Increased longevity and metabolic correction following syngeneic BMT in a murine model of mucopolysaccharidosis type I

DA Wolf1, AW Lenander1, Z Nan2, EA Braunlin3, KM Podetz-Pedersen1, CB Whitley1,3, P Gupta4,5, WC Low2,6 and RS McIvor1

INTRODUCTION

Mucopolysaccharidosis type I (MPS I) is an autosomal recessive inherited disease caused by deficiency of the glycosidase α-L-iduronidase (IDUA). Deficiency of IDUA leads to lysosomal accumulation of glycosaminoglycans (GAG) heparan and dermatan sulfate and associated multi-systemic disease, the most severe form of which is known as Hurler syndrome. Since 1981, the treatment of Hurler patients has often included allogeneic BMT from a matched donor. However, mouse models of the disease were not developed until 1997. To further characterize the MPS-I mouse model and to study the effectiveness of BMT in these animals, we engrafted a cohort (n = 33) of 4-8-week-old Idua^-/-^ animals with high levels (88.4 ± 10.3%) of wild-type donor marrow. Engrafted animals displayed an increased lifespan, preserved cardiac function, partially restored IDUA activity in peripheral organs and decreased GAG accumulation in both peripheral organs and in the brain. However, levels of GAG and GM3 ganglioside in the brain remained elevated in comparison to unaffected animals. As these results are similar to those observed in Hurler patients following BMT, this murine-transplantation model can be used to evaluate the effects of novel, more effective methods of delivering IDUA to the brain as an adjunct to BMT.

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1Gene Therapy Program, Institute of Human Genetics, Department of Genetics, Cell Biology and Development, University of Minnesota, Minneapolis, MN, USA; 2Department of Neurosurgery, University of Minnesota, Minneapolis, MN, USA; 3Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA; 4Hematology-Oncology Section, Veterans Administration Medical Center, Minneapolis, MN, USA; 5Hematology/Oncology/Transplantation Division, Department of Medicine, University of Minnesota, Minneapolis, MN, USA and 6Department of Integrative Biology and Physiology, University of Minnesota, Minneapolis, MN, USA. Correspondence: Professor RS McIvor, Department of Genetics, Cell Biology and Development, University of Minnesota, 6-160 Jackson Hall, 321 Church St. SE, Minneapolis, MN 55455, USA.

E-mail: mcivo001@umn.edu

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INTRODUCTION

Mucopolysaccharidosis type I (MPS I) is an autosomal recessive inherited disease caused by deficiency of the glycosidase α-L-iduronidase (IDUA). Deficiency of IDUA leads to lysosomal accumulation of glycosaminoglycans (GAG) heparan and dermatan sulfate and deficiency of the enzyme leads to lysosomal accumulation of these substrates. MPS I affects approximately 1 in 125,000 live human births, and homozygosity for specific mutations (for example, W402X, Q70X) leads to the most severe phenotype, Hurler syndrome. Patients with Hurler syndrome develop progressively severe manifestations of the disease within the first year of life, including growth delay, hepatosplenomegaly, skeletal deformities, excess urinary GAG, corneal clouding and severe neurological deficits. Untreated, these patients usually succumb to the disease in the first decade of life due to complications caused by respiratory infection, cardiac failure and obstructive airway disease.

Early biochemical research led to discoveries that have provided the basis for treatment of Hurler patients by hematopoietic SCT (HSCT). After synthesis in the endoplasmic reticulum, IDUA is post-translationally modified by the addition of mannose-6 phosphate to Asn residues in the rough endoplasmic reticulum and Golgi apparatus. Most of the modified enzyme is sorted and translocated to the lysosomes, but a small proportion of IDUA escapes from the cell into the extracellular environment. Extracellular IDUA can then interact with mannose-6-phosphate receptors on the surface of neighboring cells, with subsequent endocytosis, and shuffling to the lysosomes. IDUA-deficient cells can thus be cleared of accumulated lysosomal GAG through the uptake of IDUA released by non-deficient cells. This cross-corrective mechanism constitutes the basis for development of cellular and molecular strategies to treat this disorder.

Currently, the standard of care for severe Hurler patients involves enzyme replacement therapy (ERT) by weekly infusions of recombinant enzyme following diagnosis and ultimately HSCT for patients with an HLA-matched donor. Allogeneic BMT for MPS I was first conducted in 1981 by Hobbs et al. Since then, a body of literature has accumulated describing studies involving transplantation of hematopoietic stem cells collected from bone marrow, peripheral blood or umbilical cord blood of related and unrelated donors. These and other studies have provided molecular insights into the effectiveness of these treatments and have led to continual improvement in HSCT protocols with reduced transplant complications and morbidity. The evolution of HSCT protocols has resulted in increased access to donor sources and allowed achievement of higher levels of donor chimerism and enzyme activity in transplant recipients. Following HSCT, organomegaly, upper respiratory symptoms, corneal clouding and sleep apnea are generally resolved. Cardiac function is preserved, although valvular deformities may persist. The lifespan of patients significantly improves following successful transplantation, as many patients have now survived into the third decade of life.
Furthermore, neurological outcome has improved in many patients, although they continue to exhibit subnormal IQ and impaired neurocognitive capability.\textsuperscript{17,18}

Despite the long history of HSCT to treat Hurler patients, it was not until 1997 that murine models of MPS I were introduced.\textsuperscript{8,19,20} This advance has provided the opportunity to characterize the pathobiology of IDUA deficiency in a model that can also be used to develop new approaches for the treatment of MPS I.\textsuperscript{21} Previous studies have reported some of the biochemical effects of wild-type HSCT into MPS-I mice.\textsuperscript{22,23} In this study, we further and other animal models. We engrafted treatment recapitulate results observed in human MPS-I patients and other animal models. We engrafted \textit{Idua}\textsuperscript{−/−} animals with quantifiably high levels of congenic wild-type marrow and report novel outcomes of HSCT on the lifespan, cardiac function and GM3 ganglioside accumulation in the brains of treated mice. These results provide further characterization of the MPS-I mouse model as well as additional insights into the long-term benefits of HSCT that may similarly be achieved in Hurler patients, particularly with respect to metabolic correction in the brain.

MATERIALS AND METHODS

Animals and transplantation procedure

The \textit{Idua}\textsuperscript{−/−} mouse strain \textsuperscript{24} was kindly provided by Dr Elizabeth Neufeld. The animals were routinely maintained on a C57BL/6 background and provided food and water \textit{ad libitum}. For BM, 33 CD45.2 4-8-week-old \textit{Idua}\textsuperscript{−/−} recipient mice were preconditioned by exposure to a sublethal dose of cesium irradiation (750 cGy). The following day, wild-type whole marrow was harvested by flushing the hind limbs of congenic CD45.1 wild-type C57BL/6 mice into Dulbecco’s modified Eagle medium supplemented with 10\% fetal bovine serum and 10 U/mL heparin. Harvested cells were triturated into a single-cell suspension and viable cells counted by trypan blue exclusion using a hemacytometer. Ten million donor cells were then infused into the preconditioned \textit{Idua}\textsuperscript{−/−} animals through the lateral tail-vein.

Flow cytometry

Peripheral blood was collected via the submandibular vein into heparinized tubes and the red cells lysed using a hypotonic buffer (eBioscience, San Diego, CA, USA). The remaining nucleated cells were stained with allophycocyanin-conjugated anti-murine CD45.1 (eBioscience) and evaluated by flow cytometry using a FACSCalibur bench top cytometer. The data were analyzed using FlowJo software (Tree Star Inc, Ashland, OR, USA) and donor cell engraftment was determined as the percentage CD45.1\textsuperscript{+} cells present in the gated lymphocyte compartment.\textsuperscript{25}

IDUA-activity assays

Animals were anesthetized with ketamine/xylocaine (100 mg ketamine + 10 mg xylazine per kg) and transcardially perfused with 70 mL PBS prior to euthanization. Peripheral tissue including the heart, lungs, liver, kidneys, spleen and brain were harvested. The brain was microdissected on ice into separate regions: right and left olfactory bulb, cerebellum, hippocampus, striatum, cortex and brainstem and thalamus. For the analyses included in this paper, microdissected brain samples from the left hemisphere were analyzed. The tissue samples were frozen on dry ice and stored at –80°C until use. Samples were thawed and homogenized in 1 mL of PBS (Gibco, Invitrogen, Carlsbad, CA, USA) using a motorized pestle and permeabilized by addition of 0.1% Triton X-100. IDUA activity was determined by fluorometric assay using 4MU-iduronide as the substrate, as previously described.\textsuperscript{21,26} Activity is expressed as nmol 4- -methylumbelliferone released per mg tissue per hour (nmol/mg/h) with the amount of protein in each sample determined by Bradford assay (BioRad, Hercules, CA, USA).

GAG analysis

The remainder of each tissue homogenate was incubated overnight with protease K, DNaseI and RNase (Sigma-Aldrich, St Louis, MO, USA) as previously described and clarified for 3 min at 12,000 r.p.m. using an Eppendorf tabletop microcentrifuge model Centrifuge 5415D (Eppendorf, Hauppauge, NY, USA).\textsuperscript{21,26} GAG concentration was determined using the Blysca Sulfated Glycosaminoglycan Assay (Accurate Chemical, Westbury, NY, USA), according to the manufacturer’s instructions.

Tissue staining for GM3 ganglioside

Animals distinct from those analyzed for IDUA activity and GAG levels were anesthetized with ketamine/xylocaine as described above and transcardially perfused with 70 mL ice-cold paraformaldehyde (4% w/v in 0.1 M PBS) prior to euthanization. Brains were removed, post-fixed overnight in 4\% paraformaldehyde, cryopreserved in sucrose (30\% w/v in PBS), frozen on dry ice and sectioned into coronal slices (30\% mm thickness) using a freezing microtome. Free-floating sections were washed 3 × 10 min in PBS (pH 7.4) and blocked with 10\% normal goat serum/0.3\% Triton X-100. Primary antibody was added and sections were incubated overnight at 4°C, washed 3 × 10 min in PBS and incubated for 1 h at room temperature with a fluorescently labeled secondary antibody diluted in PBS. Sections were then washed 3 × 10 min in PBS, incubated for 10 min with DAPI (Invitrogen), mounted on slides, and visualized using a Zeiss Axioplan 2 upright microscope. Primary antibody was used to bind GM3 ganglioside (1:500, Cat. no. 370695, Seikagaku Corporation, Tokyo, Japan). The secondary antibody used was a donkey anti-mouse IgG antibody conjugated to Alexa Fluor 488 (1:500, Cat. no. A-10680, Molecular Probes, Invitrogen).

Cardiac ultrasound

Mice were anesthetized by inhalant isoflurane and ultrasound was conducted using a 30 MHz probe and a Vevo 660 high-resolution ultrasound biomicroscope (VisualSonics, Toronto, Ontario, Canada).\textsuperscript{27} Doppler imaging was conducted in both the long- and short-axis beneath the aortic valve to determine the presence or absence of aortic insufficiency (AI).

Statistical analysis

Data are reported as mean ± s.d. Differences in survival were evaluated using the Kaplan-Meier product-limit method, calculating the log-rank statistic. One-way analysis of variance with Tukey’s post-test was used for determining significance between groups for GAG assays. A χ\textsuperscript{2} test with 95\% confidence interval was used to determine significance in cardiac function manifested by the presence or absence of AI. In all cases, \( P<0.05 \) was considered significant and analysis was performed using Prism 5.0 software (GraphPad Software, La Jolla, CA, USA).

RESULTS

Increased longevity of MPS-I mice following BMT with wild-type donor marrow

To evaluate the effect of BMT in MPS-I mice, we transplanted young adult \textit{Idua}\textsuperscript{−/−} mice with wild-type marrow from syngeneic C57BL/6 donors. Thirty-three CD45.2 \textit{Idua}\textsuperscript{−/−} mice between the ages of 4–8 weeks were preconditioned with 750 cGy cesium irradiation, and on the following day, transplanted with 10\(^{7}\) donor marrow cells harvested from wild-type CD45.1 mice. Mean donor-cell engraftment as determined by flow cytometry of peripheral blood for the CD45.1 congenic marker 2 months post-transplant was 88.4 ± 10.3\% (s.d.). Interestingly, we attempted to engraft a second cohort of \textit{Idua}\textsuperscript{−/−} mice at a reduced level by administering 100 cGy cesium irradiation followed by infusion of 1 × 10\(^{7}\) congenic donor marrow cells. However, donor-cell engraftment was undetectable in this cohort of animals (data not shown).

Upon extended study of these animals, we observed that the recipient \textit{Idua}\textsuperscript{−/−} mice appeared quite healthy compared with...
untreated MPS-I mice as they remained unhunched and active in their cages. The recipient animals displayed increased longevity compared with untreated control animals, with a median lifespan of 85 weeks for transplanted animals compared with a median lifespan of 49 weeks for historical untreated Idua−/− animals from the same colony (P < 0.001, log-rank test) (Figure 1). The median survival ratio of transplanted mice to untreated MPS I mice was 1.72 (95% CI, 1.09–2.36).

Partial restoration of IDUA expression in peripheral organs following BMT

Upon reaching 92 weeks of age, the longest surviving transplanted MPS-I mice were trans-cardially perfused with saline and organs were harvested and homogenized. Positive- and negative-control animals consisted of 13-month-old unaffected Idua+/− and untreated MPS-I mice, respectively. A portion of each tissue homogenate was evaluated for IDUA activity using a fluorometric assay. BMT-recipient animals displayed long-term partial restoration of IDUA activity in peripheral tissues 20 months post-transplantation (Figures 2a and b). Activity levels detected in the heart, lungs, spleen, kidneys and liver were 12%, 37%, 74%, 26% and 45%, respectively, of those detected in unaffected heterozygous animals. However, IDUA activity was below the lower limit of detection for this assay in the brains of BMT recipients (Figure 2c).

Reduced GAG storage material in both peripheral organs and the brain following BMT

As previously reported,26 we found that Idua−/− mice displayed increased levels of GAG storage in peripheral organs and in different sections of the brain in comparison to unaffected heterozygous animals. Additionally, Idua−/− animals engrafted with IDUA-positive donor marrow exhibited a statistically significant reduction in GAG storage material in the lungs (**P < 0.01), spleen (**P < 0.001), kidney (**P < 0.001) and liver (*P < 0.05) (Figure 3). There was also a trend towards reduced GAGs in the heart of BMT recipients, but the difference was not statistically significant. The mean reduction in GAG storage material in the heart, lung, spleen, kidney and liver of treated animals was 63%, 89%, 96%, 75% and 93%, respectively, compared with that detected in untreated MPS-I animals. The mean percent reduction in storage material was plotted vs the mean percent of heterozygous IDUA activity detected in the peripheral organs of transplanted animals (Figure 4). A best-fit curve was applied to the data set and yielded a hyperbolic relationship between the two variables with a coefficient of determination (R²) value = 0.95. This relationship between the level of IDUA activity vs the level of GAG reduction supports previous observations whereby a very small amount of IDUA enzymatic activity is sufficient to provide a substantial reduction in lysosomal GAG accumulation.2,22

Although IDUA activity was undetectable in brain samples from transplanted animals, the mean level of GAGs detected was slightly, although not significantly, lower than that observed in untreated animals in all portions of the brain including the olfactory bulb, cerebellum, hippocampus, striatum, cerebral cortex and brainstem and thalamus (Figure 5a). When the data from all portions of the brain were compiled, total GAG accumulation in the brain was significantly reduced in the BMT recipients (Figure 5b). These results were likely an underestimation of the actual reduction in GAG storage material, as untreated Idua−/− mice did not survive to the age of the transplanted animals and thus the BMT-treated animals studied were much older than the control animals.

Focal aggregates of GM3 ganglioside in the brains of BMT recipients

GM3 gangliosides were visualized as focal aggregates in grey matter areas throughout the brains of untreated Idua−/− mice by immunofluorescence microscopy. Representative images of GM3 ganglioside accumulation were taken from the dentate gyrus and septal nucleus (Figure 6). Interestingly, the aggregates of GM3 ganglioside in the dentate gyrus appear concentrated within the
subgranular zone, which provides a niche for neural stem cells. It is not known if this results in dysfunction of these neural stem cells and alters their ability to divide and differentiate; this warrants further investigation. GM3 ganglioside accumulation was absent from the grey matter of unaffected heterozygous mice. Although total brain GAG levels were modestly reduced in the brains of BMT-recipient mice, focal aggregates of GM3 gangliosides were detected in the grey matter of these animals with the pathology indistinguishable from that observed in untreated MPS-I animals.

Preserved valvular heart function in BMT recipients
BMT recipient and control mice were analyzed by high-resolution ultrasound biomicroscopy to assess cardiac valve function. Aortic insufficiency (AI) was observed in 9 of 16 (56%) 7.5-month-old male untreated MPS-I mice, whereas AI was not present in age-matched unaffected male heterozygous animals (n = 6). Six male BMT recipient mice were analyzed and none of the animals displayed AI, demonstrating a significant improvement in aortic function compared with untreated Idua−/− animals (**P < 0.01 by χ² test).

DISCUSSION
Engraftment of wild-type donor marrow into Idua−/− mice resulted in a prolonged lifespan and improvement in valvular heart function, consistent with what has been observed in Hurler patients following successful HSCT. We also observed partial restoration of enzymatic activity in the heart, liver, kidney, lungs and spleen of transplanted animals, with a resultant dramatic reduction in GAG storage material in these organs. These results are consistent with data generated from BMT studies in large animals of MPS-I disease, including both canine and feline models. Upon plotting the mean level of GAG reduction achieved vs the mean IDUA activity detected in each peripheral organ, we constructed a best-fit curve to depict the relationship between IDUA activity and GAG accumulation in tissues. The relationship validates previous observations whereby very small amounts of IDUA resulted in dramatic reduction in tissue GAGs.

Although some BMT studies in MPS-I animals have indicated that IDUA activity can be detected in the brains of transplanted dogs and mice, brain IDUA was below the lower limit of
detection in this study. Nonetheless, total GAG accumulation in the brain was significantly reduced in our study, as reported in cats following BMT.\textsuperscript{33} This suggests that hematopoietic cells may have engrafted in the brain and differentiated into microglia,\textsuperscript{36} providing a sufficient amount of enzyme to reduce lysosomal GAG accumulation. However, although this reduction was statistically significant, brain GAG levels were still elevated compared with unaffected heterozygous animals (*\(P\) < 0.05). Furthermore, punctate aggregates of GM3 ganglioside remained in the treated animals. This demonstrates that although some clearance of storage material occurred following BMT, there is room for improvement in the extent of biochemical correction that can be achieved in the brain. Because the relationship between the level of biochemical storage in the nervous system and the extent of neurocognitive dysfunction in LSD has yet to be elucidated, experiments in animal models constitute an important step in understanding the degree of intervention that may be required to preserve or restore brain function.

The results from this study corroborate the usefulness of the MPS-I mouse as a disease model that recapitulates the human disease. As the current standard of care for Hurler children involves HSCT from a matched donor, the development and assessment of new therapeutic strategies for improved outcomes should be based on those achieved following HSCT. Additionally, as many patients receive enzyme-replacement therapy in combination with HSCT,\textsuperscript{15} it will be important to understand the effect of this combined therapeutic approach on the disease in animal models such as the MPS-I mouse. As one of the major challenges in the treatment of Hurler patients remains efficient delivery of IDUA to the central nervous system, the results of this study provide a benchmark against which novel therapies directed at the CNS in the MPS-I mouse can be compared.

Figure 5. GAG levels in the brain. (a) Levels of GAG storage material detected in microdissected regions of brain tissue collected from MPS I (MPS I, circles), heterozygous (Het, squares) and BMT-recipient mice (MPS I + BMT, triangles). The mean is indicated by a solid line. (b) Mean (+ s.d.) GAG content detected in the brains of MPS I (MPS I, white bar), heterozygous (Het, black bar) and BMT recipient mice (MPS I + BMT, grey bar) upon compiling all data points in part (a). *\(P\) < 0.05 (MPS I vs MPS I + BMT), ***\(P\) < 0.001 (MPS I vs Het) by one-way analysis of variance.

Figure 6. GM3 ganglioside accumulation in the brain. GM3 ganglioside, a substrate that accumulates in neurons and glia of MPS-I animals,\textsuperscript{26,37} was visualized by immunofluorescence microscopy as punctate aggregates (white arrows) within grey matter throughout the brains of untreated MPS-I mice (a, d). Representative images demonstrate focal accumulation of GM3 ganglioside in the dentate gyrus region (a) of the hippocampus and within the septal nucleus (d), both parts of the limbic system. These GM3 ganglioside aggregates were absent from the grey matter of \(Idua^{-/-}\) mice (b, e), but persisted in the brains of BMT-recipient mice (c, f).
CONFLICT OF INTEREST
The authors declare no conflict of interest.

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REFERENCES
1 Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scrivir ALB CR, Sly WS, Beaudet AL, Valle D (eds). The Metabolic and Molecular Bases of Inherited Disease. McGraw Hill: New York, 2001, pp 3421 - 3452.
2 Scott HS, Litjens T, Nelson PV, Thompson PR, Brooks DA, Hopwood JJ et al. Identification of mutations in the alpha-L-iduronidase gene (IDUA) that cause Hurler and Scheie syndromes. Am J Hum Genet 1993; 53: 973 - 986.
3 Kornfeld S. Trafficking of lysosomal enzymes. Faseb J 1987; 1: 462 - 468.
4 Fratantoni JC, Hall CW, Neufeld EF. Hurler and Hunter syndromes: mutual correction of the defect in cultured fibroblasts. Science 1968; 162: 570 - 572.
5 Unger EG, Durrant J, Anson DS, Hopwood JJ. Recombinant alpha-L-iduronidase: characterization of the purified enzyme and correction of mucopolysaccharidosis type I fibroblasts. Biochem J 1994; 304 (Pt 1): 43 - 49.
6 Tsukimura T, Tajima Y, Kawashima I, Fukushige T, Kanzaki T, Kanezuka T et al. Uptake of a recombinant human alpha-L-iduronidase (laronidase) by cultured fibroblasts and osteoblasts. Biol Pharm Bull 2008; 31: 1691 - 1695.
7 Rome LH, Weissmann B, Neufeld EF. Direct demonstration of binding of a lysosomal enzyme, alpha-L-iduronidase, to receptors on cultured fibroblasts. Proc Natl Acad Sci USA 1979; 76: 2331 - 2334.
8 Hobbs JR, Hugh-Jones K, Barrett A, Byrom N, Chambers D, Henry K et al. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. Lancet 1981; 2: 709 - 712.
9 Boelens JJ, Rocka V, Aldenhooven M, Wynn R, O'Meara A, Michel G et al. Risk factor analysis of outcomes after unrelated cord blood transplantation in patients with huer syndrome. Biol Blood Marrow Transplant 2009; 15: 618 - 625.
10 Staba SL, Escolar ML, Poe M, Kim Y, Martin PL, Szabolcs P et al. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med 2004; 350: 1960 - 1969.
11 Bjoraker KJ, Delaney K, Peters C, Krivit W, Shapiro EG. Long-term outcomes of adaptation for functions for children with mucopolysaccharidosis I (Hurler syndrome) treated with hematopoietic stem cell transplantation. J Dev Behav Pediatr 2006; 27: 290 - 296.
12 Dusing SC, Rosenberg A, Hiemenz JR, Piner S, Escolar M et al. Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome. Bone Marrow Transplant 2008; 41: 531 - 535.
13 Prasad VK, Kurtzberg J. Transplant outcomes in mucopolysaccharidoses. Semin Hematol 2010; 47: 59 - 69.
14 Vellodi A, Young E, Cooper A, Lichdi V, Winchester B, Wraith JE. Long-term follow-up following bone marrow transplantation for Hunter disease. J Inherit Metab Dis 1999; 22: 638 - 648.
15 Ziegler R, Shapiro E. Metabolic and neurodegenerative diseases across the life span. In: Donder J, Hunter SJ (eds) Principles and Practice of Lifespan Developmental Neuropsychology. Cambridge University Press: New York, 2007, pp 427 - 448.
16 Clarke LA, Russell CS, Powall S, Warrington CL, Borowsk A, Dimmick JE et al. Murine mucopolysaccharidosis type I targeted disruption of the murine alpha-L-iduronidase gene. Hum Mol Genet 1997; 6: 503 - 511.
17 Ohmi K, Greenberg D, Rajavel K, Ryuazantsev S, Li H, Neufeld E. Activated microglia in cortex of mouse models of mucopolysaccharidosis I and IIIB. PNAS 2003; 100: 1902 - 1907.
18 Garcia-Rivera MF, Colvin-Wanshura LE, Nelson MS, Nan Z, Khan SA, Rogers TB et al. Characterization of an immunodeficient mouse model of mucopolysaccharidosis type I suitable for preclinical testing of human stem cell and gene therapy. Brain Res Bull 2007; 74: 429 - 438.
19 Zheng Y, Rozengurt N, Ryazantsev S, Kohn DB, Satake N, Neufeld EF. Treatment of the mouse model of mucopolysaccharidosis I with retrovirotransduced bone marrow. Mol Genet Metab 2003; 79: 233 - 244.
20 Visigalli I, Delai S, Politi LS, Di Domenico C, Cerrli F, Mirk A et al. Gene therapy augments the efficacy of hematopoietic cell transplantation and fully corrects mucopolysaccharidosis type I phenotype in the mouse model. Blood 2010; 116: 5130 - 5139.
21 Ohmi K, Greenberg DS, Rajavel KS, Ryazantsev S, Li HH, Neufeld EF. Activated microglia in cortex of mouse models of mucopolysaccharidoses I and IIIB. Proc Natl Acad Sci USA 2003; 100: 1902 - 1907.
22 Gori JL, Podetz-Pedersen S, Swanson D, Karlen AD, Gunther R, Sonia NV et al. Protection of mice from methotrexate toxicity by ex vivo transduction using lentivirous vectors expressing drug-resistant dihydrofolate reductase. J Pharmacol Exp Ther 2007; 322: 989 - 997.
23 Wolf DA, Lenander AW, Nan Z, Belur LR, Whitley CB, Gupta P et al. Direct gene transfer to the CNS prevents emergence of neurologic disease in a murine model of mucopolysaccharidosis type I. Neurobiol Dis 2011; 43: 123 - 133.
24 Tolar J, Braunlin E, Riddle M, Peacock B, McElmurry RT, Orchard PJ et al. Gender-related dimorphism in aortic insufficiency in murine mucopolysaccharidosis type I. J Heart Valve Dis 2009; 18: 524 - 529.
25 Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 1996; 16: 2027 - 2033.
26 Braunlin E, Mackey-Bojaci S, Panoskittis-Mortari A, Berry JM, McElmurry RT, Riddle M et al. Cardiac functional and histopathologic findings in humans and mice with mucopolysaccharidosis type I: implications for assessment of therapeutic interventions in huer syndrome. Pediatr Res 2006; 59: 27 - 32.
27 Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood 1996; 87: 4984 - 4985.
28 Souillet G, Guffon N, Maire I, Pujol M, Taylor P, Sevin F et al. Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic stem cell sources. Bone Marrow Transplant 2003; 31: 1105 - 1117.
29 Breider MA, Shull RM, Constantopolous G. Long-term effects of bone marrow transplantation in dogs with mucopolysaccharidosis I. J Inherit Metab Dis 1998; 21: 59 - 69.
30 Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood 1996; 87: 4984 - 4985.
31 Souillet G, Guffon N, Maire I, Pujol M, Taylor P, Sevin F et al. Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic stem cell sources. Bone Marrow Transplant 2003; 31: 1105 - 1117.
32 Breider MA, Shull RM, Constantopolous G. Long-term effects of bone marrow transplantation in dogs with mucopolysaccharidosis I. J Inherit Metab Dis 1998; 21: 59 - 69.
33 Ellinwood NM, Colle MA, Weil ML, Casal ML, Vite CH, Wiemelt S et al. Bone marrow transplantation for feline mucopolysaccharidosis I. Mol Genet Metab 2007; 91: 239 - 250.
34 Shull RM, Breider MA, Constantopolous G. Long-term neurological effects of bone marrow transplantation in a canine lysosomal storage disease. Pediatr Res 1988; 24: 347 - 352.
35 Shull R, Lu X, Dube I, Lutzko C, Kruth S, Abrams-Ogg A et al. Humoral immune response limits gene therapy in canine MPS I. Blood 1996; 88: 377 - 379.
36 Krivit W, Sung JH, Shapiro EG, Lockman MA. Microglia: the effector cell for reconstitution of the central nervous system following bone marrow transplantation for lysosomal and peroxosomal storage diseases. Cell Transplant 1995; 4: 385 - 392.
37 Walkley SJ. Secondary accumulation of gangliosides in lysosomal storage disorders. Semin Cell Dev Biol 2004; 15: 433 - 444.