Update on Antisense Oligonucleotide Treatment for HD

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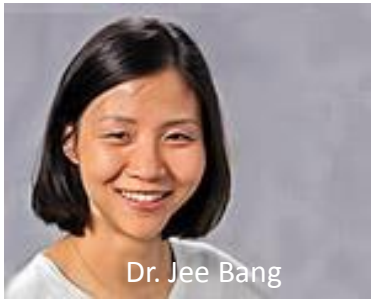
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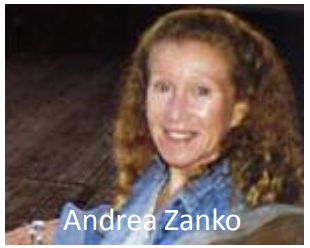
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Current HD Clinical Studies at UCSF

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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In animals with HD genetics, ASOs can dramatically reduce disease symptoms; in humans ASOs are already being tried for other genetic diseases

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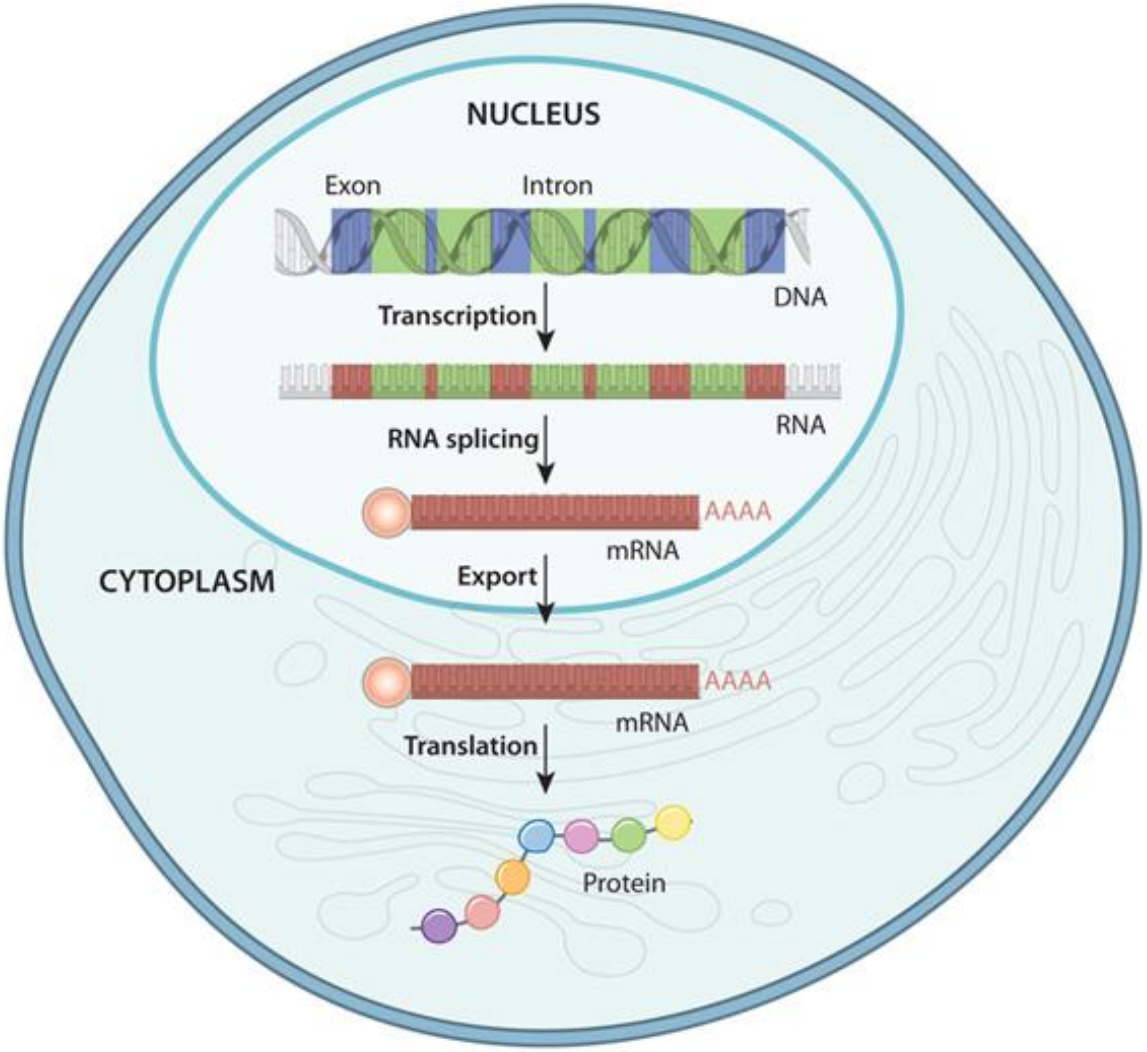
- What is happening with ASOs in HD?

First (small) human trial is ongoing in Europe and Canada

What is an Antisense Oligonucleotide?

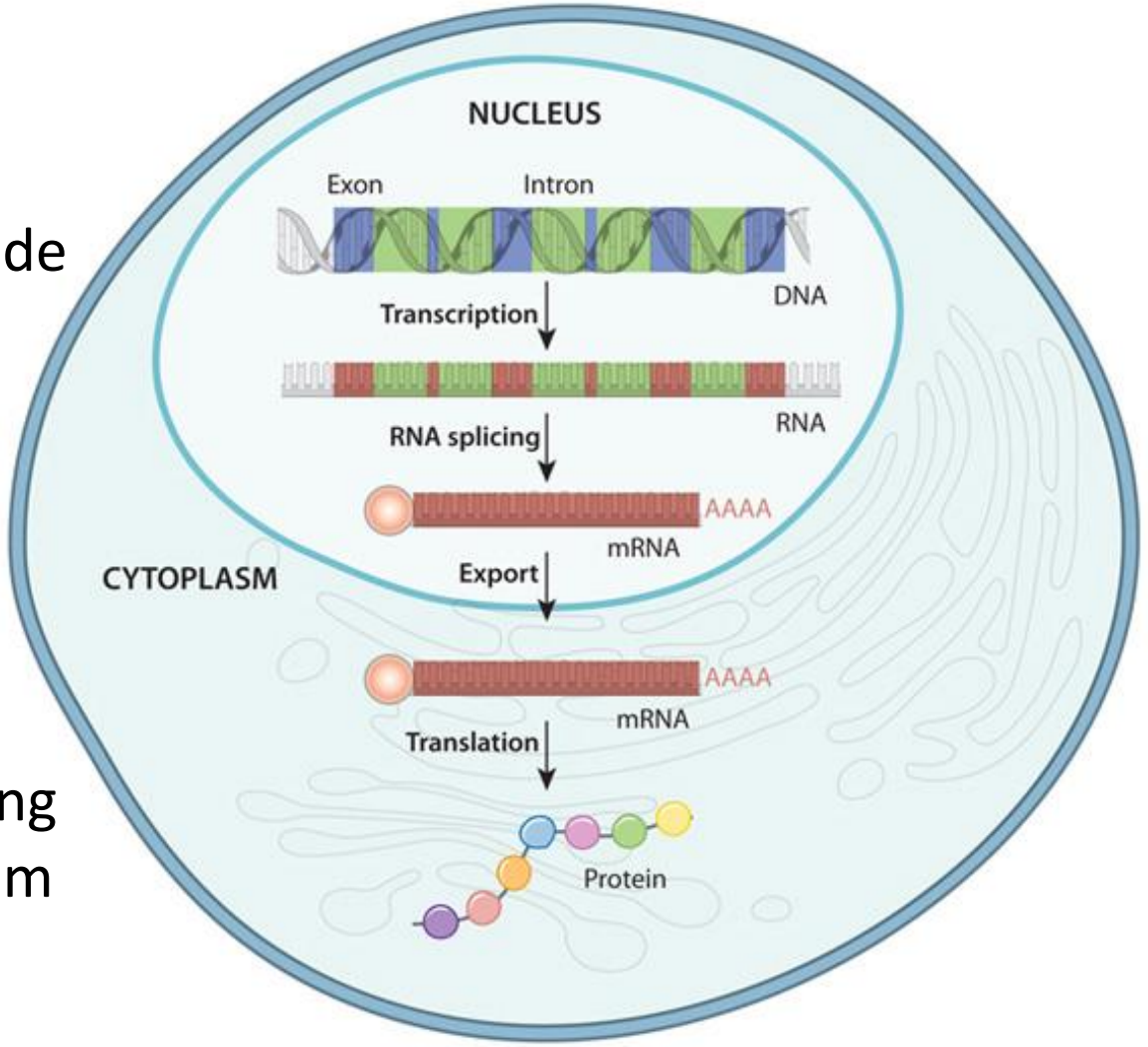


The HD Gene Gets Made Into Protein

DNA = The Master Code

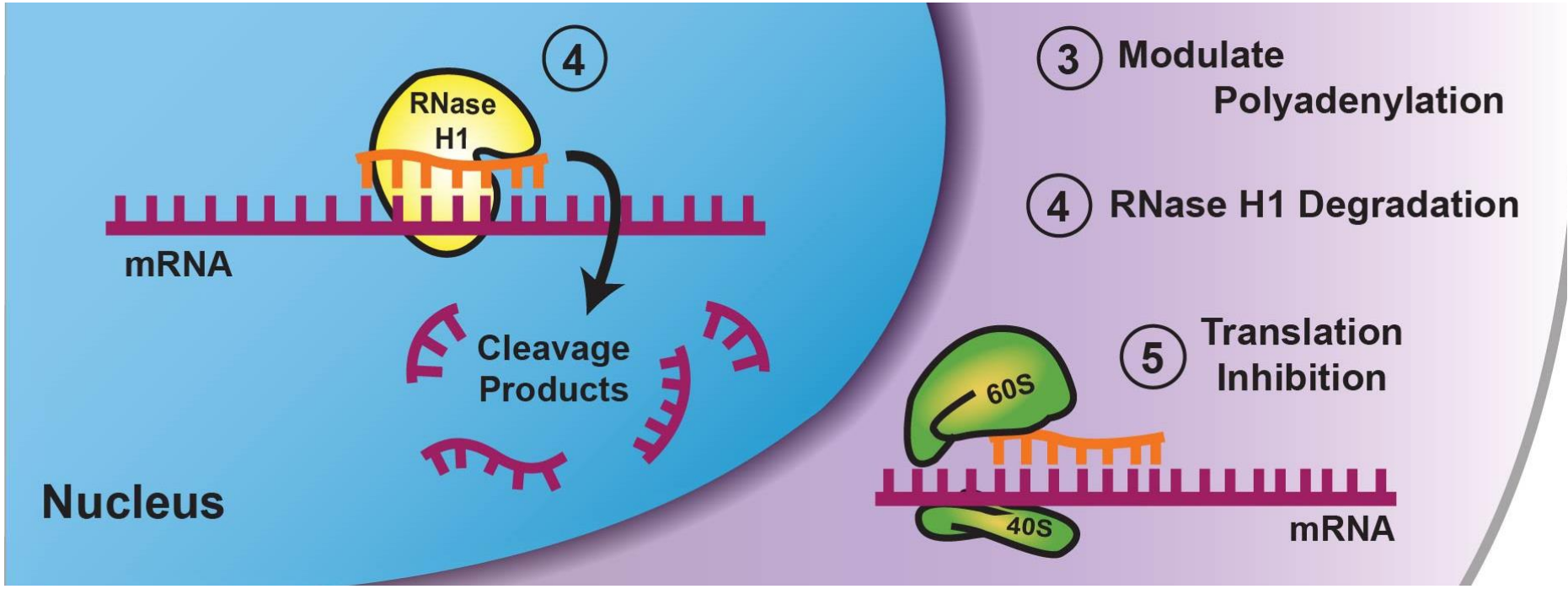
RNA = Temporary Copy of the Code

Protein = The Building Block Translated From the Code



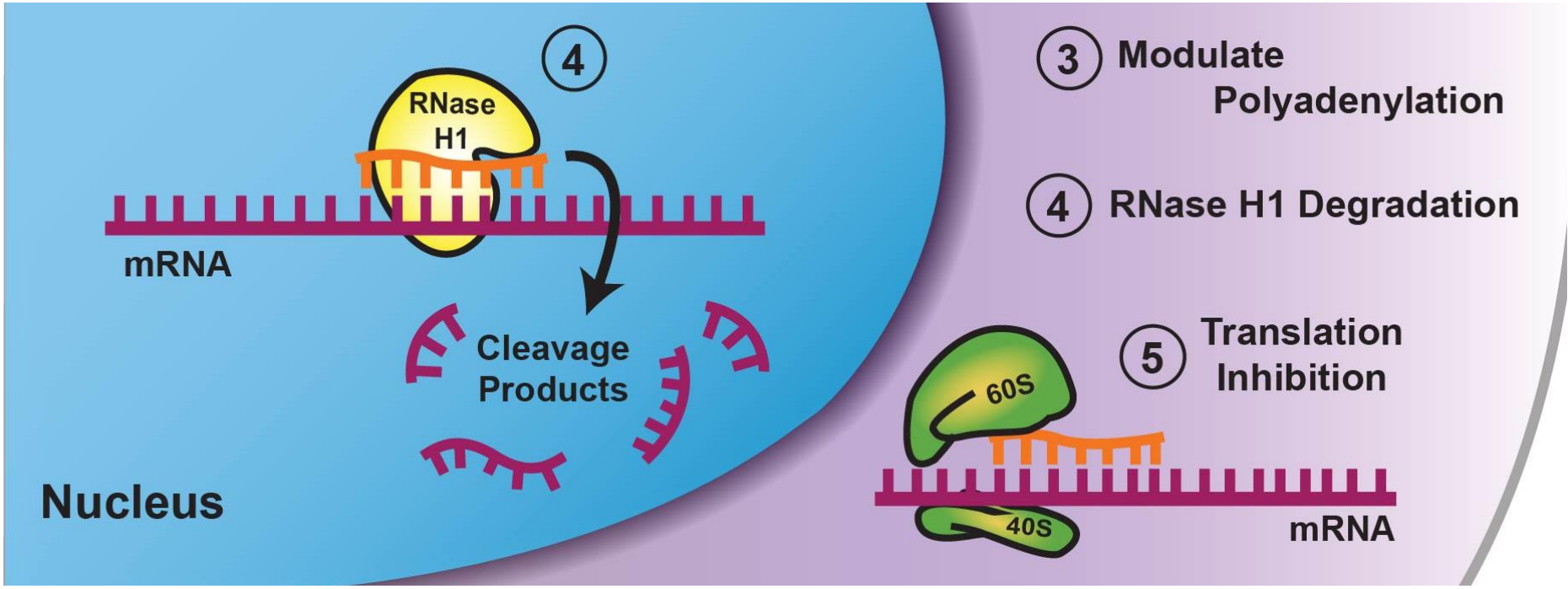
Nature (Journal) 2016

Antisense Oligonucleotides Destroy Specific RNA



Devos and Miller, 2013

Antisense Oligonucleotides Destroy Specific RNA

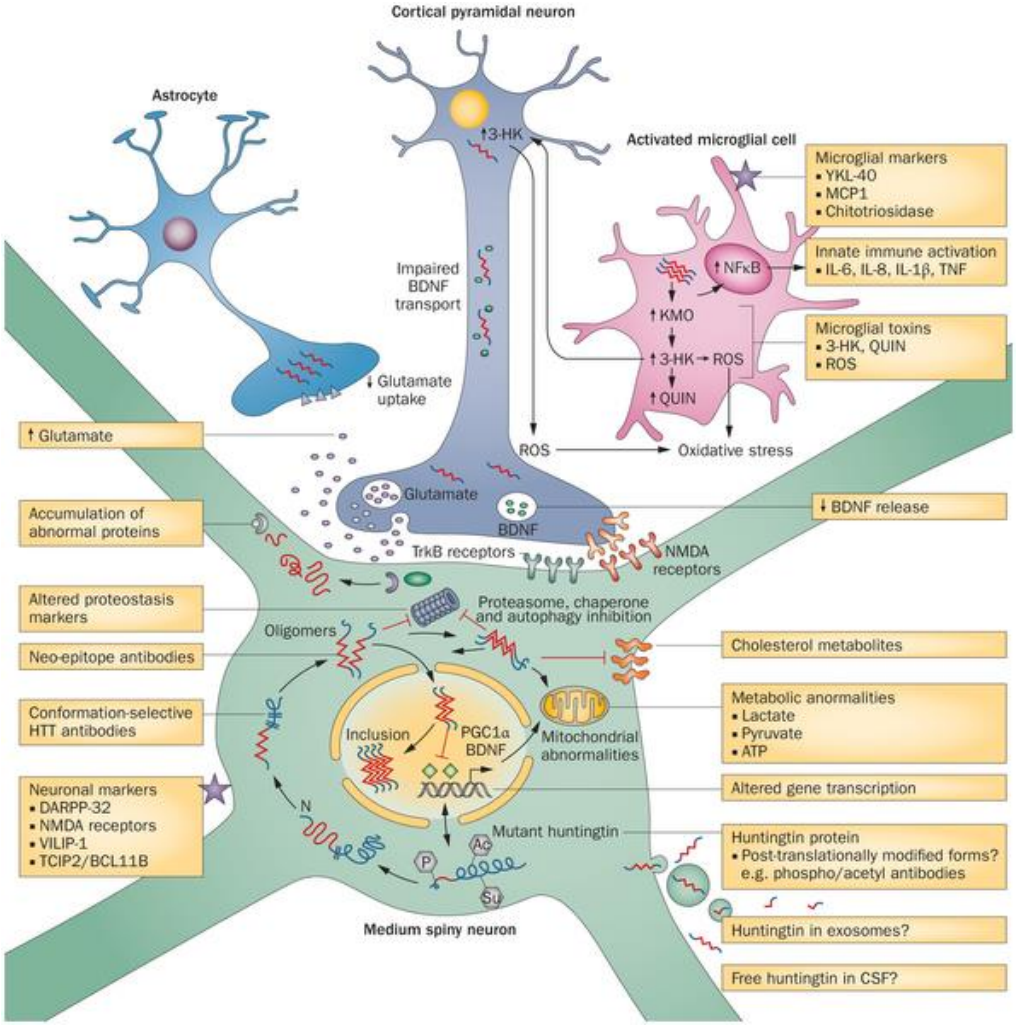


Meaning Less Protein Can Be Made

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

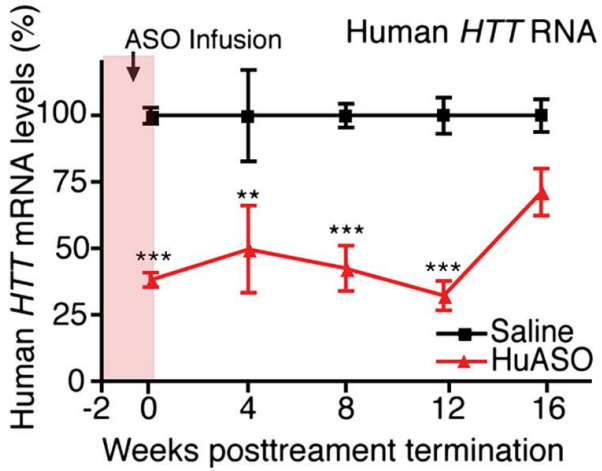


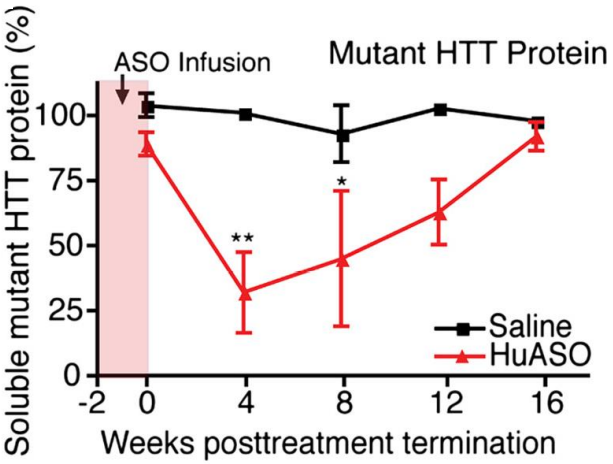
Ross et al, Nature Rev Neurology 2014

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

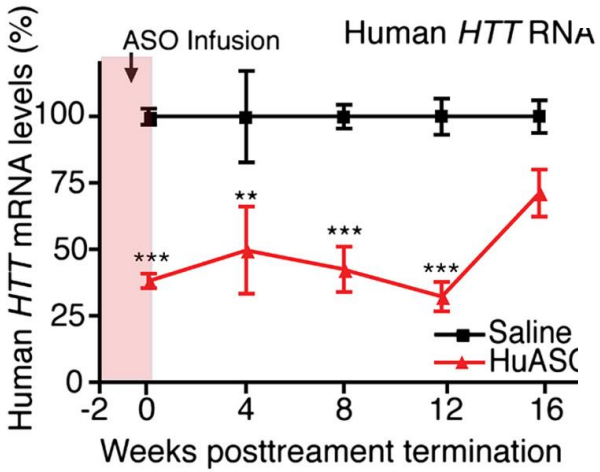
Mouse HD ASO Study

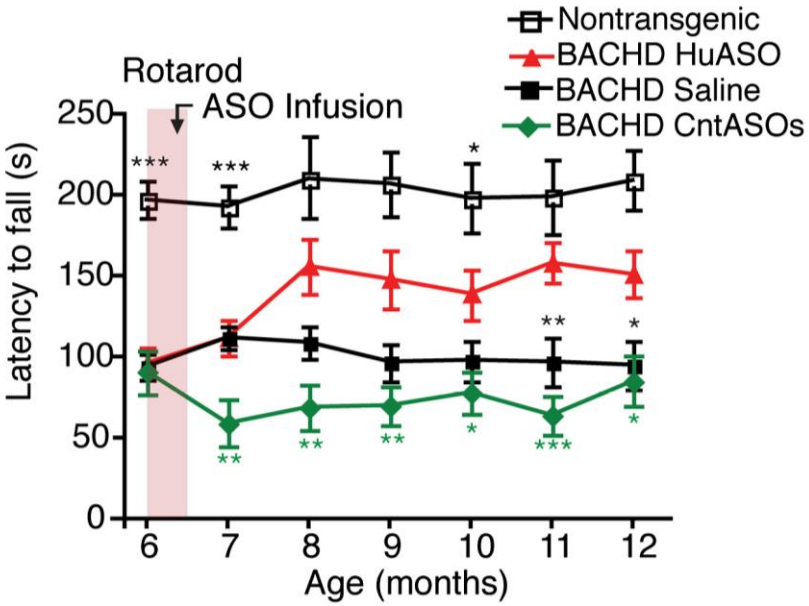


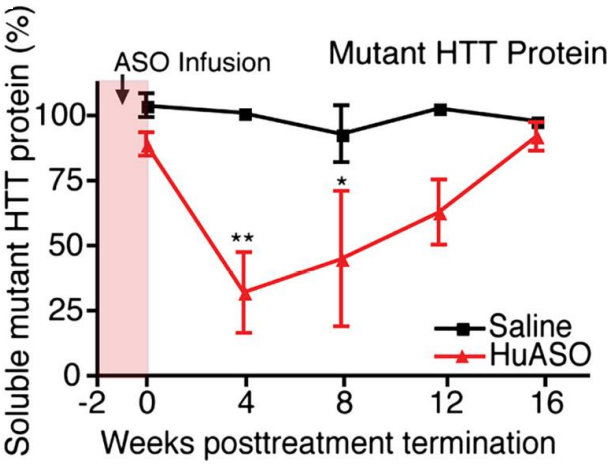


Kordasiewicz et al, 2012

ASO Improves Balance in Mouse HD

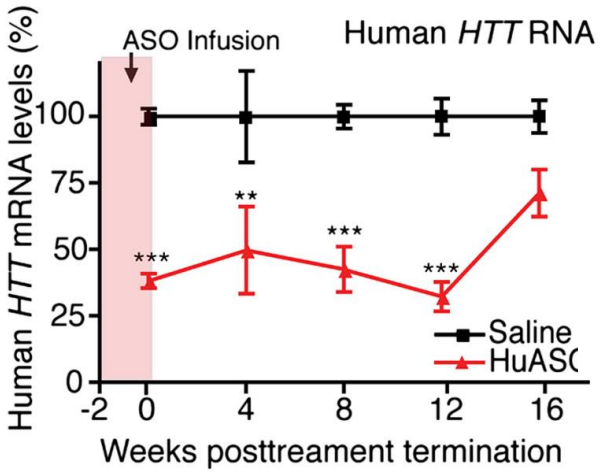


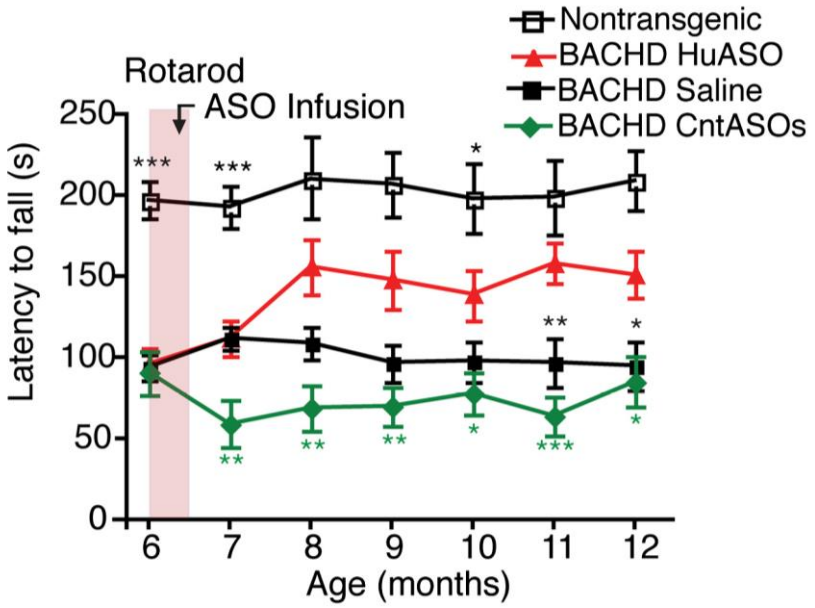


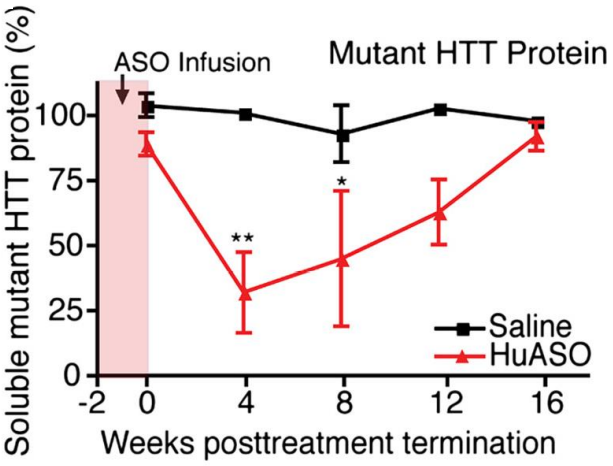


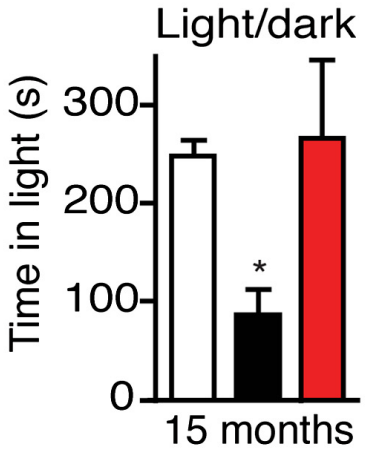
Kordasiewicz et al, 2012

ASO Improves Anxiety in Mouse HD



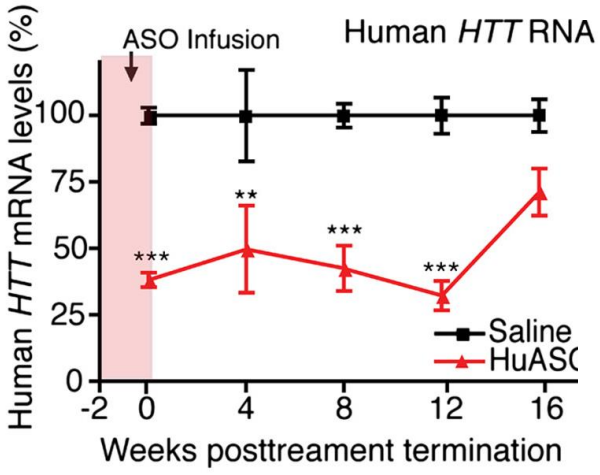


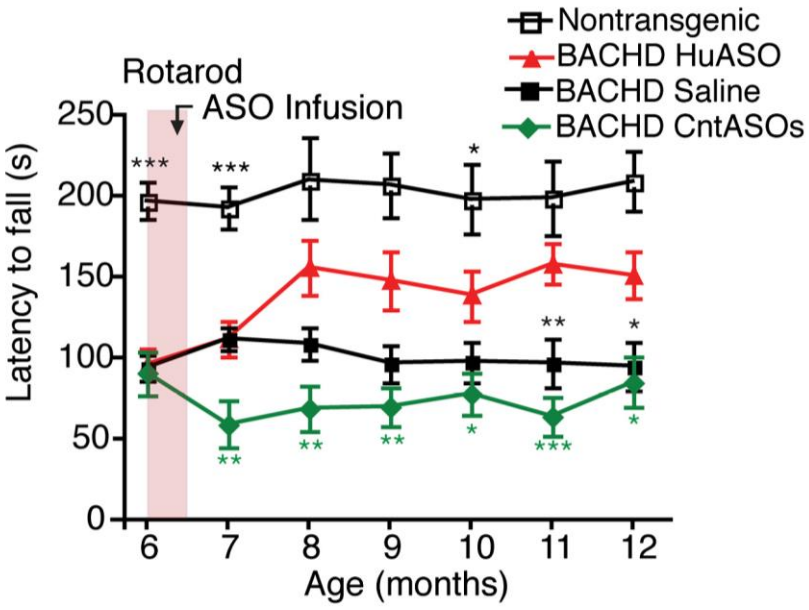


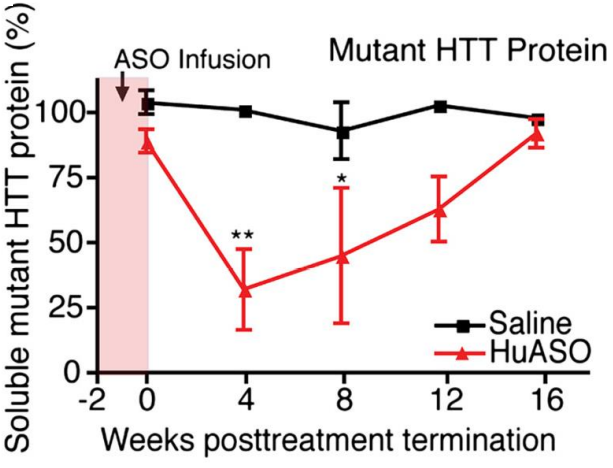


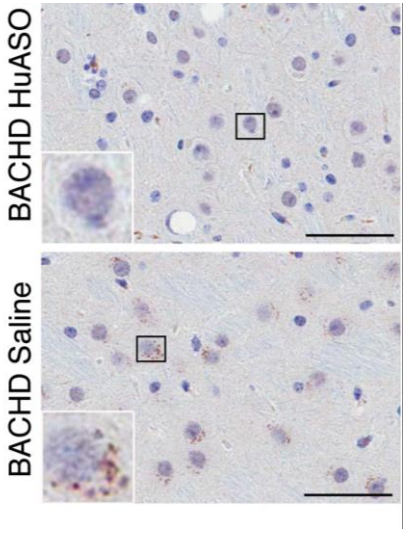
Kordasiewicz et al, 2012

ASO Reduces HD Brain Pathology



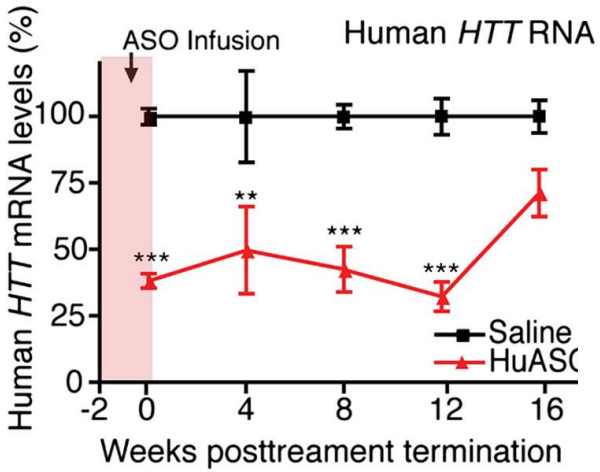


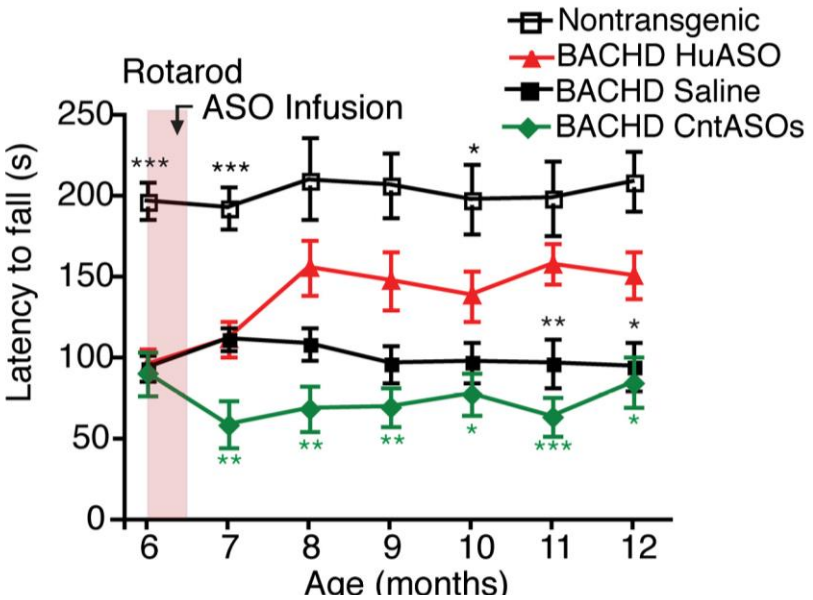


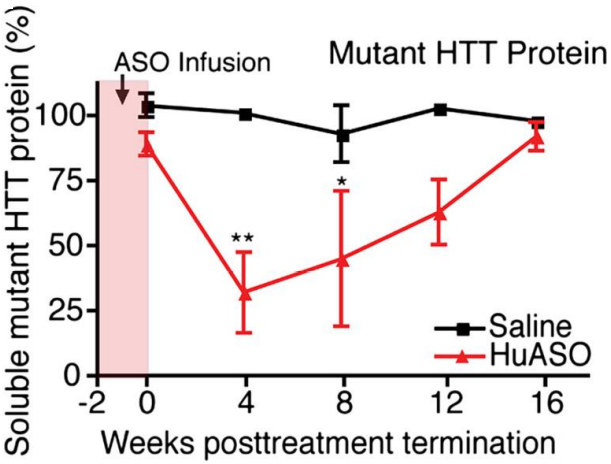


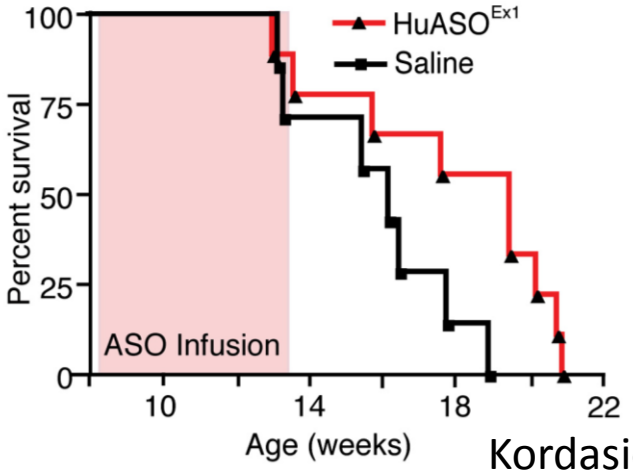
Kordasiewicz et al, 2012

ASO Reduces Mortality in HD Mice





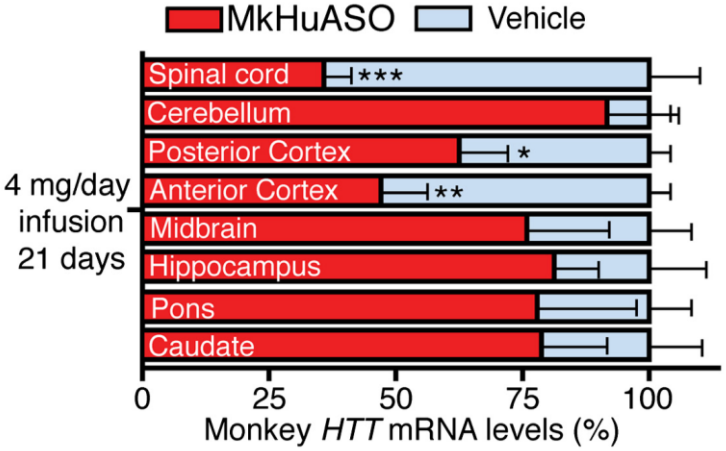


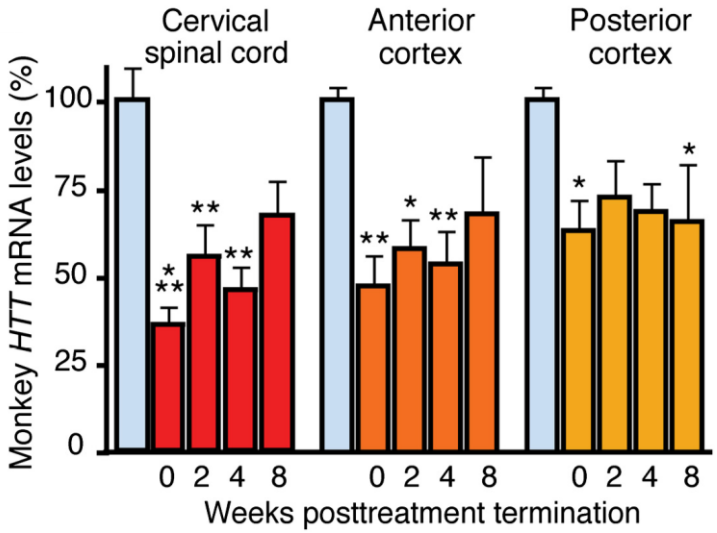


Kordasiewicz et al, 2012

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