices in methylmalonic acidemia raises concerns about the safety of medical foods. Part 1: Isolated methylmalonic acidemias. *Genet. Med.,* **2016**, *18*(4), 386-395.

[211] Randle, P.J. Regulatory interactions between lipids and carbohydrates: The glucose fatty acid cycle after 35 years. *Diabet. Metab. Rev.*, **1998**, *14*, 263-283.

[212] Ugarte, M.; Perez-Cerda, C.; Rodriguez-Pombo, P.; Desviat, L.R.; Perez, B.; Richard, E.; Muro, S.; Campeau, E.; Ohura, T.; Gravel, R.A. Overview of mutations in the PCCA and PCCB genes causing propionic acidemia. *Hum. Mutat.*, **1999**, *14*, 275-282.

[213] Desviat, L.R.; Perez, B.; Perez-Cerda, C.; Rodriguez-Pombo, P.; Clavero, S.; Ugarte, M. Propionic acidemia: Mutation update and functional and structural effects of the variant alleles. *Mol. Genet. Metab.*, **2004**, *83*, 28-37.

[214] Gupta, D.; Bijarnia-Mahay, S.; Kohli, S.; Saxena, R.; Puri, R.D.; Shigematsu, Y.; Yamaguchi, S.; Sakamoto, O.; Gupta, N.; Kabra, M.; Thakur, S.; Deb, R.; Verma, I.C. Seventeen novel mutations in PCCA and PCCB genes in indian propionic acidemia patients, and their outcomes. *Genet. Test Mol. Biomarkers,* **2016**, *20*(7), 373-382.

[215] Childs, B.; Nyhan, W.L.; Borden, M.; Bard, L.; Cooke, R.E. Idiopathic hyperglycinemia and hyperglycinuria: A new disorder of amino acid metabolism. I. *Pediatrics,* **1961**, *27*, 522-538.

[216] Hsia, Y.E.; Scully, K.J.; Rosenberg, L.E. Defective propionate carboxylation in ketotic hyperglycinaemia. *Lancet*, **1969**, *1*, 757-758.

[217] Brandt, I.K.; Hsia, Y.E.; Clement, D.H.; Provence, S.A. Propionicacidemia (ketotic hyperglycinemia): Dietary treatment resulting in normal growth and development. *Pediatrics,* **1974**, *53*(3), 391-395.

[218] Hillman, R.E.; Keating, J.P.; Williams, J.C. Biotin-responsive propionic acidemia presenting as the rumination syndrome. *J. Pediatr.,* **1978**, *92*(3), 439-441.

[219] Morrow, G., 3rd; Barness, L.A.; Cardinale, G.J.; Abeles, R.H.; Flaks, J.G. Congenital methylmalonic acidemia: Enzymatic evidence for two forms of the disease. *Proc. Natl. Acad. Sci. USA,* **1969**, *63*(1), 191-197.

[220] Barness, L.A.; Morrow, G., 3rd. Methylmalonic aciduria, a newly discovered inborn error. *Ann. Intern. Med.,* **1968**, *69*(3), 633-635.

[221] Wasserstein, M.P.; Gaddipati, S.; Snyderman, S.E.; Eddleman, K.; Desnick, R.J.; Sansaricq, C. Successful pregnancy in severe methylmalonic acidaemia. *J. Inherit. Metab. Dis.,* **1999**, *22*(7), 788-794.

[222] Andersson, H.C.; Shapira, E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). *J. Pediatr.*, **1998**, *132*, 121-124.

[223] Ampola, M.G.; Mahoney, M.J.; Nakamura, E.; Tanaka, K. Prenatal therapy of a patient with vitamin-B12-responsive methylmalonic acidemia. *N. Engl. J. Med.,* **1975**, *293*(7), 313-317.

[224] Newman, C.G.; Wilson, B.D.; Callaghan, P.; Young, L. Neonatal death associated with isovalericacidaemia. *Lancet*, **1967**, *2*, 439-442.

[225] Tanaka, K.; Budd, M.A.; Efron, M.L.; Isselbacher, K.J. Isovaleric acidemia: A new genetic defect of leucine metabolism. *Proc. Natl. Acad. Sci. USA,* **1966**, *56*(1), 236-242.

[226] Budd, M.A.; Tanaka, K.; Holmes, L.B.; Efron, M.L.; Crawford, J.D.; Isselbacher, K.J. Isovaleric acidemia. Clinical features of a new genetic defect of leucine metabolism. *N. Engl. J. Med.,* **1967**, *277*(7), 321-7.

[227] Sidbury, J.B., Jr.; Smith, E.K.; Harlan, W. An inborn error of short-chain fatty acid metabolism. The odor-of-sweaty-feet syndrome. *J. Pediatr.,* **1967**, *70*(1), 8-15.

[228] Cohn, R.M.; Yudkoff, M.; Rothman, R.; Segal, S. Isovaleric acidemia: Use of glycine therapy in neonates. *N. Engl. J. Med.,* **1978**, *299*(18), 996-999.

[229] Naglak, M.; Salvo, R.; Madsen, K.; Dembure, P.; Elsas, L. The treatment of isovaleric acidemia with glycine supplement. *Pediatr. Res.,* **1988**, *24*(1), 9-13.

[230] Dancis, J.; Levitz, M.; Westall, R.G. Maple syrup urine disease: Branched-chain keto-aciduria. *Pediatrics,* **1960**, *25*, 72-79.

[231] de Baulny, H.O.; Saudubray, J.-M. Branched-Chain Organic Acidurias. In: *Inborn Metabolic Diseases: Diagnosis and Treatment*, Fernandes, J.; Saudubray, J.-M.; Van den Berghe, G., Eds. Springer: Berlin, Heidelberg, **2000**; pp. 196-212.

[232] Kalyanaraman, K.; Chamukuttan, S.; Arjundas, G.; Gajanan, N.; Ramamurthi, B. Maple syrup urine disease (branched-chain ketoaciduria) variant type manifesting as hyperkinetic behaviour and mental retardation. Report of two cases. *J. Neurol. Sci.*, **1972**, *15*, 209-217.

[233] Schulman, J.D.; Lustberg, T.J.; Kennedy, J.L.; Museles, M.; Seegmiller, J.E. A new variant of maple syrup urine disease (branched

chain ketoaciduria). Clinical and biochemical evaluation. *Am. J. Med.*, **1970**, *49*, 118-124.

[234] Schadewaldt, P.; Bodner-Leidecker, A.; Hammen, H.W.; Wendel, U. Whole-body L-leucine oxidation in patients with variant form of maple syrup urine disease. *Pediatr. Res.,* **2001**, *49*(5), 627-635.

[235] Scriver, C.R.; Mackenzie, S.; Clow, C.L.; Delvin, E. Thiamine-responsive maple-syrup-urine disease. *Lancet*, **1971**, *1*, 310-312.

[236] Duran, M.; Tielens, A.G.; Wadman, S.K.; Stigter, J.C.; Kleijer, W.J. Effects of thiamine in a patient with a variant form of branched-chian ketoaciduria. *Acta Paediatr. Scand.,* **1978**, *67*(3), 367-372.

[237] Duran, M.; Wadman, S.K. Thiamine-responsive inborn errors of metabolism. *J. Inherit. Metab. Dis.,* **1985**, *8*(Suppl 1), 70-75.

[238] Zhang, B.; Wappner, R.S.; Brandt, I.K.; Harris, R.A.; Crabb, D.W. Sequence of the E1 alpha subunit of branched-chain alpha-ketoacid dehydrogenase in two patients with thiamine-responsive maple syrup urine disease. *Am. J. Hum. Genet.,* **1990**, *46*(4), 843-846.

[239] Hong, Y.S.; Kerr, D.S.; Craigen, W.J.; Tan, J.; Pan, Y.; Lusk, M.; Patel, M.S. Identification of two mutations in a compound heterozygous child with dihydrolipoamide dehydrogenase deficiency. *Hum. Mol. Genet.*, **1996**, *5*, 1925-1930.

[240] Morton, D.H.; Strauss, K.A.; Robinson, D.L.; Puffenberger, E.G.; Kelley, R.I. Diagnosis and treatment of maple syrup disease: A study of 36 patients. *Pediatrics,* **2002**, *109*(6), 999-1008.

[241] Engel, K.; Hohne, W.; Haberle, J. Mutations and polymorphisms in the human argininosuccinate synthetase (ASS1) gene. *Hum. Mutat.,* **2009**, *30*(3), 300-307.

[242] Li, C.M.; Chao, H.K.; Liu, Y.F.; Su, T.S. A nonsense mutation is responsible for the RNA-negative phenotype in human citrullinaemia. *Eur. J. Hum. Genet.,* **2001**, *9*(9), 685-689.

[243] Kobayashi, K.; Shaheen, N.; Terazono, H.; Saheki, T. Mutations in argininosuccinate synthetase mRNA of Japanese patients, causing classical citrullinemia. *Am. J. Hum. Genet.,* **1994**, *55*(6), 1103-1112.

[244] Diez-Fernandez, C.; Wellauer, O.; Gemperle, C.; Rufenacht, V.; Fingerhut, R.; Haberle, J. Kinetic mutations in argininosuccinate synthetase deficiency: Characterisation and *in vitro* correction by substrate supplementation. *J. Med. Genet.*, **2016**; *53*, 710-719.

[245] Vilaseca, M.A.; Kobayashi, K.; Briones, P.; Lambruschini, N.; Campistol, J.; Tabata, A.; Alomar, A.; Rodes, M.; Lluch, M.; Saheki, T. Phenotype and genotype heterogeneity in Mediterranean citrullinemia. *Mol. Genet. Metab.*, **2001**, *74*, 396-398.

[246] Gucer, S.; Asan, E.; Atilla, P.; Tokatli, A.; Caglar, M. Early cirrhosis in a patient with type I citrullinaemia (CTLN1). *J. Inherit. Metab. Dis.,* **2004**, *27*(4), 541-542.

[247] Alfadhel, M.; Mutairi, F.A.; Makhseed, N.; Jasmi, F.A.; Al-Thihli, K.; Al-Jishi, E.; AlSayed, M.; Al-Hassnan, Z.N.; Al-Murshedi, F.; Haberle, J.; Ben-Omran, T. Guidelines for acute management of hyperammonemia in the Middle East region. *Ther. Clin. Risk Manag.,* **2016**, *12*, 479-487.

[248] Williams, R.A.; Mamotte, C.D.; Burnett, J.R. Phenylketonuria: An inborn error of phenylalanine metabolism. *Clin. Biochem. Rev.,* **2008**, *29*(1), 31-41.

[249] Blau, N.; van Spronsen, F.J.; Levy, H.L. Phenylketonuria. *Lancet*, **2010**, *376*, 1417-1427.

[250] Folling, I. The discovery of phenylketonuria. *Acta Paediatr. Suppl.,* **1994**, *407*, 4-10.

[251] Scriver, C.R. The PAH gene, phenylketonuria, and a paradigm shift. *Hum. Mutat.,* **2007**, *28*(9), 831-845.

[252] Christ, S.E. Asbjorn Folling and the discovery of phenylketonuria. *J. Hist. Neurosci.,* **2003**, *12*(1), 44-54.

[253] van Spronsen, F.J. Phenylketonuria: A 21st century perspective. *Nat. Rev. Endocrinol.*, **2010**, *6*, 509-514.

[254] Dyer, C.A. Pathophysiology of phenylketonuria. *Ment. Retard. Dev. Disabil. Res. Rev.,* **1999**, *5*(2), 104-112.

[255] Smith, I.; Beasley, M.G.; Ades, A.E. Intelligence and quality of dietary treatment in phenylketonuria. *Arch. Dis. Child.,* **1990**, *65*(5), 472-478.

[256] Loeber, J.G. Neonatal screening in Europe; the situation in 2004. *J. Inherit. Metab. Dis.,* **2007**, *30*(4), 430-438.

[257] Wolf, B.; Grier, R.E.; Secor McVoy, J.R.; Heard, G.S. Biotinidase deficiency: A novel vitamin recycling defect. *J. Inherit. Metab. Dis.,* **1985**, *8*(Suppl 1), 53-58.

[258] Pomponio, R.J.; Hymes, J.; Reynolds, T.R.; Meyers, G.A.; Fleischhauer, K.; Buck, G.A.; Wolf, B. Mutations in the human biotinidase gene that cause profound biotinidase deficiency in symptomatic children: Molecular, biochemical, and clinical analysis. *Pediatr. Res.,* **1997**, *42*(6), 840-848.

[259] Pindolia, K.; Jordan, M.; Wolf, B. Analysis of mutations causing biotinidase deficiency. *Hum. Mutat.,* **2010**, *31*(9), 983-991.

[260] Muhl, A.; Moslinger, D.; Item, C.B.; Stockler-Ipsiroglu, S. Molecular characterisation of 34 patients with biotinidase deficiency ascertained by newborn screening and family investigation. *Eur. J. Hum. Genet.,* **2001**, *9*(4), 237-243.

[261] Zempleni, J.; Barshop, B.A.; Cordonier, E.L.; Baier, S.R.; Gartsman, I. Disorders of biotin metabolism. In: *The metabolic and molecular bases of inherited disease*, Valle, D.; Beaudet, A.L.; Vogelstein, B.; Kinzler, K.W.; Antonarakis, S.E.; Ballabio, A.; Gibson, K.M.; Mitchell, G., Eds. McGraw-Hill: New York, **2001**; 39353962.

[262] Wolf, B.; Grier, R.E.; Allen, R.J.; Goodman, S.I.; Kien, C.L. Biotinidase deficiency: The enzymatic defect in late-onset multiple carboxylase deficiency. *Clin. Chim. Acta*, **1983**, *131*, 273-281.

[263] Burri, B.J.; Sweetman, L.; Nyhan, W.L. Mutant holocarboxylase synthetase: Evidence for the enzyme defect in early infantile biotin-responsive multiple carboxylase deficiency. *J. Clin. Invest.,* **1981**, *68*(6), 1491-1495.

[264] Baumgartner, E.R.; Suormala, T.; Wick, H.; Bausch, J.; Bonjour, J.P. Biotinidase deficiency: Factors responsible for the increased biotin requirement. *J. Inherit. Metab. Dis.,* **1985**, *8*(Suppl 1), 59-64.

[265] Hymes, J.; Wolf, B. Biotinidase and its roles in biotin metabolism. *Clin. Chim. Acta.*, **1996**, *255*, 1-11.

[266] Roth, K.S.; Yang, W.; Foremann, J.W.; Rothman, R.; Segal, S. Holocarboxylase synthetase deficiency: A biotin-responsive organic acidemia. *J. Pediatr.,* **1980**, *96*(5), 845-849.

[267] Dupuis, L.; Campeau, E.; Leclerc, D.; Gravel, R.A. Mechanism of biotin responsiveness in biotin-responsive multiple carboxylase deficiency. *Mol. Genet. Metab.*, **1999**, *66*, 80-90.

[268] Wolf, B. Biotinidase Deficiency: New Directions and Practical Concerns. *Curr. Treat. Options Neurol.,* **2003**, *5*(4), 321-328.

[269] Pindolia, K.; Jordan, M.; Guo, C.; Matthews, N.; Mock, D.M.; Strovel, E.; Blitzer, M.; Wolf, B. Development and characterization of a mouse with profound biotinidase deficiency: A biotin-responsive neurocutaneous disorder. *Mol. Genet. Metab.,* **2011**, *102*(2), 161-169.

[270] El-Hattab, A.W.; Adesina, A.M.; Jones, J.; Scaglia, F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. *Mol. Genet. Metab.*, **2015**, *116*, 4-12.

[271] Uusimaa, J.; Moilanen, J.S.; Vainionpaa, L.; Tapanainen, P.; Lindholm, P.; Nuutinen, M.; Lopponen, T.; Maki-Torkko, E.; Rantala, H.; Majamaa, K. Prevalence, segregation, and phenotype of the mitochondrial DNA 3243A>G mutation in children. *Ann. Neurol.,* **2007**, *62*(3), 278-287.

[272] Hirano, M.; Pavlakis, S.G. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS): Current concepts. *J. Child Neurol.,* **1994**, *1*, 4-13.

[273] Wallace, D.C. Diseases of the mitochondrial DNA. *Annu. Rev. Biochem.,* **1992**, *61*, 1175-212.

[274] Pfeffer, G.; Majamaa, K.; Turnbull, D.M.; Thorburn, D.; Chinnery, P.F. Treatment for mitochondrial disorders. *Cochrane Database Syst. Rev.,* **2012**, (4), CD004426.

[275] Koga, Y.; Akita, Y.; Nishioka, J.; Yatsuga, S.; Povalko, N.; Tanabe, Y.; Fujimoto, S.; Matsuishi, T. L-arginine improves the symptoms of strokelike episodes in MELAS. *Neurology*, **2005**, *64*, 710-712.

[276] Koga, Y.; Akita, Y.; Nishioka, J.; Yatsuga, S.; Povalko, N.; Katayama, K.; Matsuishi, T. MELAS and L-arginine therapy. *Mitochondrion*, **2007**, *7*, 133-139.

[277] Kubota, M.; Sakakihara, Y.; Mori, M.; Yamagata, T.; Momoi-Yoshida, M. Beneficial effect of l-arginine for stroke-like episode in MELAS. *Brain Dev.,* **2004**, *26*(7), 481-483.

[278] El-Hattab, A.W.; Hsu, J.W.; Emrick, L.T.; Wong, L.J.; Craigen, W.J.; Jahoor, F.; Scaglia, F. Restoration of impaired nitric oxide production in MELAS syndrome with citrulline and arginine supplementation. *Mol. Genet. Metab.,* **2012**, *105*(4), 607-614.

[279] El-Hattab, A.W.; Emrick, L.T.; Hsu, J.W.; Chanprasert, S.; Almannai, M.; Craigen, W.J.; Jahoor, F.; Scaglia, F. Impaired nitric oxide production in children with MELAS syndrome and the effect of arginine and citrulline supplementation. *Mol. Genet. Metab.,* **2016**, *117*(4), 407-412.

[280] El-Hattab, A.W.; Almannai, M.; Scaglia, F. Arginine and citrulline for the treatment of MELAS syndrome. *J. Inborn Errors Metab.*

Screen., **2017**, *5*, doi: 10.1177/2326409817697399. Epub 2017 Mar 24.

[281] Abe, K.; Matsuo, Y.; Kadekawa, J.; Inoue, S.; Yanagihara, T. Effect of coenzyme Q10 in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): Evaluation by noninvasive tissue oximetry. *J. Neurol. Sci.*, **1999**, *162*, 65-68.

[282] Glover, E.I.; Martin, J.; Maher, A.; Thornhill, R.E.; Moran, G.R.; Tarnopolsky, M.A. A randomized trial of coenzyme Q10 in mitochondrial disorders. *Muscle Nerve,* **2010**, *42*(5), 739-748.

[283] Ikejiri, Y.; Mori, E.; Ishii, K.; Nishimoto, K.; Yasuda, M.; Sasaki, M. Idebenone improves cerebral mitochondrial oxidative metabolism in a patient with MELAS. *Neurology,* **1996**, *47*(2), 583-585.

[284] Napolitano, A.; Salvetti, S.; Vista, M.; Lombardi, V.; Siciliano, G.; Giraldi, C. Long-term treatment with idebenone and riboflavin in a patient with MELAS. *Neurol. Sci.,* **2000**, *21*(5 Suppl), S981-982.

[285] Parikh, S.; Goldstein, A.; Koenig, M.K.; Scaglia, F.; Enns, G.M.; Saneto, R.; Anselm, I.; Cohen, B.H.; Falk, M.J.; Greene, C.; Gropman, A.L.; Haas, R.; Hirano, M.; Morgan, P.; Sims, K.; Tarnopolsky, M.; Van Hove, J.L.K.; Wolfe, L.; DiMauro, S. Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial medicine society. *Genet. Med.,* **2015**, *17*(9), 689-701.

[286] Ohashi, T. Enzyme replacement therapy for lysosomal storage diseases. *Pediatr. Endocrinol. Rev.,* **2012**, *10*(Suppl 1), 26-34.

[287] Ruiz de Garibay, A.P.; Solinis, M.A.; Rodriguez-Gascon, A. Gene therapy for fabry disease: A review of the literature. *BioDrugs,* **2013**, *27*(3), 237-246.

[288] Aronovich, E.L.; Hackett, P.B. Lysosomal storage disease: Gene therapy on both sides of the blood-brain barrier. *Mol. Genet. Metab.,* **2015**, *114*(2), 83-93.

[289] Chandler, R.J.; Venditti, C.P. Gene therapy for metabolic diseases. *Trans. Sci. Rare Dis.,* **2016**, *1*(1), 73-89.

[290] Rastall, D.P.W.; Amalfitano, A. Recent advances in gene therapy for lysosomal storage disorders. *Appl. Clin. Genet.,* **2015**, *8*, 157-169.

[291] Esteban Alberto, G.; Guilherme, B. Gene therapy for lysosomal storage disorders: Recent advances and limitations. *J. Inborn Error Metab. Screen.,* **2017**, *5*.

[292] Penati, R.; Fumagalli, F.; Calbi, V.; Bernardo, M.E.; Aiuti, A. Gene therapy for lysosomal storage disorders: Recent advances for metachromatic leukodystrophy and mucopolysaccaridosis I. *J. Inherit. Metab. Dis.,* **2017**, *40*(4), 543-554.

[293] Lee, K.; Jin, X.; Zhang, K.; Copertino, L.; Andrews, L.; Baker-Malcolm, J.; Geagan, L.; Qiu, H.; Seiger, K.; Barngrover, D.; McPherson, J.M.; Edmunds, T. A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease. *Glycobiology*, **2003**, *13*, 305-313.

[294] Dumont, J.; Euwart, D.; Mei, B.; Estes, S.; Kshirsagar, R. Human cell lines for biopharmaceutical manufacturing: History, status, and future perspectives. *Crit. Rev. Biotechnol.,* **2016**, *36*(6), 1110-1122.

[295] Beck, M. Alglucosidase alfa: Long term use in the treatment of patients with Pompe disease. *Ther. Clin. Risk Manag.,* **2009**, *5*, 767-772.

[296] Griebel, D. Approval package for application number BLA 125291/136. United States Food and Drug Administration: **2014**.

[297] Miebach, E. Enzyme replacement therapy in mucopolysaccharidosis type I. *Acta Pædiatrica,* **2005**, *94*, 58-60.

[298] Lourenço, C.M.; Giugliani, R. Evaluation of galsulfase for the treatment of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *Expert Opin. Orphan Drugs*, **2014**, *2*(4), 407-417.