Developing Treatments for Dysferlin Deficiency

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Goal: Establish a first therapy for LGMD2B

**Ideal**
An intervention that can reverse the disease course – aka “a Cure”

**Practical**
Anything that can help improve the quality of life of LGMD2B patients by slowing down disease progression.

**Priority**
Find something soon
Where we started

- 1998 Gene discovered
- 1999 1st Mouse model described
- 2003 1st function (membrane repair)
- 2005 Jain Foundation founded
- 2007 JF assumes leadership of field
What it takes to get a drug to market

- Assumes knowledge of the disease is sufficient to ID drug targets.
- Assumes animal models exist and symptoms can be measured.
- Assumes patients are available and methods to study them are in place.

Pharma is driven by profit

Drug price x #patients >> Development costs.
Building a knowledge base

Understanding a disease is essential for building a therapy.

Fundamentals required to start searching for a therapy

- Establish requisite scientific tools (genetically modified mice, cell lines, DNA clones, antibodies) in the research community
- Determine what goes wrong in a muscle when dysferlin is missing and the possible intervention points.
- Find symptoms related to disease progression that can be measured and tracked in cells, mice and people.

Philosophy

- Pursue all options
- Learn from other diseases when possible
- Focus funding on dysferlin specific issues related to finding and testing therapies
The situation today

Progress toward building a therapy.

- The Jain Foundation acts as a central distributor of research tools many of which we built based on anticipated need.
- Our research program has identified multiple intervention points that are being evaluated for their therapeutic potential.
- Symptoms related to dysferlin’s loss have been identified in cells, and are being used in High throughput drug screens.
- Symptoms related to dysferlin’s loss have been identified in mice, and are being used in preclinical studies to test the therapeutic value of different interventions.
- A growing number of patients are genetically diagnosed and clinical trial ready.
- Our Clinical Outcome Study is underway and we hope to have a suite of defined measures that can track disease progression, and improvement and in patients.
- Progress in key areas is now the basis for partnerships with 4 different pharma companies.
1998 Gene discovered

1999 1st Mouse model described

2002 2003 1st function (membrane repair)

2007 JF assumes leadership of field

2010 dysferlin gene therapy in mice

2012 COS begins

2012 start of CRO partnerships

2014 1st preclinical drug trial

2015 Biomarker study to be completed

2018 COS to be completed

Emerging Therapeutic Options

Part 1 - Slow down disease progression.
Pro - Repurposing approved drugs may be rapid (can be prescribed “off label”)
Con - Benefits maybe mild

Part 2 – Put dysferlin back
Pro - Conceptually simple. Returning dysferlin to muscle should fix the problem and “cure” the disease.
Cons -
• Technically difficult to deliver dysferlin to muscle in adequate amounts.
• Relies on new therapeutic paradigms that are moving slowly through regulatory processes.
Part 1 - Slow down disease progression.

Possible intervention points

- Absence of dysferlin protein
  - Unrepaired membrane damage
    - Muscle fiber death
      - Loss of Strength
      - Increased regeneration
      - Reduced myogenesis
    - Repair mediating proteins, drugs
  - Membrane stabilization
  - Membrane damage
  - Calcium regulation
  - Increased regeneration
  - Inflammation
  - Immune modulation
  - ???

- Membrane stabilization
- Membrane damage
Part 1 - Slow down disease progression.

Membrane stabilization
- Some success in artificial systems and cells, but none in animals.
- Continuing to pursue the concept in an academic setting.

Immune modulation
- Many approved drugs.
- Need to selectively prevent damaging effects and not interfere with beneficial effects.
- Best options being tested in pre-clinical trials in animals in collaboration with Pharma companies.
- Access to some options blocked by the companies that own them.
- Academic studies are attempting to refine what aspects of the immune system can be targeted to provide a benefit.

Repair mediating proteins, drugs
- Main therapeutic candidate doesn’t look promising.
- Additional candidates are not obvious.
- A better understanding of membrane repair is required to identify new candidates. "Basic Science" projects continue to discover new aspects of membrane repair that may turn up new candidates.
Part 1 - Slow down disease progression.

**Calcium regulation**
- Many approved drugs that might be repurposed from the cardiovascular field.
- Best options are being tested in pre-clinical trials in animals, one in collaboration with a Pharma company.
- Academic work refining the contribution of calcium to the disease process may reveal additional drug candidates.

**Increased regeneration**
- Pharma is leading the development of drugs for sarcopenia (age related muscle loss).
- Applicability to LGMD2B is being tested in animals.
Dysferlin mutation:
- Stop/frameshift
- Missense

Gene Editing

Dysferlin mutation:
- Stop codon read through
- Exon skipping

Chaperones

Truncated protein

Misfolded protein

Degradation

Absence of dysferlin protein

Protein therapy

Gene therapy

Stem cell therapy

Part 2 – Put dysferlin back
Putting dysferlin back  
(Permanent and Irreversible)

Gene therapy

- AAV delivery of MD genes are moving through clinical trials.
- AAV-dysferlin is more complicated - requires a dual vector strategy
- Dr. Mendell will discuss in more detail

Gene editing

- Field is moving quickly with major breakthroughs in the ability to edit genomes.
- Efficiency is currently too low to be considered a therapy.
- Major ethical considerations to be worked out.
- No active projects, but keeping a close eye on this field

Stem cell therapy

- Successful proof of concept studies, but efficiency remains too low to be an effective therapy.
- Major hurdle is effective delivery/engraftment.
- No active projects, but keeping a close eye on this field
Putting dysferlin back (transient and reversible)

- Ataluren conditionally approved for use in Europe and on the market in Germany for DMD.
- Benefit may be small due to low efficiency
- Only applicable to patients with “nonsense” or “stop” mutations

- Clinical trials underway for DMD and showing promise
- Assessing applicability to dysferlin – which dysferlin exons can be skipped?
- Only applicable to patients with mutations in specific exons

- Proof of concept studies successful but limited to single specific point mutation
- One approved drug on the market
- Limited clinical trials in Europe
- Applicable only to patients with specific point mutations

- Proof of concept studies failed in animals
- Abandoned the approach for now
The Road Ahead

• No single emerging therapy is a sure thing, so we will continue to pursue all options.

• Several therapies are reaching the clinical trial stage of development. Enthusiastic and committed patient participation is necessary to keep them moving forward!

• New therapeutic opportunities continue to surface as we learn more about LGMD2B and we are now in a much better position to pursue them.