Review Article

J Mucopolysacch Rare Dis 2021;5(1):22-28
https://doi.org/10.19125/jmrd.2021.5.1.22
pISSN 2465-8936 · eISSN 2465-9452

JMRD
Journal of Mucopolysaccharidosis and Rare Diseases

Novel Therapeutic Approaches to Mucopolysaccharidosis Type III

Aram Yang

Department of Pediatrics, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Mucopolysaccharidosis type III (MPS III) or Sanfilippo disease is an orphan-inherited lysosomal storage disease. It is one of the most common MPS subtypes. The classical presentation is an infantile-onset neurodegenerative disease characterized by intellectual regression, behavioral and sleep disturbances, loss of ambulation, and early death. Unlike other MPS, no disease-modifying therapy has been approved. Here, we review the curative therapy developed for MPS III, from historically ineffective hematopoietic stem cell transplantation and substrate reduction therapy to the promising enzyme replacement therapy or adeno-associated/lentiviral vector-mediated gene therapy. Preclinical studies are presented with recent translational first-in-man trials. We also present experimental research with preclinical mRNA and gene-editing strategies. Lessons from animal studies and clinical trials have highlighted the importance of early therapy before extensive neuronal loss. Disease-modifying therapy for MPS III will likely mandate the development of new early diagnosis strategies.

Keywords: Mucopolysaccharidosis type III, Sanfilippo disease, Lysosomal storage disease, Heparin sulfate, Gene therapy, Substrate reduction therapy

Introduction

Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) is a rare, autosomal recessive, inborn error of glycosaminoglycan (GAG) metabolism with an estimated incidence of 0.28–4.1 per 100,000 live births. This condition belongs to a group of genetic disorders called MPS, which are caused by different single-enzyme defects affecting lysosomal GAG breakdown. MPS III is caused by the deficient activity of any one of four enzymes involved in GAG heparan sulfate (HS) breakdown in lysosomes. The disease is divided into four distinct subtypes based on the gene defect and corresponding enzyme deficiency, as follows: MPS IIIA (SGSH (N-sulfoglucosamine sulfohydrolase) gene; heparan N- sulfatase deficiency), MPS IIIB (NAGLU (N-acetyl-alpha-glucosaminidase) gene; N-acetyl-α-glucosaminidase deficiency), MPS IIIC (HGSNAT (heparan-α-glucosaminide N-acetyltransferase) gene; acetyl CoA:α-glucosaminide N-acetyltransferase deficiency), and MPS IIID (GNS (N-acetyl-glucosamine-6-sulfatase) gene; N-acetylglucosamine 6-sulfatase deficiency)[1]. These enzymatic defects result in progressive intralysosomal accumulation of HS, which may lead to or initiate a cascade of events causing cellular damage and progressive tissue and organ dysfunction. Currently, there are no approved disease-modifying therapies for MPS III.

MPS III primarily affects the central nervous system (CNS). The natural history and rate of progression of neurologic manifestations are not well characterized in any of the four MPS III subtypes. Some limited natural history information is available in MPS IIIA. In general, genotype alone is not a reliable sole predictor of disease severity or neurological progression in MPS III[1,2]. However, in MPS IIIA, patients with early childhood onset signs and symptoms may have a more rapidly progressive course (severe MPS IIIA) compared to patients diagnosed later in childhood or adolescence (attenuated MPS IIIA). In severe MPS IIIA, clinical symptoms manifest in early childhood (two to six years of age) and include developmental delays (primarily of speech and lan-

Received May 24, 2021; **Revised** June 1, 2021; **Accepted** June 9, 2021
Correspondence to: Aram Yang
Department of Pediatrics, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-2001-1980, E-mail: aram.yang@samsung.com

guage) and behavioral problems (e.g., hyperactivity, inattention, anxiety, autistic features, aggression, lack of fear). Other symptoms include normal sleep cycle disturbances, frequent upper respiratory and ear infections, hearing and visual impairment, and motor deficits. Hepatomegaly is found in some patients (splenomegaly is rare), but it is generally much less common and less severe in MPS III compared to other mucopolysaccharidoses.

Severely affected patients (rapid progressors) with MPS IIIA follow a typical disease trajectory[3]. Typically, a patient with MPS IIIA has an initial period of normal or near-normal development (up to two years of age), followed by a period of slower developmental progression (between two and four years of age). Development appears to arrest around four years of age in severely affected patients. Subsequently, patients enter a phase of progressive neurocognitive decline characterized by developmental regression and loss of previously acquired skills, which eventually leads to complete loss of cognitive, language, and motor abilities. This typically culminates in dementia. Motor abilities are usually not affected until later in the disease course. The median age at death in MPS IIIA is reported as 15 years of age, ranging between 8.5 and 25.5 years of age[1]. There is insufficient information on the general disease trajectory and natural history of manifestations in patients with MPS IIIB, IIIC, and IIID.

MPS IIIA

MPS IIIA mice received recombinant human sulfamidase (rhSGSH) via direct injection in the cisterna magna, which showed declining cerebral and medullar HS levels and improved behavior[4]. Moreover, intermittent cisternal or spinal bolus rhSGSH injection provided greater reductions in substrate storage and neuroinflammation than slow continual spinal enzyme infusion in dogs with MPS IIIA[5]. In mice with MPS IIIA, intracerebroventricular (ICV) administration was more effective in decreasing substrate levels and reducing microglial activation than intrathecal (IT) injections[6]. The safety of rhSGSH was successfully assessed in juvenile Cynomolgus monkeys via an IT drug delivery device (IDDD)[7] and in dogs with MPS IIIA after IT injection[8]. These promising preclinical studies paved the way to early-phase clinical trials.

A Shire-sponsored open-label, phase I/II, safety trial of IT rhSGSH via IDDD (NCT01155778) recruited 12 patients aged three years and older receiving monthly administration for six months in escalating doses. No safety concerns were observed, but seven patients experienced serious adverse effects, with all but one related to non-functioning IDDD, that is, migration, disconnection, or pin break. Although plasma anti-rhSGSH antibodies were detected in six patients, CSF HS and uGAG levels were reduced in all tested patients in a dose-response pattern. Neurocognitive assessments showed a decline in four patients and stabilization in six patients (no data available in two patients) with no dose differences. Brain MRIs showed worsening cortical atrophy in all dose groups, although this six-month study was too short to adequately assess clinical efficacy[9]. Patients were subsequently recruited in an open-label extension study (NCT01299727) to determine the initial established dose; however, the study was terminated as pre-specified efficacy criteria were not met.

Furthermore, a 48-week, phase IIb, open-label, randomized, safety, and efficacy study of rhSGSH administration via IDDD was initiated in early-stage pediatric patients with MPS IIIA in 2014 (NCT02060526)[10]. A total of 21 patients (12 females and 9 males) with a mean age of 32 months were randomly divided into three groups: one administered IT at 45 mg rhSGSH every two weeks (Q2W), one administered IT administration at 45 mg rhSGSH every four weeks (Q4W), and one group that received no treatment. The primary endpoint was set as a maximum 10-points decline of DQ after 48 weeks. A satisfactory rhSGSH safety profile was observed and all serious SAEs were related to IDDD. A clinical response to rhSGSH was observed only in three treated patients (two in the Q2W group and one in the Q4W group) with no significant difference noted between the treatment and control groups. Contrasting with a reduction of CSF HS and uGAG levels in all treated patients, efficacy endpoints were not met and the trial was terminated in 2016[10].

A Swedish Orphan Biovitrum (SOBI)-sponsored open-label, phase I/II study (NCT03423186) is ongoing and includes weekly IV administration of SOBI003 in three dose-escalating cohorts of chemically modified rhSGSH for 24 weeks. Glycan modification of rhSGSH using the proprietary technology Modifa may extend the half-life of the enzyme. The primary objective of this study is to assess the safety of SOBI003. Secondary outcomes focus on pharmacokinetics, immunogenicity, and efficacy based on neurocognition, behavior, neuroimaging, and quality of life changes. Patients in the first dose group showed good tolerability after completing 24 weeks of infusions. An extension study (NCT03811028) is set up for a further 80 weeks[11].

MPS IIIB

Recombinant human α-N-acetyl glucosaminidase (rhNAGLU) has reduced cellular uptake due to limited cation-independent mannose 6 phosphorylation[12,13]. Given that the M6P receptor is

also the IGF2 receptor at another binding site[14], the rhNAGLU enzyme was attached to insulin-like growth factor 2's (IGF2) receptor-binding motif (rhNAGLU-IGF2) to improve its cellular uptake. Preliminary in vitro work has shown a feasible improvement in neuronal and astrocytic targeting by the rhNAGLU-IGF2 fusion[15].

A Biomarin-sponsored, open-label, phase I/II dose-escalation study to evaluate the safety and efficacy of BMN-250 (rhNAGLU-IGF2) in MPS IIIB patients (NCT02754076; long-term extension study NCT03784287) began in 2016 with an initial dose escalation (30, 100, and 300 mg/infusion) via weekly ICV infusion until the maximum tolerated tested dose was reached. The study was then extended for 48 months. BMN-250 or tralesinidase alfa is a development program that was out-licensed to Allievex Corporation in 2019. The extension study (NCT03784287) began in 2018, and weekly ICV administration of 300 mg doses will continue for up to 240 weeks.

Current Clinical Trials to Improve the Targeting of Corrective Enzymes to the Central Nervous System

Until now, no effective disease-modifying treatment has been identified, and supportive treatment addressing various multisystem problems is the mainstay of therapy. This requires a multidisciplinary approach to disease management, anticipating the likely problems that will arise over time.

1. Enzyme replacement therapy (ERT)

Enzyme replacement therapy (ERT) provides a recombinant functional enzyme to deficient cells via the mannose 6 phosphate (M6P) receptor endocytosis pathway, which targets extracellular M6P-tagged proteins to the lysosome. ERT has become the standard of care in several lysosomal storage diseases (LSDs)[16], especially in MPS type I, II, IVA, VI, and VII. Although systemic ERT has demonstrated improvement in skeletal problems and somatic manifestations[17-19], it has limited ability to cross the blood-brain barrier (BBB)[20] and does not modify the neurological phenotype[21]. In MPS III, neurologic regression is the main clinical sign requiring efficient therapeutic penetrating BBB[20]. Therefore, efforts to overcome CNS penetration problems have been proposed, such as direct intraparenchymal (IP), IT, or ICV administration[22].

2. Substrate reduction therapy

Substrate reduction therapy (SRT) aims to reduce toxic accumulation by reducing biosynthesis upstream of the substrates of insufficient enzymes[23,24]. Considering the limited effects of ERT on multiple tissues and the difficulty of crossing the BBBs, SRT has emerged as an alternative to LSD, particularly in neurodegenerative diseases[24].

Rhodamine B, an inhibitor of polysaccharide chain formation in GAG synthesis[25], is a small molecule of 479 Da that can penetrate the BBB[26]. Rhodamine B effectively eliminates GAG storage, which decreased liver size in mice with MPS IIIA and decreased GAG levels in the brain and somatic tissues[27]. These encouraging findings were hampered by toxic effects reported in the literature, such as skin lacerations, gastrointestinal and liver tumors, and decreased fertility[28].

Genistein, a protein-tyrosine-kinase inhibitor in the isoflavone group, inhibits GAG synthesis by inhibiting epidermal growth factor receptor-dependent signals, a concept described by "Gene Expression Target Isoflavone Therapy" (GETIT)[29]. Genistein has limited ability to pass through the BBB, with an estimated CNS delivery of less than 10%[30]. In vitro proof was observed in the fibroblasts of patients with MPS I, MPS II, MPS IIIA, and MPS IIIB[31]. Oral administration of Genistein in mice with MPS IIB increased GAG cleaning rates after eight weeks and improved behavior[32], neuropathology, and partial HS clearance after nine months of daily administration at high doses (160 mg/kg/day)[33].

An open-label pilot study was performed in a pediatric population of five patients with MPS IIIA and five patients with MPS IIIB who received oral administration of genistein (5 mg/kg/day) for 12 months[34]. Tolerance was satisfactory, uGAG levels decreased significantly in all patients with MPS IIIA and two patients with MPS IIIB, correlating with a significant improvement in or stabilization of cognitive function[34]. A randomized, crossover, placebo-controlled study with a genistein-enriched soy isoflavone extract (10 mg/kg/day of genistein) administered to 30 patients with MPS III for six months was followed by an open-label extension study for another six months for patients who were on genistein during the last part of the crossover. Neither clinical benefit nor a reduction in uGAGs and HS compared to placebo were observed at 12 months[35].

3. Pharmacological chaperone therapy

Pharmacological chaperone therapy (PCT) is an emerging approach based on small-molecule ligands that selectively bind to

and stabilize mutant enzymes, increase their cellular levels, and improve lysosomal trafficking and activity[36,37]. Imino and amino sugars are the most common pharmacological chaperones for LSDs, such as GM1-gangliosidosis, Fabry, Morquio B, Pompe, Gaucher, Krabbe, Niemann-Pick A/B, and C diseases[38]. Orally administered chaperones can cross the BBB. However, their effects depend on the mutation and they may only benefit a small number of patients with these orphan diseases[37].

Glucosamine, an amino sugar that competitively inhibits HGSNAT inhibitors, showed in vitro proof of concept in fibroblasts in MPS IIIC patients with missense[39] or acceptor splice-site mutations affecting the HGSNAT gene[40].

4. Gene therapy

Adeno-associated viral (AAV) gene therapy enables in vivo transduction of the targeted cell types, which can occur via vector delivery by various administration routes.

Current Clinical Trials

1. MPS IIIA

A pilot phase I/II open-label clinical trial (NCT01474343) sponsored by Lysogene was initiated in 2011. An AAVrh10 vector carrying hSGSH and hSUMF1 transgenes (AAVrh.10-SGSH-IRES-SUMF1) was injected intraparenchymally into four pediatric patients with MPS IIIA. Although there were not any serious side effects related to the injection, clinical outcomes, such as brain MRI findings, neurocognitive impairment, behavior problems, and biomarkers, were not favorable in all patients[41]. An ongoing Lysogene-sponsored open-label, single-arm phase II/III, clinical trial called AAVance (NCT03612869) aims to assess intracerebral administration of AAVrh10 encoding hSGSH in 20 patients with MPS IIIA older than six months with a DQ >50.

Based on AAV9 preclinical data, Abeona Therapeutics is administering two-phase I/II open-label clinical trials to assess the safety and efficacy of a single intravenous injection of scAAV9-U1a-hSGSH. The study will recruit 22 patients with MPS IIIA either aged six months to two years or older than two years with DQ ≥60. Preliminary data at 6, 12, and 24 months post-infusion from each of the three-dose escalation groups will be measured, including significant time- and dose-dependent reductions in HS levels and liver volume and stabilization or improvement of adaptive behaviors and/or cognitive function. Emphasis was placed on safety[42]. Study ABT-003 (NCT04088734) is another clinical trial enrolling 12 patients with MPS IIIA a DQ lower than 60 in middle and advanced disease phases.

An AAV9 vector encoding the SGSH gene administered via a single ICV injection is currently being assessed in a phase I/II clinical trial sponsored by Esteve.

2. MPS IIIB

Uniqure Biopharma and the Institut Pasteur led an open-label phase 1/2 clinical trial (NCT03300453) to evaluate the safety and efficacy of an AAV5 vector encoding hNAGLU. The vector administered IP to 16 regions of the brain through eight burr holes, for a total dose of 4×10e12vg. The accompanying immunosuppression based on tacrolimus and mycophenolate morphethyl began 14 days before gene therapy and was maintained throughout the follow-up. Four patients aged 20, 26, 30, and 53 months were recruited between 2012 and 2014. At 30 months post-injection, the administration product and procedure were well tolerated. Neurocognitive impairment improved in all patients compared to no treatment, with a better outcome in the youngest patient treated[43].

Abeona Therapeutics is sponsoring an ongoing phase 1/2 clinical trial (NCT03315182) on Transpher B to assess the safety and efficacy of ABO-101, a self-complementary AAV9 vector encoding hNAGLU (AAV9.CMV.hNAGLU) delivered via a single IV injection. This non-randomized, open-label, dose-escalation study is recruiting 12 patients. Currently, eight patients have been enrolled in the low, medium, and high dose cohorts. There have been two and four patients enrolled in the low and medium dose cohorts, respectively, which has shown good safety after a median follow-up of 15 and three months, respectively. Sustained reduction in CSF and urine HS levels, urine GAGs, and liver volume were observed in up to 18 months of follow-up[44].

Conclusion

Some other MPS subtypes may benefit from approved treatments that target systemic and CNS symptoms, respectively, such as ERT (MPS I, II, IVA, VI, and VII). However, no disease modification therapy has yet been approved for MPS III. Continued ERT clinical trials and, in particular, gene therapy, have promising preclinical studies. This offers patients, families, and clinical teams hope. At the same time, a new research strategy based on gene editing is sought to develop mutant-specific and personalized medicines for vulnerable patients. The main obstacles to the therapy development are effective BBB crossings, diffuse

cerebral biological distributions, appropriate administration, and sustained effects through early diagnosis. Early-onset of effective therapy in MPS III remains the cornerstone of successful management to prevent irreparable nerve cell loss. New disease modification therapy is expected to significantly alter the diagnostic and treatment pathways of these patients, facilitating potential newborn screening methods.

Conflict of Interest

The authors have declared that no competing interests exist.

References

1. Valstar MJ, Ruijter GJ, van Diggelen OP, Poorthuis BJ, Wijburg FA. Sanfilippo syndrome: a mini-review. J Inherit Metab Dis 2008;31:240-52.
2. Valstar MJ, Marchal JP, Grootenhuis M, Colland V, Wijburg FA. Cognitive development in patients with Mucopolysaccharidosis type III (Sanfilippo syndrome). Orphanet J Rare Dis 2011;6:43.
3. Shapiro EG, Nestrasil I, Delaney KA, Rudser K, Kovac V, Nair N, et al. A Prospective Natural History Study of Mucopolysaccharidosis Type IIIA. J Pediatr 2016;170:278-87.e1-4.
4. Hemsley KM, King B, Hopwood JJ. Injection of recombinant human sulfamidase into the CSF via the cerebellomedullary cistern in MPS IIIA mice. Molecular genetics and metabolism 2007;90:313-28.
5. King B, Marshall NR, Hassiotis S, Trim PJ, Tucker J, Hattersley K, et al. Slow, continuous enzyme replacement via spinal CSF in dogs with the paediatric-onset neurodegenerative disease, MPS IIIA. Journal of inherited metabolic disease 2017;40:443-53.
6. Beard H, Luck AJ, Hassiotis S, King B, Trim PJ, Snel MF, et al. Determination of the role of injection site on the efficacy of intra-CSF enzyme replacement therapy in MPS IIIA mice. Molecular genetics and metabolism 2015;115:33-40.
7. Pfeifer RW, Felice BR, Boyd RB, Butt MT, Ruiz JA, Heartlein MW, et al. Safety evaluation of chronic intrathecal administration of heparan N-sulfatase in juvenile cynomolgus monkeys. Drug delivery and translational research 2012;2:187-200.
8. King B, Marshall N, Beard H, Hassiotis S, Trim PJ, Snel MF, et al. Evaluation of enzyme dose and dose-frequency in ameliorating substrate accumulation in MPS IIIA Huntaway dog brain. Journal of inherited metabolic disease 2015;38:341-50.
9. Jones SA, Breen C, Heap F, Rust S, de Ruijter J, Tump E, et al. A phase 1/2 study of intrathecal heparan-N-sulfatase in patients with mucopolysaccharidosis IIIA. Molecular genetics and metabolism 2016;118:198-205.
10. Wijburg FA, Whitley CB, Muenzer J, Gasperini S, Del Toro M, Muschol N, et al. Intrathecal heparan-N-sulfatase in patients with Sanfilippo syndrome type A: A phase IIb randomized trial. Molecular genetics and metabolism 2019;126:121-30.
11. Broijersen A, Dalén P, Ezgu F, Huledal G, Lindqvist D, Wikén M, et al. Safety and tolerability of SOBI003 in pediatric MPS IIIA patients key study design features of the ongoing first-in-human study. 2019.
12. Weber B, Hopwood JJ, Yogalingam G. Expression and characterization of human recombinant and α-N-actylglucosaminidase. Protein expression and purification 2001;21:251-9.
13. Zhao K-W, Neufeld EF. Purification and characterization of recombinant human α-N-acetylglucosaminidase secreted by Chinese hamster ovary cells. Protein expression and purification 2000;19:202-11.
14. Kan S-h, Troitskaya LA, Sinow CS, Haitz K, Todd AK, Di Stefano A, et al. Insulin-like growth factor II peptide fusion enables uptake and lysosomal delivery of α-N-acetylglucosaminidase to mucopolysaccharidosis type IIIB fibroblasts. Biochemical Journal 2014;458:281-9.
15. Yogalingam G, Luu AR, Prill H, Lo MJ, Yip B, Holtzinger J, et al. BMN 250, a fusion of lysosomal alpha-N-acetylglucosaminidase with IGF2, exhibits different patterns of cellular uptake into critical cell types of Sanfilippo syndrome B disease pathogenesis. PLoS One 2019;14:e0207836.
16. Concolino D, Deodato F, Parini R. Enzyme replacement therapy: efficacy and limitations. Italian Journal of Pediatrics 2018;44:120.
17. Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J Pediatr 2004;144:581-8.
18. Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genetics in Medicine 2006;8:465-73.
19. Fox JE, Volpe L, Bullaro J, Kakkis ED, Sly WS. First human treatment with investigational rhGUS enzyme replacement

therapy in an advanced stage MPS VII patient. Molecular genetics and metabolism 2015;114:203-8.
20. Gaffke L, Pierzynowska K, Piotrowska E, Węgrzyn G. How close are we to therapies for Sanfilippo disease? Metabolic brain disease 2018;33:1-10.
21. Muenzer J, Bodamer O, Burton B, Clarke L, Frenking GS, Giugliani R, et al. The role of enzyme replacement therapy in severe Hunter syndrome—an expert panel consensus. European journal of pediatrics 2012;171:181-8.
22. Fecarotta S, Gasperini S, Parenti G. New treatments for the mucopolysaccharidoses: from pathophysiology to therapy. Italian journal of pediatrics 2018;44:135-43.
23. Platt FM, Butters TD. Substrate reduction therapy. Lysosomal storage disorders 2007:153-68.
24. Coutinho MF, Santos JI, Alves S. Less is more: substrate reduction therapy for lysosomal storage disorders. International journal of molecular sciences 2016;17:1065.
25. Kaji T, Kawashima T, Sakamoto M. Rhodamine B inhibition of glycosaminoglycan production by cultured human lip fibroblasts. Toxicology and applied pharmacology 1991;111:82-9.
26. Pardridge WM. CNS drug design based on principles of blood-brain barrier transport. Journal of neurochemistry 1998;70:1781-92.
27. Roberts AL, Thomas BJ, Wilkinson AS, Fletcher JM, Byers S. Inhibition of glycosaminoglycan synthesis using rhodamine B in a mouse model of mucopolysaccharidosis type IIIA. Pediatric research 2006;60:309-14.
28. Nainggolan-Sihombing G. The toxic effect of rhodamine B in rats. Paediatr Indones 1984;24:125-38.
29. Jakóbkiewicz-Banecka J, Piotrowska E, Narajczyk M, Barańska S, Węgrzyn G. Genistein-mediated inhibition of glycosaminoglycan synthesis, which corrects storage in cells of patients suffering from mucopolysaccharidoses, acts by influencing an epidermal growth factor-dependent pathway. Journal of biomedical science 2009;16:1-9.
30. Tsai T-H. Concurrent measurement of unbound genistein in the blood, brain and bile of anesthetized rats using microdialysis and its pharmacokinetic application. Journal of Chromatography A 2005;1073:317-22.
31. Piotrowska E, Jakobkiewicz-Banecka J, Barańska S, Tylki-Szymańska A, Czartoryska B, Węgrzyn A, et al. Genistein-mediated inhibition of glycosaminoglycan synthesis as a basis for gene expression-targeted isoflavone therapy for mucopolysaccharidoses. European Journal of Human Genetics 2006;14:846-52.
32. Malinowska M, Wilkinson FL, Bennett W, Langford-Smith KJ, O'Leary HA, Jakobkiewicz-Banecka J, et al. Genistein reduces lysosomal storage in peripheral tissues of mucopolysaccharide IIIB mice. Molecular genetics and metabolism 2009;98:235-42.
33. Malinowska M, Wilkinson FL, Langford-Smith KJ, Langford-Smith A, Brown JR, Crawford BE, et al. Genistein improves neuropathology and corrects behaviour in a mouse model of neurodegenerative metabolic disease. PloS one 2010;5:e14192.
34. Piotrowska E, Jakóbkiewicz-Banecka J, Tylki-Szymanska A, Liberek A, Maryniak A, Malinowska M, et al. Genistin-rich soy isoflavone extract in substrate reduction therapy for Sanfilippo syndrome: An open-label, pilot study in 10 pediatric patients. Current therapeutic research 2008;69:166-79.
35. de Ruijter J, Valstar MJ, Narajczyk M, Wegrzyn G, Kulik W, IJlst L, et al. Genistein in Sanfilippo disease: a randomized controlled crossover trial. Annals of neurology 2012;71:110-20.
36. Bernier V, Bichet DG, Bouvier M. Pharmacological chaperone action on G-protein-coupled receptors. Current opinion in pharmacology 2004;4:528-33.
37. Parenti G, Andria G, Valenzano KJ. Pharmacological chaperone therapy: preclinical development, clinical translation, and prospects for the treatment of lysosomal storage disorders. Molecular Therapy 2015;23:1138-48.
38. Suzuki Y. Emerging novel concept of chaperone therapies for protein misfolding diseases. Proceedings of the Japan Academy, Series B 2014;90:145-62.
39. Feldhammer M, Durand S, Pshezhetsky AV. Protein misfolding as an underlying molecular defect in mucopolysaccharidosis III type C. PloS one 2009;4:e7434.
40. Matos L, Canals I, Dridi L, Choi Y, Prata MJ, Jordan P, et al. Therapeutic strategies based on modified U1 snRNAs and chaperones for Sanfilippo C splicing mutations. Orphanet J Rare Dis 2014;9:1-12.
41. Tardieu M, Zérah M, Husson B, de Bournonville S, Deiva K, Adamsbaum C, et al. Intracerebral administration of adeno-associated viral vector serotype rh. 10 carrying human SGSH and SUMF1 cDNAs in children with mucopolysaccharidosis type IIIA disease: results of a phase I/II trial. Human gene therapy 2014;25:506-16.
42. Flanigan K, Simmons T, Mcbride K, Kunkler K, Alyward S, Couce M, et al. Phase 1/2 clinical trial of systemic gene transfer of scAAV9. U1a. hSGSH for MPS IIIA demonstrates 2 years of safety, tolerability, and biopotency. Molecular Ge-

netics and Metabolism 2019;126:S54.
43. Tardieu M, Zérah M, Gougeon ML, Ausseil J, de Bournonville S, Husson B, et al. Intracerebral gene therapy in children with mucopolysaccharidosis type IIIB syndrome: an uncontrolled phase 1/2 clinical trial. Lancet Neurol 2017;16:712-20.
44. McBride KL, Smith N, Couce M, Flanigan K, Truxal K, Simmons T, et al. Safety, Tolerability, and Preliminary Evidence of Biopotency in Transpher B, a Multicenter, Singledose, Phase 1/2 Clinical Trial of ABO-101 Gene Therapy for Sanfilippo Syndrome Type B (Mucopolysaccharidosis IIIB) (5175). AAN Enterprises; 2020.