On the Verge of Fixing DM1

Some things to consider

Bruce M. Wentworth, PhD
It’s the year 2013 - we’ve come a long way

- 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…

Preclinical testing

Develop understanding of drug mechanism, potential for efficacy, dose, and evidence for toxicity

Phase 1
Demonstration of safety

Phase 2
Determine appropriate dose and gain evidence for efficacy

Phase 3
Confirmatory studies

Seek Approval
However, the reality is often very complex ...

- **Lengthy**
  - 4.3 yrs
  - 6.8 yrs
  - 1.3 yrs
  - 12.4 Years

- **Costly**
  - w/o failures: $170M
  - w/ failures: $560M
  - w/ failures: $1.2B (11.5% Discount Rate)

- **Risky**
  - very low preclinical success rate
  - 30.2% clinical success rate
  - 85% ph1 to ph2
  - 45% ph2 to ph3
  - 70% ph3 to approval

**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*
Why do trials fail?

"Oh, if it were only so simple"

Because we never 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.
Targeting nuclear RNA for *in vivo* correction of myotonic dystrophy

Thurman M. Wheeler¹,², Andrew J. Leger³, Sanjay K. Pandey⁴, A. Robert MacLeod⁴, Masayuki Nakamori¹,², Seng H. Cheng³, Bruce M. Wentworth³, C. Frank Bennett⁴ & Charles A. Thornton¹,²
**ISIS DMPK**

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

- Generation 2.5 Antisense Drug

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

![Diagram of the mechanism of action of ISIS DMPKRx](image)
Drug strength’s and weaknesses

Tissues the drug will treat

- CNS – No
- Heart – Maybe
- Viscera – maybe
- Muscle - Yes
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, it’s 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 Garcia-López⁴, Beatriz Llamusi⁴, Mar Orzáez⁵, Enrique Pérez-Payá⁶, and Ruben D. Artero⁷

⁴Department of Genetics, University of Valencia, Burjassot E-46100, Spain; ⁵Peptide and Protein Chemistry Laboratory, Centro de Investigación Príncipe Felipe, Valencia E-46012, Spain; and ⁶Instituto 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

Systemic disease
Clinical trial

Learn how to treat the CNS

Both directions!
We need you on the team!

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

2013 World Series Champs