Update on Antisense Oligonucleotide Treatment for HD

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Current HD Clinical Studies at UCSF

1) Enroll-HD

2) Legato-HD

3) Decision Making in HD
Update on Antisense Oligonucleotide (ASO) Treatment for HD

• What is an ASO?

• Why use an ASO approach in HD?

• What science has been done with ASOs already?

• What is happening with ASOs in HD?
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  A way to “knock down” a gene of interest

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• What is happening with ASOs in HD?
First (small) human trial is ongoing in Europe and Canada
What is an Antisense Oligonucleotide?
The HD Gene Gets Made Into Protein

**DNA** = The Master Code

**RNA** = Temporary Copy of the Code

**Protein** = The Building Block Translated From the Code
Antisense Oligonucleotides Destroy Specific RNA

1. RNase H1
2. Cleavage Products
3. Modulate Polyadenylation
4. RNase H1 Degradation
5. Translation Inhibition

Devos and Miller, 2013
Antisense Oligonucleotides Destroy Specific RNA

Meaning Less Protein Can Be Made

Devos and Miller, 2013
Why Use an ASO Approach in HD?

- We suspect the HD gene causes numerous downstream problems.
- We know the disease is caused by ONE gene.
- We don’t need to know how the disease works to treat the gene.

What Science Has Been Done with ASOs Already?

• HD Mice have been treated with anti-HD ASOs, with reduction of HD protein and slowed disease progression

• Monkeys have been treated with anti-HD ASOs, which reduces HD protein

• ASOs have been used in humans with other genetic diseases, and appear safe
Mouse HD ASO Study

Kordasiewicz et al., 2012
ASO Improves Balance in Mouse HD

Kordasiewicz et al, 2012
ASO Improves Anxiety in Mouse HD

Kordasiewicz et al, 2012
ASO Reduces HD Brain Pathology

Kordasiewicz et al, 2012
ASO Reduces Mortality in HD Mice

Kordasiewicz et al, 2012
Potential Limitations of ASOs in Humans

- Cannot cross blood-brain barrier, so need to be given in spinal fluid
- The human brain is BIG – how to deliver the ASO?
- ASOs are likely to help in preventing progression, so they may be most effective early in the disease
- We don’t know yet how knocking down the normal gene will affect people
- Potential side effects: inflammation, liver enzyme changes
First ASO Clinical Trial in HD

- Drug called ISIS-HTT$_{Rx}$ developed by Ionis/Roche
- Study began in July 2015 in Europe and Canada
- Small (Phase 1 / 2) randomized, placebo-controlled study, 1/month infusion x 3, total trial 29 weeks, in early HD patients
- ASO is administered in the CSF
- Goal of medication is to slow the progression of HD in the brain, and to reduce symptoms
- Goal of study is to assess safety and tolerability
- Planned end of trial in 2017
Conclusions

• Given the many different ways the HD protein affects the brain, developing a drug which stops them all may be difficult

• ASOs are an innovative way to get around this problem in genetic diseases like HD

• ASOs show promise in animal models of disease

• We will know soon about the safety of ASOs in HD