

Workshop Updates

Gene Delivery and New Developments

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One of the most conceptually appealing options for treating and even curing

Huntington's disease (HD) is to target its root cause by eliminating, or reducing, mutant huntingtin. As explained by HDF's Executive Director for Science Carl Johnson, the main options for achieving this goal are targeting huntingtin messenger RNA (mRNA) using RNA silencing techniques, or targeting the huntingtin protein using anti-huntingtin intrabodies. How, when, and where to deliver these cargoes for maximum efficacy and minimal side-effects, however, remains uncertain. In this workshop, participants identified outstanding issues to be discussed in greater depth at an upcoming workshop dedicated to establishing a research agenda for gene delivery as a treatment for HD.

Participants agreed that viruses are the most developed delivery systems and, thus, probably closest to being tested in HD clinical trials.

Viruses are also appealing carriers because they circumvent the need for multiple dosing. Because HD is a chronic disease involving the brain, the problem of delivering therapeutic molecules continuously or repeatedly into the brain is significant, not only for patients, but for performing preclinical tests in mice.

Participants agreed that the most important and immediate task to be accomplished is to clearly define the open questions and issues that need to be addressed to move gene delivery into the clinic. The first clinical trial will mark the beginning of a long process of development, and it will be important to identify at the outset the aims of this process as clearly as possible.

One key issue will be defining which of the several delivery options to pursue. As previously mentioned, participants agreed that initial studies should probably focus on viral vectors, given their more advanced stage of clinical development. However, participants also stressed the importance of continuing work on other alternatives, particularly due to the irreversibility of viral infections.

The how, when, and where of gene delivery also emerged as key open issues. For example, should delivery be global or selectively targeted? If targeted, where and when? How will a balance be reached between targeting vulnerable brain regions and targeting regions that are sufficiently healthy to benefit from gene therapy? How will a balance be reached between early treatments that are more likely to rescue cells before they are damaged beyond repair, and later treatments involving patients more willing to accept the risks of an experimental treatment and who may show quicker and clearer signs of improvement? How important will it be to reach non-neural targets, including glia and peripheral tissues? How should minimizing invasivity be factored in to the optimization of other delivery parameters? What options should be pursued to develop regulatable gene therapies? A key to answering many of these questions, noted participants, will be the use and refinement of HD models in large species.

The importance of identifying robust and reproducible biomarkers and outcome measures was also strongly emphasized.

To streamline the resolution of the multiple unresolved issues, participants proposed recruiting experts in a variety of fields. They emphasized the need for the advice of physicians, in particular neurosurgeons and HD clinicians, along with experts from various companies working on siRNA technologies, such as Alnylam, Medtronic, Isis, Merck and Genzyme, and experts in business and regulatory affairs. The need for building partnerships was also stressed.

It is clear that the path ahead will not be easy. Many open questions remain and much work remains to be done, and there is a risk of moving too quickly without a thorough understanding of the efficacy and safety of gene delivery technologies. It was feared that HD research may suffer from some of the problems Parkinson's disease research has experienced, such as premature testing of experimental therapies in humans, sometimes without appropriate controls. However, most participants were enthusiastic about the future. The advances made just in the last year are impressive, and with the help of the HDF putting careful, rigorous people to work hard in this field, it is likely that progress will continue at a rapid, yet responsible, pace.

An additional follow-up workshop entitled "Clinical trials of RNAi-based therapy in HD" is planned for July 16-17, 2008 in New York, NY to address many of these questions and accelerate the pace of progress. ■