GENE THERAPY AS A TREATMENT FOR HUNTINGTON’S DISEASE

Huntington’s disease (HD) is a progressive, neurodegenerative disease that affects about 5-10 out of 100,000 individuals and for which there is no cure. The disease is due to an excessive number of CAG repeats (>35) on the J1 region of the HD gene, which results in an expanded polyglutamine (polyQ) region on the Huntington protein (HTT) sequence. The mutant form of Huntington (mHTT) acquires toxic function through altering several processes within neurons, especially in the striatum and cortex, leading to cell death. The only drug that has been approved by the FDA is Tetrabenazine, used to suppress the chorea syndrome associated to these patients. Currently, multiple strategies are being tested for the treatment of HD, being gene therapy the most promising one, since it makes possible to stop all the downstream effects caused by mutant Huntington.

OBJECTIVES
1. To understand the genetic and molecular mechanisms that lead to Huntington’s disease phenotype.
2. To catch up with the most relevant treatment strategies that are currently being tested, and the experimental models used to gain insight on the role of gene therapy and on the different approaches that are being studied.
3. To get the opinion of experts in the field on the research status, and the possibility of obtaining a cure soon.
4. To learn how to obtain information from various sources, and how to manage the time to organize and process this information.

RESULTS

GENETIC ANIMAL MODELS

Table 1. Most used animal models

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Transgenic</td>
<td>5’ fragment of human HD gene + 2 copies of the endogenous gen</td>
<td>They manifest most symptoms. Fast progression of the disease. Smaller experiments.</td>
<td>No reproduction of human HD.</td>
</tr>
<tr>
<td>Knock-in</td>
<td>1 full length human HD gene + 1 endogenous gene. Physiological HTT levels.</td>
<td>No overexpression, full human mHTT gene, slower progression.</td>
<td>Better reproduction of human HD.</td>
</tr>
</tbody>
</table>

PHARMACOLOGICAL THERAPY

Mutant Huntington affects signaling within neurons, neurotransmitters release, energy production, gene expression, protein refolding and protein degradation. Symptomatic treatments are based on the use of small drugs to inhibit or compensate of one or more altered pathways.

CURRENT PROMISING APPROACHES

<table>
<thead>
<tr>
<th>Current Promising Approaches</th>
<th>Pharmacological therapy</th>
<th>Gene therapy</th>
<th>Ex vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDAC inhibitors</td>
<td>Gene expression</td>
<td>Non-selective</td>
<td>BDNF</td>
</tr>
<tr>
<td>DNA inhibitors</td>
<td>Excitotoxicity</td>
<td>Allele selective</td>
<td>Non-selective</td>
</tr>
<tr>
<td>PDE inhibitors</td>
<td>Neuroprotection</td>
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</table>

IN VIVO GENE THERAPY FOR HUNTINGTON’S DISEASE

- Allele-specific silencing
  - The chosen target must be present in heterozygosity
  - This strategy is only being tested in vitro due to the lack of a fully humanized in vivo model.
  - mRNAs-like siRNAs: siRNAs from non-human primate mRNAs, or synthetic siRNA that contain mismatches. Selectivity of siRNAs that target the CAG sequence increases when complementarily isn’t full. These siRNAs mimic the endogenous mRNA pathway.

OUTSTANDING EXPERIMENTS

**2009:** siRNA-mediated Huntington’s suppression in adult mice for 4 months.

**2011:** Preclinical safety testing of wild type Huntington suppression in primates for 8 weeks.

**2012:** Preclinical safety of wild type Huntington suppression in primates for 8 months.

CONCLUSIONS: What are the future prospects regarding the development of a cure?

Although gene therapy is giving positive results, there are several challenges that must be overcome. One of them is that the current animal models aren’t completely reliable when it comes to extrapolate the results to humans. In addition, all functions involved by normal and mutant HTT are still not known, making it more difficult to predict the consequences of inhibiting a certain pathway or the wild type HTT. Finally, RNAs and ASOs must be optimized in order to improve efficiency, selectivity, and safety.

DISCUSSION: What are the main obstacles in the research?

The real purpose of this project was to collect enough information in order to answer one question: how long before a cure for Huntington’s disease? Nevertheless, the answer is uncertain. Further research is still needed before any of the gene therapy strategies can enter clinical phases, but at the same time the required steps are being made. Since 2011 non-selective siRNAs are being tested in non-human primates for safety evaluation giving promising results, and recently there have been attempts to create better animal models, with apparent success. Gene therapy for HD might not be such a distant reality. Meanwhile, there is a relatively considerable activity regarding the use of small drugs, and probably the next approved treatments will be symptomatic.