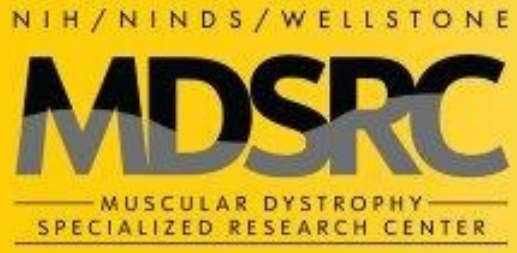


Introduction to clinical trials and therapeutic options for dystroglycanopathies

Katherine D Mathews

Outline

- Introduction to clinical trials and trial participation
- General approaches to potential treatments

Steps to a treatment trial

- Identify patients
  - Accurate diagnosis
  - Registries (CMDIR, Global FKRP Registry[see video for more information])
- Know the natural history of the disease
- Understand the cellular and molecular basis of disease (usually)
- Have a consistent standard of care to minimize variability that is not related to the intervention being tested
- Identify a possible treatment
- Test in cells and animal model(s) of the disease

Steps to a treatment trial—how are we doing across dystroglycanopathies?

- Identify patients
  - Accurate diagnosis ✓
  - Registries ✓
- Know the natural history of the disease ✓
- Understand the cellular and molecular basis of disease (usually) ✓
- Have a consistent standard of care to minimize variability that is not related to the intervention being tested ✓
- Identify a possible treatment ✓
- Test in cells and animal model of the disease ✓

✓ Doing well!

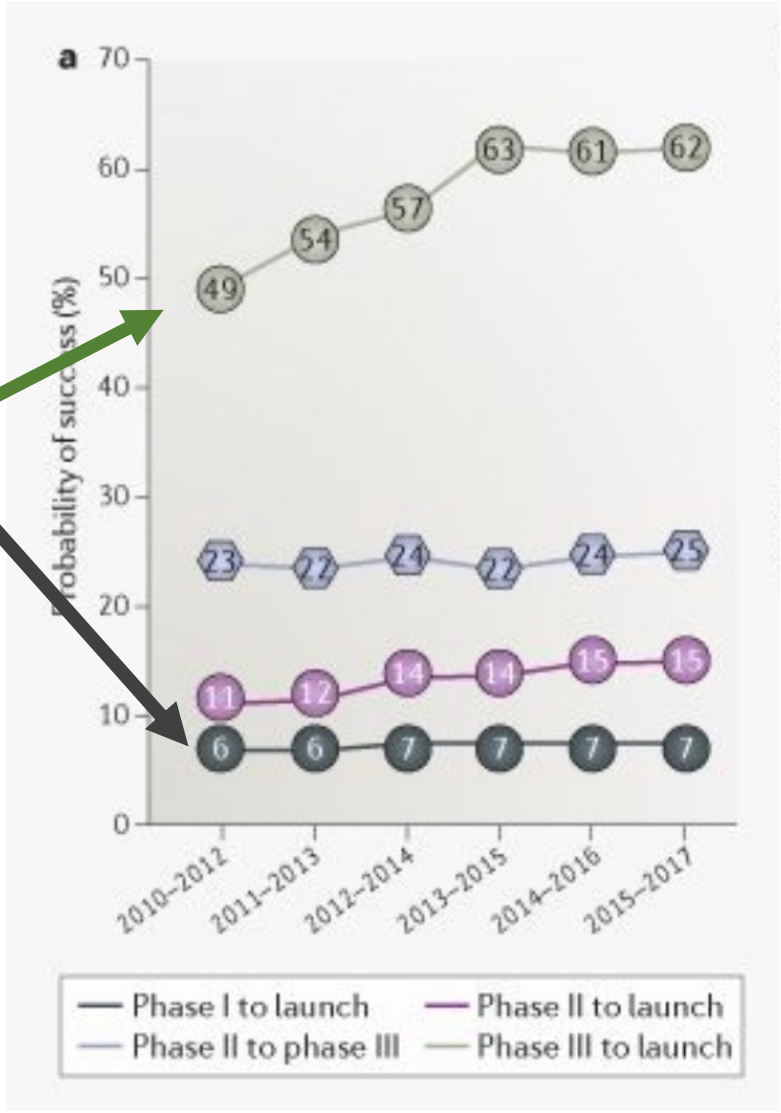
✓ Making progress, varies across genes

Human Trials of a Possible New Treatment

- Phase I Investigation (few subjects, often healthy)
  - Look for toxicity
- Phase II Investigation (small study)
  - Establish dose
  - Assess for safety
  - Look for hint of therapeutic effect
- Phase III Investigation
  - Large number of patients
  - Control population (placebo group)
  - Determines if treatment is effective
    - a good study should provide a clear answer about whether or not the treatment works
- Phase IV (post-marketing surveillance)
- Phases may be combined in rare diseases
- Millions of dollars required for large Phase III trial
- This sequence typically takes several years

Success rate for a new drug

- For a compound entering Phase I trials, <10% get FDA approval and commercial release
- Compounds that make it to Phase III
  - Historically <50% get FDA approval
  - Rate appears to be rising
- Most drug failures are due to problems with efficacy and/or safety.
  - *D. Lowe, Science Translational Medicine, 2019*



Placebo controlled trials

- Needed to demonstrate a difference that is due to the drug rather than something else
  - Change in national practice
  - Increased attention/therapy due to being in trial
  - Practice effect on outcome measures
  - Other
- Placebo controlled phase 3 trial often followed by access to active drug for <u>all</u> participants until
  - It is commercially available
  - It is determined to be unsafe/not effective

Participation in a clinical treatment trial

- Clinical trial participation a major commitment!
  - Helping others is often one of the reasons people participate
- Dystroglycanopathies are rare diseases, so enrolling enough subjects will be a challenge
- Things to consider:
  - Do you have the time and willingness to attend study visits and travel (if needed)?
    - Costs associated with travel are paid by the study in most cases
  - Are you willing to accept the possibility of a placebo?
  - Do you understand the risks and are they acceptable, understanding that the treatment being studied might not work?

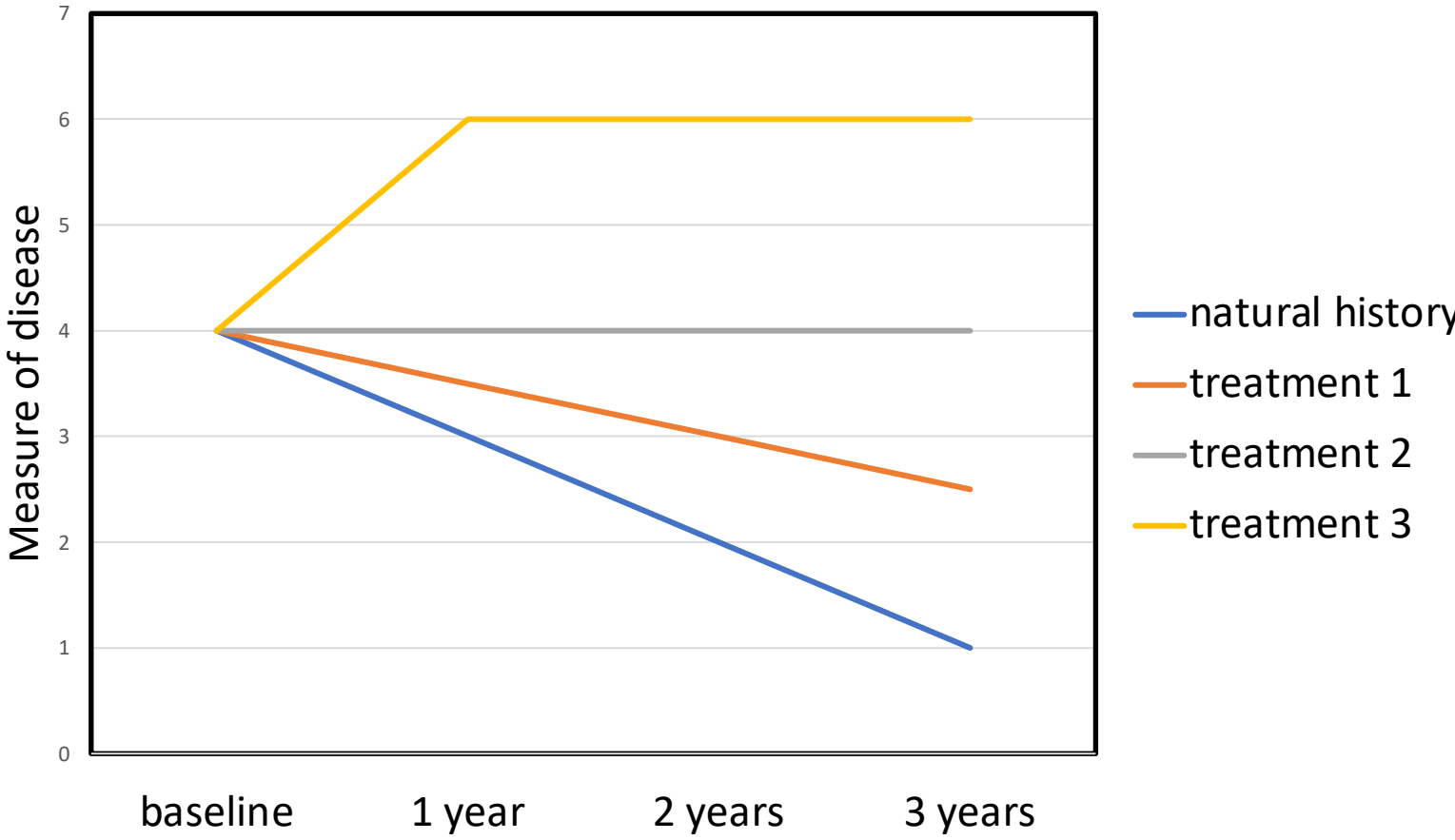
Treatment strategies (not an exhaustive list)

- Treat symptoms
- Drugs to modify some or all of disease process, nonspecific
  - Decrease fibrosis
  - Increase muscle bulk
  - Anti-oxidants
  - Anti-inflammatories
  - Improve muscle repair and regeneration
  - Upregulate related genes, such as LARGE
- Drugs to target disease-specific metabolic pathway
- Gene replacement
- Edit the genetic basis of disease, typically mutation-specific
- Cell-based therapy (stem cell/myoblasts)

- Combination therapies are likely

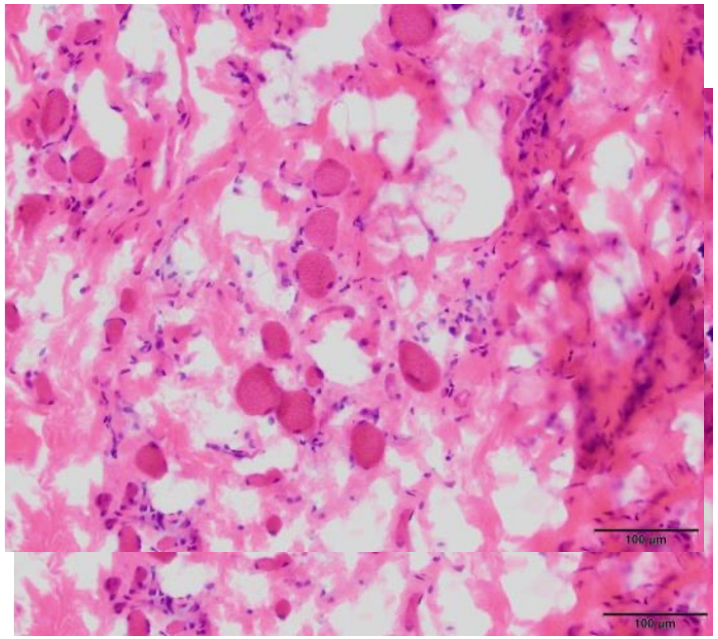
Potential goals of treatment

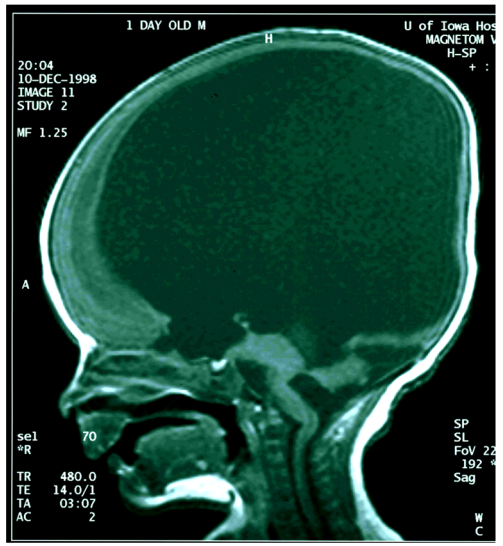
- Disease progression
  - Slow disease progression
  - Stop disease progression
  - Improve disease and stop progression
- Expected effect helps determine the number of people in the trial and duration of trial



Goals of treatment in dystroglycanopathies

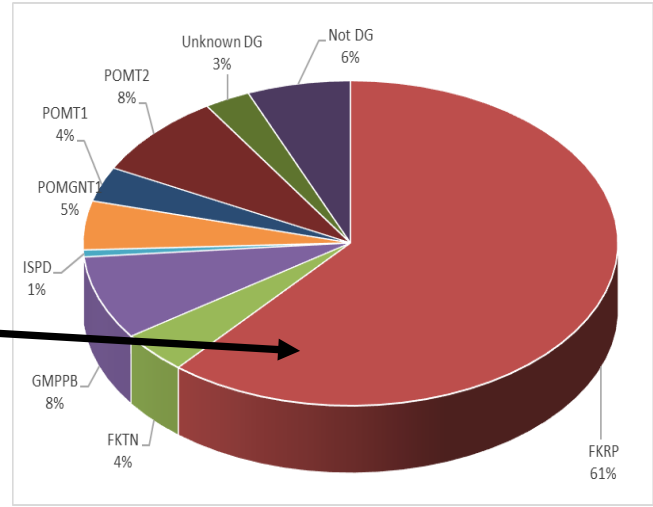
- Tissue to be treated
  - Skeletal muscle (includes breathing)
  - Heart muscle
  - Smooth muscle (bowel, bladder, blood vessels)?
  - Brain?

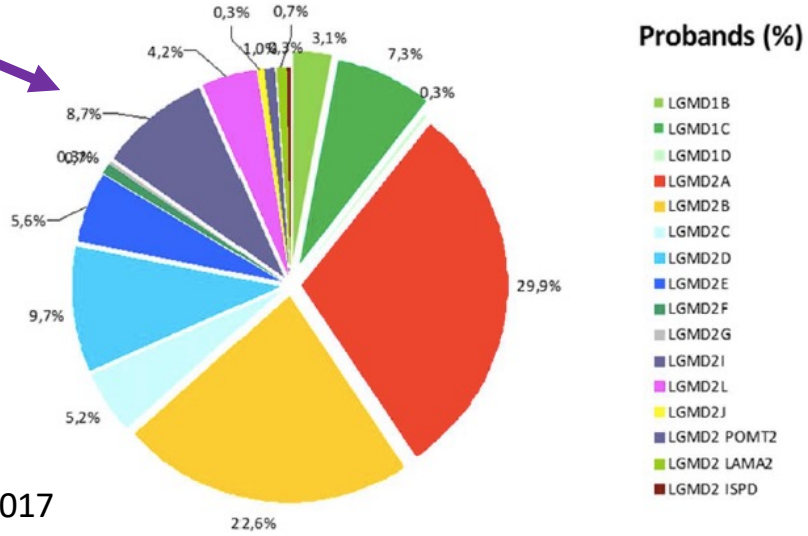




Studies thus far primarily focused on FKRP related MD

- The most common gene affected so easier to study than very rare diseases
  - LGMD2I/R9 accounts for ~10% of LGMD patients
- The principles will apply to at least some of the other dystroglycanopathies
- Effective treatment in one disease will drive progress in another





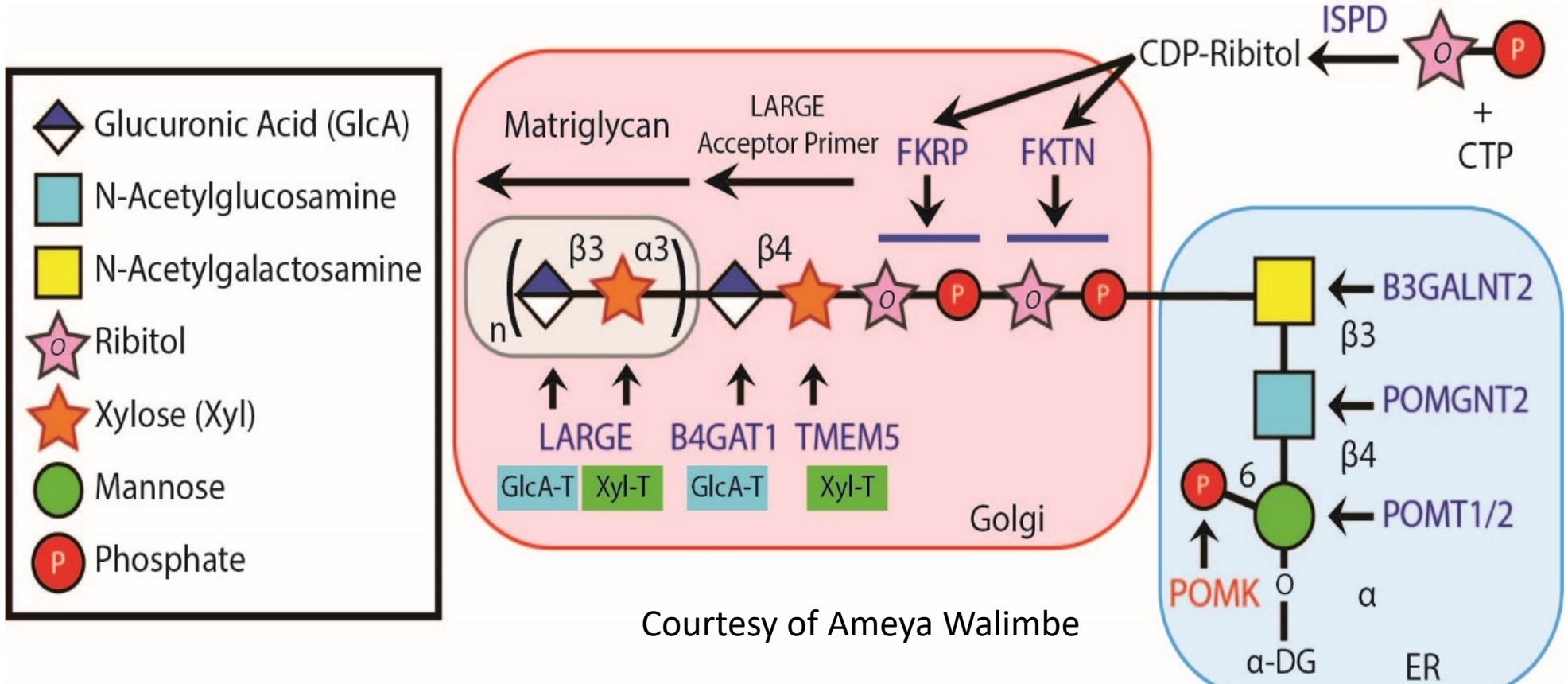
MAGRI, et al, MUSCLE & NERVE 2017

Trials in LGMD2I/R9 that are closed

- Myostatin inhibitor
  - Non-specific
  - Designed to increase muscle bulk
  - Not effective in clinical trial
- Deflazacort trial closed due to insufficient enrollment

CDP-ribitol: target metabolic pathway with FKRP mutations

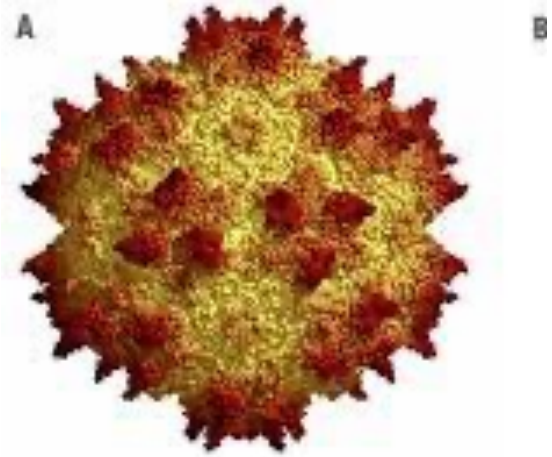
- Everyone has some FKRP activity
- FKRP uses CDP-ribitol to add ribitol to the alpha-dystroglycan sugar chain
  - Concept: Increase the amount of CDP-ribitol in the cell, drive the residual FKRP to work harder and increase glycosylation



Courtesy of Ameya Walimbe

Gene replacement

- Gene replacement in neuromuscular diseases
  - The gene is packaged inside a modified virus (AAV)
  - Given as an IV infusion
  - Currently, can only get once due to immune response
- Several companies are exploring gene replacement in LGMD2I/R9
- The only genetic disease with FDA approved gene replacement with systemic delivery is SMA



http://signagen.com/images/AAV_Size_EM.jpg

Considerations with gene replacement

- Does dosage matter?
  - Some mouse evidence suggests that too much FKRP is harmful to muscle
  - There are human examples in nature where either too much or too little of a gene causes disease
    - 1 copy PNP22 → hereditary predisposition to pressure palsies
    - 2 copies → healthy
    - 3 copies → Charcot Marie Tooth disease type 1A
- Immune response to viral load
- Is the heart targeted?

Summary

- Some ideas or treatments that are promising, even in Phase 2 human trials, don’t work or are not safe
- A phase 3 trial is designed to determine if a treatment works
- There are many potential approaches to treating a dystroglycanopathy
  - Combinations might ultimately be the most effective
- Every success in treating a neuromuscular disease is a success for the whole larger community—proves it can be done

Industry Q and A

- Dr Nguyen, AskBio
- Dr. Rudnicki, Satellos
- Dr. Sproule, ML Bio

- Videos from each speaker are available in the Whova App

- Thanks to all of them for participating!