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Large Animal Models of Neurological Disorders for Gene Therapy

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Abstract

The development of therapeutic interventions for genetic disorders and diseases that affect the central nervous system (CNS) has proven challenging. There has been significant progress in the development of gene therapy strategies in murine models of human disease, but gene therapy outcomes in these models do not always translate to the human setting. Therefore, large animal models are crucial to the development of diagnostics, treatments, and eventual cures for debilitating neurological disorders. This review focuses on the description of large animal models of neurological diseases such as lysosomal storage diseases, Parkinson's disease, Huntington's disease, and neuroAIDS. The review also describes the contributions of these models to progress in gene therapy research.

Keywords

gene therapy; Huntington's disease; large animal model; lysosomal storage disease; neuroAIDS; neurologic disease; Parkinson's disease

Introduction

The discovery of therapeutic interventions for genetic disorders and diseases that affect the central nervous system (CNS[1]) has proven challenging. The development and testing of such interventions often begin in animal models, which enable scientists to (1) test the safety and efficacy of new therapeutic agents in vivo, (2) acquire a detailed understanding of mechanisms of action for new drugs, and, most importantly, (3) collect essential data to advance therapies to human clinical trials. Animals with homologous genetic diseases thus play a vital role in the testing of new gene and stem cell–based strategies for therapy.

Naturally occurring and knockout mice models of disease have been invaluable for early studies. Most types of mice readily breed, permitting the rapid production of large numbers of affected animals for gene therapy studies. In addition, the affected mice have a uniform and well-understood genetic background and the disease pathology in the mouse model is typically well characterized. But, although these models are excellent test systems for gene therapy

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[2]Importantly, MPTP does not affect rats (Riachi et al. 1988), underscoring the point that nonhuman primates are valuable models of human neurological disease.

[1]Abbreviations used in this article: 6-OHDA, 6-hydroxydopamine; AADC, amino acid decarboxylase; AAV, adeno-associated virus; BMT, bone marrow transplant; CNS, central nervous system; CNTF, ciliary neurotrophic factor; GAG, glycosoaminoglycan; GALC, galactocerebrosidase; GDNF, glial cell line–derived neurotrophic factor; HIV, human immunodeficiency virus; IDUA, alpha-L-iduronidase; LSD, lysosomal storage disease; LV, lentivirus; MPS, mucopolysaccharidosis; MPTP, 1 methyl-4 phenyl 1,2,3,6 tetrahydropyridine; NHP, nonhuman primate

because they are true homologues of the human disease, gene therapy investigations in murine models have not always predicted the results of higher-order models. For example, in an investigation of the transduction patterns of adeno-associated virus (AAV[1]) 5, both mice and cats received direct injection of the vector in the brain: the results demonstrated successful gene transfer to the mouse CNS by AAV5, but none in the cat (Vite et al. 2003). Thus variations in the biology, development, and architecture of the mouse CNS compared to that of humans, differences in the tropism of recombinant virus vectors, and the lack of relatedness of these models to humans all warrant the development and testing of CNS gene transfer strategies in large animal models. Such models enable scientists to assess the tropism, biodistribution, and persistence of gene therapy vectors and make rational decisions about vector design for human clinical trials.

Moreover, although mouse models have played a central role in the development of gene therapy strategies for numerous disorders, the application of gene therapy for CNS diseases can pose a unique problem, especially for the lysosomal storage diseases (LSDs[1]). The central challenge for treating the brain in inherited metabolic disorders is the global delivery of the gene or its protein product. Investigators have reported widespread correction in the mouse brain, but it is much more difficult in a large brain (Bosch et al. 2000;Brooks et al. 2002;Daly et al. 1999;Passini and Wolfe 2001). The brain of a newborn child, when LSD diagnosis is most likely and treatment is believed to be most effective, is 1000 to 2000 times larger than the mouse brain (BAB personal communication with JH Wolfe, University of Pennsylvania, August 2008). As gene therapy strategies move from mouse models toward human clinical trials, it is essential to demonstrate the delivery of a gene or gene product to large regions of the brain in large animal models.

The most widely investigated large animal species and disease models are cats and dogs, especially for gene therapy studies. More importantly, various institutions (e.g., the veterinary schools at the University of Pennsylvania and Auburn University) have undertaken both the continued identification of new disease models in these species and concerted breeding efforts for these models. Additional large animal models for gene therapy research include sheep and nonhuman primates (NHPs[1]), but although there have been reports of the characterization of genetic diseases in these species, they have not yet been widely used for therapeutic gene therapy studies. Instead, these models most often serve for the development of gene transfer protocol development, gene marking studies for analysis of tropism, biodistribution, and persistence, and analysis of the toxicity and safety of gene therapy protocols. However, concerted breeding efforts are under way to more fully develop nonhuman primate models of Krabbe disease and Huntington's disease for the testing of therapeutic gene delivery.

The number of large animal models of human disease is quite extensive and new models are added regularly. It is evident that large animal models will be crucial to the development of diagnostics, treatments, and eventual cures for CNS disorders such as inborn metabolic diseases (e.g., lysosomal storage disorders), Parkinson's disease, Huntington's disease, and neuroAIDS.

Viral Vectors for Gene Delivery to the CNS

Modification of a specific cell type or tissue requires efficient delivery of the therapeutic gene to the tissue or cell in a way that enables expression of the gene at therapeutic levels and for an extended duration. Most often, gene therapy studies focus on replication-defective viral vectors because viruses can infect cells, often with great specificity, and are very efficient at introducing their own DNA into the host cell. Replacement of the viral genes with foreign genes of interest enables the recombinant viral vectors to effectively transduce cells. Despite the development of a number of vectors, a large number of studies have demonstrated that the potential of gene therapy applications for CNS disorders has been most successful using

recombinant lentiviral (LV[1]) or adeno-associated viral vectors. Interest has centered on LV and AAV vectors because of their ability to persist in the host cell and thus potentially provide life-long correction of a genetic disorder (Bunnell and Morgan 1996;Kafri et al. 1999;Miller et al. 1993;Naldini 1998;Rabinowitz and Samulski 1998;Robbins and Ghivizzani 1998;Xiao et al. 1997;Zufferey et al. 1998).

Lentiviruses, such as the human immunodeficiency virus (HIV[1]) type 1, are a subfamily of retroviruses that are biologically distinct because they can efficiently infect both proliferating and nonproliferating cells (Naldini 1998). Thus, vector systems derived from lentiviruses may offer a solution to gene delivery in populations of quiescent cells, such as those in the CNS. But disease pathology associated with replication-competent HIV gives rise to concerns about the clinical use of HIV-derived vectors. These concerns have led to the construction of self-inactivating vectors based on HIV-1, and these vectors are safer and have broader applicability as a means of high-level gene transfer and expression in nondividing cells (Miyoshi et al. 1998).

It is possible to target LV vectors to specific cell types either by specific promoter elements that are active only in the target cell type or by envelope proteins that bind specific receptors on the target cell type (Jakobsson and Lundberg 2006). Researchers have used glycoproteins from strains of vesicular stomatitis virus (VSV), rabies virus, Mokola virus, lymphocytic choriomeningitis virus, and Ross River virus to pseudotype lentiviral vectors (Kang et al. 2002; Mazarakis et al. 2001; Watson et al. 2002; Wong et al. 2004), and one study showed that the rabies-G envelope confers retrograde axonal transport to the vector and CNS access after delivery to the periphery (Mazarakis et al. 2001).

Naldini and colleagues (1996) described efficient and stable transduction of beta-galactosidase and green fluorescent protein (GFP) by an LV vector in rat neurons after single intracerebral injections into adult rats. Further, use of the LV vector system produced no detectable decrease in expression or toxicity over several months (Blomer et al. 1997). Lentiviral gene delivery of nerve growth factor leading to gene expression was detectable in nonhuman primate brains for at least 1 year after gene delivery, with no detectable adverse effects over that time and without expression beyond the targeted brain region (Nagahara et al. 2009).

Like lentiviruses, AAV vectors are capable of transducing both dividing (Russell et al. 1994) and nondividing cells (Podsakoff et al. 1994). AAV is a nonpathogenic, replication-deficient human parvovirus that commonly infects humans (Berns 1990); infection by wild-type AAV is asymptomatic (Blacklow et al. 1968,1971). AAV is dependent for replication on help from other viruses, usually adenovirus or herpes virus (Buller 1981; Hoggan et al. 1966). It is unique among the human DNA viruses because wild-type virus integrates in a site-specific fashion on human chromosome 19 (Giraud et al. 1994; Kotin et al. 1992; Linden et al. 1996).

AAV2 was the first AAV serotype harnessed for gene therapy applications and is by far the most commonly used in studies assessing AAV as a vector system. More recently, investigators have isolated several novel AAV serotypes and over 100 AAV variants from stocks of adenovirus or from human and nonhuman primate tissue samples (Gao et al. 2002,2004; Mori et al. 2004; Schmidt et al 2006). A total of nine novel AAV serotypes have been isolated from a number of species, including nonhuman primates (AAV7, AAV8, and AAV rh10) (Gao et al. 2002,2005). These serotypes differ from one another primarily by their capsid proteins, and all but AAV6 are unique based on antibody cross-reactivity studies; AAV6 appears to be closely related to AAV1.

The specific serotypes of AAV differ in the amino acid content of their capsid proteins and these differences result in variable cellular tropism in murine tissues such as the liver, skeletal muscle, and brain (Gao et al. 2002). Numerous AAV serotypes have been examined for their

gene transfer efficiency, persistence, and biodistribution in the mouse CNS, and several have revealed distinct transduction patterns in the rodent brain. AAV1 and 5 vectors mediate greater transduction frequencies than AAV2 in all CNS regions that receive injections (Alisky et al. 2000; Burger et al. 2004). AAV2 shows widespread transduction throughout the midbrain, whereas AAV4 appears to transduce specific cell types, such as the ependyma and astrocytes in the subventricular zone (Liu et al. 2005). In the mouse brain, AAV7, 8, 9, and Rh10 vectors transduce neurons, but not astrocytes or oligodendrocytes, in the cortex, striatum, hippocampus, and thalamus (Cearley and Wolfe 2006). In direct comparison with AAV2, pseudotyped vectors derived from AAV7 and AAV8 have increased transduction efficiency in the murine CNS (Harding et al. 2006). AAV8 mediated higher levels of gene expression and vector spread than AAV2, AAV5, or AAV1 in the adult rat hippocampus and substantia nigra (Klein et al. 2006). In a subsequent study, the same group compared AAV serotypes 8, 9, Rh10, and Rh43 in the rat brain and found that AAV9 was superior to AAV8 at mediating expression of the GFP reporter gene (Klein et al. 2008). In a study performed in the cat brain, the administration of AAV serotypes 1, 2, and 5 revealed that AAV1 mediated greater gene transfer efficiency in the gray matter than AAV2 as well as transduction of the white matter, whereas AAV5 did not result in detectable transduction (Vite et al. 2003). In a dog model, the subretinal delivery of an AAV8 pseudotyped vector delivered by intraocular injection resulted in efficient gene transfer in the retinal pigment epithelium (RPE), photoreceptors, and the neurons of the lateral geniculate nucleus of the brain (Stieger et al. 2008).

Lysosomal Storage Diseases

There are more than 40 different forms of inherited lysosomal storage diseases known to occur in humans. These diseases, which progress rapidly and are associated with high morbidity and mortality, result from the loss of function of enzymes coupled with the proper function of lysosomes, causing the accumulation of undegraded or partially degraded macromolecules. Although individually rare, inherited LSDs and leukodystrophies, such as mucopolysaccharidoses and Krabbe disease, collectively occur in approximately 1 in 5,000 live births. Most of these disorders have a marked CNS pathologic component, so correction of the CNS-associated disease in LSD patients will be critical, as many of them suffer from severe mental retardation. Treatment options for these and other CNS disorders are primarily limited to supportive care, but researchers have explored a spectrum of therapeutic avenues. One such approach is enzyme replacement therapy (direct administration of functional recombinant enzyme), as gene therapy and stem cell transplantation are among the only viable treatment options potentially available. Thus, direct CNS gene transfer may provide the best opportunity for eliminating the pathology associated with these conditions. Analysis of gene therapy strategies for the CNS in valid animal models will be essential for successful and predictable clinical outcomes. The focus of this review is naturally occurring models of LSDs in dogs, cats, and nonhuman primates.

Mucopolysaccharidosis Type I

Mucopolysaccharidosis (MPS[1]) type I is a family of lysosomal storage diseases caused by a lack of specific lysosomal enzymes involved in the degradation of glycosaminoglycans (GAGs[1]), or mucopolysaccharides. The enzyme alpha-L-iduronidase (IDUA[1]), which normally breaks down GAGs, is deficient or absent in MPS-I, and the glycosoaminoglycans dermatan sulfate and heparan sulfate accumulate in cells. The IDUA deficiency can result in three major recognized clinical entities with a wide range of phenotypic involvement: Hurler (MPS-IH), Scheie (MPS-IS), and Hurler-Scheie (MPS-IH/S) syndromes. Hurler syndrome is the most severe form, Scheie syndrome represents the mild phenotype of the MPS-I clinical spectrum, and the Hurler-Scheie syndrome is intermediate in phenotypic expression (McKusick et al. 1972). The clinical symptoms of Hurler syndrome include severe retardation

of mental and physical growth, skeletal deformities, umbilical hernias, joint abnormalities, corneal clouding, cardiovascular disease, and death usually in late childhood. It is possible to treat humans with MPS-I by injection of recombinant human enzyme, denoted as enzyme replacement therapy (Starzyk et al. 2007;Wraith et al. 2008). However, most MPS-I patients that receive recombinant human alpha-L-iduronidase develop anti-iduronidase antibodies within weeks of exposure, and these immune responses can interfere with the effectiveness of the therapy and be challenging to manage.

Both canine and feline models of MPS-1 clinically resemble most closely the intermediate form of human MPS-I. The mutation in the MPS-I dogs is a null mutation—specifically, a G>A transition in the donor splice site of intron 1, causing the mRNA retention of intron 1 and consequent formation of a premature termination codon at the exon-intron junction (Menon et al. 1992). The disease in the dogs is strikingly similar to the human disease, but the dogs show thickening and prolapse of the third eyelid (membrana nictitans), joint laxity instead of joint stiffness, and no obvious cognitive impairment. Cats with MPS-I have clinical signs of disease similar to those of the dog, but their skeletal disease is not as significant, although they have facial deformity, lameness, corneal opacity, and cardiac murmurs. The mutation in the cats is a three base pair deletion, leading to the loss of a conserved aspartate residue (He et al. 1999).

One of the earliest attempts to develop a gene therapy for MPS-I transduced myoblasts from MPS-I dog skeletal musle with a retrovirus vector expressing the canine IDUA gene driven by the muscle creatine kinase enhancer that resulted in the expression of high levels of IDUA enzyme (Shull et al. 1996a,b). However, upon the reintroduction of the genetically engineered myoblasts in dogs, the levels of IDUA production declined rapidly. The research group determined that there was a simultaneous production of antibodies specific for IDUA and that there was an infiltration of infl ammatory cells, both lymphocytes and plasma cells, at injection sites, suggesting both humoral and cellular immune responses to the IDUA enzyme produced by the transplanted myoblasts.

Investigators who performed a bone marrow transplant (BMT[1]) for canine MPS-I using allogeneic hematopoietic stem cells (HSCs) (Breider et al. 1989) reported a substantial decrease in the severity of MPS-I-related lesions in the transplanted MPS-I dogs. These dogs had only slight cardiac valvular thickening, no meningeal thickening, no renal tubular epithelial vacuolation, decreased neuronal vacuolation, decreased corneal stromal vacuolation, and greatly diminished arterial medial thickening. The BMT dogs also showed a decrease in the severity and incidence of degenerative arthropathy; however, their vertebral lesions were similar to those of nontransplanted affected dogs. Ultrastructurally, the liver and kidney tissue in the BMT recipients had no appreciable lysosomal accumulation of GAGs. The animals also had near normal levels and electrophoretic patterns of GAGs. This study demonstrates that BMT is capable of substantially diminishing the severity of MPS-I-related lesions in this canine model.

The results of BMT with autologous marrow cells retrovirally transduced to express the canine iduronidase cDNA in vitro were not as promising, however (Lutzko et al. 1999a,b). Gene-modified cells, expressing more than 10 times the IDUA enzyme levels of normal dogs, were infused into nonmyeloablated recipients. Unfortunately, neither enzyme nor mRNA was detectable in any transplanted dog. However, vector sequences were detectable in 0.01% of peripheral blood leukocytes for 2 to 3 years after the infusion. The researchers determined that the presence of humoral and cellular immune responses against IDUA enzyme apparently abrogated the therapeutic potential of HSC gene therapy in this study and, in an attempt to avoid the immune response, they transplanted in vitro IDUA-transduced MPS-I long-term marrow culture cells in preimmune midgestation pups. Although retrovirus transduced cells

remained present in the bone marrow and peripheral blood for up to 1 year, neither enzyme nor vector-derived mRNAs were present in the marrow or peripheral blood leukocytes of any MPS-I dog, and there was no evidence of amelioration of the disease. Unlike the postnatal BMT study, there was no evidence of humoral immune responses to the IDUA in neonates, suggesting that potent immune responses may be avoided using the in utero transfer.

In an alternative gene therapy strategy, investigators directly injected recombinant viral vectors expressing human IDUA in an attempt to assess the effectiveness of this vector for in utero gene transfer and expression in multiple tissues in the canine model (Meertens et al. 2002). They observed successful gene delivery to a spectrum of cell types and tissues but no enzyme activity in the adult tissues of most of the animals. Although gene transfer efficiency to multiple tissues after in utero injection was high, the vector was not able to mediate sustained in vivo gene expression.

Neonatal MPS-I dogs that received intravenous (IV) injections of a gamma-retroviral vector containing a complete long-terminal repeat (LTR) and an internal human alpha 1-antitrypsin (hAAT) promoter upstream of the canine IDUA complementary DNA had stable enzyme expression and a marked reduction of disease signs (Traas et al. 2007). The animals produced stable serum IDUA enzyme activity primarily from cells transduced in the liver for up to 1.8 years. The vector-treated dogs had decreased severity and/or incidence of hernias, chest deformities, joint disease, facial dysmorphia, corneal clouding, valvular heart disease, and aortic dilation as compared with untreated MPS-I dogs, even though the enzyme levels were only 18% of the native levels. The reason for the marked reduction in the levels of lysosomal storage in the brain of the treated dogs is unclear, though it may have been, in part, the result of expression from the LTR of the vector in the brain.

Researchers attempting to avoid immune responses to IDUA enzyme in the MPS-I dogs combined the direct intracerebral injections of rAAV vector (with the IDUA gene) with an immunosuppressive regimen (Ciron et al. 2006). They detected a broad dispersion of AAV vector genomes in the CNS of efficiently immunosuppressed dogs and noted that the delivery or spread of IDUA throughout a large portion of the brain resulted in a drastic reduction of neuropathology in the encephalon and the prevention of GAG accumulations. Demonstrating the importance of the immunosuppressive regimen in the success of this approach, vector injections in animals on partial immunosuppression resulted in the development of subacute encephalitis, generation of IDUA antibodies in the brain, and elimination of genetically modified cells.

As part of the above-mentioned MPS-I dog study involving neonatal gene delivery, neonatal MPS-I kittens received injections of a retrovirus vector expressing the canine IDUA cDNA, and shortly afterward had high levels of canine IDUA in the serum (Ponder et al. 2006). However, by 60 days these levels had decreased to baseline levels because of a CTL response to the canine IDUA. A second set of kittens that received injections of the identical vector as well as transient injections of the immunosuppressive agent CTLA4-Ig did not develop a detectable CTL response. Thus in higher-order animal models the direct administration of gene therapy vectors in the neonatal setting can reduce, but not eliminate, immune responses.

While it is evident that both enzyme replacement therapy and/or gene therapy for IDUA successfully reduces lysosomal storage in canines and humans with MPS-I, both of these therapeutic strategies induce antibodies specific for the functional enzyme that may reduce its efficacy in the long term. To understand the potential impact of IDUA-specific antibodies, Dickson and colleagues (2008) studied whether induction of antigen-specific immune tolerance to iduronidase could improve the effectiveness of recombinant IDUA treatment in the MPS-I dogs. All canines received recombinant IDUA enzyme intravenously at the FDA-

approved human dose or a higher dose for a period ranging from 9 to 44 weeks. The canines that were tolerized achieved increased tissue enzyme levels and a reduction in tissue GAG levels and lysosomal pathology. Nontolerized dogs developed IDUA-specific antibodies that proportionally reduced iduronidase uptake in vitro. It is evident that the induction of immune tolerance to IDUA improved the efficacy of enzyme replacement therapy with recombinant IDUA in canine MPS-I and could eventually improve outcomes for gene therapy strategies in dogs and perhaps clinical outcomes in humans.

Mucopolysaccharidosis Type VII

Mucopolysaccharidosis type VII (MPS-VII) or Sly disease is an autosomal recessive LSD characterized by the inability to degrade glucuronic acid-containing GAGs. The enzyme betaglucuronidase (GUSB), which normally degrades glucuronic acid-containing glycosoaminoglycans (dermatan sulfate, heparan sulfate, and chondroitin sulfate), is deficient or absent in MPS-VII. The phenotype is highly variable, ranging from severe lethal hydrops fetalis to mild forms with survival into adulthood. The symptoms for most patients involve multiple organ systems and tissues and include organomegaly, umbilical hernias, skeletal anomalies, coarse features, ocular impairment, and variable degrees of CNS impairment (Shipley et al. 1993).

Both canine and feline models of MPS-VII are highly homologous to the disease in humans. Haskins and colleagues (1984) were the first to identify and characterize an animal model of MPS-VII in German shepherd dogs, whose pathologic features of the disease are very similar to those of humans except that the hepatosplenomegaly is less pronounced and the extent of mental retardation cannot be assessed. MPS-VII dogs have a single nucleotide substitution in the GUSB gene, which results in a guanine to adenine base change at nucleotide position 559 in the canine cDNA sequence, which in turn causes an arginine to histidine substitution at amino acid 166 in the canine GUSB (cGUSB) protein (Ray et al. 1998). The feline MPS-VII model has a missense mutation, specifically a guanine to adenine transition, that results in the change of glutamic acid to lysine at position 351 of the protein, eliminating GUSB enzymatic activity (Fyfe et al. 1999).

The development of successful gene therapy strategies for MPS-VII in the mouse model led to the testing of multiple gene therapy strategies in the dog and cat models. Researchers have reported clinical improvements in MPS-VII dogs that received canine GUSB-expressing retrovirus vectors (RV) as neonates (Ponder et al. 2002; Wang et al. 2006). Because studies in MPS-VII mice had shown that high levels of enzyme can be secreted by the liver and substantially improve clinical symptoms (Kosuga et al. 2000; Ohashi et al. 1997), two dogs in the 2002 study by Ponder and colleagues received human hepatocyte growth factor (HGF), which can induce canine hepatocyte replication (Kobayashi et al. 1996), in addition to RV-GUSB, while five dogs received RV-GUSB alone. All seven dogs showed similar clinical improvements at 6 to 17 months after treatment, although those that also received hepatocyte growth factor had much higher serum GUSB levels. All of the treated animals had bone and joint improvements, little or no corneal clouding, and no mitral valve thickening (Ponder et al. 2002). A follow-up study reported that the RV-GUSB-treated dogs maintained improved facial morphology, reduced lysosomal storage in osteocytes and synovium, and stable serum GUSB activity levels after 3 years (Mango et al. 2004). In addition, an assessment of the cardiovascular and skeletal features of the dogs several years after RV-GUSB treatment showed increased cervical vertebrae (C2) and femur lengths compared to untreated animals, although neither was as long as those of normal animals (Herati et al. 2008). A subsequent study called for the treatment of MPS-VII-affected dogs with the same RV-GUSB vector and monitoring of its effect on their cardiovascular disease (Sleeper et al. 2004); all of the dogs showed marked

improvements in this area. In addition, after RV-GUSB, animals showed correction in both mitral regurgitation and mitral valve thickening.

Alpha-Mannosidosis

Alpha-mannosidosis is an autosomally recessive inherited lysosomal storage disease (Malm and Nilssen 2008). Affected individuals are deficient in lysosomal acidic alpha-mannosidase enzyme activity, resulting in the accumulation of undegraded mannose-rich oligosaccharides and deterioration of the CNS. The age of onset and severity of disease vary, with many individuals developing symptoms over several decades. Clinical symptoms of the disease include hearing impairment, skeletal abnormalities, recurrent infection, and mental retardation. Complete absence of the enzyme leads to early death.

Researchers identified alpha-mannosidosis in cows (Hocking et al. 1972) and, later, Burditt and colleagues (1980) reported a kitten with a nervous disorder and very low levels of alpha-mannosidase in its brain and high amounts of mannose-rich oligosaccharides in its urine. The mutation in the feline model is a 4 base pair deletion, leading to a frame shift and premature termination codon (Berg et al. 1997). Vite and colleagues (2001) described the clinical signs of disease in affected cats—action tremors, loss of balance, nystagmus, spinal ataxia, and dysmetria, all of which were associated with myelin loss.

The transplantation of heterologous bone marrow is a highly effective treatment of the CNS components of alpha-mannosidosis in the feline model (Walkley et al. 1994). Bone marrow and hematopoietic stem cell transplantation have also been successful treatments for a small number of human patients (Grewal et al. 2004; Wall et al. 1998). In an effort to avoid the complications associated with bone marrow transplantation and to mediate a therapeutic effect in the CNS, Vite and colleagues (2005) used a gene therapy approach in the cat model injecting recombinant AAV1 vector into the brain at multiple sites. The treated cats had a significant increase in life span and showed remarkable improvements in clinical neurological signs and in brain myelination (assessed by magnetic resonance imaging, MRI). Postmortem assessment showed a significant reduction in the extent of storage lesions throughout the brain, but gene transfer and expression were restricted to brain tissue immediately surrounding the injection sites. The results from this study were among the first to clearly demonstrate that widespread improvement of neuropathology in a large mammalian brain was possible with multiple injections in one surgical procedure.

Krabbe Disease

Krabbe disease, or globoid cell leukodystrophy, is a rapidly progressing neurological disease (Suzuki 1998,2003; Wenger et al. 1974,1997) that is an autosomal recessive inherited disorder and a type of lysosomal storage disease. In Krabbe disease, a mutation in the galactocerebrosidase ($GALC^1$) gene prevents the formation of functional GALC enzyme (Wenger et al. 1997), which normally breaks down galactolipids such as galactosylceramide and psychosine in the nervous system (Jesionek-Kupnicka et al. 1997). In the absence of GALC, undegraded galactolipids accumulate in macrophages to form characteristic globoid cells (Jesionek-Kupnicka et al. 1997) and toxic levels of psychosine cause myelinating oligodendrocytes and Schwann cells to die (Svennerholm et al. 1980; Vanier and Svennerholm 1976). Although it can present at any age, Krabbe disease most often affects infants and progresses rapidly; symptoms such as irritability, hypersensitivity, hypotonicity, blindness, and deafness usually present before 6 months of age and affected infants typically die before age 2 (Hagberg et al. 1963). There is no cure, and the only treatment for patients with Krabbe disease is bone marrow transplantation.

Researchers have described Krabbe disease in large animal species such as cats, dogs, sheep, and rhesus macaques (Baskin et al. 1998; Luzi et al. 1997; Victoria et al. 1996; Wenger 2000; Wenger et al. 1999). The dog models of Krabbe disease include the West Highland white and Cairn terriers (Victoria et al. 1996; Wenger et al. 1999); their presenting symptoms are dysmetria, weakness, and tremor, typically between 6 and 12 weeks of age, and they have a marked deficiency in GALC activity and progressively increasing levels of psychosine in the CNS. As in humans with Krabbe disease, MRI of the dogs demonstrates an increased signal in T2 weighted images and can be used to monitor the demyelination progression in vivo (McGowan et al. 2000). The spontaneous GALC mutation has been identified as a missense mutation, as indicated by the A>C transversion at position 473, which changes a tyrosine to a serine. The dogs' significant disease pathology is evident in the accumulation of psychosine in the white matter of the brain, loss of myelin, gliosis, and the presence of extensive numbers of globoid cells, all ofwhich are highly similar to the pathologic effects in human patients.

The rhesus monkey Krabbe disease model is significant in that it was the first spontaneously occurring lysosomal storage disease identified in a nonhuman primate species. In terms of genes, morphology, physiology, hematopoiesis, immunology, and development, monkeys are most similar to humans and are therefore an essential and appropriate animal model of human development and disease. They are further similar to humans in their "complex cognitive capabilities, great social complexity, details of reproductive biology and intricacy of brain organization" (Capitanio and Emborg 2008) and for those reasons are valuable tools for the study of human development, disease, and behavior. In addition, they have long life spans for long-term evaluation of treatments, and large brains that facilitate the investigation of injection strategies (Ellinwood et al. 2004).

The human brain size, anatomy, circuitry, and development are far more similar to those of nonhuman primates than of rodents. During fetal development, rhesus monkeys have longer cell cycles, produce substantially more rounds of cell divisions, and therefore generate a larger neocortex than rodents (Kornack and Rakic 1998). The CNS of nonhuman primates has been well characterized functionally, anatomically, and physiologically, making it an ideal model for neurologic studies in humans (Capitanio and Emborg 2008). The same anatomical criteria serve to locate the auditory and visual cortex in humans and nonhuman primates, suggesting homologous cortical regions; and there are similarities between the MRI T1 and T2 values of the human and NHP (specifically macaque) brain (Dubowitz et al. 2001; Hackett et al. 2001). In addition, the genetic heterogeneity among nonhuman primates is similar to the genetic diversity in humans. The recent creation of a population-average MRI-based atlas collection for rhesus macaques (McLaren et al. 2008) may be invaluable for the development of gene therapy protocols.

The most significant benefit of gene therapy studies in nonhuman primates may be the ability to use sensitive neuromotor and behavioral testing to assess alterations brought about by a therapeutic intervention. Analogous and often identical neuromotor tasks are applicable for both NHP and human studies. For example, the same computerized cognitive test batteries have been effective for characterizing and comparing the neuropsychological performance of both species—e.g., to assess AIDS-related (Gibbie et al. 2006; Weed et al. 2004) and drug-related (Paule 2005) changes in cognition and motor abilities in macaques—and the same neonatal neurobehavioral test has been used to directly compare NHP and human development (Bard 1992) and to model factors that infl uence development in the young of both species (Schneider et al. 2006).

The monkey model of Krabbe disease has a high degree of clinical similarity to the human disease, as the monkeys exhibit the same clinical signs (tremors, hypertonia, and in-coordination) and pathological signs (characteristic globoid cells) of the disease (Baskin et al.

1989; Borda et al. 2008). However, Borda and colleagues (2008) found that affected rhesus monkeys experience variable disease progression, despite a common disease-causing mutation, and that onset age varied from 19 days to 140 days, and survival time from 52 days to 642 days. According to their findings, early signs of the disease include tremors and difficulty grasping items, and symptoms eventually progress to complete inability to use the hind limbs and to clenched hands and feet. Histopathologically, all of the Krabbe monkeys had accumulation of globoid cells, gliosis, and demyelination in the white matter, although the gray matter appeared normal. The group also noted cellular immune activation and high expression of inducible nitric oxide synthase (iNOS), suggesting an infl ammatory component to the pathogenesis of Krabbe disease.

Researchers in 1997 identified the disease-causing mutation, a deletion of two nucleotides, in the rhesus monkey (Luzi et al. 1997). Not unlike the mutations of human patients, this deletion results in no active enzyme. Gene therapy can replace the mutated gene with a normal copy, but because of the rapid progression and early onset of Krabbe disease, therapeutic levels of functioning enzyme have been difficult to achieve.

With regard to gene therapy strategies, reports indicate that a retroviral vector carrying a normal GALC gene can transfer normal activity to Krabbe-affected cells in vitro (Meng et al. 2005; Rafi et al. 1996), and that the enzyme produced by transduced cells was taken up by neighboring, non-transduced cells (Rafi et al. 1996). Researchers have attempted several therapeutic strategies in the (twitcher) mouse model of the disease: bone marrow transplantation (Hoogerbrugge et al. 1988a,b; Ichioka et al. 1987; Yeager et al. 1984,1993), adenoviral vector delivery of the GALC cDNA (Shen et al. 2001), lentiviral vector transfer of the GALC gene (Dolcetta et al. 2006), and AAV vector-mediated delivery of GALC (Lin et al. 2005,2007; Rafi et al. 2005). These studies showed some improvement in the neuropathology of the disease and prolonged the life span of the treated mice. One group, using a BAC clone encoding the entire human GALC gene, reported twitcher mice that have lived for over 1 year with no sign of the disease (De Gasperi et al. 2004). None of these strategies have yet been studied in the dog model nor in the Krabbe disease monkey colony.

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder, the genetics of which are not clear, although several genes have been linked to the disease (Belin and Westerlund 2008). There is currently no therapy for treating or preventing the neurodegeneration observed in PD. The selective degeneration of the neurons that produce dopamine (DA) in the substantia nigra is the primary neuropathological feature, but the disease also entails the loss of non-DA cells. Other prominent neuropathological features include the aggregation of alpha-synuclein in cytoplasmic inclusions called Lewy bodies in DA neurons of the substantia nigra and, in some cases, in nondopaminergic neurons located elsewhere, although the origin of these pathologies is not known. Symptoms of the disease include resting tremor, rigidity, bradykinesia, and impaired balance.

A naturally occurring large animal model of PD has not been documented, but investigators have identified similar symptoms in aged nonhuman primates (Emborg et al. 1998; Zhang et al. 2000) and there are methods of inducing a similar disorder in NHPs. Neurotoxins 6-hydroxydopamine (6-OHDA[1]) and 1 methyl-4 phenyl 1,2,3,6 tetrahydropyridine (MPTP[1]) destroy dopaminergic neurons and are frequently used to induce a Parkinson's-like disease in animals (Emborg 2007[),2] Gene transfer–mediated overexpression of the human alpha-synuclein gene also produces PD in marmoset monkeys (Eslamboli et al. 2007; Kirik et al. 2003). The transgenic model has advantages over the neurotoxin models in that it provides neuropathological features, similar to the Lewy bodies seen in humans (Kirik et al. 2003;

Mandel et al. 2005). In addition, the MPTP and 6-OHDA models cause an acute onset of disease symptoms, whereas the alpha-synuclein model develops more slowly, as in human patients. However, one specific disease model may not completely mirror the human disease, suggesting that each may offer a unique insight to the search for a cure.

The body synthesizes dopamine from the amino acid L-tyrosine, which is converted to L-dopa by the enzyme tyrosine hydroxylase along with the cofactor tetrahydrobiopterin (BH4). Dopa decarboxylase, or aromatic L-amino acid decarboxylase (AADC[1]), then converts L-dopa to dopamine (tyrosine hydroxylase is the rate-limiting enzyme in the synthesis of dopamine). Current treatment of the symptoms of PD entails administration of L-dopa, which, unlike dopamine, can enter the CNS across the blood brain barrier. Endogenous enzymes in the brain then convert L-dopa to dopamine to reduce symptoms. Side effects of L-dopa treatment include gastrointestinal distress, hypotension, and dyskinesias, and result from conversion to dopamine in the periphery, where enzyme is also available. These side effects can be reduced by coadministering a decarboxylase inhibitor, which cannot enter the brain and prevents conversion to dopamine in the periphery. Unfortunately, as the disease progresses, L-dopa becomes ineffective, necessitating higher, more frequent doses, while side effects become unmanageable and incapacitating (Bravi et al. 1994;Marsden and Parkes 1977;Nutt and Holford 1996) as the high doses of L-dopa overstimulate regions of the brain that have less AADC.

Patients taking L-dopa initially respond very well to the drug but, as mentioned above, after continuous administration of it over years, they need more and more to achieve the same clinical benefit because the enzyme that converts L-dopa into dopamine is depleted as the neurons that synthesize the AADC are lost (Marsden and Parkes 1977). AADC is present in numerous regions of the brain as well as peripheral tissues—the liver, kidney, adipose, heart, adrenal gland, and keratinocytes. The loss of AADC makes it significantly more difficult for the brain to make sufficient amounts of dopamine. For patients receiving L-dopa treatment the tyrosine hydroxylase component of the synthesis pathway is bypassed and AADC becomes the rate-limiting step.

One strategy to restore dopamine to PD patients involves transplanting tissue or cells that produce tyrosine hydroxylase in order to achieve consistent levels of factors for dopamine synthesis that are not possible with intermittent L-dopa injections. Fetal tissue transplants have been attempted for treating PD patients (Spencer et al. 1992), but fetal tissue is not a reliable, abundant material and rejection of foreign cells may also be an issue. A similar approach is to use viral vectors to deliver components of the dopamine synthesis pathway that have broken down. The tyrosine hydroxylase gene has been successfully expressed in 6-OHDA-lesioned rat brains using AAV vectors (Kaplitt et al. 1994). Tyrosine hydroxylase coexpression with GTP-cyclohydrolase I (GCH), the primary synthetic enzyme for BH4, produced measurable amounts of striatal L-dopa in rats, but without significant behavioral improvement (Mandel et al. 1998). Using an ex vivo approach, Anton and colleagues (1994) transplanted immortalized cells that had been engineered to overexpress the tyrosine hydroxylase gene into MPTP-lesioned nonhuman primates and reported amelioration of disease symptoms.

A number of research groups have explored whether replacement of sufficient AADC in the putamen, which does not produce sufficient levels of AADC, might normalize response to low doses of L-dopa (Bankiewicz et al. 2000,2006; During et al. 1998; Forsayeth et al. 2006; Ozawa et al. 2000). Bankiewicz and colleagues (2000) demonstrated that administration of an AAV vector expressing the human AADC gene into the striatum of MPTP-lesioned monkeys leads to restoration of response to L-dopa and renewed dopamine production. They further reported that the transgene expression and improved response endures for more than 2 years

(Bankiewicz et al. 2006). In fact, the AAV-AADC provided clinical improvement in Parkinsonian monkeys for over 6 years (Bankiewicz et al. 2006).

The combination of tyrosine hydroxylase and AADC is another potential treatment option under investigation in monkey models of PD. Combined AAV-mediated expression of tyrosine hydroxylase and AADC in MPTP-treaded African green monkeys led to increased dopamine levels and low toxicity (During et al. 1998), suggesting improved results with the combined expression. And expression of three genes—tyrosine hydroxylase, AADC, and GCH—induced behavioral improvements in a Parkinsonian rat model for up to 1 year (Shen et al. 2000). Similar gene therapy has been attempted in human trials; in an early trial, five patients with moderate to severe disease received an infusion of AAV-hAADC directly into the brain, but showed modest improvement (Eberling et al. 2008).

Deep brain stimulation relieves the motor symptoms of Parkinson's disease by inhibiting the overactive glutaminergic neurons in the brain. A similar, potentially safer strategy is to use AAV vectors to deliver glutamic acid decarboxylase (GAD; During et al. 2001; Emborg et al. 2007). GAD is the rate-limiting step for the production of γ-aminobutyric acid (GABA), the main inhibitory signal in the brain. Direct administration of a GABA agonist has been reported to ameliorate symptoms in nonhuman primates (Baron et al. 2002). Delivery of AAV-GAD for long-term therapy was well tolerated by MPTP-lesioned macaques (Emborg et al. 2007).

Instead of restoring dopamine or inhibiting the overactive neural activity to relieve symptoms of PD, another strategy involves preventing and restoring damaged neurons. Delivery of glial cell line–derived neurotrophic factor (GDNF[1]) enhances the survival of dopaminergic neurons in vitro (Lin et al. 1993). Gash and colleagues (1996) demonstrated that intracerebral injections of GDNF to MPTP-lesioned monkeys resulted in sustained improvement in symptoms. In a subsequent study, direct GDNF infusion into the putamen of aged nonhuman primates improved the metabolism of dopamine without side effects (Maswood et al. 2002). Encapsulated GDNF-producing cells have also been shown to be safe and effective in MPTP-lesioned baboons (Kishima et al. 2004). On the other hand, clinical trials with intraventricular administration of GDNF did not improve the disease progression of Parkinson's patients (Kordower et al. 1999;Nutt et al. 2003), and intraputamenal infusion led to only modest improvement (Patel et al. 2005).

Direct injection of GDNF seemed promising, but a more effective method for sustained long-term dosing may be gene transfer. A lentiviral vector was a successful method of delivery of GDNF to both aged and MPTP-lesioned monkeys (Kordower et al. 2000), preventing motor deficits when given before MPTP administration and, in aged monkeys, resulting in increased dopaminergic activity compared with control animals. Gene delivery of GDNF has also been successful in 6-OHDA-lesioned marmoset monkeys using a rAAV vector (Eslamboli et al. 2003). Eslamboli and colleagues (2005) reported that rAAV-GDNF-treated monkeys showed reduced or lesion-induced impairments or even none at all. One study reported that, in rats, GDNF expression led to downregulation of tyrosine hydroxylase expression (Georgievska et al. 2002), but a subsequent study showed that low levels of GDNF expression both reduced symptoms and increased tyrosine hydroxylase protein in 6-OHDA-lesioned nonhuman primates (Eslamboli et al. 2005).

In addition to gene replacement therapy through vector delivery, cell replacement therapy using embryonic stem cells is a treatment option for PD. Investigators have generated DA neurons from cynomolgus monkey embryonic stem cells (Kawasaki et al. 2002) and have shown that these neurons attenuate MPTP-induced neurological symptoms in the monkeys (Takagi et al. 2005). The long-term efficacy and safety of embryonic stem cells has not yet been fully

investigated, but they may provide relief from a wide range of neurological diseases as well as diseases affecting other systems.

Huntington's Disease

Huntington's disease (HD), an autosomal dominant neurodegenerative disease, is characterized clinically by abnormal body movements, a lack of coordination, and impaired motor, cognitive, and psychiatric functions. It is typically detected during the fourth or fifth decade of life, and patients then have a mean survival of 15 to 20 years. HD is the result of a genetic mutation that causes an expansion of CAG-encoded polyglutamine repeats in a protein called huntingtin (Huntington's Disease Collaborative Research Group 1993; Rubinsztein et al. 1993; Yang et al. 2008). In unaffected humans, there are typically 10 to 29 (median 18) repetitions of the CAG triplet at 5′ end, which, upon translation, result in polyglutamine stretch; in contrast, HD patients have a significantly expanded number—36 to 121 (median 44)—of trinucleotide repeats. The length of the CAG/polyglutamine repeat is inversely correlated with the age of disease onset: the higher number of expanded trinucleotide repeats results in an earlier onset of the disease, and a lower number a later onset.

The huntingtin protein may be involved in cellular metabolism and protein trafficking (Truant et al. 2006). The manifestation and progression of HD are thought to involve the altered conformation of the mutant huntingtin protein resulting from the polyglutamine expansion and changed protein-protein interactions, including abnormal huntingtin aggregation, leading to transcriptional dysregulation and excitotoxicity, all of which cause extensive loss of neurons in the striatum and cerebral cortex (Gil and Rego 2008; Imarisio et al. 2008; Li and Li 2004; Walling et al. 1998). The degeneration of striatal neurons characteristic of HD patients may be due to impairments of N-methyl-D-aspartate (NMDR) receptors, disruption of intracellular energy processes, or a combination of both. There is currently no cure for Huntington's disease; symptoms cannot be prevented but can be managed (Adams and Jankovic 2008; Bonelli and Hofmann 2004).

There are no known naturally occurring animal models of HD, but administration of excitotoxic agents (e.g., quinolinic acid, kainic acid, ibotenic acid, and malonic acid) or mitochondrial disruptors (e.g., 3-nitropropionic acid, 3NP) reproduces the progressive neurodegenerative symptoms of the disease in rodents and nonhuman primates (Borlongan et al. 1997; Brouillet and Hantraye 1995; Ramaswamy et al. 2007a; Roitberg et al. 2002). Researchers have used these methods to induce the disease in baboons (Hantraye et al. 1990), capuchin monkeys (Roitberg et al. 2002), cynomolgus monkeys (Beal et al. 1986), and rhesus monkeys (Burns et al. 1995; Ferrante et al. 1993). Roitberg and colleagues (2002) compared 3NP-treated capuchin monkeys to animals treated with quinolinic acid and found that both types of lesioned animals had behavioral characteristics of HD, although the two toxins create the lesions in different ways. The researchers speculate that the pathophysiology of the disease may include a deficit in the energy balance of the cell—either an increased demand, as in the excitotoxin model, or a decline in supply, as in the 3NP model. Although these models produce some symptoms and neuronal loss similar to those of the human disease, it is not clear whether the mechanism of action is an exact mimic of the disease, and none is ideal.

Neurotrophic factors, such as brain-derived neural factor (BDNF), nerve growth factor (NGF), neurotrophin, and ciliary neurotrophic factor (CNTF[1]), may offer some neuroprotection, and have had beneficial effects in small animals (Anderson et al. 1996;Kells et al. 2004;Ramaswamy et al. 2007b). NHP models will be necessary to determine the optimal dose, delivery, and safety of these factors in a larger, more complex, and long-lived species.

Direct infusion of CNTF protein into the brain has been effective in small animals (Anderson et al. 1996), but the inability of the protein to pass the blood brain barrier, necessitating

intracerebral delivery, and its short half-life, necessitating frequent injections, have made human therapy by this method unlikely (Emerich and Thanos 2006). To overcome the obstacles associated with direct administration of CNTF, scientists developed polymer-encapsulated fibroblasts, genetically modified to secrete human CNTF (Emerich and Thanos 2006), and these were neuroprotective in cynomolgus monkeys that were later induced to develop Huntington's-like disease (Emerich et al. 1997). The engineered cells allow for the continuous low-dose delivery of CNTF, not possible with systemic injections. In addition, Mittoux and colleagues (2000) used encapsulated transgenic cells implanted in the cynomolgus striatum to deliver CNTF, a procedure that arrested degeneration and restored cognitive and motor function in the animals. But there are no reports of long-term animal studies, and the frequency with which capsules would require replacement is not clear. Phase I clinical trials using encapsulated engineered cells (Bloch et al. 2004) replaced the capsules every 6 months; there was variable cell survival over 2 years, but the safety of the encapsulated cells was demonstrated.

Because HD results from aberrant expression from just one allele, silencing of the mutant copy may be a solution. Studies have reported that RNA interference reduced mutant protein production in a mouse model of Huntington's disease (Harper et al. 2005; Wang et al. 2005), suggesting that gene silencing may indeed be a viable approach. Viral vectors may be an effective means to deliver RNAi to the affected areas of the brain; the critical obstacle to this therapy will be targeting of the mutant allele without affecting expression of the normal allele (Ralph et al. 2006).

Recent reports have described two rhesus macaque models for HD (Palfi et al. 2007; Yang et al. 2008). Palfi and colleagues (2007) induced HD symptoms in cynomolgus monkeys by injecting lentiviral vectors carrying a short N-terminal fragment of the huntingtin gene into the putamen. They compared huntingtin genes that encoded either 19 (wild-type) or 82 (mutated) polyglutamine trinucleotide repeats (as previously described in rats; de Almeida et al. 2002) and reported that delivery of the gene encoding the mutant huntingtin protein led to spontaneous and apomorphine-induced choreiform movements along with neuronal protein aggregates and a significant loss of neuronal markers in the striatum. Klawans and colleagues (1980) found that apomorphine, a dopamine receptor agonist, can cause abnormal movements in presymptomatic HD patients and speculated that, although the toxin-induced models are still necessary, their NHP HD model may provide an opportunity to study the higher-order cognitive dysfunction as well as the relationship between the protein aggregates and the behavioral manifestations of the disease.

For the second model, Yang and colleagues (2008) injected lentiviruses carrying exon 1 of the human huntingtin gene with 84 repeats and the green fl uorescent protein (GFP) gene directly into rhesus oocytes before in vitro fertilization. They transferred 30 embryos to 8 surrogates, 6 of which became pregnant and gave birth to five live infants, three of which died within 1 month. The other two infants were 6 months old at the time of publication, and are still being monitored for cognitive and behavioral changes. Symptoms of the affected monkeys included swallowing and respiratory difficulties, chorea, and dystonia. The early deaths of three of the transgenic monkeys did not allow for analysis of the progression of the disease. All of the infants carried both the human huntingtin gene and the GFP gene. Interestingly, the transgenic animals had variable-length repeats (27 to 88) and multiple integration sites (1 to 4). One of the surviving infants has repeats within the normal range of healthy humans and does not appear to be affected. The monkeys with the highest number of repeats and integration sites seemed to have more severe levels of disease, suggesting that the mutant huntingtin protein causes the disease phenotype. The authors suggest that a few male transgenic HD monkeys can serve as founders for the establishment of a transgenic colony, which will enable the long-term evaluation of pathogenesis and diagnostic and treatment strategies. In addition, the technology

used to create the transgenic HD monkey may be applicable to model other human diseases linked to known genetic mutations.

NeuroAIDS

The human immunodeficiency virus (HIV) can cause neurological symptoms such as impaired memory, leg weakness, personality changes, reduced concentration, and dementia (González-Scarano and Martín-García 2005). These symptoms, collectively called neuroAIDS, may affect up to 30% of people infected with HIV (González-Scarano and Martín-García 2005). Conventional retroviral therapies cannot cross the blood brain barrier and therefore cannot control viral replication in the CNS. The mechanism of neurological deterioration is not clear, and identifying the mechanism in humans can be complicated due to confounding factors such as simultaneous coinfections or concurrent drug use.

HIV does not directly infect neurons; rather, mononuclear phagocytes carry the virus across the blood brain barrier, act as reservoirs for virus replication in the brain, and promote monocyte/macrophage infiltration across the blood brain barrier (Gendelman et al. 1994; Kaul et al. 2001; Koenig et al. 1986; Persidsky et al. 2000; Persidsky and Gendelman 2003). The eventual neurodegeneration and neurological symptoms may be the result of a bystander effect, whereby a small number of infected cells spread toxic signals throughout the brain to kill cells that are uninfected (Eugenin and Berman 2007; Nuovo and Alfieri 1996; Persidsky and Gendelman 2003).

HIV does not infect monkeys, but simian immunodeficiency virus (SIV) produces AIDS in infected animals (Kestler et al. 1990; Kindt et al. 1992). SIV-infected macaques have both CNS dysfunction (Murray et al. 1992) and PNS neuropathy (Laast et al. 2007), similar to those of human HIV patients, and also exhibit infection-related behavioral impairments (Weed et al. 2004). The SIV-macaque model is a well-established model for the investigation of HIV-induced CNS disease (Fox et al. 1997; Gardner and Luciw 2008; Prospéro-García et al. 1996; Rausch et al. 1999; Simon et al. 1992; Weed and Steward 2005; Zink and Clements 2002). Like HIV, SIV is a lentivirus that causes an AIDS-like disease in Asian monkeys that are not naturally exposed to the virus, such as rhesus and cynomolgus monkeys (Gardner and Luciw 1989). In addition to the neurological symptoms, infected animals experience wasting and opportunistic infections much like what is seen in HIV patients. The NHP model of neuroAIDS can be an extremely valuable asset for the study of early infections and for the development of viral strains that preferentially infect neurons for experimental use (Capitanio and Emborg 2008).

Researchers have used SIV-infected nonhuman primates in studies showing that CNS infection occurs early in the disease course (Chakrabarti et al. 1991; Hurtrel et al. 1991), that the extent of neurological symptoms is related to the strain (Demuth et al. 2000), and that specific neuroinvasive strains can be isolated and passed to other animals (Wantry et al. 1995). Further, studies in monkeys have led to the identification of specific cells, perivascular macrophages, that are predominantly infected in the CNS (Williams et al. 2001). A brain-adapted SIV strain that has shown vigorous in vivo infection of macrophages and microglia (Gaskill et al. 2005) may lead to insights on the establishment of neuroAIDS. The SIV-infected neuroAIDS model has also been used to demonstrate that therapeutic agents that increase dopamine availability may potentiate neurological effects of the virus (Czub et al. 2001; Koutsilieri et al. 2002, 2004).

In addition to studies of mechanism and virulence, the NHP model of neuroAIDS can be a critical tool for the evaluation of potential therapies; for example, SIV-infected animals have been used for both therapeutic and toxic evaluation of retroviral drugs. NeuroAIDS models will be needed to test new therapies intended to treat CNS symptoms. Studies have already

shown that delivery of antioxidant enzymes using rSV40 vectors is neuroprotective in rats (Agrawal et al. 2006; Louboutin et al. 2007), and ginkgo biloba extract has prevented HIV-induced neurotoxicity in mice (Zou et al. 2007). Nonhuman primates can be used to assess the potential of novel delivery methods that bypass the blood brain barrier of antiretroviral drug delivery, such as intranasal delivery (Hanson and Frey 2006).

Conclusion

Large animal models of CNS genetic disorders have been and will continue to be valuable assets for gene therapy research, playing a central role in the development of diagnostics and treatment options for numerous debilitating diseases, such as Parkinson's disease, Huntington's disease, Krabbe disease, and neuroAIDS as well as other disorders.

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