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Discov Med. Author manuscript; available in PMC 2017 August 14.

Published in final edited form as:

Discov Med. 2013 February ; 15(81): 111–119.

Recent Gene Therapy Advancements for Neurological Diseases

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Abstract

The past few years have seen rapid advancements in vector-mediated gene transfer to the nervous system and modest successes in human gene therapy trials. The purpose of this review is to describe commonly-used viral gene transfer vectors and recent advancements towards producing meaningful gene-based treatments for central nervous system (CNS) disorders. Gene therapy trials for Canavan disease, Batten disease, adrenoleukodystrophy, and Parkinson's disease are discussed to illustrate the current state of clinical gene transfer to the CNS. Preclinical studies are under way for a number of diseases, primarily lysosomal storage disorders, using a newer generation of vectors and delivery strategies. Relevant studies in animal models are highlighted for Mucopolysaccharidosis IIB and Krabbe disease to provide a prelude for what can be expected in the coming years for human gene transfer trials, using recent advancements in gene transfer technology. In conclusion, recent improvements in CNS gene transfer technology are expected to significantly increase the degree of disease rescue in future CNS-directed clinical trials, exceeding the modest clinical successes that have been observed so far.

Introduction

Neurological disorders are among the most difficult to treat with traditional pharmacological approaches due to the complexity of the nervous system and the physical barriers (such as the blood-brain barrier, BBB) that limit the distribution of many compounds into the central nervous system (CNS) after peripheral administration. Vector-mediated gene transfer is an alternative strategy to treat CNS disorders that holds much promise, especially for monogenic diseases.

Although significant advancements have been made using oligonucleotides to treat a variety of diseases and the use of either naked DNA or nanoparticle delivery of DNA, this review will focus on the development of viral vectors and their use in treating neurological disorders. The intent of this review is to provide a basic background on the most commonly used viral vectors and their uses in preclinical and clinical research, so that a reader can gain

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Disclosure

The authors report no conflicts of interest.

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a concise view of where the field stands and seek additional detailed information in the cited references.

Gene Delivery Vectors

Viruses have the natural ability to deliver genetic material to cells, which makes them an excellent vector for gene delivery. Lentivirus, Herpes Simplex Virus, Adenovirus and Adeno-Associated virus (AAV) are some of the commonly used vectors for gene delivery to the CNS (Table 1).

Retroviruses are a family of single-stranded (ss) RNA viruses that use reverse transcription to produce DNA which is randomly inserted into the host genome as a part of their life cycle. These viruses code for the *gag*, *pol*, and *env* genes which are contained in a capsid surrounded by a phospholipid bilayer (Leis *et al.*, 1988). Lentivirus is a complex retrovirus that can transduce both non-dividing and proliferating cells (Lewis and Emerman, 1994). Retroviruses can integrate their genetic material into the host genome of quiescent cells of the CNS and confer long-term gene expression (Escors and Breckpot, 2010; Jakobsson and Lundberg, 2006; Wong *et al.*, 2006). Pseudotyping, which involves modifying the envelope proteins on the capsid surface, can change the tropism of these viruses and also improve transduction efficiency (Colin *et al.*, 2009; Desmaris *et al.*, 2001; Greenberg *et al.*, 2007; Jakobsson *et al.*, 2006; Rahim *et al.*, 2009). Lentiviruses have a packaging capacity of 8 kb of foreign DNA once the *gag* and *pol* genes are removed. The biggest advantage of retroviral vectors is their ability to incorporate the target gene of interest into the host chromosome of dividing cells, which ensures faithful transmission of the transgene to progeny cells. This advantage is critical when targeting a dividing cell population, such as hematopoietic cells.

Herpes Simplex Virus I (HSV-I) is a member of the Herpesviridae family which carries a large, linear, double-stranded (ds) DNA genome encoding about 80 viral genes (Roizman, 1996). The glycoproteins on the capsid facilitate entry of the virion into host cells (Shieh *et al.*, 1992), and once inside the cell, the virus uncoats and circularizes its linear genome into an episome in the nucleus without integration (Garber *et al.*, 1993; Strang and Stow, 2005). Properties of HSV-1 that make it a suitable vector in treating CNS disorders include high transduction efficiency, large transgene capacity (152 kb), its ability to enter a state of latency in neurons, and its high neural tropism via retrograde axonal transport to dorsal root ganglia and trigeminal ganglions (Bearer *et al.*, 2000; Berges *et al.*, 2007). Replication-conditional or attenuated HSV vectors are capable of transgene expression in dividing cells but not in non-dividing cells (Wu *et al.*, 1996). The application of this vector is limited due to its high inflammatory profile but it has been used in gene delivery to cancers such as glioblastoma multiforme (Andreansky *et al.*, 1997; Lou, 2003; Markert *et al.*, 2009; Mineta *et al.*, 1995).

Another vector used in clinical applications is Adenovirus. Although it shows a high neural tropism (Jager and Ehrhardt, 2009), the use of this vector in the CNS is limited due to its high toxicity in the CNS (Lozier *et al.*, 2002; Thomas *et al.*, 2001). This vector is more commonly seen in cancer treatments and is capable of packaging 25 kb of foreign DNA (Kochanek *et al.*, 1996).

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Arguably the most prominent vector for gene delivery to the brain is AAV. It is an ssDNA virus whose genome consists of 3 capsid genes, 4 replication genes, and a gene called AAP contained within 3 open reading frames, flanked by inverted terminal repeats (ITRs) that serve in genome replication and packaging. Recombinant AAV (rAAV) is generated by flanking up to ~4.7 kb of foreign DNA with the ITRs and providing the viral genes in *trans*, to package the foreign DNA (but not viral genes) within the AAV capsid (Dong *et al.*, 1996; Lai *et al.*, 2010; Wu *et al.*, 2010). The risks associated with AAV are highly reduced due to its non-pathogenic nature (Atchison *et al.*, 1965) and its dependence on co-infection with a helper virus such as adenovirus in order to replicate and execute a lytic infection (Goncalves, 2005; McCarty *et al.*, 2004). The viral capsid proteins facilitate binding of the virion to cell surface receptors, which can vary considerably between the >100 AAV variants that have been identified (Gao *et al.*, 2005). The availability of many different capsids with differing tropisms provides a level of cell/organ specificity that can be modulated by the choice of capsid. High neural tropism of some serotypes adds to other advantages of AAV which include its ability to confer long-term transgene expression in non-dividing cells and its ability to deliver genes as an extra-chromosomal episome which highly reduces the possibility of insertional mutagenesis and oncogenesis (Choi *et al.*, 2006; Duan *et al.*, 1998).

For a detailed review of viral vectors used in gene therapy, see Gray *et al.*, 2010b and Lentz *et al.*, 2011.

Current State of Clinical Research

Two primary strategies have emerged as a means to advance gene therapy into the clinical arena. *In vivo* gene transfer focuses on using viral or chemical reagents to deliver genes directly to patients through a single injection. *Ex vivo* gene transfer relies on externally transducing cultured cells with a therapeutic vector and placing them back into patients (Suhr and Gage, 1993). This section will focus on current examples of CNS gene delivery trials made possible through rAAV and lentiviral vectors (Table 2). Additionally, shortcomings associated with each approach will be discussed to emphasize areas where vector improvements may lead to a more meaningful clinical outcome.

The first CNS gene therapy trial utilizing AAV began in 2001 for Canavan's disease -- an inherited leukodystrophy that leads to toxic accumulation of N-acetyl-aspartate (NAA) in the CNS, interfering with the formation of myelin sheaths (Janson *et al.*, 2002; Kumar *et al.*, 2006; Leone *et al.*, 1999). Thirteen of the 28 patients received intraparenchymal injections of an AAV2 vector carrying the enzyme ASPA into six brain regions. Five and ten years post-procedure, no long-term adverse effects were detected in treated patients, and host immune responses to the vector were minimal. Decreased levels of NAA accumulation in the brain suggested a functional copy of ASPA could be delivered to the CNS (Leone *et al.*, 2012; McPhee *et al.*, 2006). Though modest phenotypic improvements could be observed in treated patients such as hand-grasping and increased cognitive recognition, all patients still relied on assistance to walk, converse, and even acknowledge people around them (Leone *et al.*, 2012). A similar result was observed in the 2008 trial to treat late infantile neuronal ceroid lipofuscinosis (LINCL), or Batten disease. Ten patients were injected with twelve stereotaxic injections of CLN2/AAV2 vector into six brain regions (Worgall *et al.*, 2008).

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While four subjects exhibited mild humoral responses to the vector, the remaining subjects exhibited significantly decreased rates of decline compared to untreated control subjects (Worgall *et al.*, 2008). However, like the Canavan trial, only modest phenotypic improvements were observed in these patients without complete reversal of disease pathology. In conclusion, though these studies were some of the first to demonstrate the safety of rAAV-mediated gene delivery for CNS disorders, the breadth of gene transfer achieved with direct brain injections appeared insufficient to achieve a substantial rescue.

Parkinson's disease (PD) is a neurological disease triggered by the loss of dopaminergic neurons in the substantia nigra and the striatum. In the context of disease pathology, PD is a good candidate for gene therapy. However the involvement of several genes and neurotrophic factors has made PD anything but a simple therapeutic goal (Gray *et al.*, 2010). Despite these setbacks, PD gene therapy has pushed its way into seven different phase I and phase II clinical trials, demonstrating the high enthusiasm for gene therapy (Xiao *et al.*, 2012). Six out of the seven trials utilized AAV2 as a vehicle for delivering neurotrophic factors such as GDNF or glutamic acid decarboxylase (GAD) while the seventh utilizes a lentiviral vector (Feng and Maguire-Zeiss, 2010). Treated patients have reported improvements in motor function, but the treatment efficacy has been difficult to evaluate in the absence of an extended phase III, placebo-controlled study.

Lastly, for disorders where loss of a secreted protein results in CNS defects, *ex vivo* gene therapy offers a way to reprogram isolated patient cells for functional protein synthesis. An example is a 2009 trial to treat adrenoleukodystrophy (ALD) -- a demyelinating disorder caused by the loss of an enzyme critical for metabolizing fatty acid chains in the CNS. Autologous CD34+ cells were isolated from two ALD boys, genetically reprogrammed using a lentiviral vector carrying the missing *ABCD1* gene, and then reinjected into the patients. Follow-up studies showed that demyelination was halted 14–16 months following treatment, and 24–30 months later ALD protein expression was still retained in several cell types (Cartier *et al.*, 2012; 2010).

While several clinical trials have occurred, the degree of patient improvement has been limited. A major limitation in all of these trials is the current vector technology and the ongoing challenge of how to widely, efficiently, and safely transduce cells within the CNS. Vector technology has made considerable advancements over what is currently used in the clinic, and these improvements are poised to greatly improve treatment efficacy. Some of these advancements are outlined below.

Advancements in Vector Technology for *In Vivo* Gene Transfer

An ideal vector would provide widespread distribution of the transgene, large packaging capacity, stable gene expression, high transduction efficiency, target cell specificity, and low immunological responses in order to overcome current limitations. Except for the packaging capacity, recent advancements have been made for AAV in each of these regards. Improvements in other vectors have also been made in most of these areas, but will not be discussed in detail. For more information on Adenovirus and HSV vectors, see Lentz *et al.*, 2011.

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Identification of the optimal capsid is critical to effectively target the desired cells and tissues. Over 100 AAV variants have been identified with varying tropisms providing a broad toolkit for optimized delivery to target tissue/organs (Gao *et al.*, 2005; Wu *et al.*, 2006). Several variants of AAV have been used in CNS applications including AAV1, AAV2, AAV4, AAV5, AAV6, AAV8, and AAV9 (Gray, 2012). Although AAV2 is the most studied serotype in clinical applications, it performs relatively poorly compared to more recently characterized serotypes. Direct injection in the brain parenchyma with AAV1 and AAV9 provides an almost exclusive neuronal tropism, a mix of neurons and glia with AAV5, and mostly astrocytes with AAV4 (Burger *et al.*, 2004; Cearley and Wolfe, 2006; Davidson *et al.*, 2000). More recently, AAV9 has been shown to cross the BBB and transduce neurons and glia in the brain and spinal cord following intravenous injection (Duque *et al.*, 2009; Foust *et al.*, 2009; Gray *et al.*, 2011b). Current challenges to intravenous delivery of AAV9 include high peripheral tropism, high doses required, and limited neuronal transduction in non-human primate cells due to the existence of pre-existing neutralizing antibodies (NAbs) (Gray *et al.*, 2011b). To circumvent these problems AAV9 can be injected into the cerebrospinal fluid (CSF) via the lumbar cistern or cisterna magna. Using this route of administration still provides widespread CNS gene transfer in non-human primates, but avoids anti-AAV NAbs, greatly reduces the peripheral biodistribution, and uses a considerably lower dose (Samaranch *et al.*, 2012; Gray et al., in press) compared to intravenous injection.

Tissue/cell specificity can be further manipulated by engineering the viral capsid beyond what is found in nature. Strategies to modify the capsid include rational mutagenesis, peptide insertion, and directed evolution/DNA shuffling. By introducing rational mutations in the capsid, novel variants of AAV can be produced which are not only optimized for transduction but also increase target specificity, prevent the production of circulating antibodies to the vector, and/or improve intracellular trafficking. As an example, AAV9.47 is a variant of AAV9 that is liver-detargeted but still retains high CNS tropism (Pulicherla *et al.*, 2011).

To increase the specificity of the viral vector, known ligands for target cells can be incorporated on the capsid. This approach has been used to modify AAV2's ability to deliver genes to the CNS. Unmodified AAV2 normally has limited capability for axonal transport, but when peptides derived from an NMDA receptor agonist and a dynein binding motif were incorporated on the capsid, a 10–100 fold increase of retrograde transport delivery to the CNS was observed (Xu *et al.*, 2005). Similarly, novel CNS-targeted AAV vectors have been created by incorporating peptides obtained through phage-display biopanning (Chen *et al.*, 2009). When these peptides were incorporated into an AAV2 capsid, peptides generated in disease models specifically targeted the CNS vasculature in those models but not in wild-type mice, and *vice versa*. This demonstrates the high specificity that these approaches can confer upon the vectors.

As opposed to rational mutagenesis, directed evolution is a process of selecting novel capsid variants without *a priori* knowledge of physical determinants. This process was developed by Schaffer and Maheshri (Maheshri *et al.*, 2006; Schaffer and Maheshri, 2004) and allows for the recovery of clones that are highly selective for a given characteristic, above that of the

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parent serotypes. Error-prone polymerase chain reaction of a single serotype, DNA shuffling by randomly mixing multiple serotypes, and a combination of these two methods are used to generate library clones with various mutations (Stemmer, 1994a; 1994b). These library clones are pooled together and subjected to multiple rounds of selective pressure. This technique was successful in the isolation of two clones for delivering therapeutic genes to areas of the brain that suffered damage from kainic acid seizures after intravenous injection (Gray *et al.*, 2010a). These clones had the benefit of near-complete loss of tropism for liver, heart, and muscle conferring a more favorable biodistribution profile, leading to a higher degree of safety.

A major rate-limiting step in gene expression, and conversion of the genome into a stable episome in ssAAV, is the synthesis of the second strand for transcription following the uncoating of AAV in the cell (McCarty *et al.*, 2003). Transduction efficiency has been increased over 100-fold with the use of self-complementary (sc) AAV (McCarty *et al.*, 2001). scAAV vector genomes are composed of complementary copies of the DNA insert linked in *cis* through a mutated AAV inverted terminal repeat (ITR). The main disadvantage of using scAAV is the reduced packaging capacity of 2.3 kb. This limitation has led to the development of new compact promoters and polyadenylation elements (Gray *et al.*, 2011a).

Advancements in *Ex Vivo* Gene Transfer: Lentiviral Correction of Bone Marrow Stem Cells

Successful treatment options for lysosomal storage diseases include enzyme replacement therapy (ERT) (Desnick and Schuchman, 2002), hematopoietic cell transplantation (HCT) (Peters *et al.*, 2003; Souillet *et al.*, 2003), or a combination of the two as seen in Hurler's syndrome (Cox-Brinkman *et al.*, 2006). The main problem with ERT is the efficacy of the enzyme to cross the BBB which limits the access of systemically injected enzyme. Allogeneic HCT can be used to overcome this. Hematopoietic cells, such as activated lymphocytes, monocytes, and microglial precursors, are able to cross the BBB and can be used to deliver enzymes to the CNS (Asheuer *et al.*, 2004; Priller *et al.*, 2001). Following hematopoietic stem cell (HSC) transplantation, donor derived cells migrate to the CNS and differentiate to form perivascular and parenchymal microglia. These cells could mediate the cross-correction of the enzyme in neighboring neurons and glial cells. However, the benefit is limited to a small subset of lysosomal storage diseases (LSDs) and is not effective in patients with overt neurological or aggressive infantile forms (Rovelli, 2008). Another limitation of allogeneic HCT is the development of Graft-vs-Host Disease (GVHD) or Host-vs-Graft Disease (HVGD), where the immune cells are activated and cause wide-spread inflammation (Hwang *et al.*, 2007).

Transplantation of autologous HSCs modified with lentiviral vectors to express the missing enzyme or protein may circumvent the problems associated with allogeneic HSCT (Biffi *et al.*, 2011; Cartier and Aubourg, 2008; Cartier and Aubourg, 2010; Cartier *et al.*, 1996).

Random insertion of the transgene into the host genome, initially seen as advantage of lentiviral vectors due to the propagation of the transgene among dividing cells, has the risk of insertional mutagenesis as seen in the patients treated for X-linked SCID who developed leukemia as a side effect of treatment (Bokhoven *et al.*, 2009; Hacein-Bey-Abina *et al.*, 2003; Pike-Overzet *et al.*, 2007). Lentiviral vectors have been made significantly safer by

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reducing or eliminating its integration into the host genome. Directing integration to heterochromatin regions minimizes the risk of gene activation (Gijsbers *et al.*, 2010) and increases the safety of lentiviral vectors. Other advancements in lentiviral vectors are self-inactivating (SIN) mutations, which knock out the promoter activity of the LTR (Miyoshi *et al.*, 1998; Zufferey *et al.*, 1998), as well as non-integrating lentiviral (NIL) vectors, which carry mutant integrase or mutations in their LTRs that inhibit integrase binding (Apolonia *et al.*, 2007; Philippe *et al.*, 2006; Sarkis *et al.*, 2008). These viral genomes exist in linear and circular forms episomally (Cara and Reitz, 1997; Philpott and Thrasher, 2007). These new technologies aim to improve safety of the vectors and overcome risks of cancer. For a detailed review on gene transfer in HSC, see Cartier and Aubourg, 2010.

Gene Therapy for Lysosomal Storage Disorders

Lysosomal storage diseases (LSDs) are a set of inherited, metabolic disorders characterized by reduced or absent levels of soluble lysosomal enzyme activity. Over time, loss of enzyme activity results in accumulation of toxic metabolic substrates, which in 70% of LSD patients results in debilitating neurological symptoms (Gritti, 2011; Neufeld, 1991; Sands and Davidson, 2006). Genzyme Corporation currently offers recombinant enzyme replacement therapy (ERT) for four different LSDs -- Gaucher disease, Fabry disease, Mucopolysaccharidosis I, and Pompe disease. ERT requires regular infusions of enzyme, whereas gene therapy offers a permanent source of the missing enzyme within the body after a single administration.

Normally when an enzyme or protein is first translated, it is trafficked to the endoplasmic reticulum and the Golgi apparatus to undergo post-translational modifications. A small percentage of modified proteins eventually become trafficked out of the lysosome and find their way to the cell surface to be secreted out of the cell. This secreted enzyme can be taken up by neighboring cells, providing cross-correction (Sands and Davidson, 2006). Gene therapy can take advantage of this system by transducing a small population of cells, correcting them to permanently produce the functional soluble enzyme and thereafter, by inherent cellular trafficking, pass on the therapeutic product to neighboring cells. Data from *in vitro* cross-correction and *in vivo* clinical studies have demonstrated that missing LSD enzyme expressed at levels 1–10% of normal levels can be therapeutic (Leimig *et al.*, 2002; Sands and Davidson, 2006). Therefore, cross-correction allows even sub-optimal gene expression to make a strong impact on LSDs. However, there are a number of LSDs where the mutation is not in a soluble enzyme. Mutations in non-enzymatic proteins like GM2 activators or saposins can lead to an inability of cells to activate specific lysosomal enzymes (Sands and Davidson, 2006). Other LSD types are characterized by mutations in integral lysosomal membrane proteins or proteins that assist in the intracellular trafficking of lysosomal enzymes. LSDs caused by a missing soluble enzyme, that is capable of cross-correction, represent the easiest targets for gene therapy.

Several proof-of-principle studies have validated the therapeutic potential of cross-correction, as long as the transgene is widely distributed across the CNS. One example is Mucopolysaccharidosis (MPS) IIB disease -- an LSD caused by a deficiency in the alpha-N-acetyl-glucosaminidase (NAGLU) enzyme responsible for breaking down heparan sulfate in

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the lysosome. In 2011, Fu et al. (2011) demonstrated that a single intravenous injection of rAAV9-NAGLU significantly improved the behavioral phenotypes and increased survival of treated MPS IIIB disease mice. Histological staining of target CNS tissues showed diffuse global transduction and pathological correction, demonstrating that gene delivery to a small percentage of widely distributed cells could provide therapeutic enzyme activity levels across the CNS (Fu *et al.*, 2011). In Krabbe disease, a neurodegenerative disorder characterized by a deficiency in galactocerebrosidase (GALC), Rafi *et al.* (2012) demonstrated the potential of utilizing multiple CNS injections to optimize delivery and overall cross-correction. By injecting neonate mice intracerebroventricularly, intracerebellarly, and intravenously with rAAVrh10-GALC, high enzyme activity was achieved in the brain and cerebellum, and moderate to high activity was detected in the spinal cord and the sciatic nerve. In addition, treated mice successfully lived up to 8 months and gained the ability to mate and care for new-borns, among other phenotypic corrections (Rafi *et al.*, 2012).

The disease paradigm of LSDs lends itself well for gene therapy applications. Encouraging preclinical results from murine models of MPSIIB and Krabbe disease have demonstrated the capacity in which new global gene transfer approaches are proving beneficial for this family of diseases.

Summary

In an ideal scenario, a single administration of the vector (containing the therapeutic gene) would confer permanent correction of the target disease. Monogenic CNS disorders, especially LSDs that can benefit from cross-correction, are particularly amenable to this approach. Clinical trials spanning the prior decade have shown positive effects resulting from gene transfer, but the benefit to the patients has been relatively modest. The vector technology, both for *in vivo* and *ex vivo* gene transfer, has advanced rapidly in the last few years and new approaches have been developed to significantly improve the scope and efficiency of gene transfer. The effectiveness of these strategies for *in vivo* and *ex vivo* gene transfer is being realized in preclinical animal studies, and they are poised to rapidly transition into the clinical realm. Clinical successes, however modest, will continue to generate optimism and drive the field forward. If the preclinical successes now being realized translate to the clinical arena, the coming years should be quite exciting indeed.

Acknowledgments

S.J.G. would like to acknowledge support from the International Rett Syndrome Foundation, the New Hope Research Foundation, Hannah's Hope Fund, Bee for Batten, Jasper Against Batten, and the Krabbe Translational Research Network sponsored by the Legacy of Angels Foundation.

References

Andreansky S, Soroceanu L, Flotte ER, Chou J, Markert JM, Gillespie GY, Roizman B, Whitley RJ. Evaluation of genetically engineered herpes simplex viruses as oncolytic agents for human malignant brain tumors. Cancer Res. 1997; 57(8):1502–1509. [PubMed: 9108452]

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Apolonia L, Waddington SN, Fernandes C, Ward NJ, Bouma G, Blundell MP, Thrasher AJ, Collins MK, Philpott NJ. Stable gene transfer to muscle using non-integrating lentiviral vectors. Mol Ther. 2007; 15(11):1947–1954. [PubMed: 17700544]

Asheuer M, Pflumio F, Benhamida S, Dubart-Kupperschmitt A, Fouquet F, Imai Y, Aubourg P, Cartier N. Human CD34+ cells differentiate into microglia and express recombinant therapeutic protein. Proc Natl Acad Sci U S A. 2004; 101(10):3557–3562. [PubMed: 14990803]

Atchison RW, Casto BC, Hammon WM. Adenovirus-associated defective virus particles. Science. 1965; 149(3685):754–756. [PubMed: 14325163]

Bearer EL, Breakefield XO, Schuback D, Reese TS, Lavail JH. Retrograde axonal transport of herpes simplex virus: evidence for a single mechanism and a role for tegument. Proc Natl Acad Sci U S A. 2000; 97(14):8146–8150. [PubMed: 10884436]

Berges BK, Wolfe JH, Fraser NW. Transduction of brain by herpes simplex virus vectors. Mol Ther. 2007; 15(1):20–29. [PubMed: 17164771]

Biffi A, Aubourg P, Cartier N. Gene therapy for leukodystrophies. Hum Mol Genet. 2011; 20(R1):R42–53. [PubMed: 21459776]

Bokhoven M, Stephen SL, Knight S, Gevers EF, Robinson IC, Takeuchi Y, Collins MK. Insertional gene activation by lentiviral and gammaretroviral vectors. J Virol. 2009; 83(1):283–294. [PubMed: 18945765]

Burger C, Gorbatyuk OS, Velardo MJ, Peden CS, Williams P, Zolotukhin S, Reier PJ, Mandel RJ, Muzyczka N. Recombinant A AV viral vectors pseudotyped with viral capsids from serotypes 1, 2, and 5 display differential efficiency and cell tropism after delivery to different regions of the central nervous system. Mol Ther. 2004; 10(2):302–317. [PubMed: 15294177]

Cara A, Reitz MS Jr. New insight on the role of extrachromosomal retroviral DNA. Leukemia. 1997; 11(9):1395–1399. [PubMed: 9305590]

Cartier N, Aubourg P. Hematopoietic stem cell gene therapy in Hurler syndrome, globoid cell leukodystrophy, metachromatic leukodystrophy and X-adrenoleukodystrophy. Curr Opin Mol Ther. 2008; 10(5):471–478. [PubMed: 18830923]

Cartier N, Aubourg P. Hematopoietic stem cell transplantation and hematopoietic stem cell gene therapy in X-linked adrenoleukodystrophy. Brain Pathol. 2010; 20(4):857–862. [PubMed: 20626747]

Cartier N, Hacein-Bey-Abina S, Bartholomae CC, Bougneres P, Schmidt M, Kalle CV, Fischer A, Cavazzana-Calvo M, Aubourg P. Lentiviral hematopoietic cell gene therapy for X-linked adrenoleukodystrophy. Methods Enzymol. 2012; 507:187–198. [PubMed: 22365775]

Cartier N, Hacein-Bey-Abina S, Von Kalle C, Bougneres P, Fischer A, Cavazzana-Calvo M, Aubourg P. Gene therapy of x-linked adrenoleukodystrophy using hematopoietic stem cells and a lentivi-ral vector. Bulletin de l'Academie Nationale de Medecine. 2010; 194(2):255–264. discussion 264–258.

Cartier N, Miclea JM, Chomienne C, Bougneres PF, Aubourg P. Gene therapy of adrenoleukodystrophy. Archives de Pediatrie. 1996; 3(Suppl 1):77s–81s. [PubMed: 8795973]

Cearley CN, Wolfe JH. Transduction characteristics of adeno-associated virus vectors expressing cap serotypes 7, 8, 9, and Rh10 in the mouse brain. Mol Ther. 2006; 13(3):528–537. [PubMed: 16413228]

Chen YH, Chang M, Davidson BL. Molecular signatures of disease brain endothelia provide new sites for CNS-directed enzyme therapy. Nat Med. 2009; 15(10):1215–1218. [PubMed: 19749771]

Choi VW, Mccarty DM, Samulski RJ. Host cell DNA repair pathways in adeno-associated viral genome processing. J Virol. 2006; 80(21):10346–10356. [PubMed: 17041215]

Colin A, Faideau M, Dufour N, Auregan G, Hassig R, Andrieu T, Brouillet E, Hantraye P, Bonvento G, Deglon N. Engineered lentiviral vector targeting astrocytes in vivo. Glia. 2009; 57(6):667–679. [PubMed: 18942755]

Cox-Brinkman J, Boelens JJ, Wraith JE, O'meara A, Veys P, Wijburg FA, Wulffraat N, Wynn RF. Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant. 2006; 38(1):17–21. [PubMed: 16715104]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Davidson BL, Stein CS, Heth JA, Martins I, Kotin RM, Derksen TA, Zabner J, Ghodsi A, Chiorini JA. Recombinant adeno-associated virus type 2, 4, and 5 vectors: transduction of variant cell types and regions in the mammalian central nervous system. Proc Natl Acad Sci U S A. 2000; 97(7):3428–3432. [PubMed: 10688913]

Desmaris N, Bosch A, Salaun C, Petit C, Prevost MC, Tordo N, Perrin P, Schwartz O, De Rocquigny H, Heard JM. Production and neurotropism of lentivirus vectors pseudotyped with lyssavirus envelope glycoproteins. Mol Ther. 2001; 4(2):149–156. [PubMed: 11482987]

Desnick RJ, Schuchman EH. Enzyme replacement and enhancement therapies: lessons from lysosomal disorders. Nat Rev Genet. 2002; 3(12):954–966. [PubMed: 12459725]

Dong JY, Fan PD, Frizzell RA. Quantitative analysis of the packaging capacity of recombinant adeno-associated virus. Hum Gene Ther. 1996; 7(17):2101–2112. [PubMed: 8934224]

Duan D, Sharma P, Yang J, Yue Y, Dudus L, Zhang Y, Fisher KJ, Engelhardt JF. Circular intermediates of recombinant adeno-associated virus have defined structural characteristics responsible for long-term episomal persistence in muscle tissue. J Virol. 1998; 72(11):8568–8577. [PubMed: 9765395]

Duque S, Joussemet B, Riviere C, Marais T, Dubreil L, Douar AM, Fyfe J, Moullier P, Colle MA, Barkats M. Intravenous administration of self-complementary AAV9 enables transgene delivery to adult motor neurons. Mol Ther. 2009; 17(7):1187–1196. [PubMed: 19367261]

Escors D, Breckpot K. Lentiviral vectors in gene therapy: their current status and future potential. Archivum Immunologiae et Therapiae Experimentalis. 2010; 58(2):107–119. [PubMed: 20143172]

Feng LR, Maguire-Zeiss KA. Gene therapy in Parkinson's disease: rationale and current status. CNS Drugs. 2010; 24(3):177–192. [PubMed: 20155994]

Foust KD, Nurre E, Montgomery CL, Hernandez A, Chan CM, Kaspar BK. Intravascular AAV9 preferentially targets neonatal neurons and adult astrocytes. Nat Biotechnol. 2009; 27(1):59–65. [PubMed: 19098898]

Fu H, Dirosario J, Killedar S, Zaraspe K, Mccarty DM. Correction of neurological disease of mucopolysaccharidosis IIIB in adult mice by rAAV9 trans-blood-brain barrier gene delivery. Mol Ther. 2011; 19(6):1025–1033. [PubMed: 21386820]

Gao G, Vandenberghe LH, Wilson JM. New recombinant serotypes of AAV vectors. Curr Gene Ther. 2005; 5(3):285–297. [PubMed: 15975006]

Garber DA, Beverley SM, Coen DM. Demonstration of circularization of herpes simplex virus DNA following infection using pulsed field gel electrophoresis. Virology. 1993; 197(1):459–462. [PubMed: 8212585]

Gijsbers R, Ronen K, Vets S, Malani N, De Rijck J, Mcneely M, Bushman FD, Debyser Z. LEDGF hybrids efficiently retarget lentiviral integration into heterochromatin. Mol Ther. 2010; 18(3):552–560. [PubMed: 20195265]

Goncalves MA. Adeno-associated virus: from defective virus to effective vector. Virol J. 2005; 2:43. [PubMed: 15877812]

Gray SJ. Gene therapy and neurodevelopmental disorders. Neuropharmacology. 2012

Gray SJ, Blake BL, Criswell HE, Nicolson SC, Samulski RJ, Mccown TJ, Li W. Directed evolution of a novel adeno-associated virus (AAV) vector that crosses the seizure-compromised blood-brain barrier (BBB). Mol Ther. 2010a; 18(3):570–578. [PubMed: 20040913]

Gray SJ, Foti SB, Schwartz JW, Bachaboina L, Taylor-Blake B, Coleman J, Ehlers MD, Zylka MJ, Mccown TJ, Samulski RJ. Optimizing promoters for recombinant adeno-associated virus-mediated gene expression in the peripheral and central nervous system using self-complementary vectors. Hum Gene Ther. 2011a; 22(9):1143–1153. [PubMed: 21476867]

Gray SJ, Matagne V, Bachaboina L, Yadav S, Ojeda SR, Samulski RJ. Preclinical differences of intravascular AAV9 delivery to neurons and glia: a comparative study of adult mice and nonhuman primates. Mol Ther. 2011b; 19(6):1058–1069. [PubMed: 21487395]

Gray SJ, Woodard KT, Samulski RJ. Viral vectors and delivery strategies for CNS gene therapy. Ther Deliv. 2010b; 1(4):517–534. [PubMed: 22833965]

Greenberg KP, Geller SF, Schaffer DV, Flannery JG. Targeted trans-gene expression in muller glia of normal and diseased retinas using lentiviral vectors. Invest Ophthalmol Vis Sci. 2007; 48(4):1844–1852. [PubMed: 17389520]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Gritti A. Gene therapy for lysosomal storage disorders. Expert Opin Biol Ther. 2011; 11(9):1153–1167. [PubMed: 21548845]

Hacein-Bey-Abina S, Von Kalle C, Schmidt M, Le Deist F, Wulffraat N, Mcintyre E, Radford I, Villeval JL, Fraser CC, Cavazzana-Calvo M, Fischer A. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med. 2003; 348(3):255–256. [PubMed: 12529469]

Hwang WY, Samuel M, Tan D, Koh LP, Lim W, Linn YC. A meta-analysis of unrelated donor umbilical cord blood transplantation versus unrelated donor bone marrow transplantation in adult and pediatric patients. Biol Blood Marrow Transplant. 2007; 13(4):444–453. [PubMed: 17382250]

Jager L, Ehrhardt A. Persistence of high-capacity adenoviral vectors as replication-defective monomeric genomes in vitro and in murine liver. Hum Gene Ther. 2009; 20(8):883–896. [PubMed: 19364285]

Jakobsson J, Lundberg C. Lentiviral vectors for use in the central nervous system. Mol Ther. 2006; 13(3):484–493. [PubMed: 16403676]

Jakobsson J, Nielsen TT, Staflin K, Georgievska B, Lundberg C. Efficient transduction of neurons using Ross River glycoprotein-pseudotyped lentiviral vectors. Gene Ther. 2006; 13(12):966–973. [PubMed: 16511527]

Janson C, Mcphee S, Bilaniuk L, Haselgrove J, Testaiuti M, Freese A, Wang DJ, Shera D, Hurh P, Rupin J, Saslow E, Goldfarb O, Goldberg M, Larijani G, Sharrar W, Liouterman L, Camp A, Kolodny E, Samulski J, Leone P. Clinical protocol. Gene therapy of Canavan disease: AAV-2 vector for neurosurgical delivery of aspartoacylase gene (ASPA) to the human brain. Hum Gene Ther. 2002; 13(11):1391–1412. [PubMed: 12162821]

Kochanek S, Clemens PR, Mitani K, Chen HH, Chan S, Caskey CT. A new adenoviral vector: Replacement of all viral coding sequences with 28 kb of DNA independently expressing both full-length dystrophin and beta-galactosidase. Proc Natl Acad Sci U S A. 1996; 93(12):5731–5736. [PubMed: 8650161]

Kumar S, Mattan NS, De Vellis J. Canavan disease: a white matter disorder. Mental retardation and developmental disabilities research reviews. 2006; 12(2):157–165. [PubMed: 16807907]

Lai Y, Yue Y, Duan D. Evidence for the failure of adeno-associated virus serotype 5 to package a viral genome > or = 8.2 kb. Gene Ther. 2010; 18(1):75–79.

Leimig T, Mann L, Martin Mdel P, Bonten E, Persons D, Knowles J, Allay JA, Cunningham J, Nienhuis AW, Smeyne R, D'azzo A. Functional amelioration of murine galactosialidosis by genetically modified bone marrow hematopoietic progenitor cells. Blood. 2002; 99(9):3169–3178. [PubMed: 11964280]

Leis J, Baltimore D, Bishop JM, Coffin J, Fleissner E, Goff SP, Oroszlan S, Robinson H, Skalka AM, Temin HM, et al. Standardized and simplified nomenclature for proteins common to all retroviruses. J Virology. 1988; 62(5):1808–1809. [PubMed: 3357211]

Lentz TB, Gray SJ, Samulski RJ. Viral vectors for gene delivery to the central nervous system. Neurobiol Dis. 2011

Leone P, Janson CG, Mcphee SJ, During MJ. Global CNS gene transfer for a childhood neurogenetic enzyme deficiency: Canavan disease. Curr Opin Mol Ther. 1999; 1(4):487–492. [PubMed: 11713764]

Leone P, Shera D, Mcphee SW, Francis JS, Kolodny EH, Bilaniuk LT, Wang DJ, Assadi M, Goldfarb O, Goldman HW, Freese A, Young D, During MJ, Samulski RJ, Janson CG. Long-term follow-up after gene therapy for canavan disease. Sci Transl Med. 2012; 4(165):165ra163.

Lewis PF, Emerman M. Passage through mitosis is required for oncoretroviruses but not for the human immunodeficiency virus. J Virol. 1994; 68(1):510–516. [PubMed: 8254763]

Lou E. Oncolytic herpes viruses as a potential mechanism for cancer therapy. Acta Oncol. 2003; 42(7): 660–671. [PubMed: 14690152]

Lozier JN, Csako G, Mondoro TH, Krizek DM, Metzger ME, Costello R, Vostal JG, Rick ME, Donahue RE, Morgan RA. Toxicity of a first-generation adenoviral vector in rhesus macaques. Hum Gene Ther. 2002; 13(1):113–124. [PubMed: 11779415]

Maheshri N, Koerber JT, Kaspar BK, Schaffer DV. Directed evolution of adeno-associated virus yields enhanced gene delivery vectors. Nat Biotechnol. 2006; 24(2):198–204. [PubMed: 16429148]

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Markert JM, Liechty PG, Wang W, Gaston S, Braz E, Karrasch M, Nabors LB, Markiewicz M, Lakeman AD, Palmer CA, Parker JN, Whitley RJ, Gillespie GY. Phase Ib trial of mutant herpes simplex virus G207 inoculated pre-and post-tumor resection for recurrent GBM. Gene Ther. 2009; 17(1):199–207.

McCarty DM, Fu H, Monahan PE, Toulson CE, Naik P, Samulski RJ. Adeno-associated virus terminal repeat (TR) mutant generates self-complementary vectors to overcome the rate-limiting step to transduction in vivo. Gene Ther. 2003; 10(26):2112–2118. [PubMed: 14625565]

McCarty DM, Monahan PE, Samulski RJ. Self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis. Gene Ther. 2001; 8(16):1248–1254. [PubMed: 11509958]

McCarty DM, Young SM Jr, Samulski RJ. Integration of adeno-associated virus (AAV) and recombinant AAV vectors. Annu Rev Genet. 2004; 38:819–845. [PubMed: 15568995]

McPhee SW, Janson CG, Li C, Samulski RJ, Camp AS, Francis J, Shera D, Lioutermann L, Feely M, Freese A, Leone P. Immune responses to AAV in a phase I study for Canavan disease. J Gene Med. 2006; 8(5):577–588. [PubMed: 16532510]

Mineta T, Rabkin SD, Yazaki T, Hunter WD, Martuza RL. Attenuated multi-mutated herpes simplex virus-1 for the treatment of malignant gliomas. Nat Med. 1995; 1(9):938–943. [PubMed: 7585221]

Miyoshi H, Blomer U, Takahashi M, Gage FH, Verma IM. Development of a self-inactivating lentivirus vector. J Virol. 1998; 72(10):8150–8157. [PubMed: 9733856]

Neufeld EF. Lysosomal storage diseases. Annu Rev Biochem. 1991; 60:257–280. [PubMed: 1883197]

Peters C, Steward CG. National Marrow Donor P, International Bone Marrow Transplant R, Working Party on Inborn Errors EBMTG. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. Bone Marrow Transplant. 2003; 31(4): 229–239. [PubMed: 12621457]

Philippe S, Sarkis C, Barkats M, Mammeri H, Ladroue C, Petit C, Mallet J, Serguera C. Lentiviral vectors with a defective integrase allow efficient and sustained transgene expression in vitro and in vivo. Proc Natl Acad Sci U S A. 2006; 103(47):17684–17689. [PubMed: 17095605]

Philpott NJ, Thrasher AJ. Use of nonintegrating lentiviral vectors for gene therapy. Hum Gene Ther. 2007; 18(6):483–489. [PubMed: 17523890]

Pike-Overzet K, Van Der Burg M, Wagemaker G, Van Dongen JJ, Staal FJ. New insights and unresolved issues regarding insertional mutagenesis in X-linked SCID gene therapy. Gene Ther. 2007; 15(11):1910–1916.

Priller J, Flugel A, Wehner T, Boentert M, Haas CA, Prinz M, Fernandez-Klett F, Prass K, Bechmann I, De Boer BA, Frotscher M, Kreutzberg GW, Persons DA, Dirnagl U. Targeting gene-modified hematopoietic cells to the central nervous system: use of green fluorescent protein uncovers microglial engraftment. Nat Med. 2001; 7(12):1356–1361. [PubMed: 11726978]

Pulicherla N, Shen S, Yadav S, Debbink K, Govindasamy L, Agbandje-Mckenna M, Asokan A. Engineering liver-detargeted AAV9 vectors for cardiac and musculoskeletal gene transfer. Gene Ther. 2011; 19(6):1070–1078.

Rafi MA, Rao HZ, Luzi P, Curtis MT, Wenger DA. Extended normal life after AAVrh10-mediated gene therapy in the mouse model of krabbe disease. Gene Ther. 2012; 20(11):2031–2042.

Rahim AA, Wong AM, Howe SJ, Buckley SM, Acosta-Saltos AD, Elston KE, Ward NJ, Philpott NJ, Cooper JD, Anderson PN, Waddington SN, Thrasher AJ, Raivich G. Efficient gene delivery to the adult and fetal CNS using pseudotyped non-integrating lentiviral vectors. Gene Ther. 2009; 16(4): 509–520. [PubMed: 19158847]

Roizman B. The function of herpes simplex virus genes: a primer for genetic engineering of novel vectors. Proc Natl Acad Sci U S A. 1996; 93(21):11307–11312. [PubMed: 8876131]

Rovelli AM. The controversial and changing role of haematopoietic cell transplantation for lysosomal storage disorders: an update. Bone Marrow Transplant. 2008; 41(Suppl 2):S87–S89. [PubMed: 18545253]

Samaranch L, Salegio EA, San Sebastian W, Kells AP, Foust KD, Bringas JR, Lamarre C, Forsayeth J, Kaspar BK, Bankiewicz KS. Adeno-associated virus serotype 9 transduction in the central nervous system of nonhuman primates. Hum Gene Ther. 2012; 23(4):382–389. [PubMed: 22201473]

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Sands MS, Davidson BL. Gene therapy for lysosomal storage diseases. Mol Ther. 2006; 13(5):839–849. [PubMed: 16545619]

Sarkis C, Philippe S, Mallet J, Serguera C. Non-integrating lentiviral vectors. Curr Gene Ther. 2008; 8(6):430–437. [PubMed: 19075626]

Schaffer DV, Maheshri N. Directed evolution of AAV mutants for enhanced gene delivery. Conf Proc IEEE Eng Med Biol Soc. 2004; 5:3520–3523. [PubMed: 17271049]

Shieh MT, Wudunn D, Montgomery RI, Esko JD, Spear PG. Cell surface receptors for herpes simplex virus are heparan sulfate proteoglycans. J Cell Biol. 1992; 116(5):1273–1281. [PubMed: 1310996]

Souillet G, Guffon N, Maire I, Pujol M, Taylor P, Sevin F, Bleyzac N, Mulier C, Durin A, Kebaili K, Galambrun C, Bertrand Y, Froissart R, Dorche C, Gebuhrer L, Garin C, Berard J, Guibaud P. Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic stem cell sources. Bone Marrow Transplant. 2003; 31(12):1105–1117. [PubMed: 12796790]

Stemmer WP. DNA shuffling by random fragmentation and reassembly: in vitro recombination for molecular evolution. Proc Natl Acad Sci U S A. 1994a; 91(22):10747–10751. [PubMed: 7938023]

Stemmer WP. Rapid evolution of a protein in vitro by DNA shuffling. Nature. 1994b; 370(6488):389–391. [PubMed: 8047147]

Strang BL, Stow ND. Circularization of the herpes simplex virus type 1 genome upon lytic infection. J Virol. 2005; 79(19):12487–12494. [PubMed: 16160176]

Suhr ST, Gage FH. Gene therapy for neurologic disease. Arch Neurol. 1993; 50(11):1252–1268. [PubMed: 8215983]

Thomas CE, Birkett D, Anozie I, Castro MG, Lowenstein PR. Acute direct adenoviral vector cytotoxicity and chronic, but not acute, inflammatory responses correlate with decreased vector-mediated transgene expression in the brain. Mol Ther. 2001; 3(1):36–46. [PubMed: 11162309]

Wong LF, Goodhead L, Prat C, Mitrophanous KA, Kingsman SM, Mazarakis ND. Lentivirus-mediated gene transfer to the central nervous system: therapeutic and research applications. Hum Gene Ther. 2006; 17(1):1–9. [PubMed: 16409120]

Worgall S, Sondhi D, Hackett NR, Kosofsky B, Kekatpure MV, Neyzi N, Dyke JP, Ballon D, Heier L, Greenwald BM, Christos P, Mazumdar M, Souweidane MM, Kaplitt MG, Crystal RG. Treatment of late infantile neuronal ceroid lipofuscinosis by CNS administration of a serotype 2 adeno-associated virus expressing CLN2 cDNA. Hum Gene Ther. 2008; 19(5):463–474. [PubMed: 18473686]

Wu N, Watkins SC, Schaffer PA, Deluca NA. Prolonged gene expression and cell survival after infection by a herpes simplex virus mutant defective in the immediate-early genes encoding ICP4, ICP27, and ICP22. J Virol. 1996; 70(9):6358–6369. [PubMed: 8709264]

Wu Z, Asokan A, Samulski RJ. Adeno-associated virus serotypes: vector toolkit for human gene therapy. Mol Ther. 2006; 14(3):316–327. [PubMed: 16824801]

Wu Z, Yang H, Colosi P. Effect of genome size on AAV vector packaging. Mol Ther. 2010; 18(1):80–86. [PubMed: 19904234]

Xiao PJ, Lentz TB, Samulski RJ. Recombinant adeno-associated virus: clinical application and development as a gene-therapy vector. Ther Deliv. 2012; 3(7):835–856. [PubMed: 22900466]

Xu J, Ma C, Bass C, Terwilliger EF. A combination of mutations enhances the neurotropism of AAV-2. Virology. 2005; 341(2):203–214. [PubMed: 16102794]

Zufferey R, Dull T, Mandel RJ, Bukovsky A, Quiroz D, Naldini L, Trono D. Self-inactivating lentivirus vector for safe and efficient in vivo gene delivery. J Virol. 1998; 72(12):9873–9880. [PubMed: 9811723]

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Table 1

Vectors Used in Gene Therapy.

Viral Vector	**Retroviruses, HIV**	**Herpesvirus HSV-1**	**Adenovirus**	**Adeno-Associated Virus (AAV)**
Family	Retroviridae	Herpesviridae	Adenoviridae	Parvoviridae
Disease associated with parent virus	Yes	Yes	Yes	No
Transgene capacity	8 kb	150 kb	36 kb	4.7 kb ssAAV 2.2 kb scAAV
Genome	ssRNA	dsDNA	dsDNA	ssDNA
Inserts into DNA	Yes	No (circular episome)	No	No (circular episome)
Transduction of non-dividing cells	Yes	No	Yes	Yes
Innate immunity	Yes	Yes	Yes	Limited

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Table 2

CNS Gene Delivery Trials Via rAAV and Lentiviral Vectors.

Disease	Phase	Vector/Gene	Route	Reference
Batten Disease	I	AAVrh10/CLN2	Intracranial	Worgall *et al.*, 2008
Canavan's	II	AAV2/ASPA	Intracranial	Leone *et al.*, 2012; McPhee *et al.*, 2006
Parkinson's	I	AAV2/CERE-120	Intracranial	Gasmi *et al.*, 2007; Kordower *et al.*, 2006
	I	AAV2/ GAD65/67	Intracranial	Kaplitt *et al.*, 2007
	II	AAV2/AADC	Intracranial	Christine *et al.*, 2009; Eberling *et al.*, 2008; Muramatsu *et al.*, 2010
Adrenoleukodystrophy	I	HIV-1/ABCD1	*Ex vivo*	Cartier and Aubourg, 2008; 2010