Developing Treatments for Dysferlin Deficiency

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Jain Foundation
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Goal: Establish a first therapy for LGMD2B

Ideal

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

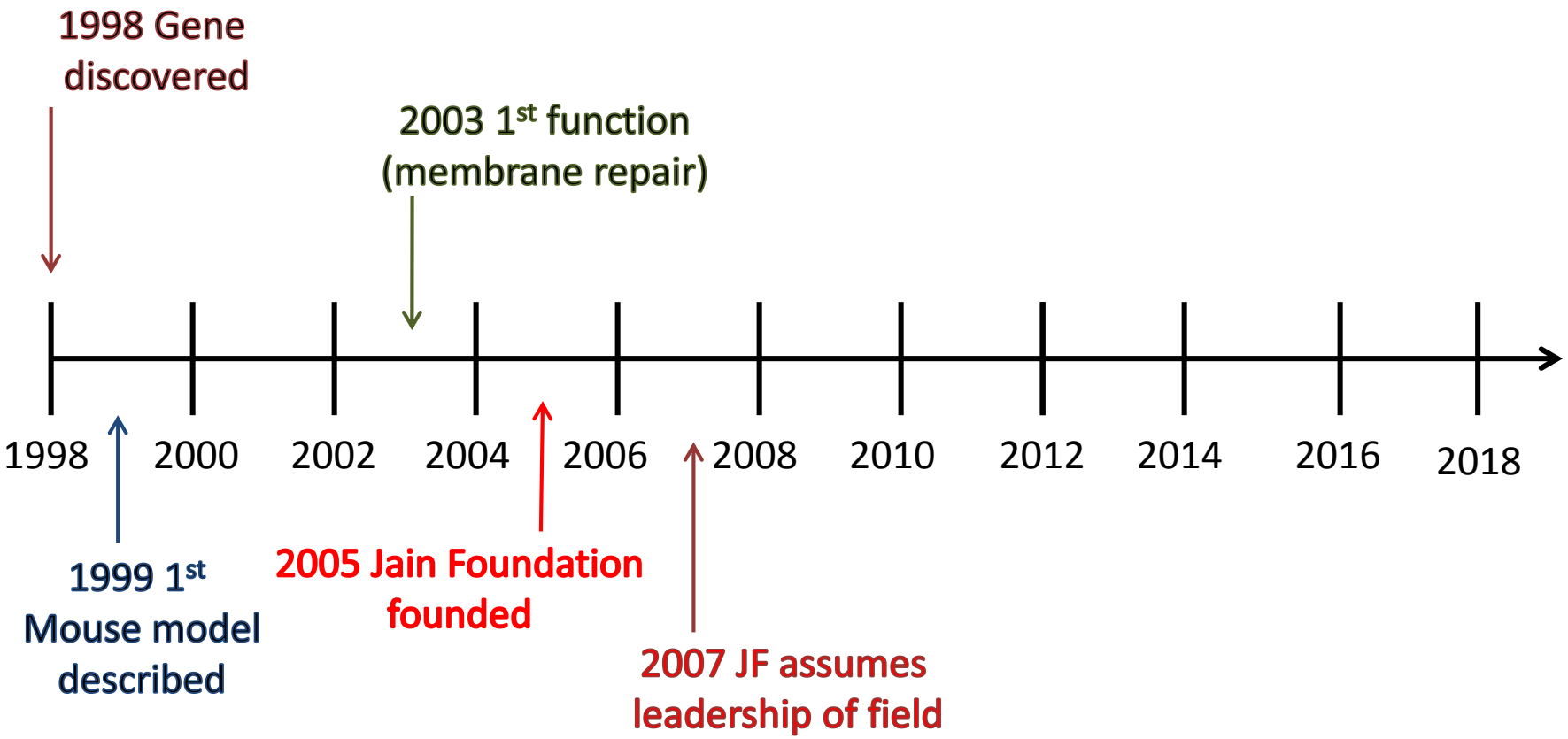
Practical

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

Priority

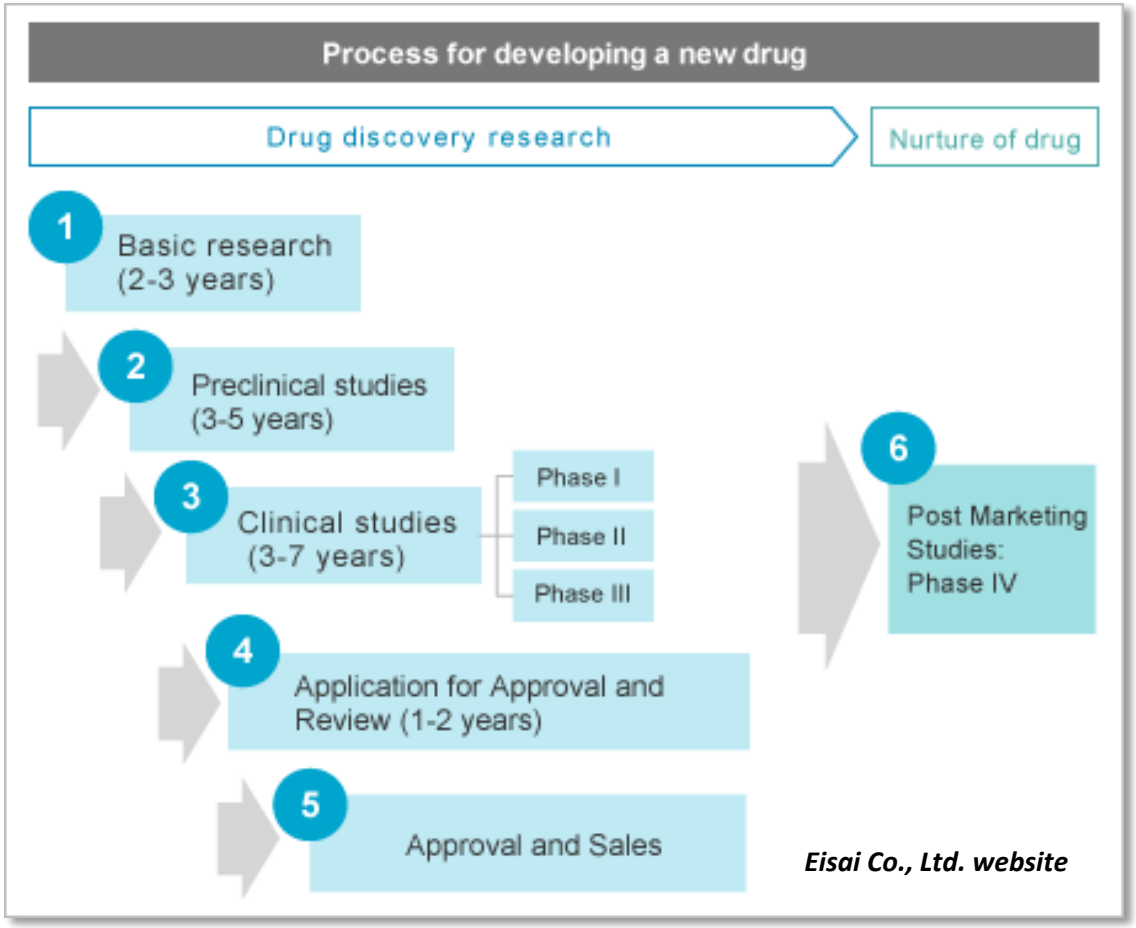
Find something soon

Where we started



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.

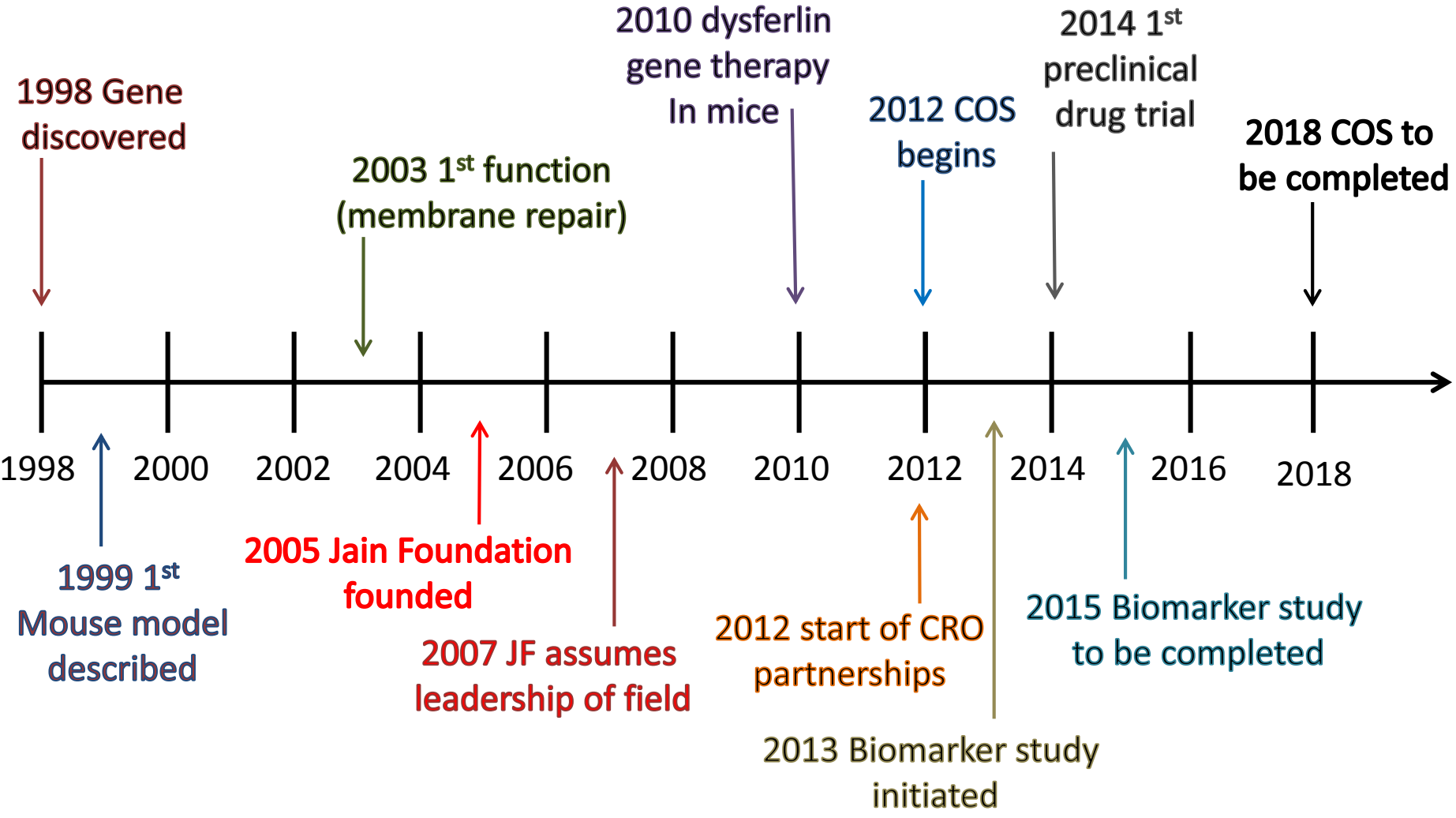
Philosophy

- 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
2003 1st function (membrane repair)
2010 dysferlin gene therapy In mice
2012 COS begins
2014 1st preclinical drug trial
2018 COS to be completed
1998
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2008
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2012
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2016
2018
1999 1st Mouse model described
2005 Jain Foundation founded
2007 JF assumes leadership of field
2012 start of CRO partnerships
2013 Biomarker study initiated
2015 Biomarker study 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

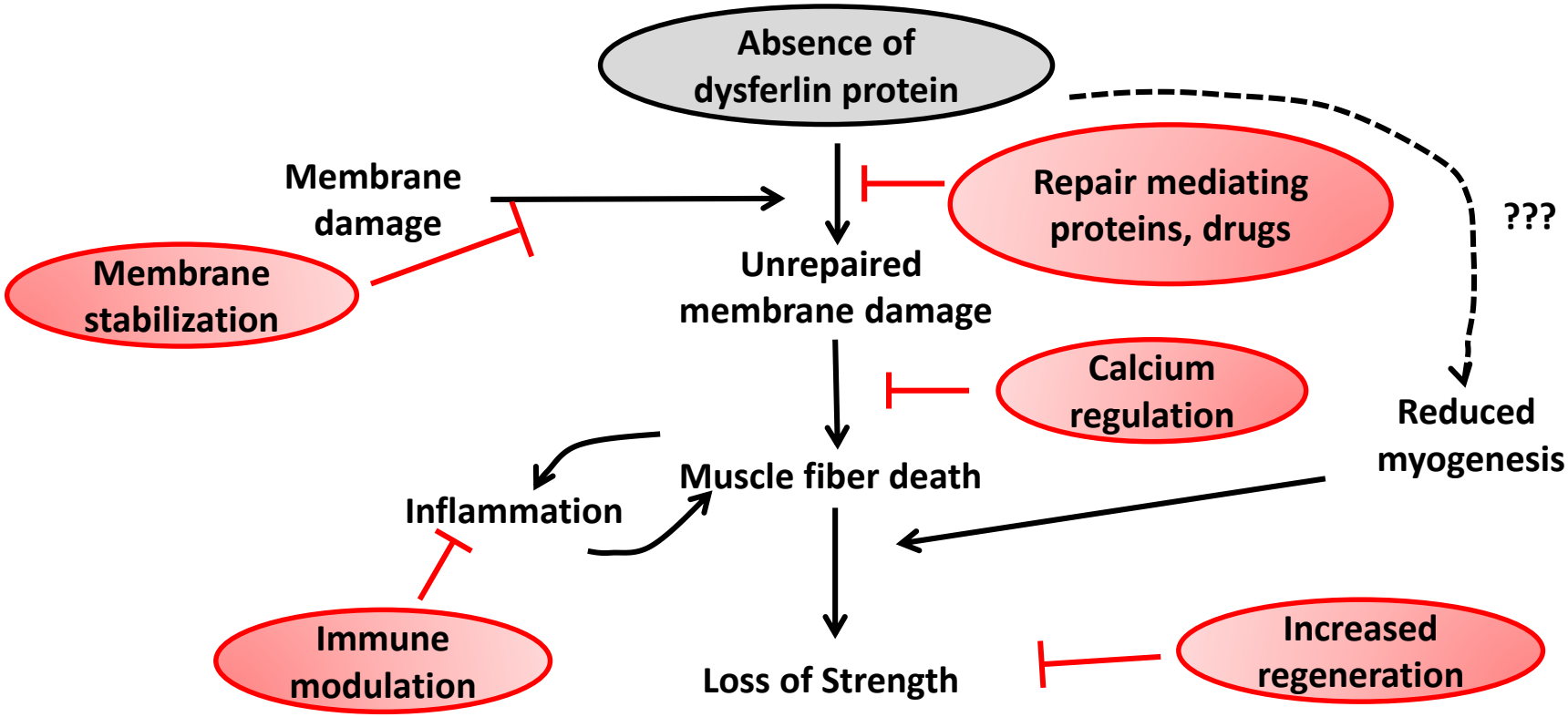
Pro - Conceptually simple. Returning dysferlin to muscle should fix the problem and “cure” the disease.

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



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.

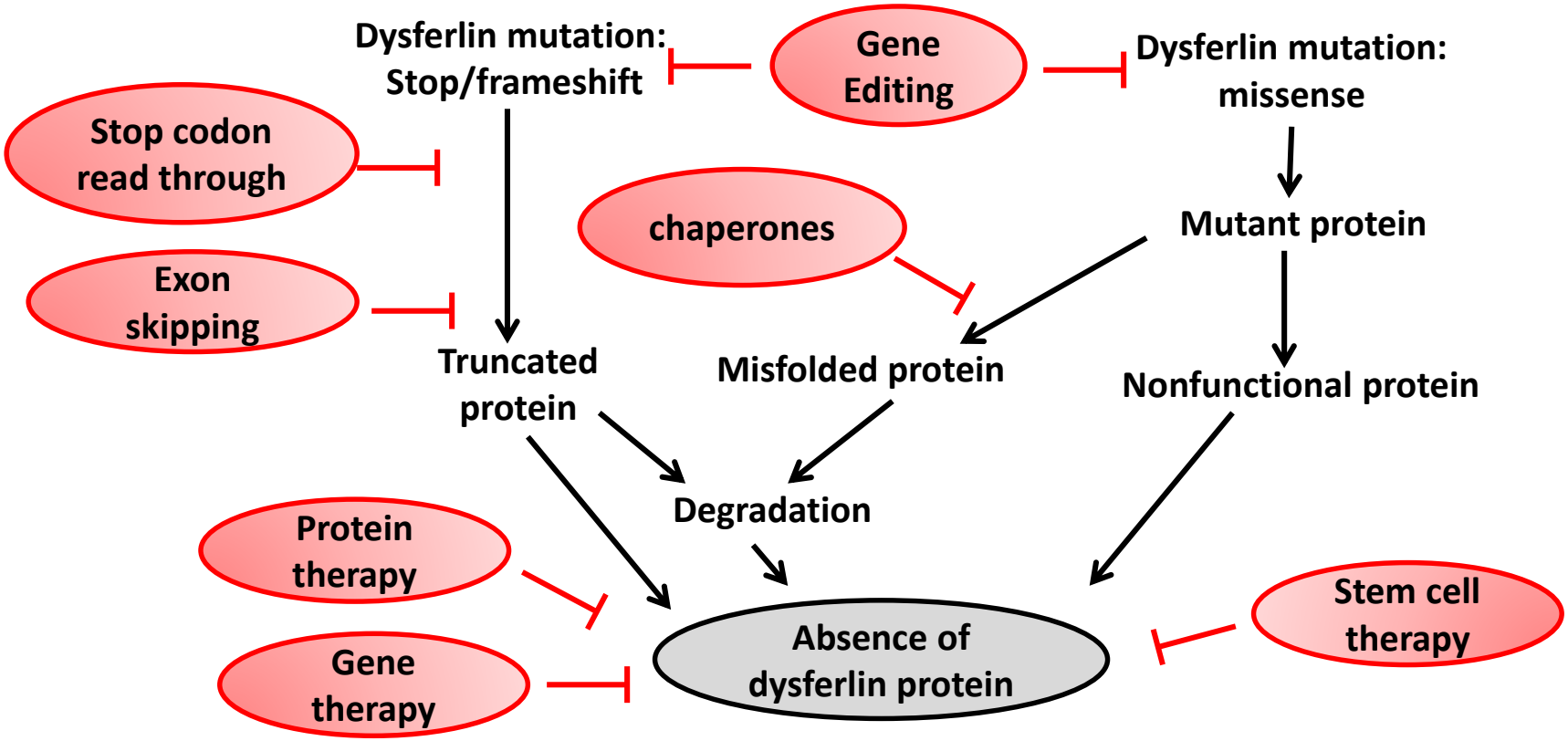
Calcium regulation

- 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.

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)

Stop codon read through

- 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

Exon skipping

- 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

chaperones

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

Protein therapy

- 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.