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The autosomal dominant polyglutamine expansion diseases, including Huntington’s disease (HD) and Spinocerebellar ataxia type 1 (SCA1), are progressive neurodegenerative disorders. Prior work in inducible mouse models of SCA1 and HD showed that repression of mutant allele expression improved disease phenotypes. Thus, therapies designed to inhibit disease gene expression would be beneficial. To accomplish this, we have optimized lentivirus- and adeno-associated virus-mediated expression of RNAi, and tested the effectiveness of these novel vector systems in cell and animal models of SCA1 and HD. Both vector systems, when optimized, can induce target gene silencing that is sustained over many months. The utility of vector mediated RNAi in these model systems will be discussed.