PERSONALIZED TREATMENT OF NEUROLOGICAL DISEASES

Michael Hayden, Israel

Huntington disease (HD) is an autosomal dominant neurodegenerative disease characterized by progressive loss of voluntary motor control, psychiatric disturbance, cognitive decline and death 15-20 years after motor onset. HD is uniquely caused by a polyglutamine encoding CAG expansion in the huntingtin gene (*HTT*), which allows for identification of pre-manifest mutation carriers as much as decades before onset and should facilitate development of disease modifying therapies. Yet nearly 20 years after identification of the HD mutation, available therapies offer only moderate symptomatic relief. Development of small molecule therapies for HD has been hindered by difficulties identifying and validating tractable drug targets within the disorder's complex pathogenesis. However, the monogenic cause of HD provides a presumably universal therapeutic target, the mutant *HTT* gene (*muHTT*). In fact there is significant evidence from transgenic mouse studies that reducing expression of *muHTT* will result in amelioration of HD. However, the HTT protein is important for neuronal health throughout life, and allele-specific silencing strategies that selectively lower mutant but not wildtype HTT are preferable and more likely to be well tolerated.

As CAG repeats are a normally occurring genetic element throughout the genome, development of *selective muHTT* silencing strategies has required identification of target sites other than the HD mutation. Maximizing patient coverage requires identification of therapeutically relevant SNPs.

We have generated a large number of antisense oligonucleotides (ASOs) targeting HD-SNPs. ASOs silence gene expression post-transcriptionally and can discriminate between SNP alleles anywhere in the pre-mRNA, including introns. Screening of candidate ASOs in HD patient derived cell lines and in the brains of mice engineered to recapitulate human HD-associated SNPs has identified several potent and highly selective molecules with which we are initiating pre-clinical efficacy studies. If successful in mice, this therapy could be rapidly translated into a similar approach for humans.