EDITORIAL
Animal Models of Neurological Disorders

The discovery of new therapies for neurological disorders is predicated on the use of animal models both to identify new therapeutic targets and to perform preclinical trials of drugs before using them in patients. In both cases, the challenge is to develop models that recapitulate the disorder. This is not as simple or straightforward as it may seem. Articles in this issue of *NeuroRx®* illustrate the choices that often need to be made between models that reproduce cardinal pathological features of the disorders by mechanisms that may not necessarily occur in humans *versus* models that are based on known pathophysiological mechanisms but may not reproduce all the features seen in patients.

This paradox is clearly illustrated by models of the neurodegenerative disorder Huntington's disease (HD). Before the identification of the gene causing the disease, animal models of HD were created by injecting neurotoxins into the striatum.[1] These models reproduced not only the cellular but also the regional selectivity of HD neuropathology, but it remained unknown whether these mechanisms reproduced the effects induced by the mutation that causes the disease. In 1993, the Huntington Disease Collaborative Group identified an expanded CAG repeat in the gene encoding huntingtin as the cause of HD.[2] This was a golden opportunity to develop accurate models of the disease because it is caused by a single mutation with 100% penetrance, which could easily be expressed in mice. We do indeed have multiple mouse models of HD (see reviews by Li et al. and by Menalled in this issue). However, although they have multiple defects and most show striatal atrophy, very few reproduce the classical pattern of cell loss that characterizes the human disease. Thus, the most faithful reproduction of the disease mechanism in a mammal often fails to reproduce the most characteristic features of the human disease. In nonmammalian models, the mutation expressed in organs where pathology is not observed in humans, such as the eye in flies (see review by Jackson in this issue) can induce neurodegeneration, but it remains uncertain that the same mechanisms are involved in humans. Does it mean that these models were not useful? Certainly not. In fact, much was learned from studying both mammalian and nonmammalian genetic models of HD, and they are now used to test neurotherapeutics. The same can be said of models for several forms of genetic ataxia, although some of these models have the added advantage of exhibiting selective neuronal loss (see reviews by Merry and by Colomer in this issue).

Curiously, although the absence of characteristic striatal cell loss has not hindered the wide use of genetic models of HD for therapeutic target discovery and preclinical trials, much controversy surrounds the lack of selective nigrostriatal dopaminergic cell loss in genetic models of Parkinson's disease (PD) (Fleming et al. in this issue). Nigrostriatal cell loss can be induced by selective toxins, and these models have been widely used to mimic the disease (Bové et al. in this issue). However, it remains unclear that toxins reproduce mechanisms operating in PD, and these models do not reproduce the extensive extra-nigral pathology present in PD. Both toxic and genetic models offer complementary windows in the physiopathology of the disease. The usefulness of similar models using rare familial mutations to produce valuable models of a frequent sporadic illness, Alzheimer disease, is described by Spires and Hyman in this issue.

Although reproducing neurodegeneration in a meaningful mechanistic way remains a challenge for models of neurodegenerative diseases, acute cell loss caused by stroke or traumatic brain injury can be readily reproduced in animals. However, as discussed by Carmichael and by Cernak in this issue, even reproducing these apparently straightforward neurological conditions in an animal presents numerous challenges. A different kind of challenge is presented by neurological conditions that, although devastating, are not associated with a clear neuropathological signature. This is in particular the case of generalized and focal dystonia. Because one cannot expect to exactly reproduce human neurological symptoms in a rat or mouse, criteria for a successful model are more difficult to establish. Reviews by Raike et al. and by Evinger illustrate the ingenuity of researchers in producing compelling models for these disorders.

The reviews gathered in this issue of *NeuroRx®* describe efforts to reproduce neurological disorders in a variety of animal models and discuss the challenges and opportunities they present for the development and testing of new therapeutics. Of course, lack of space precludes this compilation from being inclusive. New opportunities emerge for mammalian genetic models with the development of transgenic rats, and even primates, and a wider range of nonmammalian models. The development of animal models of neurological disorders is a work in progress and will continue to fuel new discoveries for neurotherapeutics.

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2. Huntington's Disease Collaborative Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 72:971–978, 1993.