

# Clinical research studies in Huntington Disease—Part 2

Gene based strategies

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# Introduction

- How the HD gene causes the disease
- Challenges of genetic approaches to treatment
- What is possible to be done to fix the problem
- An overview of what new gene associated treatments involve
- Timelines
- Summary

# The WFU HD Team: Jessica Bargoil, Vicki Hunt RN, Christine O'Neill (and Summer Harris)

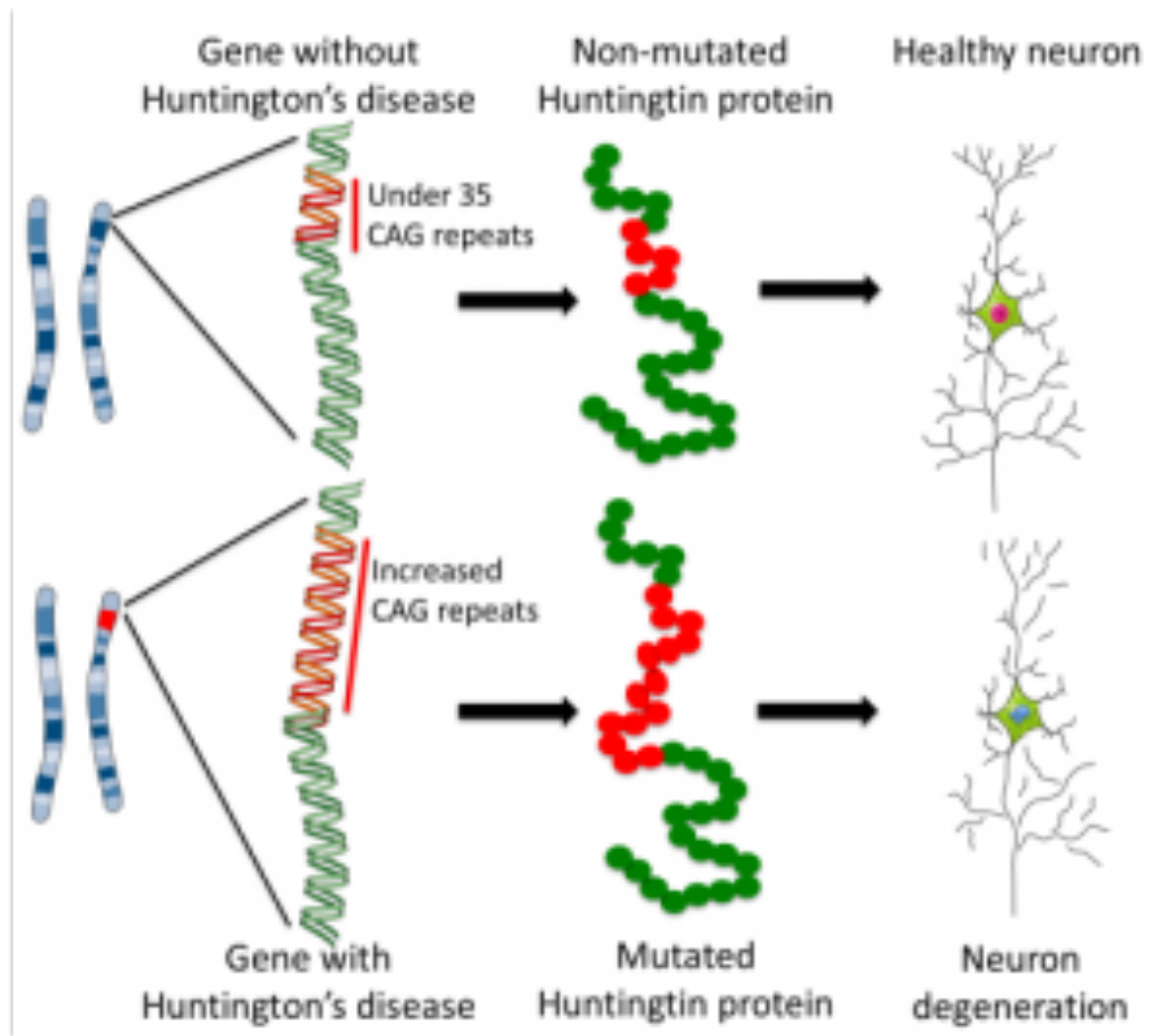


# What causes HD?

- The gene for huntingtin has an expansion of CAG repeats
- CAG codes for the amino acid glutamine
- As a result, the the huntingtin protein has an extra long stretch of glutamines (called a polyglutamine strand).

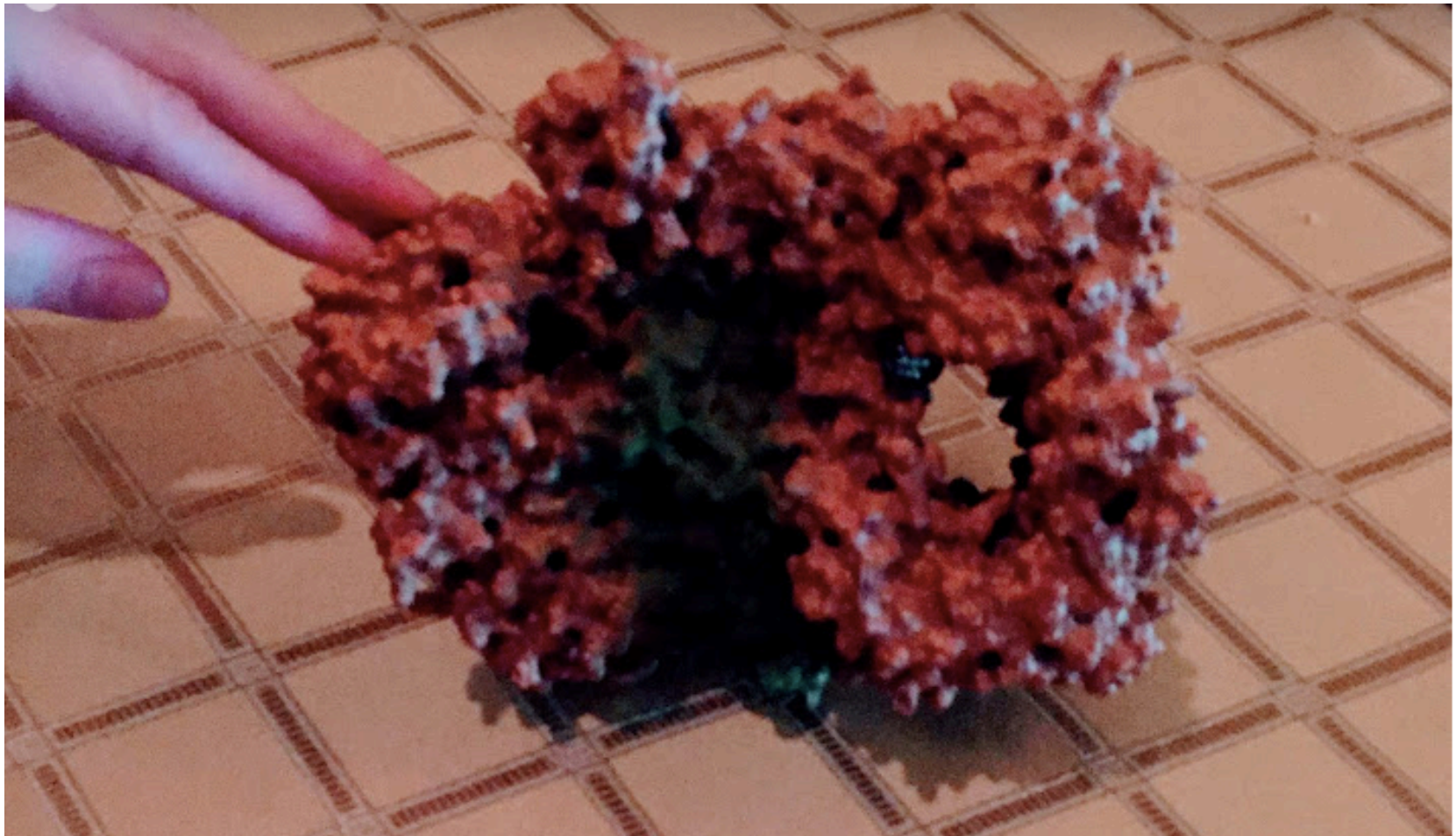
# Expanded polyglutamines in HD

Expanded  
trinucleotide  
repeat disorder

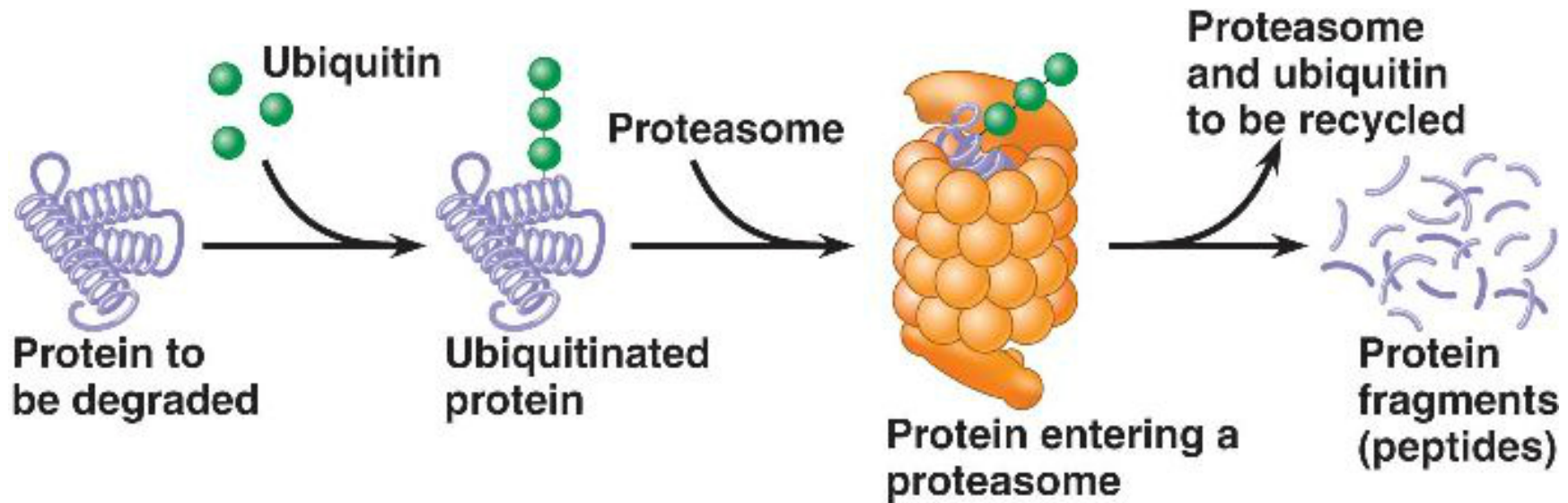




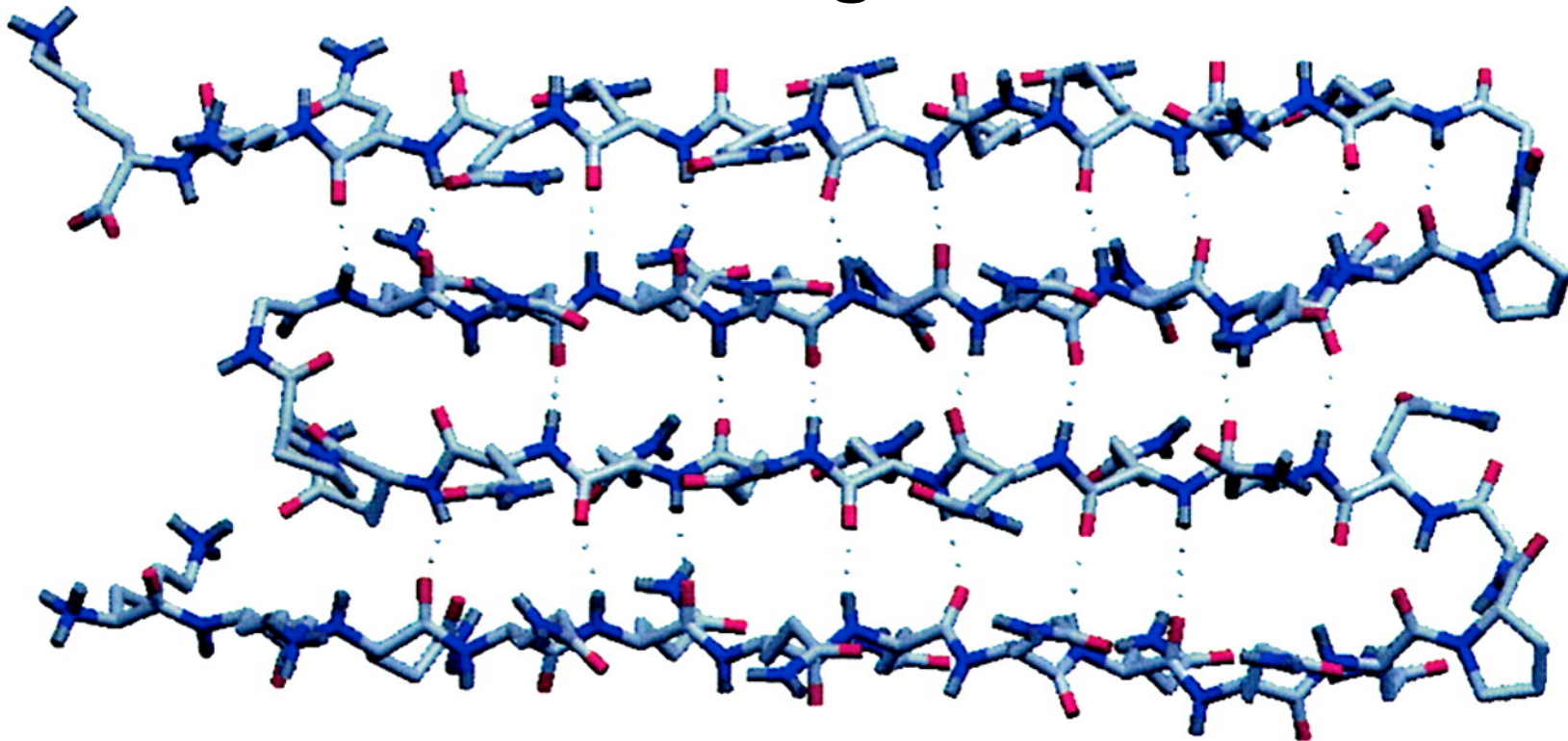
3-D model of huntingtin protein—note  
the extra strand does not hurt the  
function of this protein



Eventually, all old proteins go to the recycling bin)—which spits out little bits of the broken down protein



**One of these bits is the polyglutamine chain—which when it is of a certain length—becomes a problem—it starts to fold and tangle**



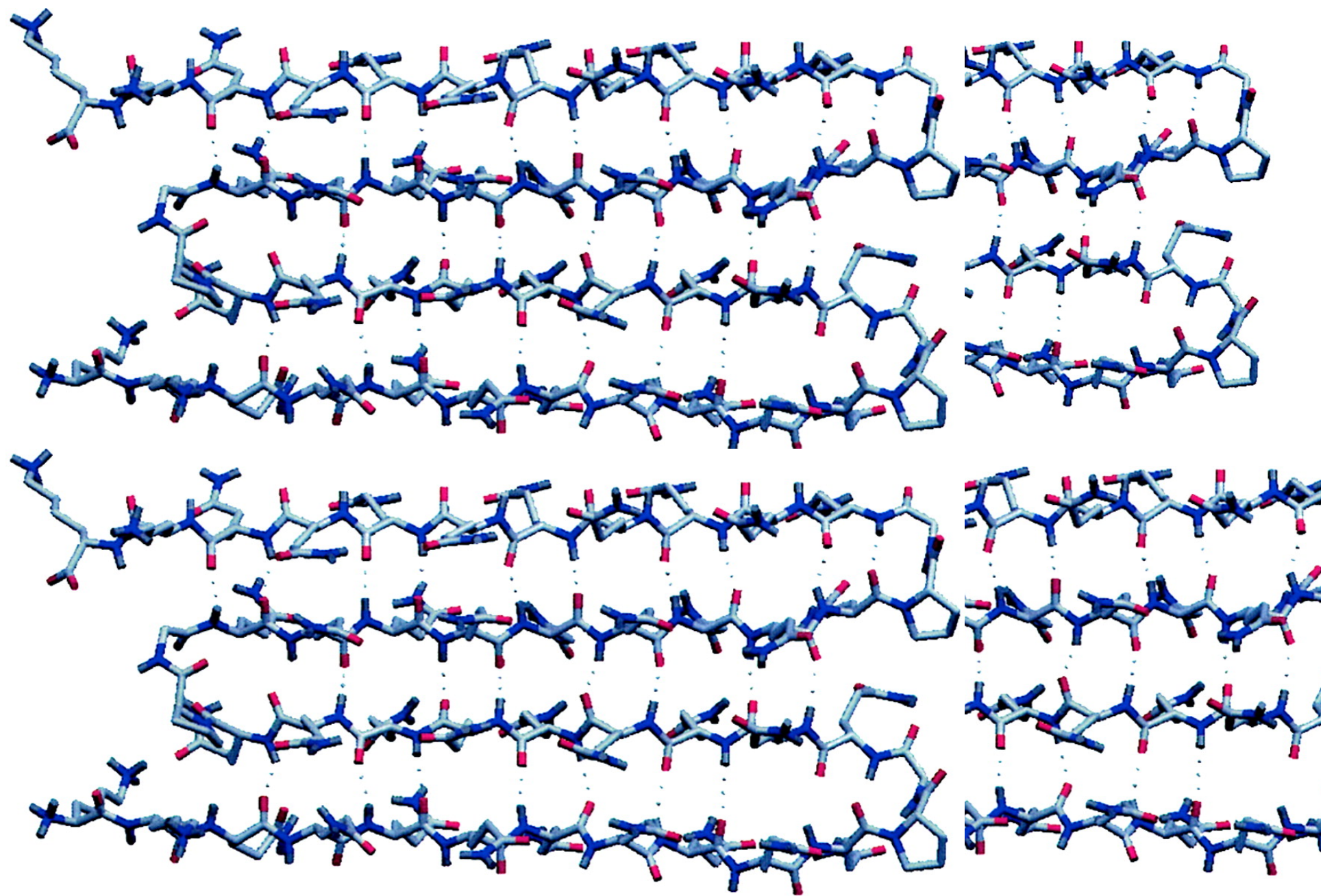
Christopher A. Ross et al. PNAS 2003;100:1:1-3

PNAS



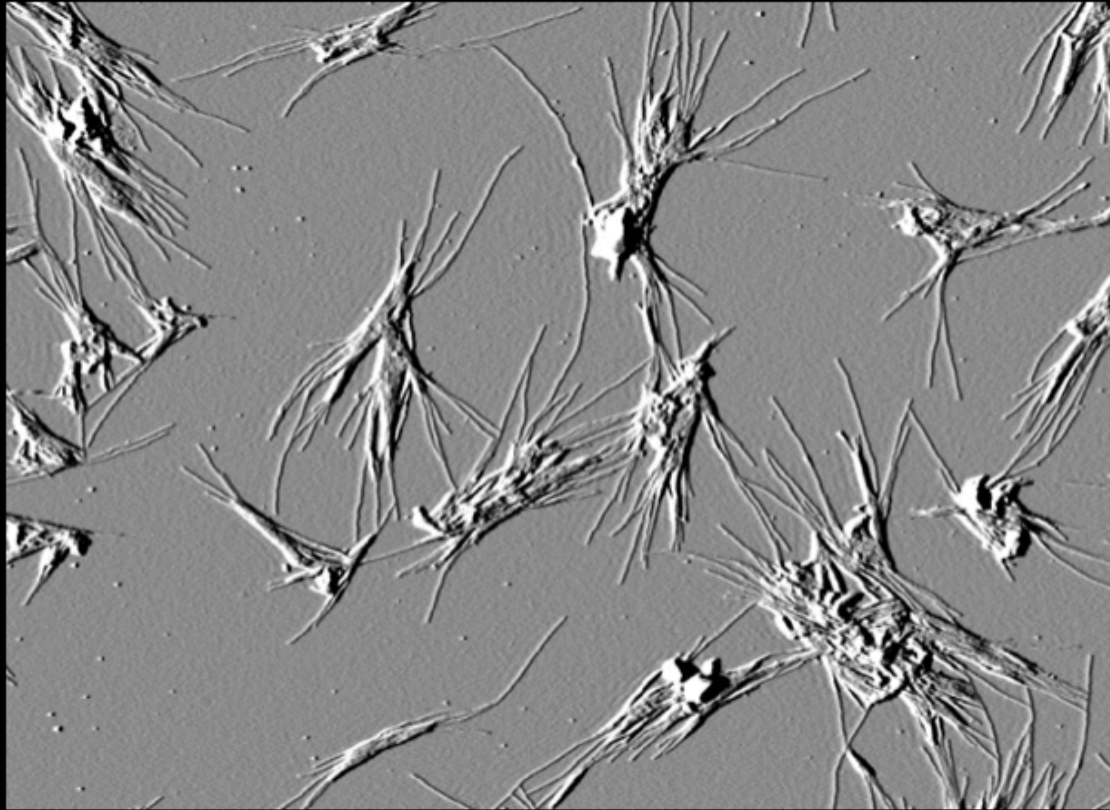
There is such a thing as one too many!





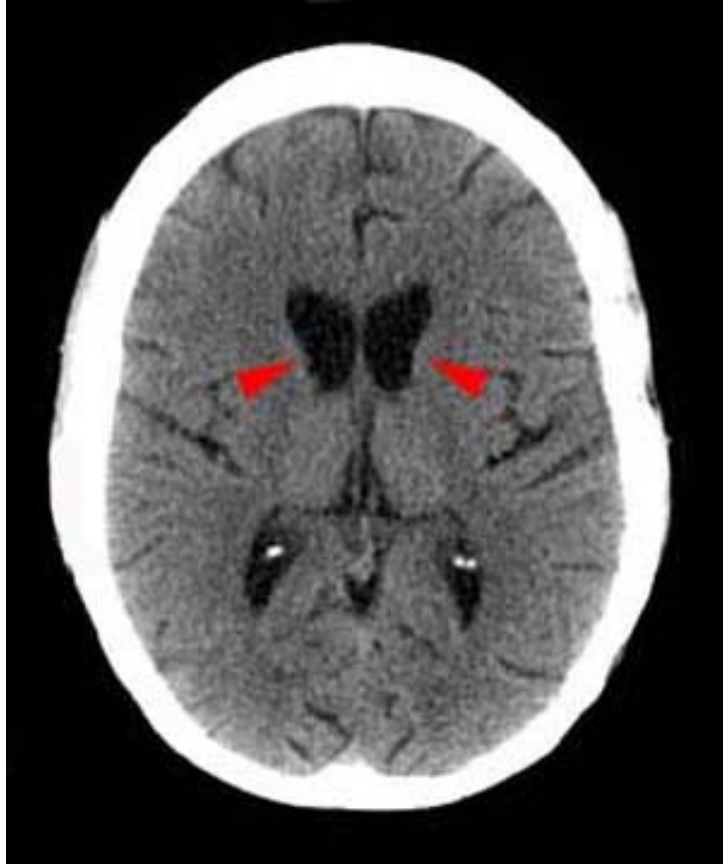


These are what polyglutamine clumps look like—and they float around, get sticky and accumulate in brain cells



On Professor Pappu's website — <http://pappulab.wustl.edu> — he features the above graphic, which

Eventually, polyglutamines cause damage



What can we do about this?

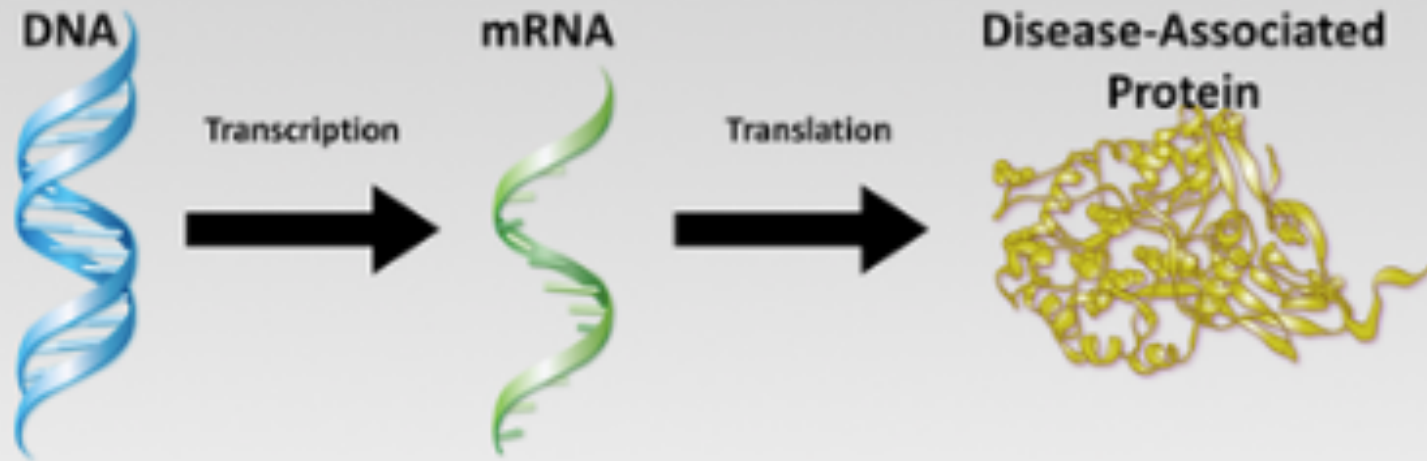


# Challenges of Gene based treatments

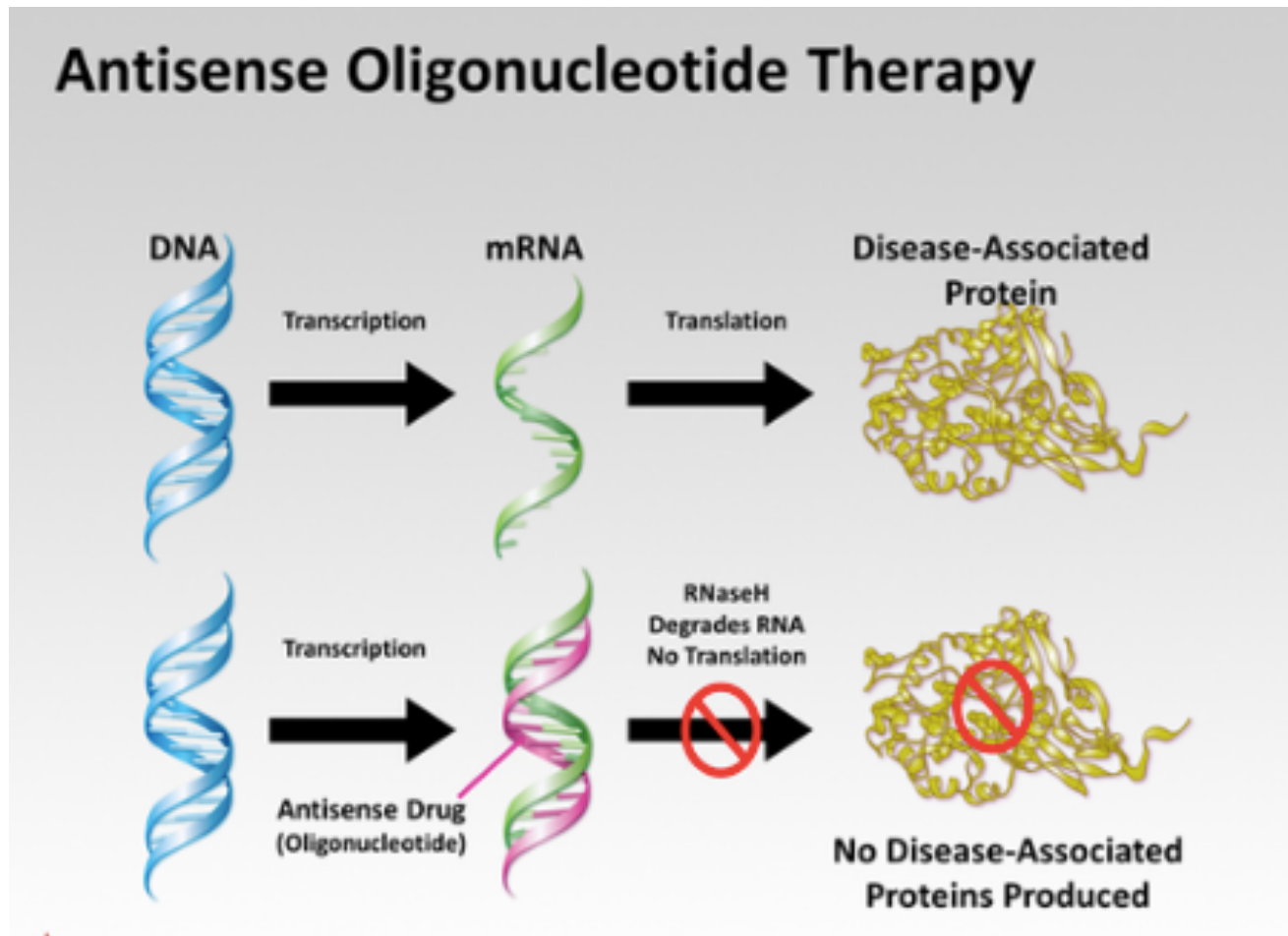
- These approaches are so new we have limited experience with them
  - Much of drug development is follow the leader
  - A lot is yet to be learned about safety and efficacy
- Getting the drug where it is needed.
- Getting treatments to work and in the right amount without side effects

So, how do we fix the problem of HD?

## Disease-Associated Protein Expression



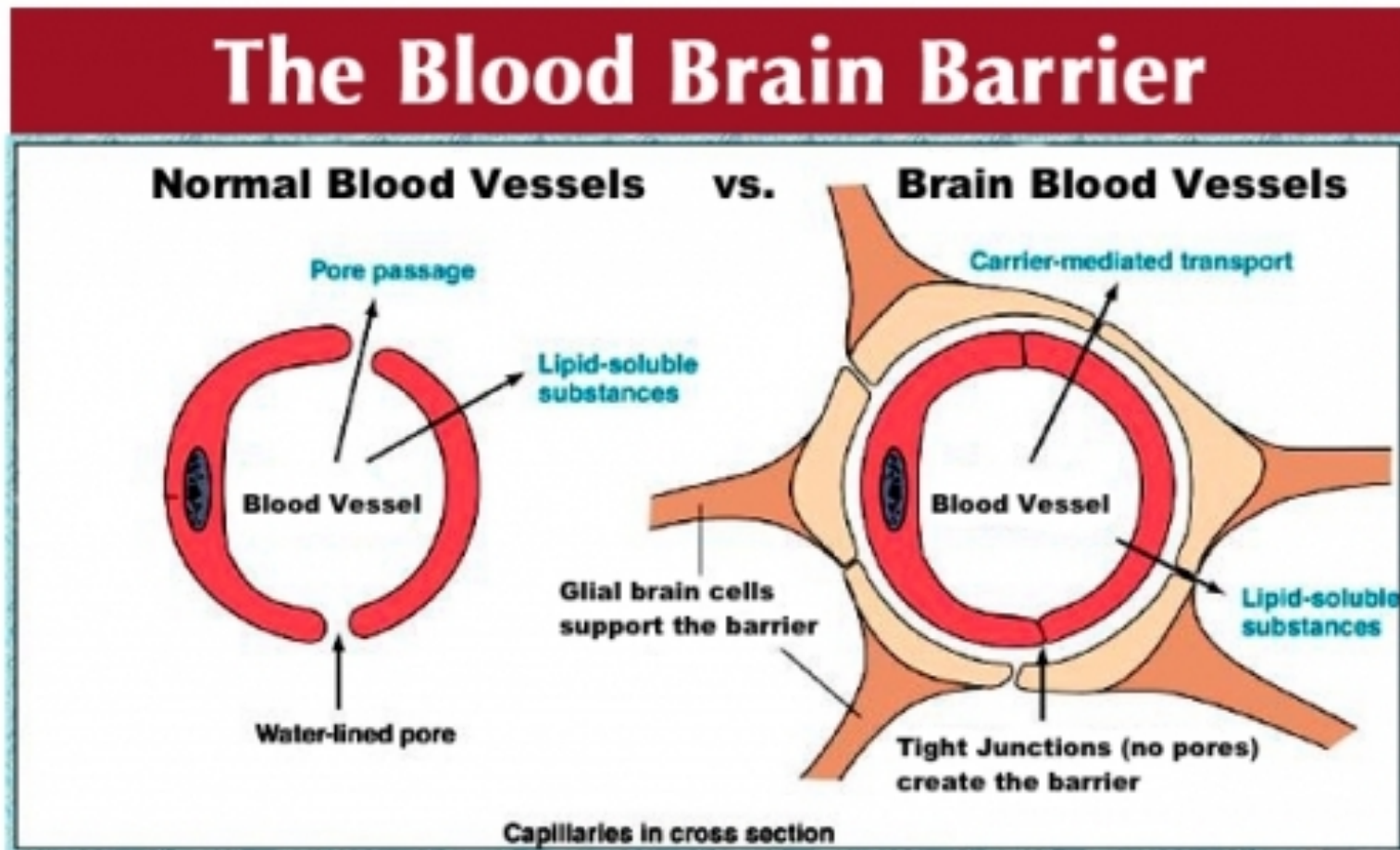
By blocking or reducing the creation of  
the mutant HD protein



# Blocking RNA

- There are now ways to do this with the magic of chemistry!
  - Create harmless but complementary micro-RNA strands to huntingtin RNA (Uniquore/Voyager)
  - Create small oligonucleotides that bind to huntingtin RNA. (Roche-Ionis/Wave)

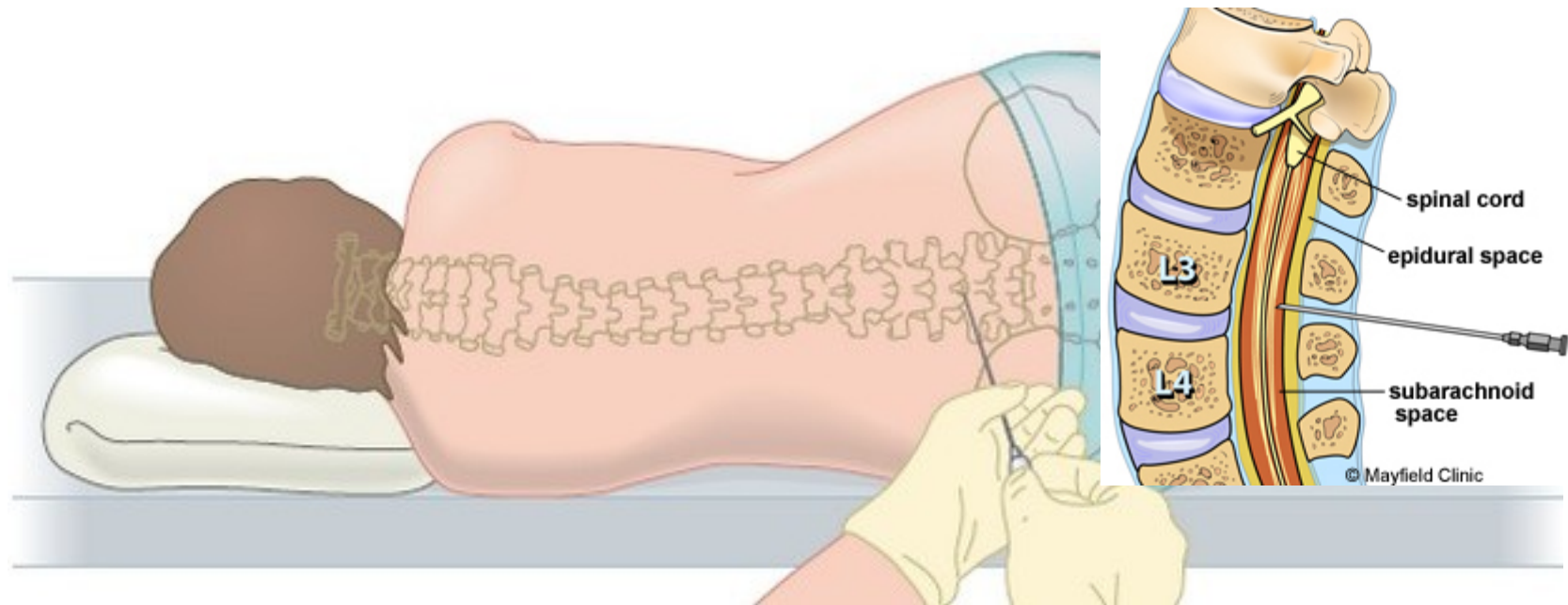
The blood brain barrier is designed to keep big molecules out of the brain



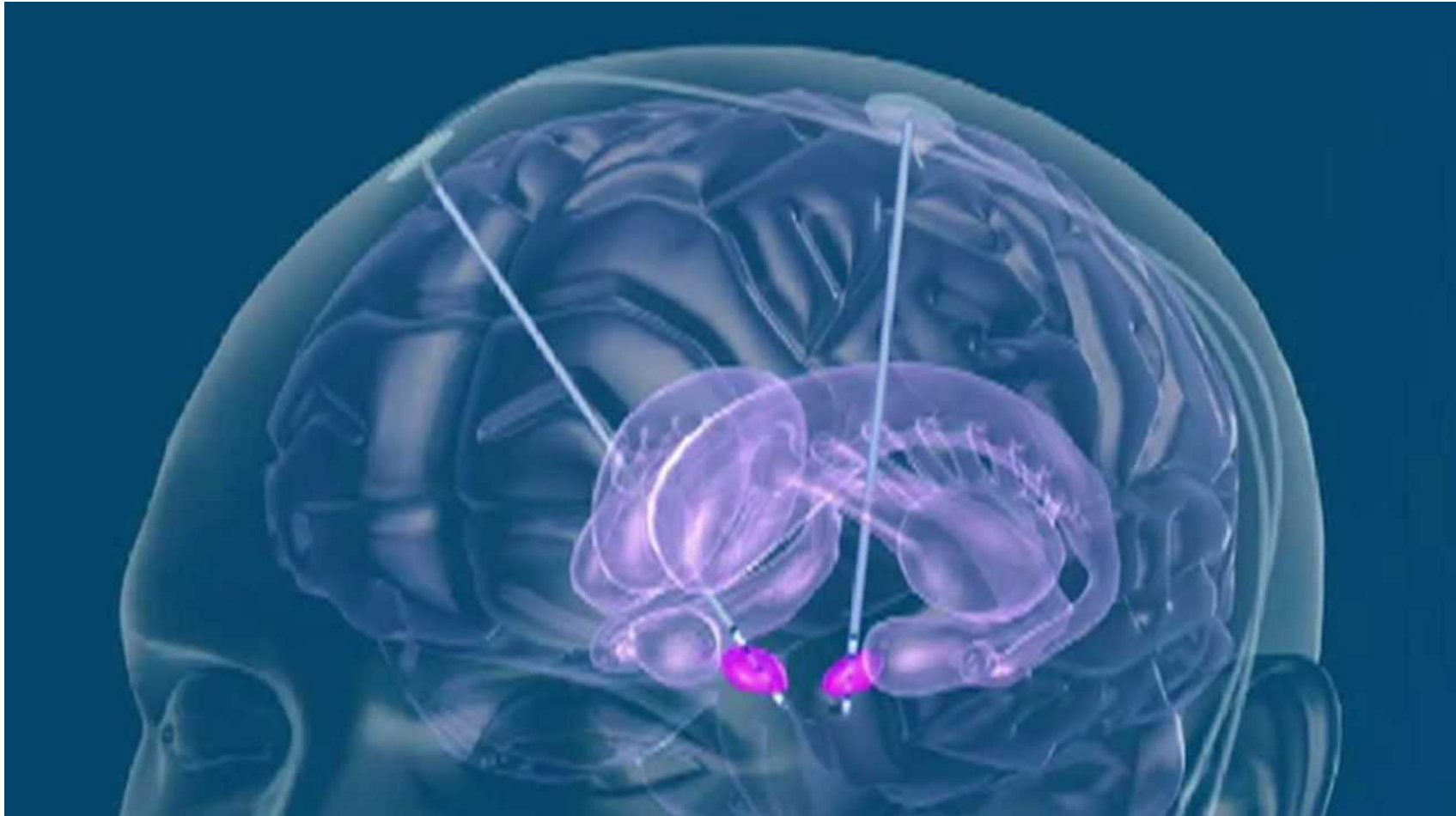


How do you get around the blood  
brain barrier?

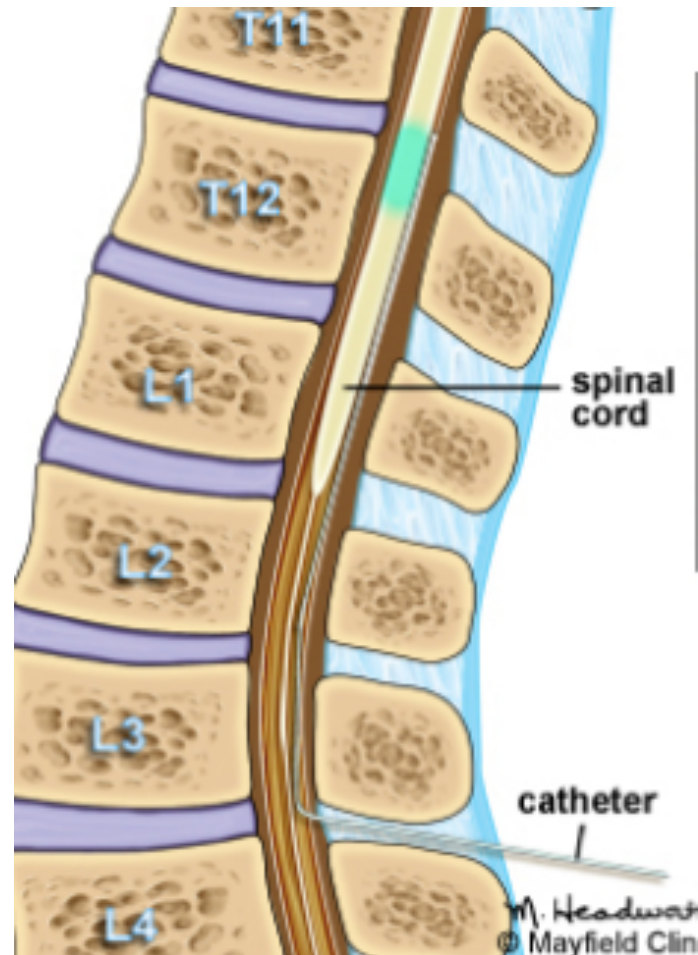
# Lumbar puncture: Spinal tap

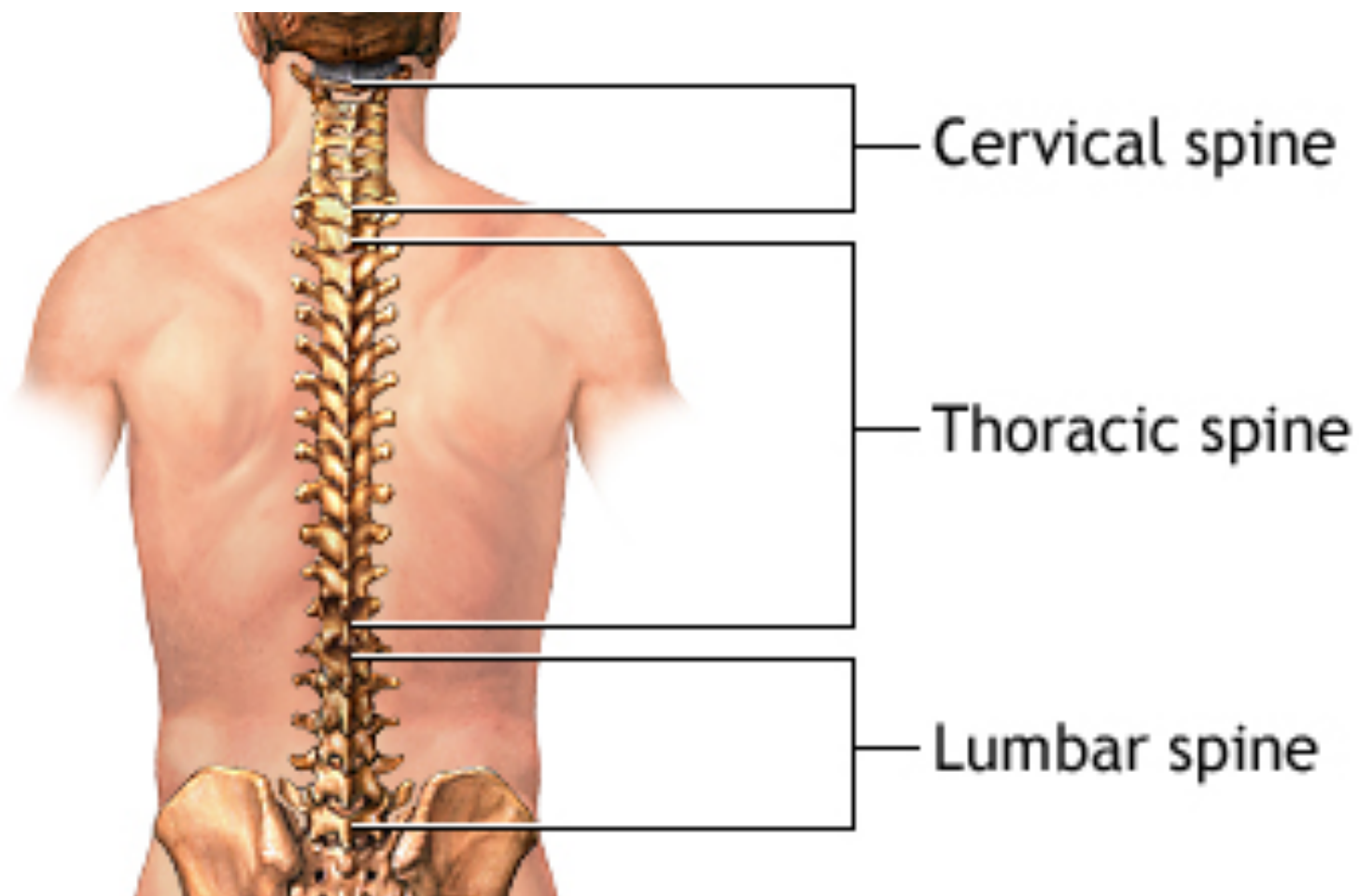


Or, direct injection into the brain



Administering therapy—Roche-Ionis/  
Wave—every 1-3 months (?)



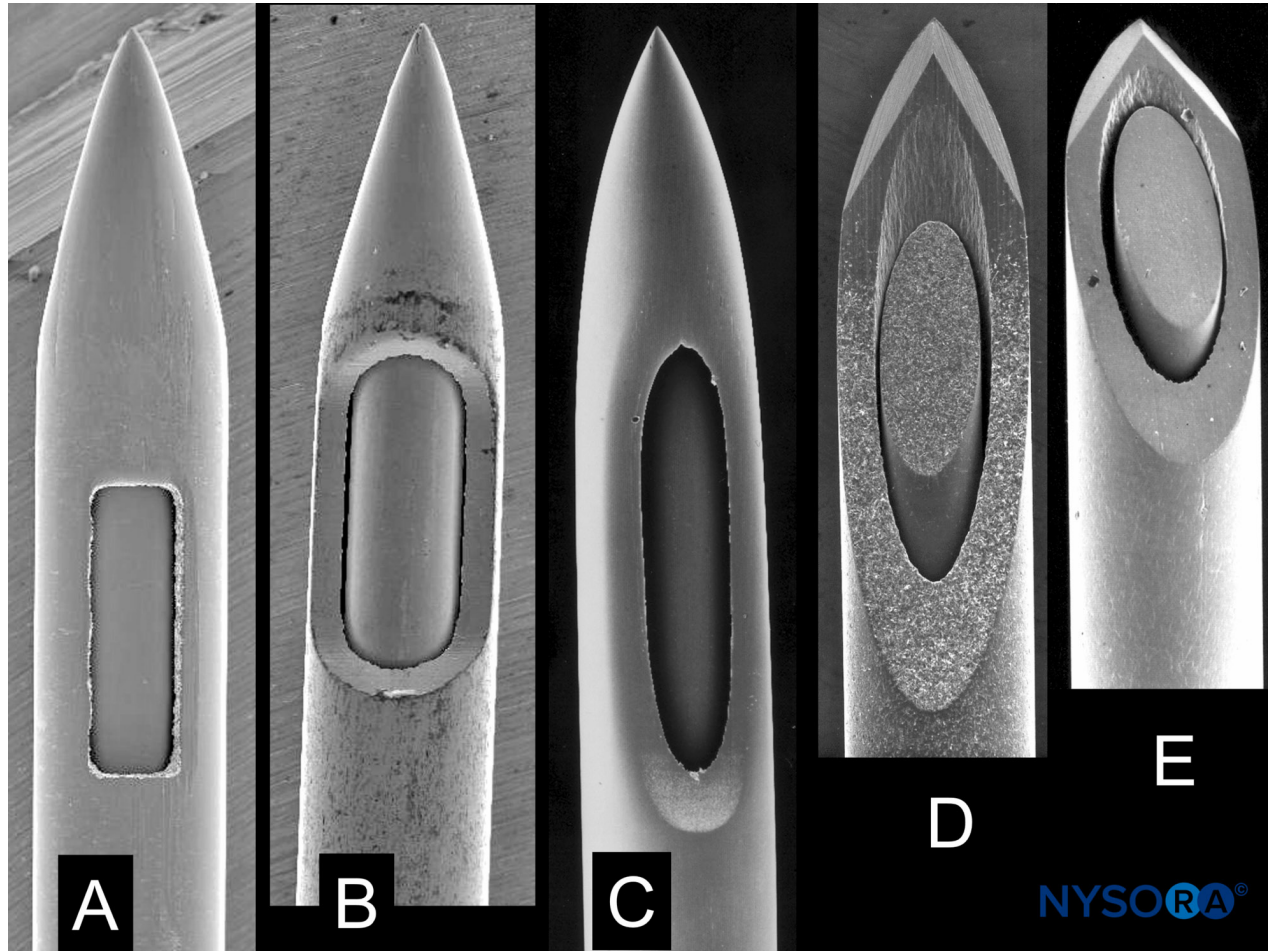




# Two risks of lumbar puncture

- Bruising/discomfort
- Spinal headache (rare, but problematic)
- Like getting an epidural for pregnancy or spinal anesthesia for a hernia repair
- One possible limitation: will the treatment spread sufficiently to cover the entire brain?

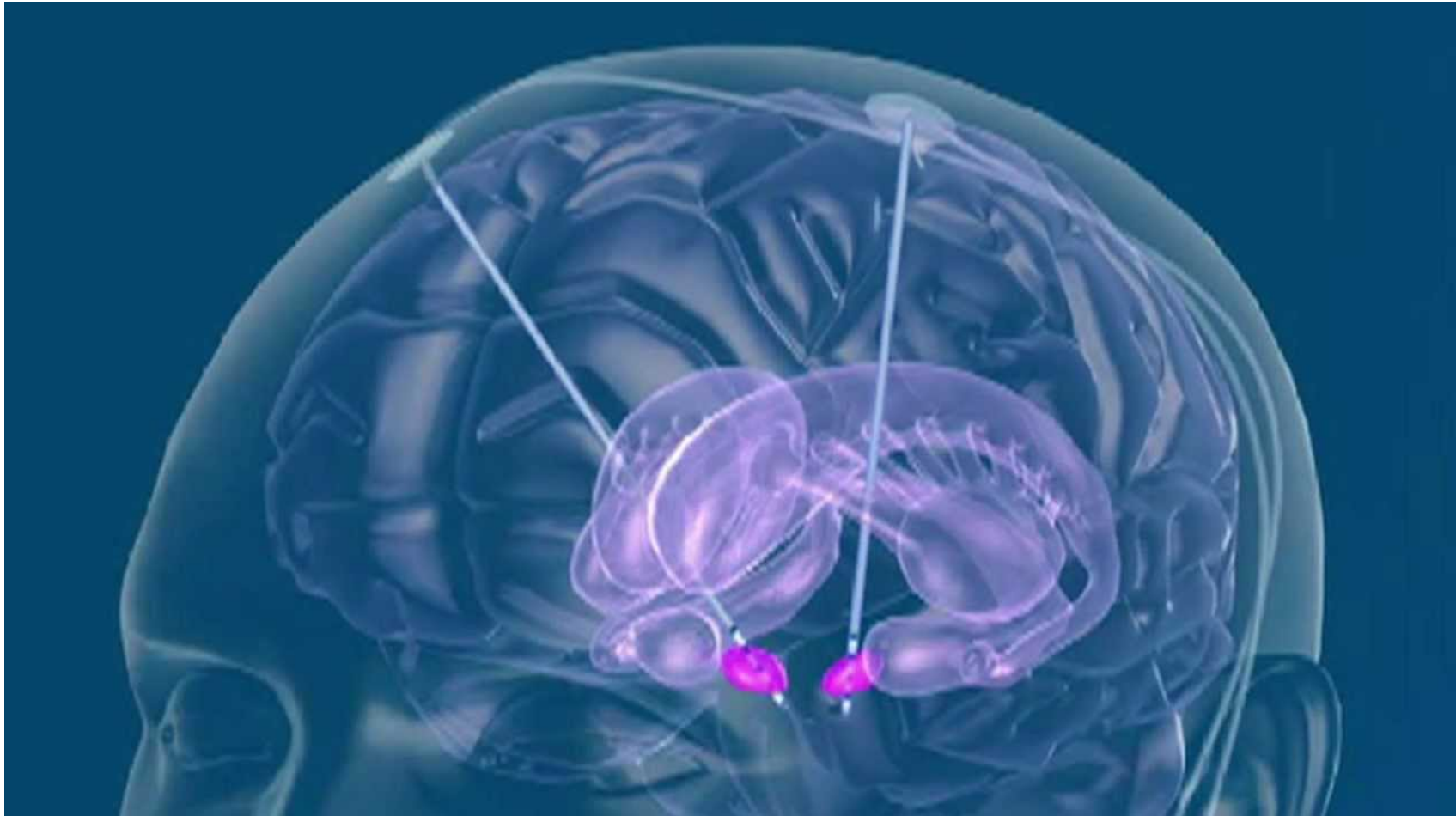
# Needles for Lumbar puncture



# Treatments minimize the risk of these problems

- Lots of local anesthetic to minimize discomfort
- Very tiny needles
- Use of special needle design to minimize headache

Or, direct injection into the brain



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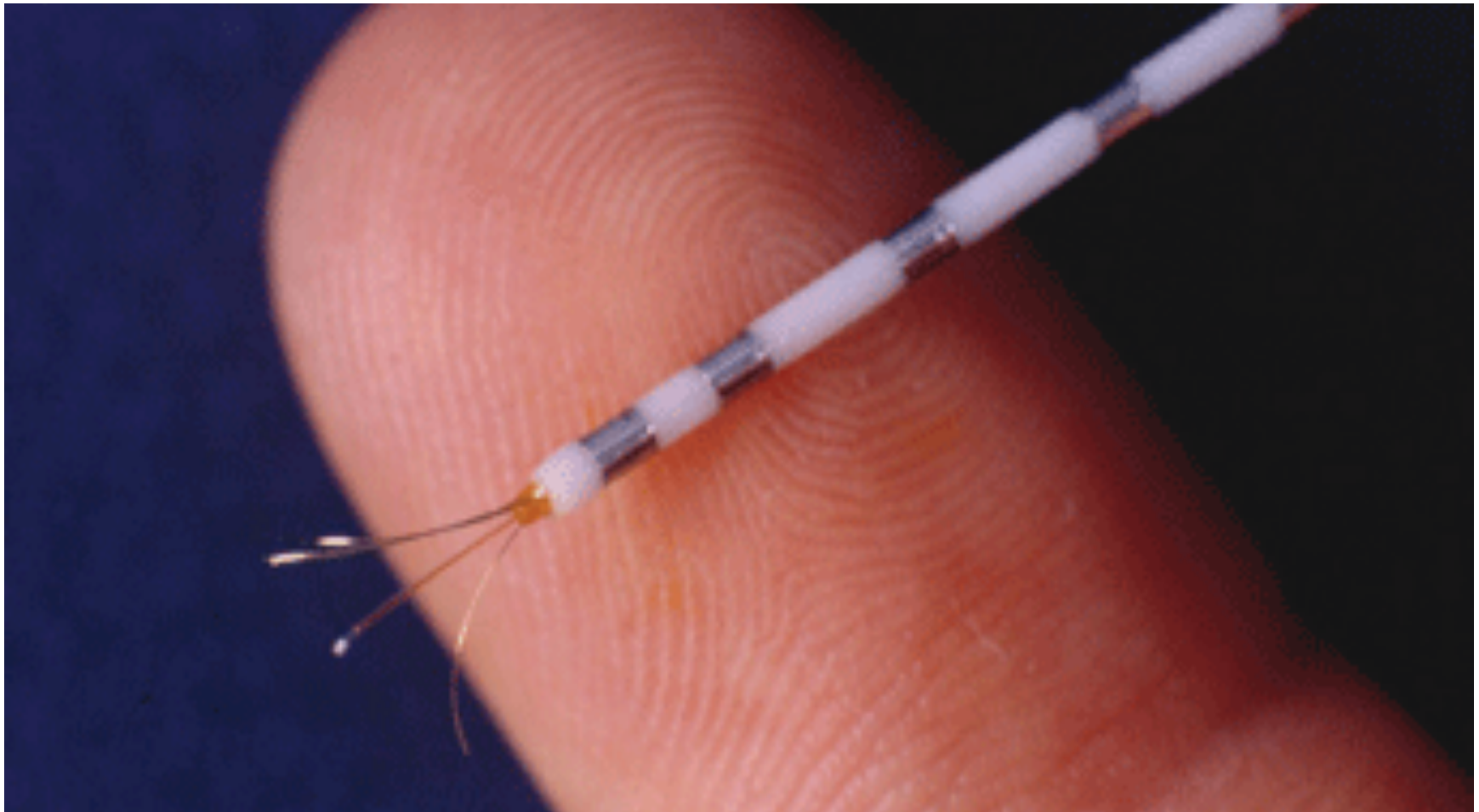
Fast track — Articles

## AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial

Prof Peter A LeWitt MD <sup>a</sup>, Prof Ali R Rezai MD <sup>b</sup>, Prof Maureen A Leehey MD <sup>c</sup>, Steven G Ojemann MD <sup>c</sup>, Alice W Flaherty MD <sup>d</sup>, Emad N Eskandar MD <sup>d</sup>, Sandra K Kostyk MD <sup>b</sup>, Karen Thomas DO <sup>b</sup>, Atom Sarkar MD <sup>b</sup>, Mustafa S Siddiqui MD <sup>e</sup>, Prof Stephen B Tatter MD <sup>e</sup>, Jason M Schwalb MD <sup>f</sup>, Kathleen L Poston MD <sup>g</sup>, Jaimie M Henderson MD <sup>g</sup>, Prof Roger M Kurlan MD <sup>h</sup>, Irene H Richard MD <sup>h</sup>, Lori Van Meter MS <sup>i</sup>, Christine V Sapan PhD <sup>j</sup> ... Dr Andrew Feigin MD <sup>l</sup>✉



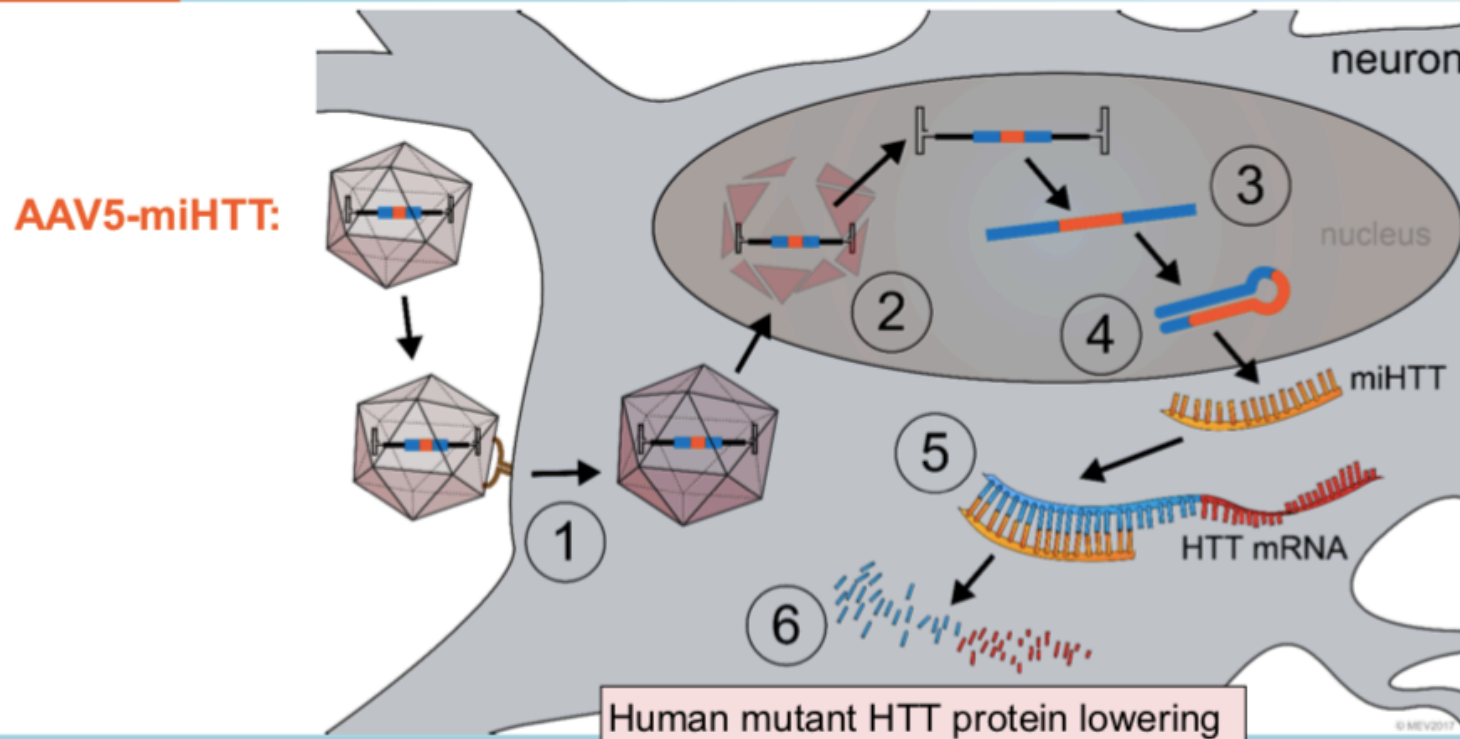
Electrodes inserted into brain for Parkinson's disease (likely for gene therapy, the cannula would be smaller)



# Approach to treatment in HD

uniQure

## AAV5-miHTT Mechanism: HTT mRNA and HTT Protein Lowering



# Risks and limitations

- Brain surgery
  - Shaving off hair on the head
  - Infection
  - Damaging a blood vessel
- 
- One limitation: Will it spread throughout the brain?

# So, where are things at?

- Roche—Ionis study ongoing—nearest site is Vanderbilt (Nashville TN)—Phase 3 just beginning
- Anticipate about two years to get it completed **and longer** to analyze data
- Wave Life Sciences study in Phase 1-2;
  - Only a few centers involved in the USA
  - Should be about a year to determine if a Phase 3 study is needed

# Uniqure

- FDA has approved the company to design a clinical trial
  - This is in progress for Phase 1 (maybe Phase1-2)
  - Possibly by the end of 2019 they will begin site selection with enrollment in 2020
  - Voyager is perhaps 2 years behind

# Conclusions

- These are exciting times
- Lots to yet be learned about safety of gene therapy
- Other drugs for HD, possibly with less risk of administration, are on the horizon
- Results of current other studies (e.g. Signal) are anticipated before too long



# Conclusions

- Treatments need to balance safety with risk, so do not expect a home run at first.
- Treatments may work better in combinations
- Peoples interest in gene testing will change if treatments for Huntington's disease show promise
- Stay tuned, we anticipate big strides in the next five years!