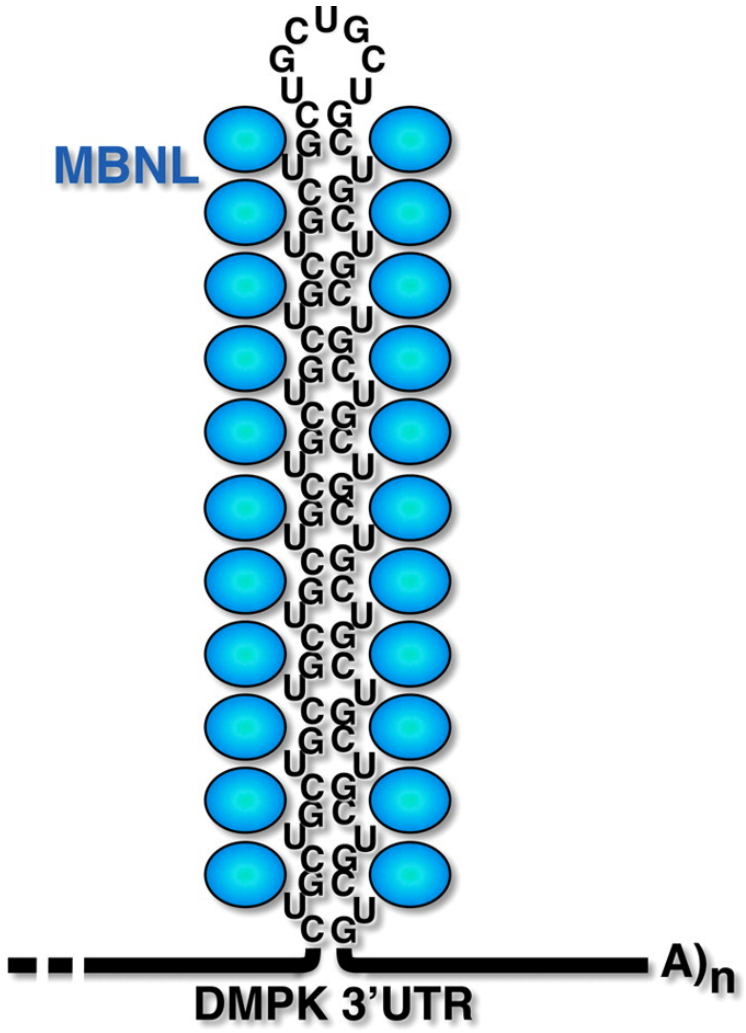
On the Verge of Fixing DM1

Some things to consider

Bruce M. Wentworth, PhD

genzyme
A SANOFI COMPANY

It's the year 2013 - we've come a long way



Cooper T A PNAS 2009;106:18433-18434

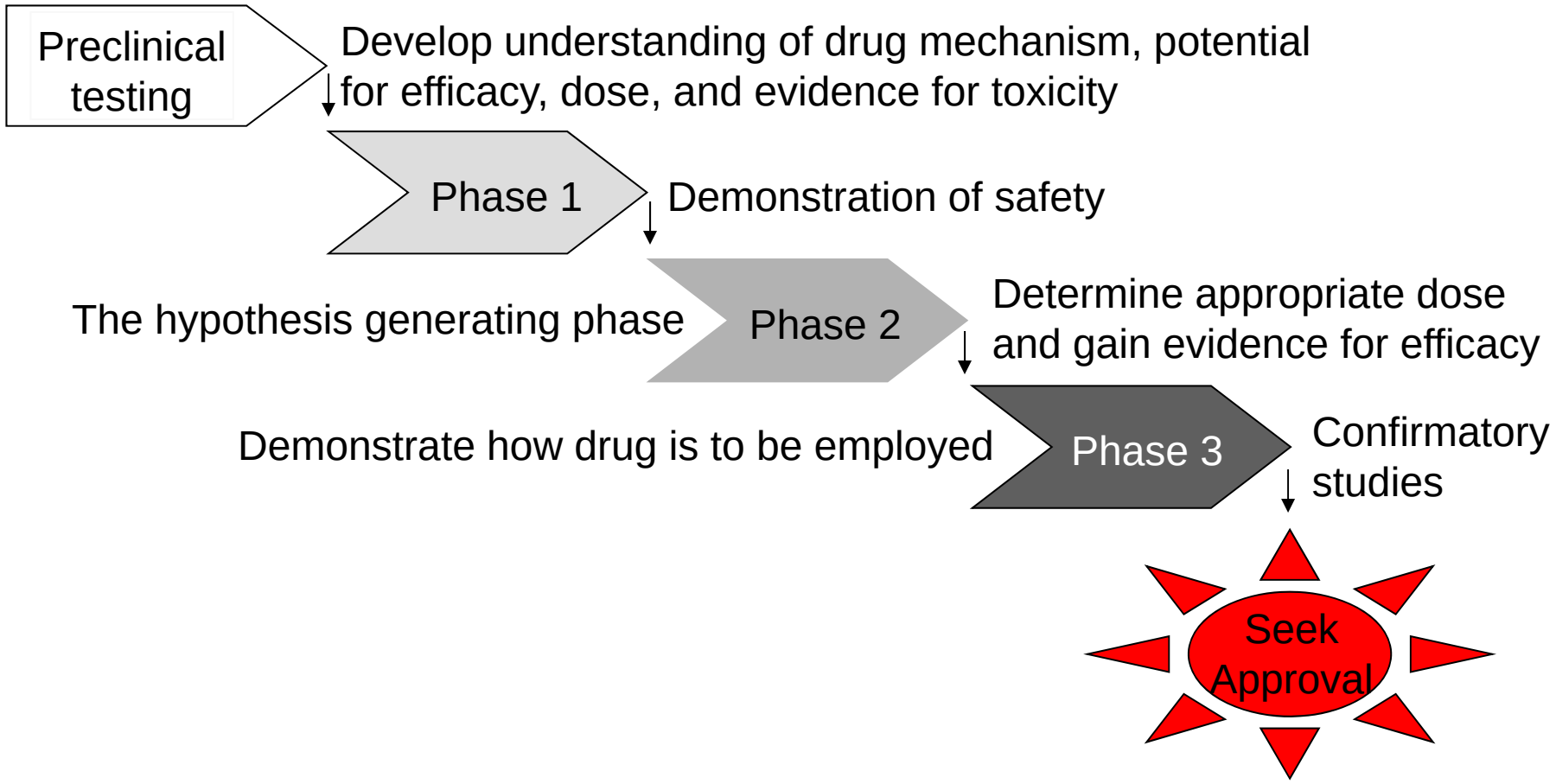
- **1909- DM1 first described**
- 1992-Mutation first described
- 1996-Proteins binding to CUG first described
- 2000-Mouse model first described as well a disease mechanism proposed
- **2002 – Toxic RNA is blamed**
- 2009 – antisense first delivered to DM1 mice i.m.
- 2012 &13 antisense first shown as plausible DM1 systemic therapy
- ***2014 first DM1 trials planned***

Some Wisdom

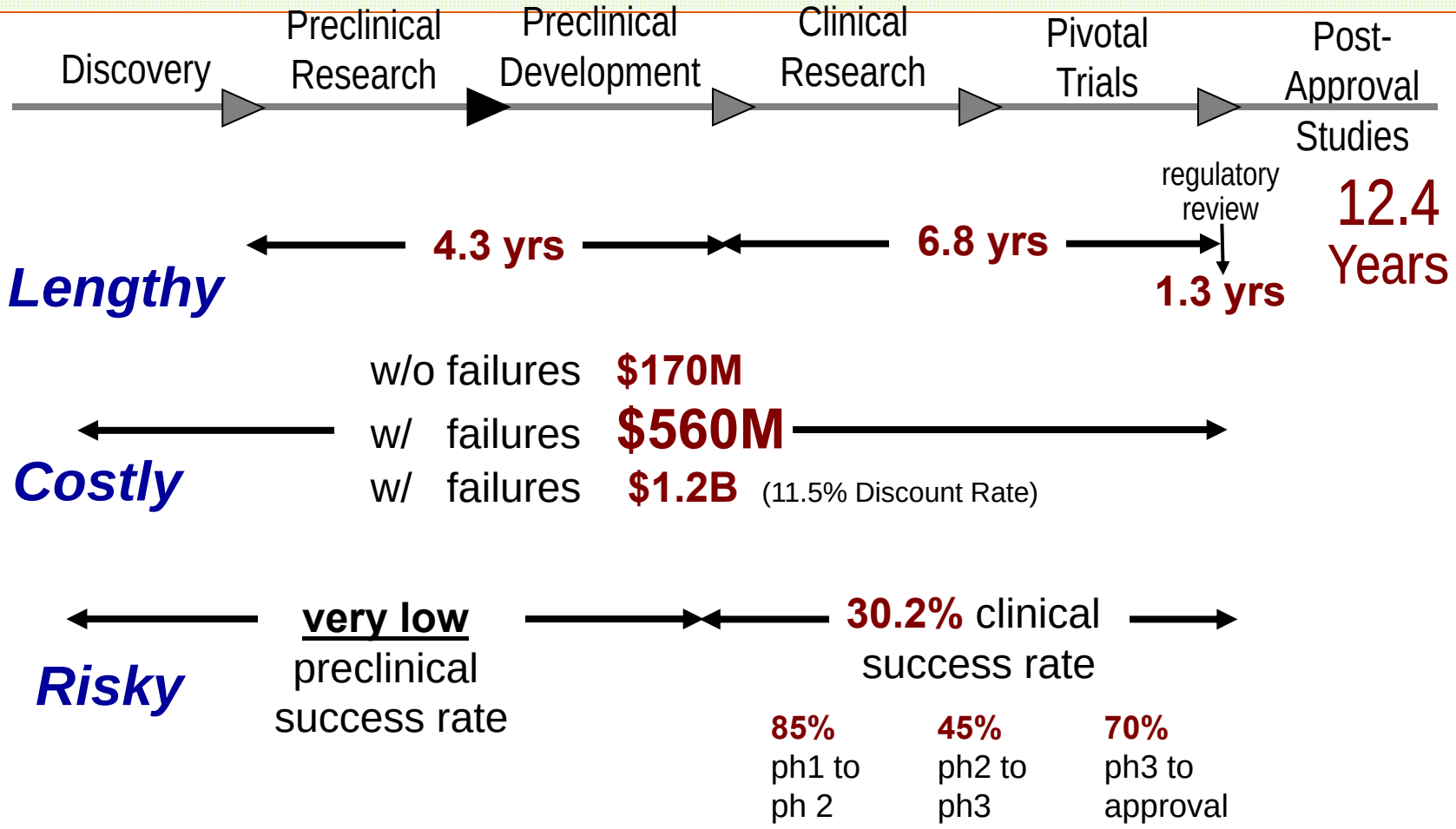
When you come to a fork in the road – take it

-Yogi Berra-

The concept of a clinical trial is simple…



However,
the reality is often very complex ...



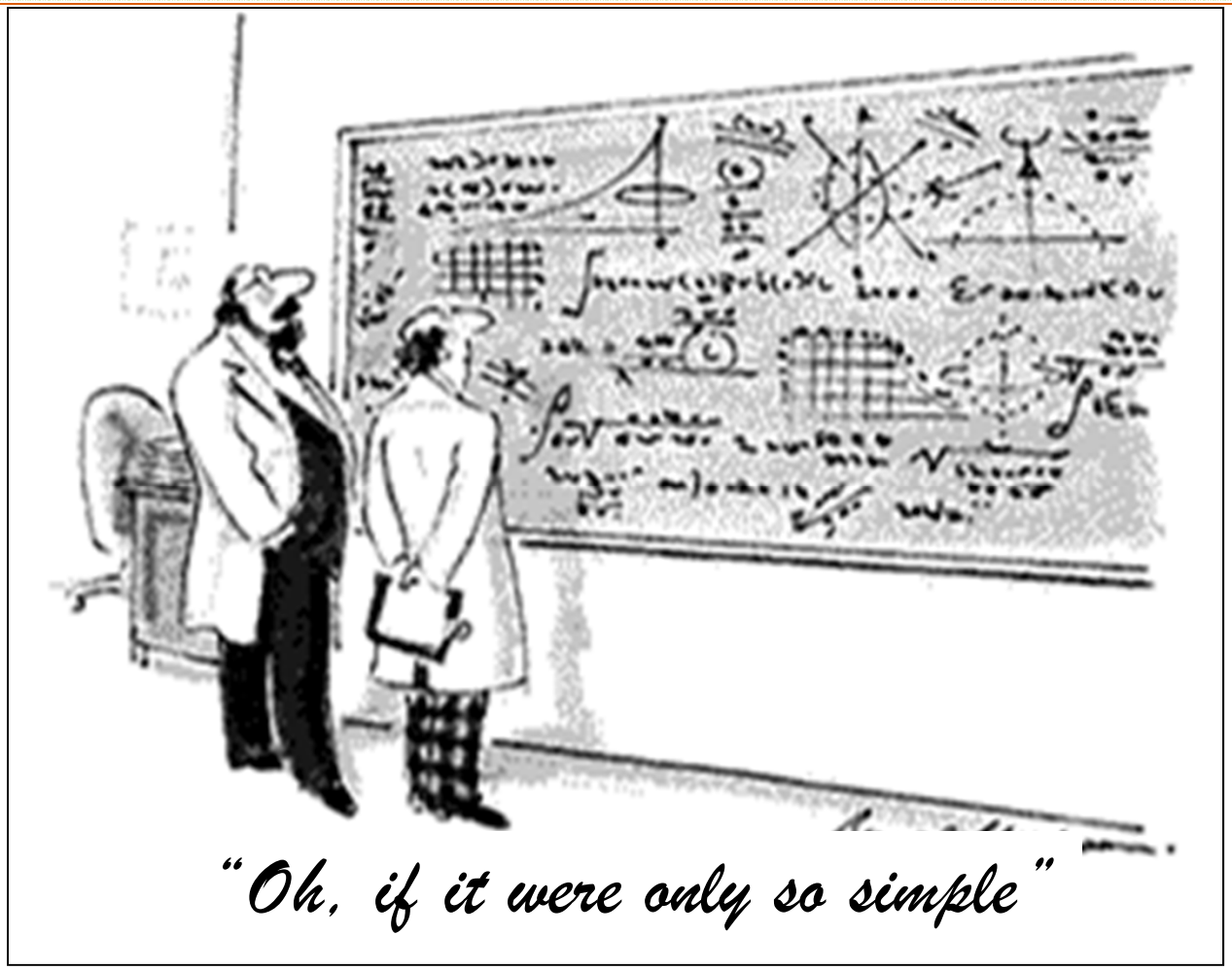
Success is rare!

Only 3 of 10 Marketed Drugs Produce Revenues ≥ Average R&D Costs

*Recent Biotechnology industry metrics, small molecule drug metrics are similar

Center for Study of Drug Development, Tufts University, 2006

Why do trials fail?



"Oh, if it were only so simple"

Because we <u>never</u> know enough!

What is a clinical trial like?

- You will be assigned to one treatment group
  - You might get the new drug
  - You might get a placebo
- You may be tested for various abilities before and after treatment
  - Maybe muscle strength
  - Or, walking ability
- You may need to give blood for testing
- You may also need to have muscle biopsies taken
- You may be asked to help with other testing related to the disease > *even if it is not part of the trial outcome*
- You will be very closely followed during and perhaps after the trial

How will we know if the drug works?

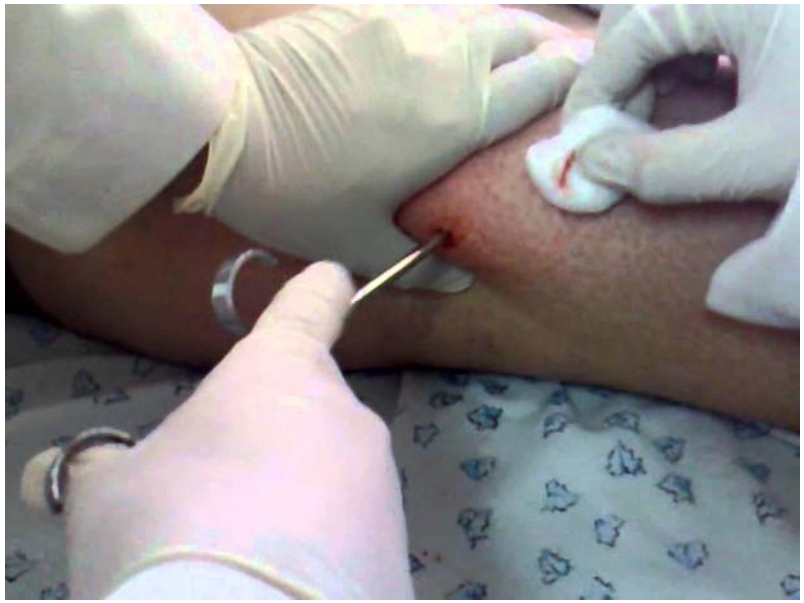
- Endpoints: An endpoint *proves* that a drug works, and makes a difference in the life of the patient

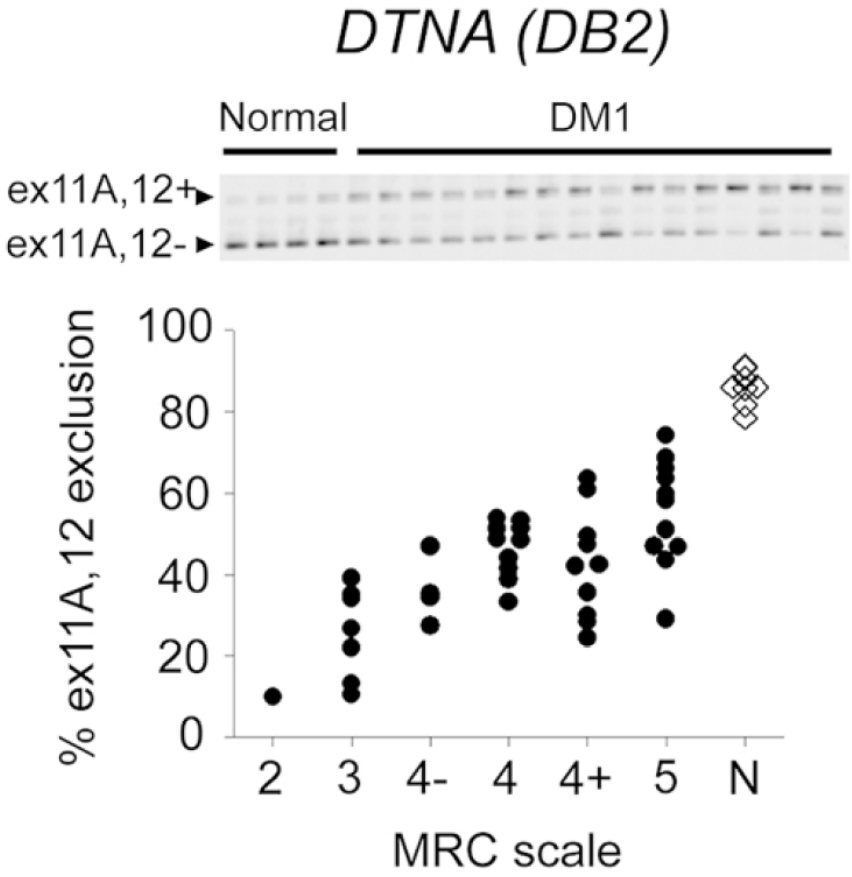
- Myotonia measurements

- Quantitative muscle testing

How will we know if the drug works?

- Biomarker: A biomarker can help by *suggesting* that a drug is working as expected





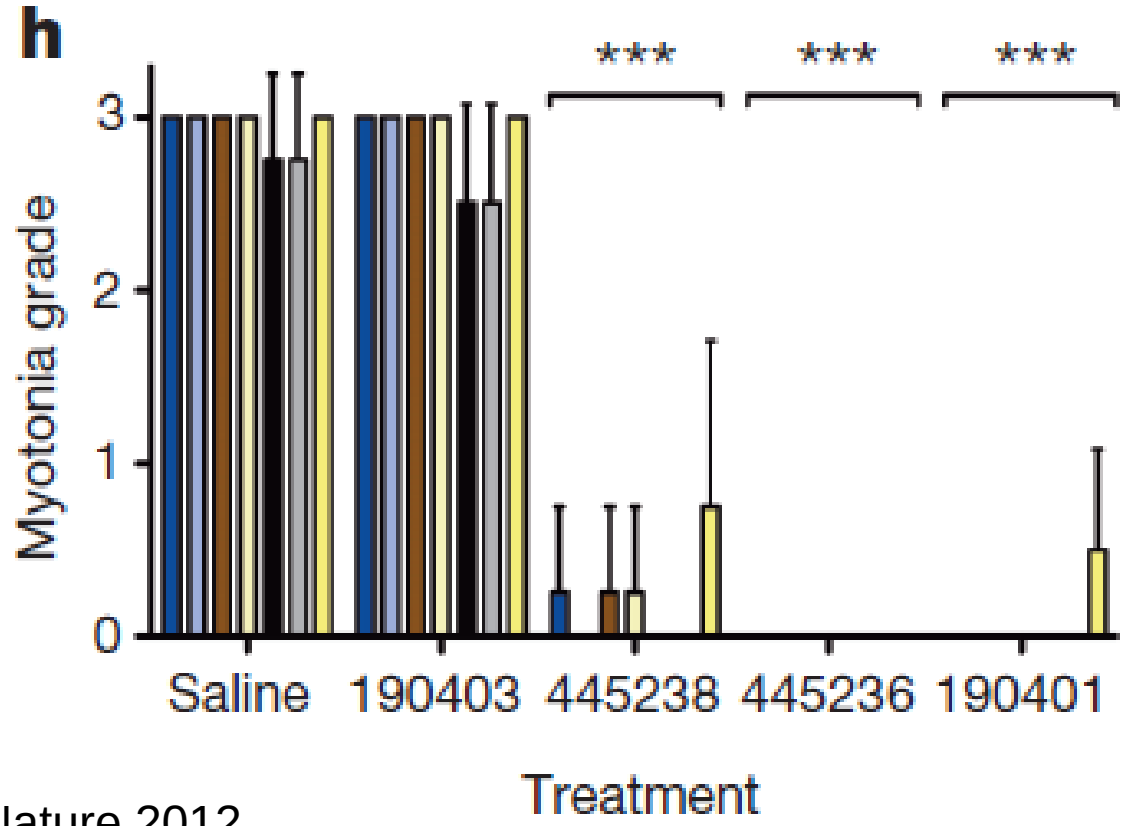
Nakamori et al 2013

LETTER

doi:10.1038/nature11362

Targeting nuclear RNA for *in vivo* correction of myotonic dystrophy

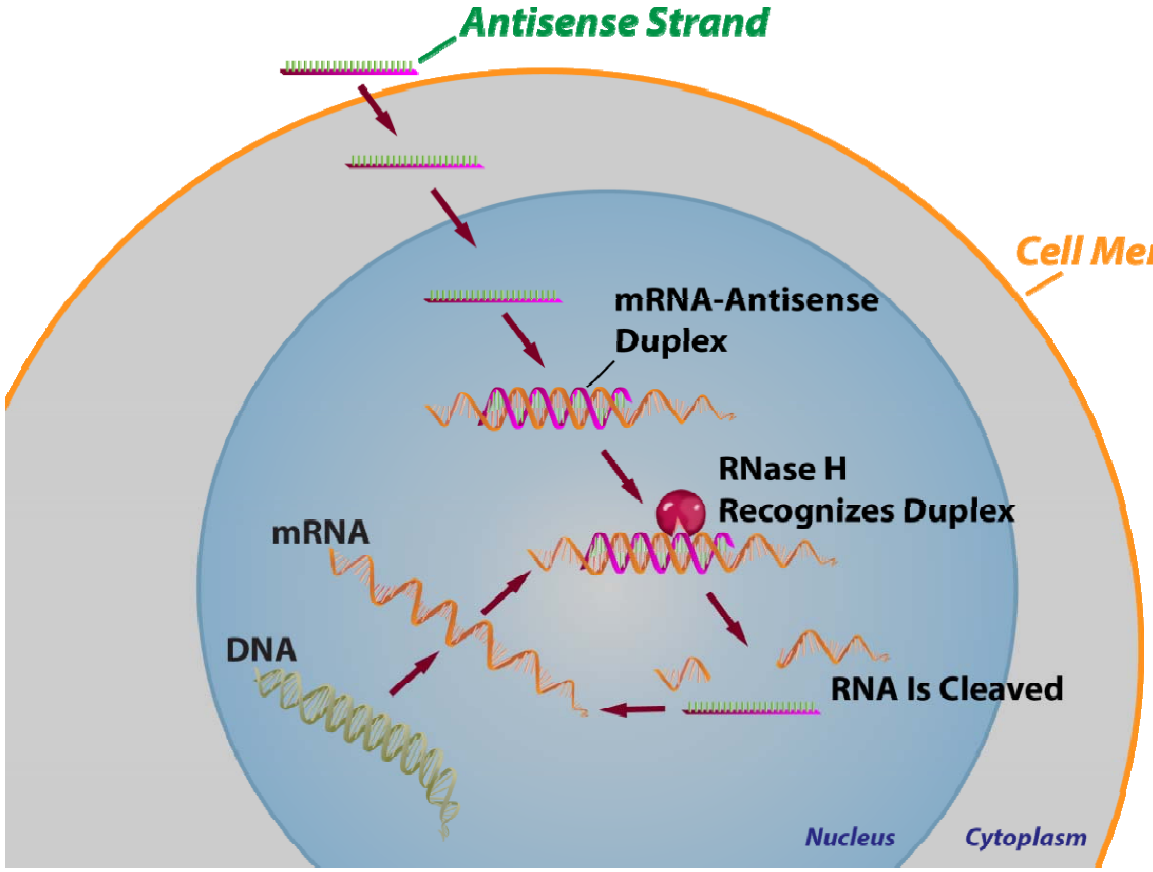
Thurman M. Wheeler[1,2], Andrew J. Leger[3], Sanjay K. Pandey[4], A. Robert MacLeod[4], Masayuki Nakamori[1,2], Seng H. Cheng[3], Bruce M. Wentworth[3], C. Frank Bennett[4] & Charles A. Thornton[1,2]



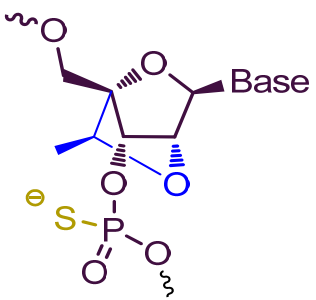
Wheeler et al Nature 2012

ISIS $DMPK_{Rx}$

- **Promotes degradation of the mutant DMPK transcript by the RNase H mechanism of action**

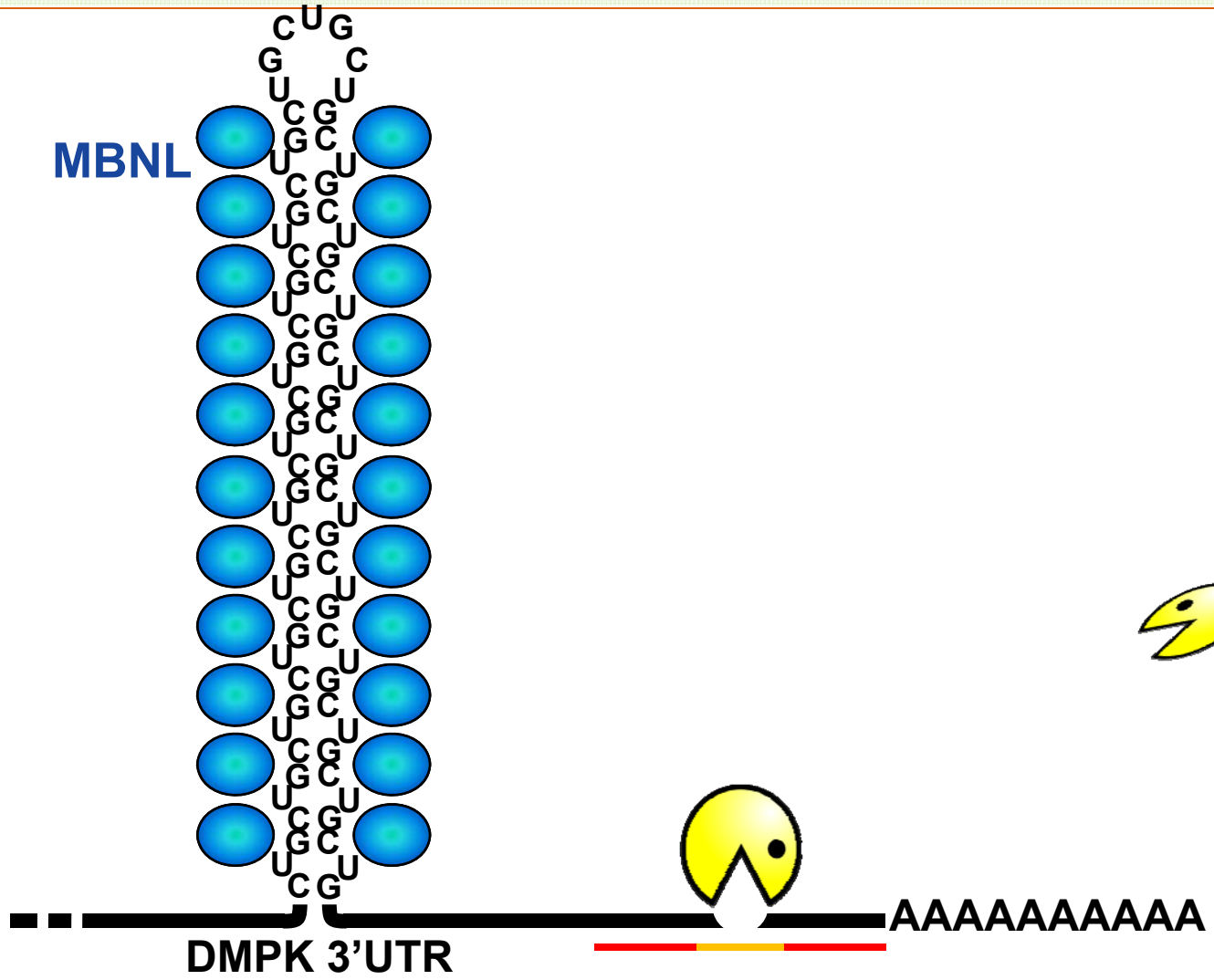


- Generation 2.5 Antisense Drug

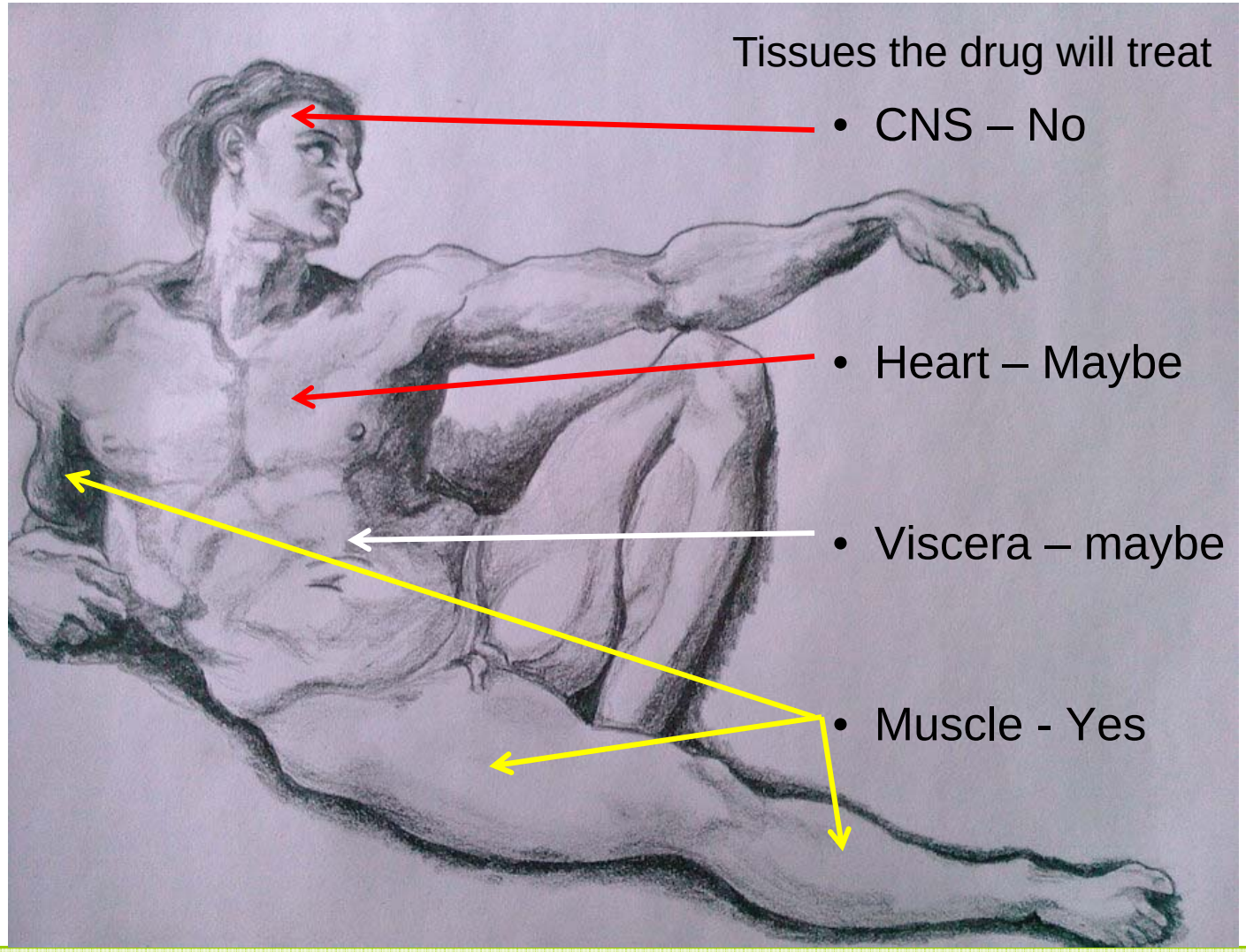


Constrained ethyl nucleotide

- **Currently in IND enabling toxicology studies**
- **If successful, first clinical trial will start in 2014**


MBNL
AAAAAAAAAA
DMPK 3'UTR

Drug strength's and weaknesses



Additional drug characteristics

- The drug being tested will be injected subcutaneously
- The drug may have a very long duration of effect
- The first trial will focus on learning if the drug is safe

A pragmatic perspective

- DM1 is complex
  - The drug under study will peel away many layers of the disease
- The CNS disease will remain
  - Exactly what that will look like is unclear

It’s the next frontier for treatment

So, its 2013 where are we?

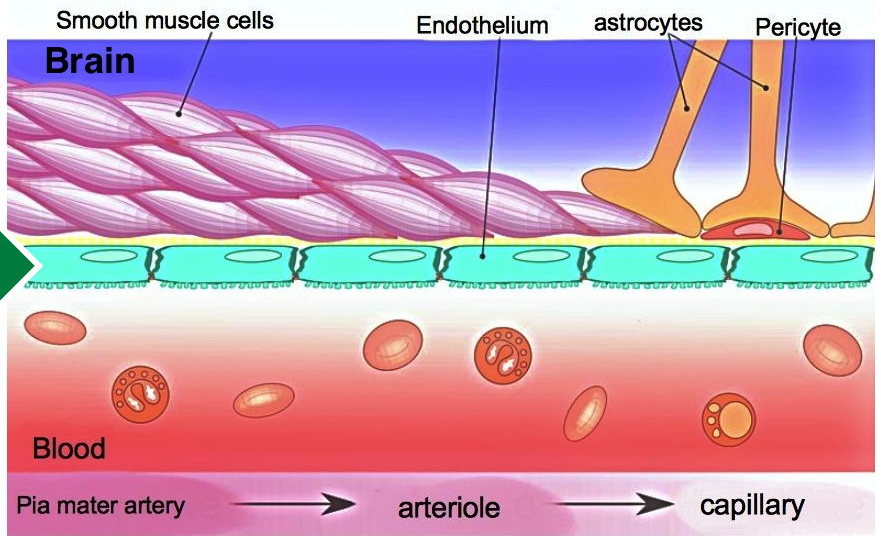
- A potentially transformative medicine is within reach
  - Fundamentally changing the disease course and/or management in clinically meaningful ways
- Ok, but, what about the CNS disease?

  Patients say it's the more significant thing in their lives

  - Treating the systemic disease will help inform us how to treat the CNS disease

Treating the CNS will be more challenging

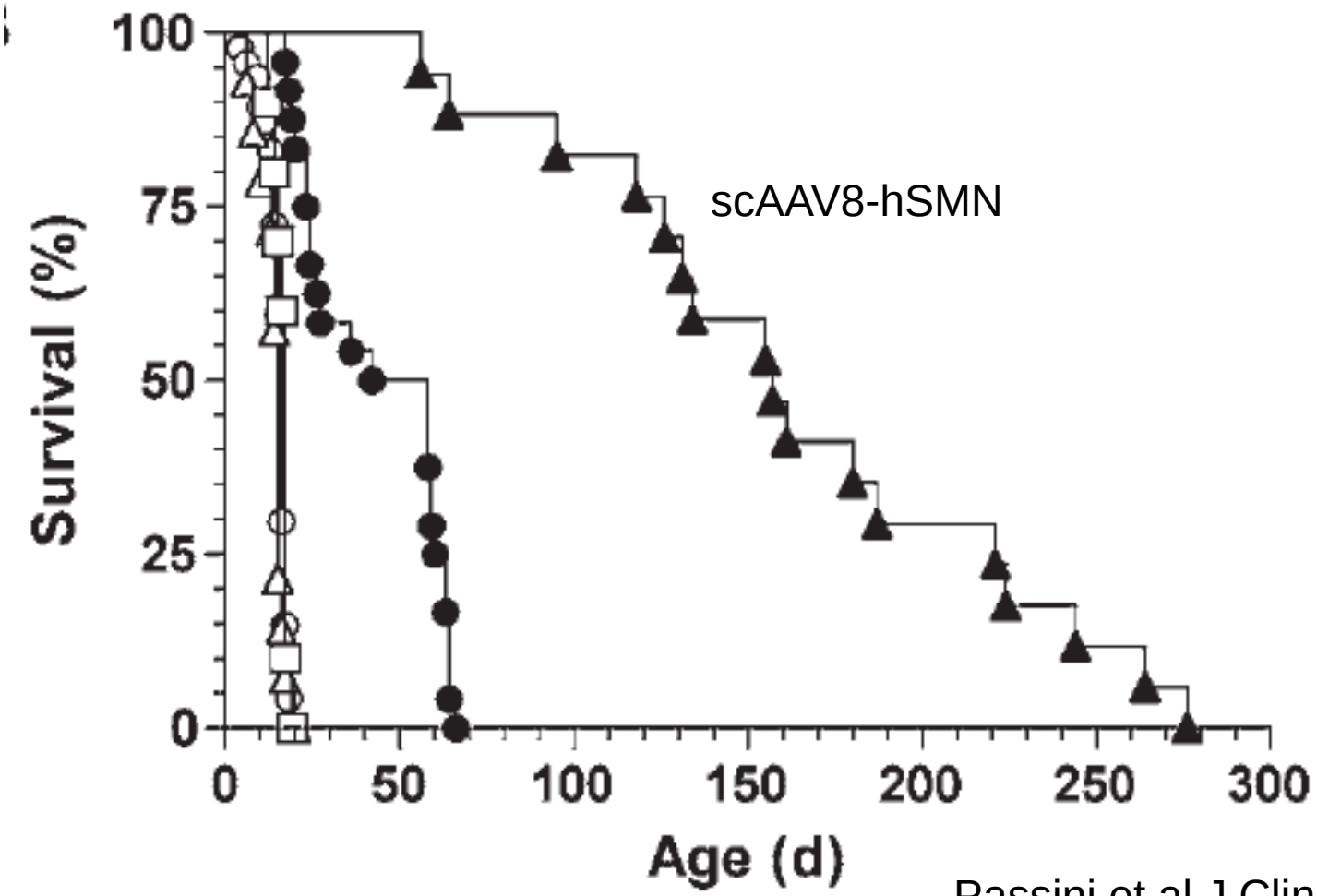
The blood-brain barrier makes drug delivery to the CNS more difficult



- Options Today
  - Direct antisense injection to the brain or spinal fluid (Isis)
  - Gene therapy with direct brain injection into the splinal fluid (Genzyme)
  - Small molecule with potential for CNS penetrance (Valentia)

Gene therapy in the CNS

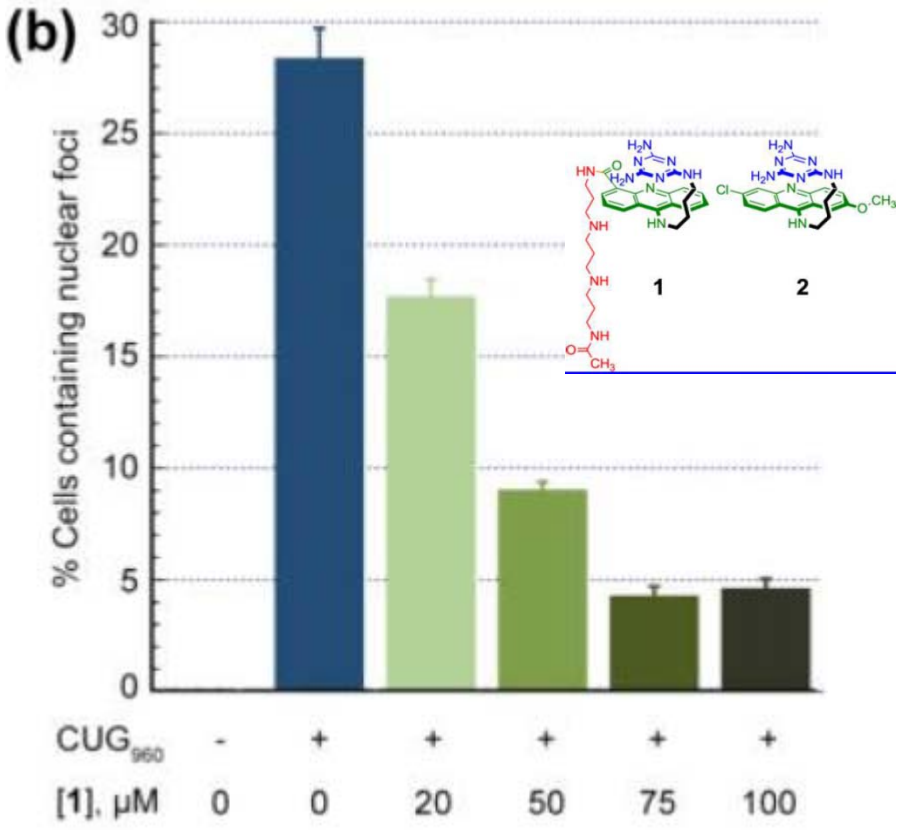
- It has shown dramatic potential in SMA

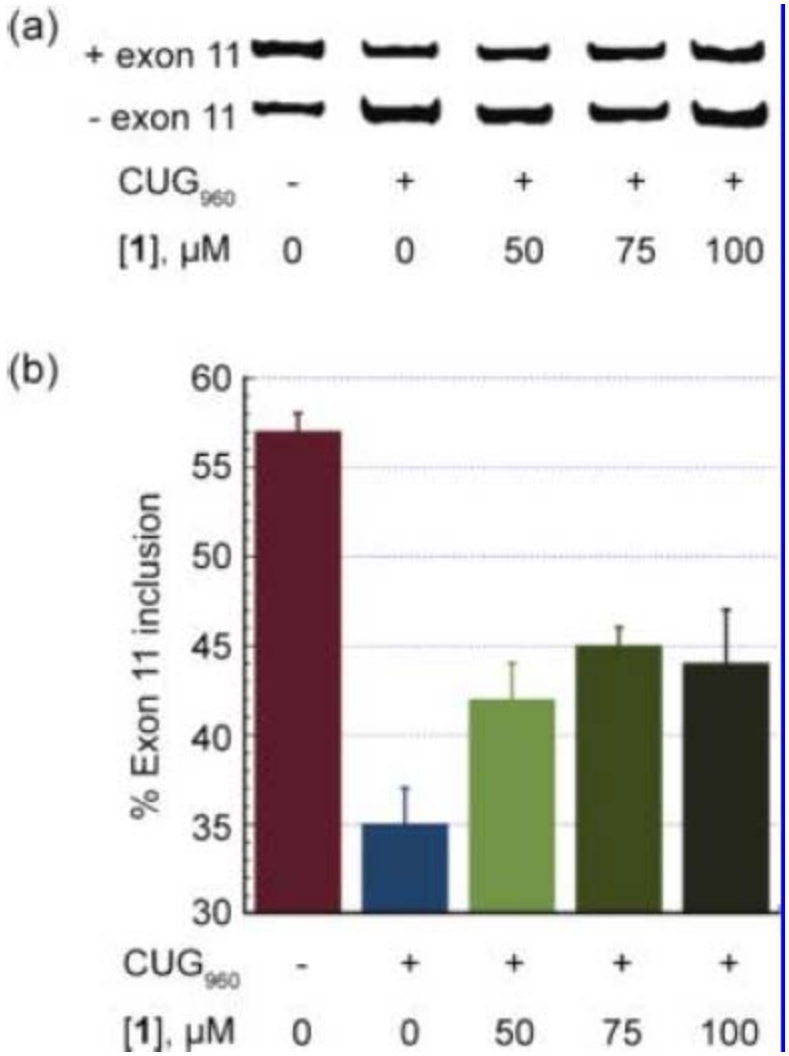


Passini et al J Clin Invest 2010

Small molecules: Perhaps the Holy Grail of DM1 therapy?

- They may work, eventually
  - Specificity and affinity are key





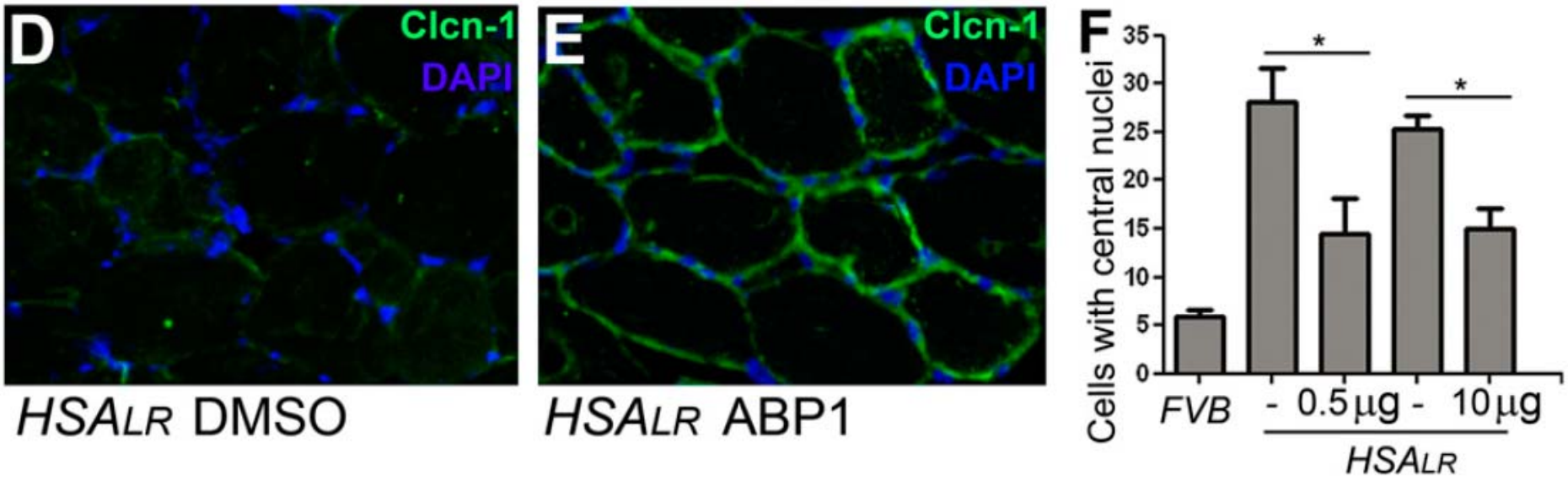
Jahromi et al ACS Chem Biol 2013

Small proteins may serve as drugs to treat DM1

In vivo discovery of a peptide that prevents CUG–RNA hairpin formation and reverses RNA toxicity in myotonic dystrophy models

Amparo García-López[a], Beatriz Llamusí[a], Mar Orzáez[b], Enrique Pérez-Payá[b,c], and Ruben D. Artero[a,1]

[a]Department of Genetics, University of Valencia, Burjassot E-46100, Spain; [b]Peptide and Protein Chemistry Laboratory, Centro de Investigación Príncipe Felipe, Valencia E-46012, Spain; and [c]Instituto de Biomedicina de Valencia, Consejo Superior de Investigaciones Científicas, Valencia E-46010, Spain



Garcia-Lopez et al 2011

-Getting Ready for a Clinical Trial in DM1-

- Understanding the patient's perspective of the disease
  - Your perspective is VERY important
- Looking for a biomarker that helps us understand if the drug is working
- Developing the best tests of muscle function

-Treating heart problems-

- Which DM1 patients are at risk for cardiac problems?
  - Known problems with heart beating ability (EKG abnormality)
  - Over 50 years old
  - About to have surgery

Speak to your physician or cardiologist

-Learning the cause of brain problems-

- DM1 patients suffer from numerous disease issues centered in the brain
  - Depression, anxiety, sleep problems, decision making problems, behavioral problems, sleep disorders
- Four tests proving very informative
  - Magnetic resonance imaging
  - Psychological testing
  - Sleep disorder studies
  - Testing cerebral-spinal fluid

We must take this fork in the road

We need you on the team!

- Be registered
  - So you can be Informed, participate and advocate