The discovery in 1993 of the genetic abnormality that causes Huntington’s disease triggered an explosion in our understanding of this inherited neurodegenerative disorder (The Huntington’s Disease Collaborative Research Group, 1993). Since the Huntington’s disease mutation is fully penetrant, everyone with the same underlying CAG triplet repeat expansion in the huntingtin (HTT) gene will develop a devastating combination of motor, cognitive and psychiatric disturbances. The monogenic nature of Huntington’s disease suggests that disease modifying therapies should be within reach. Currently, however, no such treatments exist (Mestre et al., 2009). Nevertheless, much has been done to characterize the huntingtin (Htt) protein and the effects of its toxic twin, mutant huntingtin. We know that Htt is a large and ubiquitously expressed protein with a range of possible functions, and that Huntington’s disease is predominantly caused by the damaging effects of mutant Htt on neurons. A range of animal models recapitulate the molecular, cellular and clinical phenotypes of Huntington’s disease, enhancing our understanding and facilitating the search for treatments (Ross and Tabrizi, 2011). Numerous potential pathogenic mechanisms have been identified, leading to promising therapeutic approaches in transgenic Huntington’s disease mice and other models. Although none has yet been found effective in human patients, there is optimism in the field that Huntington’s disease is a disease for which the goal of effective therapy might be achieved (Munoz-Sanjuan and Bates, 2011).

Two articles in this issue of Brain highlight the Huntington’s disease research community’s multi-faceted approach to developing new treatments for Huntington’s disease. Grondin and colleagues report success in a 6-month study of Htt gene silencing using RNA interference in the adult non-human primate brain (Grondin et al., 2012); while Labbadia et al. (2012) describe the means by which a molecular chaperone can suppress aggregation of disease-associated Htt complexes.

Gene silencing is an experimental approach to selectively modify protein expression. Custom designed nucleotide-based molecules are introduced into cells to target specific messenger RNA transcripts for removal, resulting in reduced levels of the corresponding protein. The most prominent technique for gene silencing is RNA interference, in which the silencing molecules are small interfering RNA. Other gene silencing approaches use different nucleotide chemistries such as antisense oligonucleotides, but share the same basic principles. Different silencing molecule chemistries may alter tolerability, distribution, uptake, silencing efficacy and duration of effect (Sah and Aronin, 2011). Being monogenic and fully penetrant, Huntington’s disease is an ideal candidate for the therapeutic approach of gene silencing. Several groups have now reported success using different techniques to reduce production of the Htt protein. Intracranial delivery of either RNA interference or antisense oligonucleotide compounds is capable of significantly reducing Htt production, and ameliorates both motor and neuro-pathological phenotypes in Huntington’s disease model rodents (Harper et al., 2005; Franich et al., 2008; Carroll et al., 2011).

Significant questions remain, however, before gene silencing therapeutics can be taken into trials in human patients with Huntington’s disease. The obvious issue is distribution; even using intraparenchymal delivery and viral vectors to drive expression, the penetration of RNA interference compounds is incomplete even in the mouse brain. The degree to which RNA interference can be translated to the human brain, and how the drug should be delivered, remain to be determined. Equally pressing is safety. While silencing mutant Htt is generally agreed to be desirable, debate surrounds the issue of whether it is safe to silence its wild-type partner. Silencing both Htt alleles could produce harmful effects; the function of wild-type Htt in the adult brain is unclear, but complete Htt knockout is lethal for embryos (Nasir et al., 1995), so caution is justified. It is unknown whether the partial knockdown of mutant Htt produced by RNA interference will be more beneficial than any adverse effects of reducing wild-type Htt by a similar amount. It may be desirable to target the expanded CAG tract directly, or identify individuals heterozygous for small nucleotide polymorphisms (SNPs) that enable mutant Htt messenger RNA to be targeted selectively by allele-specific silencing. However, this approach would limit treatment to those patients with Huntington’s disease who carry such SNPs, and each different SNP-targeting drug would have to be tested and licensed independently (Sah and Aronin, 2011).

The first application of Htt RNA interference in primates was recently published by McBride and colleagues (2011), who demonstrated effective partial knockdown 6 weeks after treatment. The work of Grondin and colleagues now provides stronger reassurance in the form of a 6-month non-human primate safety trial. A candidate nucleotide sequence was chosen on the basis of efficacy in human and rhesus cells, and packaged into an adeno-associated virus. Stereotactic neurosurgery was used to deliver the virus to five sites in the caudate and putamen of four healthy, wild-type rhesus macaques. The basal ganglia were
targeted for their early involvement in human Huntington’s disease. Four further animals received injections of a placebo comparator with a scrambled RNA sequence.

After this one-off treatment, the animals’ general health and motor function were monitored for 6 months before neuropathological inspection. By any measure, the trial was successful. Needle placement was shown by magnetic resonance imaging, as it would be in human patients, to have been accurate. Drug-treated animals experienced no significant change in gross or fine motor function or weight. Quantitative polymerase chain reaction demonstrated expression of the silencing and scrambled RNA function or weight. Magnetic resonance imaging showed by magnetic resonance imaging, as it would be in human patients, to have been accurate. Drug-treated animals experienced no significant change in gross or fine motor function or weight.

The Htt exon 1 inclusions in the brains of the resultant mice were reduced in size, with a parallel increase in soluble Htt. This corresponded to a modest improvement in aspects of neurological function. The effect was specific to certain aggregated Htt species; namely high molecular weight aggregates located in the nucleus. Given that cytosolic Htt inclusions were also present, it is intriguing that such aggregates were not similarly affected, perhaps indicating an important difference in their structure or composition. HSJ1a was demonstrated to interact directly with aggregated Htt, but this association did not extend to those aggregates with the very highest molecular weight. Several key domains in the HSJ1a protein were shown to be required for its interaction with Htt, including one that associates with another chaperone, HSP70, and others that bind ubiquitin. In vitro assays demonstrated that HSJ1a lowers the rate at which Htt aggregates. The authors propose a novel mechanism by which HSJ1a selectively recruits HSP70 to Htt oligomers of a certain size, where they act together physically and impede further aggregate growth.

The overexpression of chaperones has previously shown only limited success in ameliorating disease in Huntington’s disease mouse models (Hansson et al., 2003; Hay et al., 2004), but this particular class of HSP40 chaperones had not previously been tested in this way. Much debate remains as to whether large Htt aggregates have a pathogenic role in Huntington’s disease or, conversely, are formed as part of a beneficial coping mechanism to sequester smaller toxic oligomers (Arrasate and Finkbeiner, 2011). In the study reported by Labbadia et al. (2012) overexpression of HSJ1a in the R6/2 mice clearly reduces the formation of large nuclear Htt exon 1 aggregates and has a concomitant modest benefit on disease progression. This shows that, in principle, modifying chaperone function and other means of restoring protein homeostasis could be a valid therapeutic strategy in Huntington’s disease.

These papers are representative of the huge and diverse advances that are being made to understand the pathogenesis of Huntington’s disease and approaches to its treatment (Ross and Tabrizi, 2011). Strategies other than Htt lowering and restoring protein homeostasis include targeting the metabolic and transcriptional changes associated with disease. Huntington’s disease gene carriers can be identified before the onset of clinical symptoms, allowing the possibility of very early therapeutic intervention. Studies that add to the understanding of onset and progression of clinically relevant symptoms have improved our readiness for human trials (Tabrizi et al., 2012). We cannot say when such treatments will materialize, but current efforts are advancing at a rate sufficient to bring them tantalizingly closer.

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