# Sanfilippo Syndrome

Subjects: Pathology Contributor: Noelia Benetó

Sanfilippo syndrome is caused by mutations in the enzymes responsible for the degradation of heparan sulfate (HS), a specific GAG, and patients are characterized by severe neurological pathology leading to childhood dementia.

Keywords: Sanfilippo syndrome ; mucopolysaccharidosis III ; lysosomal storage disorders ; heparan sulfate ; animal models ; induced pluripotent stem cells ; cellular models ; therapeutic approaches.

#### 1. Introduction

Lysosomal storage disorders (LSDs) comprise a heterogeneous group of rare inherited metabolic diseases that are characterized by the accumulation of macromolecules inside lysosomes. LSDs are caused by deficiencies in lysosomal enzymes, leading to lysosomal dysfunction, altered recycling of macromolecules, and impaired flux of the endolysosomal system. Mucopolysaccharidoses (MPS) are a group of LSDs accounting for approximately 30% of all LSD cases and arise from mutations in genes involved in glycosaminoglycans (GAGs) degradation, which accumulate inside the lysosomes<sup>[1]</sup>. Among MPS, Sanfilippo syndrome (also known as mucopolysaccharidosis III or MPS III) is the most frequent type and it was first described more than 50 years  $ago^{[2]}$ .

### 2. Classification

There are four different subtypes of Sanfilippo syndrome based on the mutated gene and the consequent enzyme deficiency: type A (OMIM#252900), type B (OMIM#252920), type C (OMIM#252930), and type D (OMIM#252940), all of them presenting an autosomal recessive inheritance pattern<sup>[3]</sup>. Insufficient or complete loss of activity of any of the Sanfilippo syndrome causative enzymes leads to accumulation of partially degraded HS chains within lysosomes of cells in several organs and tissues<sup>[1][3][4]</sup>. In a recent study, a fifth subtype was identified in a mouse model<sup>[5]</sup> caused by **References** mutations in the *ARSG* gene; however, to date, no human cases have been described. Moreover, human patients with a 10 in eavery and the interview of the in altiseurgien of as, dvaneationas, an Santifianes, syn Banasio, anie Belaudet, A.L., Mitchell, G.A., Eds.; McGraw-Hill: New York, NY,

USA, 2001; pp. 3421-3452. Clinical symptomatology of Sanfilippo patients is similar regardless of the subtype, mainly characterized by an early-onset, 2. Severe, and progressive degeneration of the CNS with Mild somatic symptoms menerical retardation associated with acid, the first decade of life, with cortical atrophy, progressive dementia, motor detenoration, hyperactivity, learning difficulties,

aggressive behavior, sleeping problems, and pronounced mental retardation<sup>[3]</sup>. Mild somatic manifestations include arstansanda Androsofes hovis Adamization suffrées Marys phageas; Maréanlica Sigura hy Southing a sydecome logyer all review lea alteradiates to team tigs at the same tigs at the same the same attenuated cases, life 4X PARTADRY EXTENDED VISIT AND STRATE CONSTRAINTS AND A CONSTRAINTS. The Application of Clinical Genetics

**2015**, *8*, 269-281, <u>10.2147/tacg.s57672</u>. The incidence of Sanfilippo syndrome varies depending on the subtype and geographical region, but on average is ārākāno Kewalzovado Rote of Haisman ni Jubereza. At krietu Brezariza Villmanes Rauate i Remacida vardova Atace o Huinda Bilavines III. typEb9Deau DierkeinMarktusungemmeinAtazigiestheamgisisnerungendendingional eindingie aryhautigtesen Fachetisterst wire between populations, subtype A being more frequent in the Northern Europelysaccharidosis type III). Human Molecular Genetics 2014. 24, 1856-1868, 10.1093/hmg/ddu603. On the other hand, subtype C is in general less common while subtype D is very rare in all populations.

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Sutherland; C. Phillip Morris; John J. Hopwood; Cloning of the sulphamidase gene and identification of mutations in

MPSallfappGasilipponendumetgeneticscages, 10, 488-467, 510.1039691495-465, coding for sulfamidase (also known as

heparan sulfate sulfatase or N-sulfoducosamine sulfonydrolase, EC 3.10.1.1), which releases sulfate groups linked to the 15. H. G. Zhao, H. H. Li, G. Bach, A. Schmidtchen, E. F. Neuterd, The molecular basis of Santilippo syndrome type B.. amproceedings of release sulfate groups linked to the national Academy of Sciences **1996**, 93, 6101-6105, <u>10.1073/pnas.93:12,110</u>, and contains eight proceedings of the National Academy of Sciences **1996**, 93, 6101-6105, <u>10.1073/pnas.93:12,110</u>, exons. It codes for a protein of 502 amino acids with five possible glycosylation sites and a total of 155 identified 16. Fan X. Zhang H. Zhang, S. Bagshaw, R.D. Topak, M.B. Callahan, J.W. Mahuran, D. J. Identification of the gene mutations (Table 1). Samilippo syndrome type A is considered the most aggressive form, with patients surviving until 15– encoding the enzyme deficient in mucopolysaccharidosis IIIC (Sanfilippo disease type C). Am. J. Hum. Genet. 2006, 18 years old on average 4. 79, 738–744.

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Cizkova, A.; Poupetova, H.; et al. Mutations in TMEM76\* cause mucopolysaccharidosis IIIC (Sanfilippo C syndrome). MPS IIIB or Sanfilippo Syndrome type B is caused by mutations in the *NAGLU* gene, which encodes N-acetyl- $\alpha$ -Am. J. Hum. Genet. 2006, 79, 8072819. glucosaminidase (EC 3.2.1.50), a lysosomal enzyme of 720 amino acids with six possible glycosylation sites. The function

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Mutations in the HGSNAT gene are responsible for MPS IIIC or Sanfilippo syndrome type C. This gene codes for the 20. Daniel A. Robertson: Craig Freeman: Paul V. Nelson: Charles P. Morris: John J. Hopwood: Human glucosamine-6-Tysosomal membrane protein known as acetyl-CoA α-glucosaminide N-acetyltransferase (EC 2. 3.1.78). It is located at

sulfatase cDNA reveals homology with steroid sulfatase. *Biochemical and Biophysical Research Communications* chromosome 8p11.1, was identified by two independent groups in 2006<sup>10127</sup>, spans about 62.5 Kb, containing 18 exons, **1988**, 157, 218-224, <u>10.1016/s0006-291x(88)80035-4</u>. and gives rise to a protein of 635 amino acids. For some time, there was controversy about the real initiation codon<sup>[18]</sup>, but

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2.4 Suptyme in Passafaro; Samuel M. Wu; Marco Sardiello; et al. Trehalose reduces retinal degeneration,

neuroinflammation and storage burden caused by a lysosomal hydrolase deficiency. *Autophagy* **2018**, *14*, 1419-1434, Mutations in the *GNS* gene, which encodes the lysosomal enzyme N-acetylglucosamine-6-sulfatase (EC 3.1.6.14), are <u>10.1080/15548627.2018.1474313</u>. responsible for MPS IIID or Sanfilippo syndrome type D. The gene is located at 12q14.3, is 46 Kb-long, and contains 14

22xBajajr14e; 402UmBe; 172a) 552 BANAB, 2020; SAB41330 die RAUCANEO SALAISOP SAB42010 ACARSIS 2851 ARUCASARACIEM

acetyldfucbsamme residues. 73-589 now, 25 mutations have been found (Table 1). Due to the rarity of this subtype, there is

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for Sanfilippo C splicing mutations. Orphanet Journal of Rare Diseases 2014, 9, 1-12, 10.1186/s13023-014-0180-y. Currently, there is no treatment to effectively slow down or reverse Sanfilippo syndrome patients' neurodegeneration, and 26 Rosella Tomanin' Alessandra Zonettii Eva Zaccariotto; to ancesca D'Avanzo: Cinzia My Pellettato: Maurizia Scarpa: of Gene therapy approaches for lysosomal storage disorders, a good model for the treatment of mendelian diseases, approaches have been tested during the last years in cellular and animal models of the disease, focused mainly on the

Acta Paediatrica **2012**, 101, 692-701, <u>10.1111/j.1651-2227.2012.02674.x</u>, treatment of the CNS involvement. The main approaches we will review here consist of enzyme replacement therapy

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- Anita Grover; Danielle Crippen-Harmon; Lacey Nave; Jon Vincelette; Jill C. M. Wait; Andrew C. Melton; Roger Lawrence; Jillian R. Brown; Katherine A. Webster; Bryan K. Yip, et al. Translational studies of intravenous and intracerebroventricular routes of administration for CNS cellular biodistribution for BMN 259- an enzyme replacement therapy for the treatment of Sanfilippo type B. *Drug Delivery and Translational Research* 2020, 10, 425-439, <u>10.1007/s</u> <u>13346-019-00683-6</u>.
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Figure 1. Potential Mol. Genet. Metab. 2019. 126, 121–130 syndrome. Schematic representation of the main schekupeatrid, strackgevy, durrennycoeld. statigewiter, the ; treatment of sammingor main denticed some acysamite placement the approximation of the main schekupeatrid, strackgevy, durrennycoeld, statigewiter, the ; treatment of sammingor main denticed some acysamite placement the approximation of the main undet address the statige of the same statige of the statige of the statige of the statige of the same statige of undet address the statige of the statige of

glucosaminidase (SBC-103) in children with mucopolysaccharidosis IIIB. Mol. Genet. Metab. 2019, 126, 131–138 **3.1. Enzyme Replacement Therapy** 

34. Kazuki Sawamoto; Molly Stapleton; Carlos J. Alméciga-Díaz; Angela J. Espejo-Mojica; Juan Camilo Losada; Diego A.

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35.0Veithering that Gells a 35.0MeButseepters in the penerbagene: brospecel anavered as joint and conterest and a straight to the lysgorme to perform their function<sup>[26]</sup>. For non-neurological LSDs, exogenous administration of the correct form of the

enzyme mutated in patients, known as ERT (Figure 1A), has been proven to be the most successful strategy<sup>[27]</sup>. Howeyer, 36. Pineda, M.; Walterfang, M.; Patterson, M.C. Miglustat in Niemann-Pick disease type C patients: A review. Orphanet J. for diseases affecting the CNS, the existence of the blood–brain barrier (BBB), which limits the availability of the enzyme Rare Dis. 2018, 13, 140.

in the brain, has to be taken into account. In addition, antibodies targeting the enzyme can be observed in treated LSD-37 Joanna, Jakóhkiewicz-Banecka: Ewa Biotrowskaze and alena, Naraiczyk: Sylwia Barańska Grzegorz Wegrzyni patients, cleany feducing Biotrowskaze and alena, Naraiczyk: Sylwia Barańska Grzegorz Wegrzyni Genistejn-mediated inhibition of grzegorz warmon synthesis, which corrects storage in cells of patients suffering from without CNS pathology, for which ERT is currently approved and in use. On the other hand, direct brain administration for

mucopolysaccharidoses, acts by influencing an epidermal growth factor-dependent pathway. *Journal of Biomedical* the treatment of neurological disorders seems more beneficial, although it is an aggressive treatment that needs *Science* **2009**, *16*, 26-26, <u>10.1186/1423-0127-16-26</u>, continued injections. Nevertheless, clinical trials based on ERT for Sanfilippo syndrome type A and B have been carried

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European Journal of Human Genetics 2009, 18, 200-205, <u>10.1038/ejhg.2009.144</u>. One of the most studied of these molecules is genistein, a natural isoflavone that inhibits the kinase activity of epidermal <sup>4</sup>2roXenia Kaidonis: Wan ChipH is in Derrick Roberts: Madessa Ly: Bonald Anson: Sharon Ryers: Sensible for exercise of the storing activity of epidermal BETL 2 and EXTL 3 as a substrate deprivation therapy for heraan sulphate storing mucopolysaccharidoses European production. Genistein was able to reduce GAC production in Santilipo Syndrome type A and B hirdbhasts.

Journal of Human Genetics, 2009, 18, 194-199, 10, 1038/eing, 2009, 143, improve behavioral abnormalities, heuroinflammation, synaptic loss, and lysosomal storage in a Sanfilippo B mouse 430/souther Canalstitude in Banver of Burger Marine International Contract of Contra

rec<sup>39/(4)/2011)</sup> rec<sup>39/(4)/2011</sup> ed for Sanfilippo syndrome types A, B, and C. Even though these doses were safe for the patients, only a

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widely used to downregulate the expression of a large number of genes in several cell types in vitro and in vivo. In one 46. Losada Diaz, J.C.; Cepeda Del Castillo, J.; Rodriguez-Lopez, F.A.; Almeciga-Diaz, C.J. Advances in the Development study, siRNAs were used to downregulate XYLT1, XYLT2, GALTI, and GALTII, genes encoding enzymes responsible for of Pharmacological Chaperones for the Mucopolysaccharidoses. Int. J. Mol. Sci. 2019, 21, 232. the formation of the linkage region <sup>441</sup> (Figure 2). This strategy was assessed in MPS I and MPS IIIA fibroblasts, resulting
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demonstrate that the same siRNAs that were effective in Sanfilippo syndrome type C fibroblasts were not efficient in 50. Adeline A. Lau; Hanan Hannouche; Tina Rozaklis; Sofia Hassiotis; John J. Hopwood; Kim M. Hemsley; Allogeneic stem decreasing storage in IPSC-derived neurons generated from the same fibroblasts assayed in the previous study. cell transplantation does not improve neurological deficits in mucopolysaccharidosis type IIIA mice. <i>Experimental</i>
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Umbilical Cord Blood Cells Improve Disease Outcomes in a Mouse Model of Sanfilippo Syndrome Type III B. <i>Cell</i> 3.3. Pharmacological Chaperones for Enzyme-Enhancement-Therapy Transplantation 2014, 23, 1613-1630, <u>10.3727/096368914x676916</u> .
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In the case of LSDs, it has been proposed that achieving an enzyme activity around 5–15% can be sufficient to avoid the 61. Tagan A. Griffin; Hayley C. Anderson; John H. Wolfe; Ex Vivo Gene Therapy Using Patient IPSC-Derived NSCs appearance of pathological symptoms <sup>[47]</sup> . To date, several compounds with chaperone activity have been tested for Reverses Pathology in the Brain of a Homologous Mouse Model. Stem Cell Reports <b>2015</b> , 4, 835-846, <u>10.1016/j.stemC</u> diff <u>erent_LSDs2</u> , can be sufficient to avoid the Griffin and the Brain of a Homologous Mouse Model. Stem Cell Reports <b>2015</b> , 4, 835-846, <u>10.1016/j.stemC</u> diff <u>erent_LSDs2</u> , can be sufficient to avoid the Brain of a Homologous Mouse Model. Stem Cell Reports <b>2015</b> , 4, 835-846, <u>10.1016/j.stemC</u> different_LSDs2.
disease, Niemann-Pick A/B and C diseases, as well as for other types of disorders such as retinitis pigmentosa, cystic 62. Don Clarke: Yewande Pearse: Shih-Hsin Kan; Steven Qide; Valentina Sanghez; Jonathan D. Cooper; Patricia I. fibrosis, Parkinson's disease, Alzheimer disease, or cancer Dickson; Michelina Iacovino; Genetically Corrected iPSC-Derived Neural Stem Cell Grafts Deliver Enzyme
Replacement to Affect CNS Disease in Sanfilippo B Mice. Molecular Therapy - Methods & Clinical Development 2018,

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acids<sup>[25]</sup>. Further studies should be done in order to establish its efficacy and lack of toxicity in brain cells as well as its 65. M Quiviger; A Arfi; D Mansard; L Delacotte; M Pastor; D Scherman; Corinne Marie; High and prolonged sulfamidase ability to cross the BBB, secretion by the liver of MPS-IIIA mice following hydrodynamic tail vein delivery of antibiotic-free pFAR4 plasmid vector.

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order to deliver the correct form of the enzyme into the brain (Figure 1D). Allogeneic bone marrow transplantation is used 67. Alessandro Fraldi; Kim M. Hemsley; Allison Crawley; Alessia Lombardi; Adeline A Lau; Leanne Sutherland; Alberto in the treatment of different LSDs with neurological pathology, but in the case of MPS III, intravenous administration of Auricchio; Andrea Ballabio; John J. Hopwood, Functional correction of CNS lesions in an MPS-IIIA mouse model by lentiviral-transduced bone marrow stem cells were not efficient to treat a mouse model of MPS III. intravenous administration an intracerebral AAV-mediated delivery of sulfamidase and SUMF1 genes. *Human Molecular Genetics* 2007, 16, 2693insufficient or orderstring of an inefficient uptake by the host cells<sup>[51]</sup>.

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with mucopolysaccharidosis type IIIB syndrome: an uncontrolled phase 1/2 clinical trial. *The Lancet Neurology* **2017**, Administration of human umbilical cord blood cells to the MPS IIIB mouse model has been explored, resulting in an amelioration of the neurological and somatic symptoms<sup>[58]</sup>. However, it presents the inconvenience that the enzyme 70. Leanne K. Winner: Helen Beard: Sofia Hassiotis: Adeline A. Lau: Amanda J. Luck: John J. Hopwood: Kim M. Hemsley: production declines with time. On the contrary, the transplantation of syndrome. *Human Gene Therapy* **2016**, patients before the disease onset did not prevent the neurological deterioration. *Syndrome. Human Gene Therapy* **2016**, 27, 363-375, <u>10.1089/hum.2015.170</u>.

functionality IIIB model: A comparison of four hard service of the service of the

mouse models were treated with this strategy. However, for Sanfilippo C it is important to consider that HGSNAT does not
Ruzo, A.; Garcia, M.; Ribera, A.; Villacampa, P.; Haurigot, V.; Marco, S.; Ayuso, E.; Anguela, X.M.; Roca, C.; Agudo, J.; have a M6P tag and is a membrane protein, therefore secretion and uptake of this enzyme by deficient cells may not be et al. Liver production of sulfamidase reverses peripheral and ameliorates CNS pathology in mucopolysaccharidosis
Successful.
IIIA mice. *Mol. Ther.* 2012, 20, 254–266, <u>10.1038/mt.2011.220</u>.

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rAAV9-hNAGLU Delivery for Treating Mucopolysaccharidosis IIIB: Toxicology, Biodistribution, and Immunological **3.5. Gene Therapy** Assessments in Primates. *Human Gene Therapy Clinical Development* **2014**, *25*, 72-84, <u>10.1089/humc.2013.208</u>.

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promoted the GAG decrease in other tissues therapy. Human Molecular Genetics **2014**, *24*, 2078-2095, <u>10.1093/hmg/ddu</u>

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FoZeles in the storage and inflammation, and an improvement in the motor and cognitive function<sup>[67]</sup>. After these results, a phase I/II clinical trial for MPS IIIA using AAV10 expressing the deficient SGSH enzyme and the SUMF1 enzyme was statiled of from the storage and inflammation. Advision of the storage and the storage and inflammation and an improvement in the motor and cognitive function<sup>[67]</sup>. After these results, a phase I/II clinical trial for MPS IIIA using AAV10 expressing the deficient SGSH enzyme and the SUMF1 enzyme was statiled of from the storage in another clinical trial with MPS IIIB patients, and results indicate an improvement of neurocognitive progression in all patients<sup>[69]</sup>.

AAVrh10 has also been used to deliver *SGSH* in MPS IIIA mice via intraparenchymal administration<sup>[70]</sup>. This treatment reduced HS and GM3 ganglioside accumulation and microglial activation, but only in the site of injection. To increase efficacy, multiple intraparenchymal regions should be injected to ensure widespread distribution. To study SGSH distribution in the brain of large animals, the same transducing vector was injected via parenchyma in dogs and cynomolgus monkeys, and SGSH enzyme activity increase was detected<sup>[71]</sup>.

In a study comparing delivery efficiency of the *NAGLU* gene using different AAV serotypes in MPS IIIB mice<sup>[72]</sup>, a better biodistribution and transduction was found using AAV8 via direct administration of the virus to the CNS, but AAV9 showed better results for systemic or intracerebroventricular delivery. Intramuscular administration of AAV8 carrying the *SGSH* gene in Sanfilippo A mouse models showed no amelioration, while intravenous administration was effective in transducing mainly the liver, with a consequent amelioration of the pathology in somatic tissues, although with a discrete improvement in CNS symptoms of male mice<sup>[73]</sup>. To improve secretion and targeting of the CNS, another study used a fusion protein of *SGSH* with a signal peptide to boost enzyme secretion and a BBB-binding domain. This vector was administered with an AAV8, and results showed an important increase in enzyme activity in the brain that resulted in brain pathology and behavior improvements<sup>[74]</sup>.

Recently, the safety of intravenous administration of an AAV9 carrying the *NAGLU* gene was tested in unaffected primates<sup>[75]</sup>. AAV9 has been suggested to be the most efficient serotype for targeting brain cells and therefore, for the treatment of neurological disorders. Very interestingly, a consistent and long-term increase in brain enzymatic activity was detected together with low immunogenic reaction. Similar successful results using AAV9 have been achieved in mouse and canine models of MPS IIIA <sup>[76][77]</sup>. First, a clear increase in enzyme activity combined with a reduction in GAG storage and neuroinflammation was found in the mouse model treated intravenously, resulting in expanded lifespan<sup>[77]</sup>. Later, both animal models were treated with intracerebrospinal injections, showing low immunogenic reaction and resulting in a clear restoration of enzymatic activity and full body reduction of GAG storage and lysosome alterations, leading to prolonged lifespan<sup>[76]</sup> [120]. This same research group also develop a strategy to treat MPS IIIB<sup>[78]</sup> or MPS IIID<sup>[79]</sup> mice with cerebrospinal fluid delivery of AAV9 vector carrying *NAGLU* or *GNS* genes, respectively. After treatment, enzyme activity in the CNS, normalization of GAG storage, corrected behavior, and extended lifespan were observed.

All these results in different Sanfilippo subtypes encouraged the application of this approach in human patients. In relation to cerebrospinal fluid administration, Esteve Laboratories recently started a phase I/II clinical trial using AAV9-*hSGSH* in MPS IIIA patients (EudraCT Number: 2015-000359-26). Besides, although some preclinical studies have been performed before, it was recently confirmed that some AAV were able to cross the BBB<sup>[80]</sup>. Due to that, Abeona Therapeutics has started a clinical trial using an intravenous delivery of AAV9 vector carrying the human *SGSH* gene under the control of a U1a promoter (ClinicalTrials.gov: NCT02716246, NCT04088734). Preliminary data showed a dose-dependent and sustained reduction in cerebrospinal HS after 30 days. In the case of Sanfilippo syndrome types A and B, two clinical trials based on intracerebral injection of AAV have been already completed<sup>[68][69]</sup>, and another two for subtype A have started (ClinicalTrials.gov: NCT03612869, EudraCT Number: 2015-000359-26). However, as for ERT, gene therapy success for lysosomal enzymes relies in the ability of transduced cells to share the correct lysosomal enzyme through M6P receptors with non-transduced neighboring cells<sup>[23]</sup>. As mentioned above, HGSNAT is a lysosomal transmembrane protein that does not undergo the M6P pathway. For this reason, Sanfilippo C syndrome might not be the best candidate for gene therapy strategy, although some interesting results have been obtained with a novel AAV<sup>[81]</sup>.