LGMD-1D DNAJB6 Foundation

and

MYOSYND™

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The 2024 MDA Conference

The 2024 Muscular Dystrophy Association (MDA) Conference was held early March and delivered an important array of advancements, especially on the therapeutic front. I will attempt to summarize and show examples.

Duchene's, SMA, and ALS were primary features as expected with various gene therapies in the pipeline. With that said, more reported complications of genetic therapies and their mitigation were discussed. The LGMD community will benefit from these lessons as therapeutic trials continue to roll out for the autosomal recessive LGMD community.

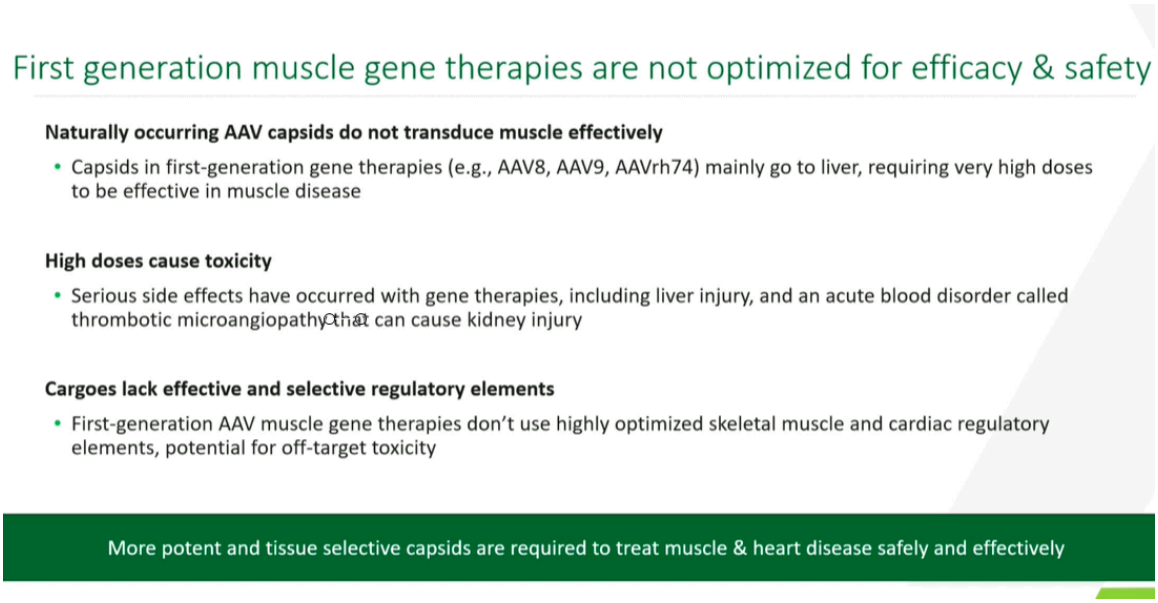
The good news for the autosomal dominant LGMD community is that therapeutic trials are starting for more common conditions such as FSHD, (Facioscapulohumeral muscular dystrophy).

Before getting into the weeds of evidence, a refresher on therapeutic options for LGMD, and will include supporting slides below. We have small molecules or a current library of drugs that might be useful if repurposed for LGMD. There are genetic options including in body (in vivo) or out of body (ex vivo) genetic editing involving CRISPR 9 and newer editions. Finally, there are small blocking nucleotides that attach to the specific bad nucleotides that are causing LGMD thus preventing further damage, (also known as antisense oligonucleotides, ASOs).

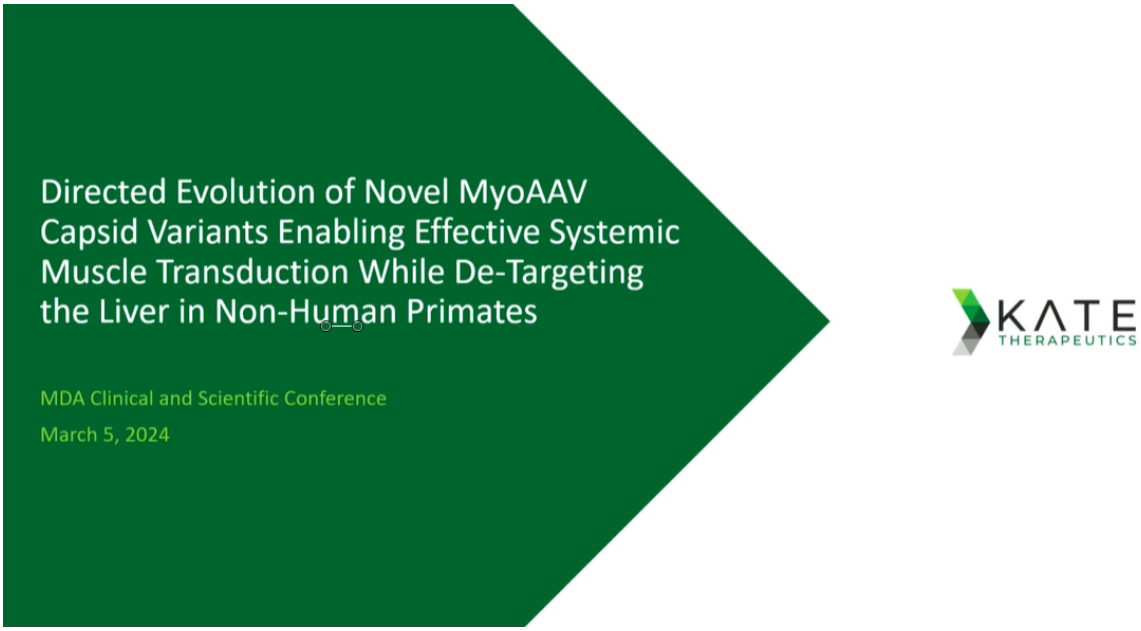
A key link in all genetic therapies for LGMD is targeting the muscle specifically and sparing other off target organs. In the past, neutered viral vehicles were relatively non selective and led to extra toxicity. Now new vehicles including highly selective muscle viral vectors, specific muscle antibodies and inert nanoparticles allow genetic packages to be delivered to and through the muscle membrane where they can correct the deficiency. See the following slides:

Viral Delivery Systems

Slide 1: Initial viral vehicles had problems.

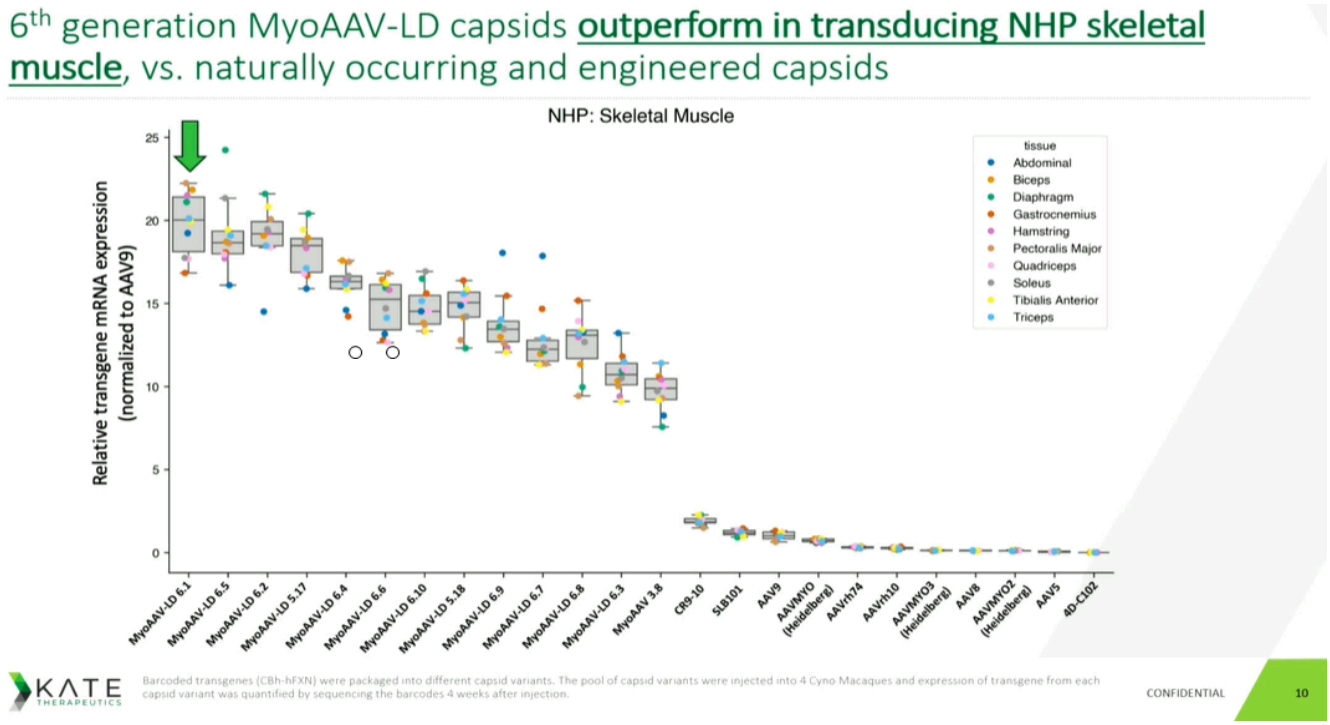


Slide 2: Enter industry, developing a better viral vehicle to deliver the genetic package.



Slide 3: Graph showing superior delivery to muscle (green arrow).

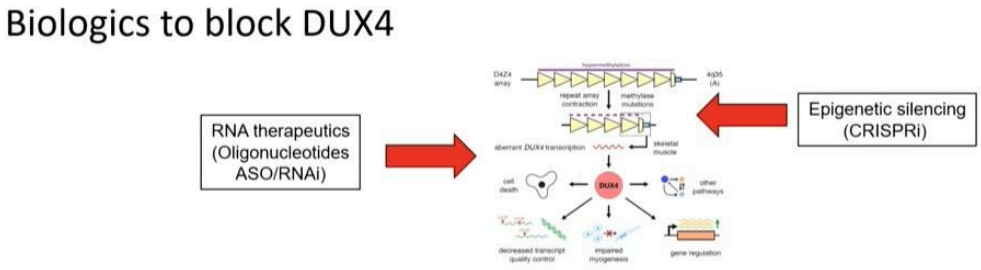
Note that all the superior vectors are "MYO" variety.

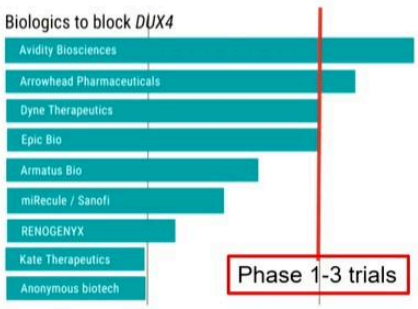


New Trials for Autosomal Dominant LGMD:

FSHD

Slide 4: FSHD, an autosomal dominant LGMD, has 7 trials using ASOs with antibody or nanoparticle to deliver ASOs (blocking mRNA) and viral (AAV) CRISPR delivery to muscle for direct gene editing. All are efforts to block pathogenic protein DUX4, the cause of FSHD. This may be the first time a rare condition has had a head to head comparison of not only the different delivery systems, but also the blocking vs editing technologies. Stay tuned!





Name	Biologics type	Deliver
AOC-1020	Oligo/RNAi	Antibody
ARO-DUX4	Oligo/RNAi	Nanoparticle
DYNE-301	Oligo/ASO	Antibody
EPI-321	CRISPRi	AAV
ARM-201	Oligo/RNAi	AAV
MC-DX4	Oligo/ASO	Antibody
CRI007	CRISPRi	AAV

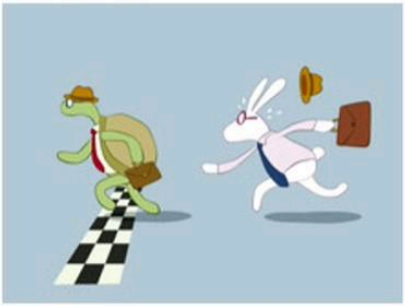
One FSHD trial HERE (Arrowhead Pharm)

Therapy: Small Molecule vs Blocking Oligonucleotides (ASOs)

Slide 6:

Small molecules: pros and cons

PROS	CONS
• Cheaper • ?Safer profile • Several clinical data available • Generally taken orally • Faster to get to the market (some *already FDA-approved)*	• Expensive over the long term (lifelong administration) • ? Long-term negative effects (widely expressed targets/multiple pathways including regeneration) • Compensatory pathway ?long term effect



Slide 7:

Oligonucleotide therapeutics: pros and cons

PROS	CONS
• Direct suppression of DUX4 • Relatively easy to produce • Sequence-based targeting (→precision medicine) • Treatment can be stopped	• Risk of off-target effects/cytotoxicity • Dysregulation of endogenous RNA-processing pathways • ?poor delivery to muscle vs liver • Lifelong administration

MDA Conference Conclusion

In summary, the MDA conference presented optimistic data for new genetic therapies and delivery systems. The amount of research and industry interest has mushroomed since last year's conference. Therapy for autosomal dominant LGMD is no longer a proof of concept and now entering well designed trials. See selected conference videos HERE.

AI, Chat GPT and LGMD Part II

This topic was featured in our last newsletter and the advances in AI have exploded over the last three months. The number of "large language models" (LLMs) has proliferated but the Open AI group whose latest model is Chat GPT 4.5 still leads the pack in performance over a broad range of intellectual performance testing.

The last three months I have trained my LGMD AI programs on many different LLMs with improvement in consistency of responses to the user. These programs allow the user to find information regarding specific genetic variants, location of university and MDA neuromuscular clinics, etc. The "Wheelchair Planner" helps organize trips to any city in the world. Please feel free to ask specific follow-up questions to get the answers you want and it is OK to compliment or criticize the response to help it learn. This is a Chat GPT 4.5 LLM application: LGMD Assistant 3.0, you may need an Open AI account to use this which may be free or paid.

These two are on a website, YouAI, which will require free registration to use: LGMD Assistant II, Wheelchair Travel Planner. They both use the Anthropic group's Claude 3.0 LLM.

I can make myself available for group ZOOM sessions to develop your own models or general instruction at: wslowery.57@lgmd1d.org .

Please try these and let me know if they are useful and any bugs that you find.

Important MDA Links

Since our inception in 2018 we have collected links to help everyone's journey. Due to the onboarding of new members and new links I am adding this as an evergreen list to our newsletter.

MDA Connect: https://www.mda.org/care/connect

MDA Connect: Helps find a neuromuscular doctor near you!

MDA gene therapy workshop HERE

MDA summer camp for attendees and volunteers HERE

MDA college scholarship program HERE

Important Patient Care Links

Sponsored Whole Genome Sequencing: (next step for VUS resolution)

NIH

Harvard

Stanford Center for Undiagnosed Diseases

Do I really have a genetic muscle disorder? See HERE

Do I have a mitochondrial muscle condition? Video1, Video2

United Mitochondrial Disease Foundation (UMDF) Genetic Testing For Suspected Mitochondrial Disease Program HERE . Sponsored testing that clinicians can order if a mitochondrial disease is strongly suspected.

Are You Having a Muscle Biopsy?

Tissue referral to University of Iowa

University of Iowa Muscle Biopsy Requisition

Gene matching sites, you must register all your VUS variants to connect with others to help establish a genetic diagnosis: MyGene2, GenomeConnect, Rare-X

Sponsored flights for rare conditions HERE and HERE.

Joe's House (discount lodging for patients with cancer and rare conditions)

Important Foundation Links

LGMD1D DNAJB6 Foundation

LGMD1D Foundation YouTube Archive

LGMD1D Foundation assisted sponsored genetic testing

LGMD1D Foundation Autosomal Dominant Registry

LGMD1D Foundation: Solving Your Variant of Uncertain Significance (VUS)

Ways to Donate

1. OUR WEBSITE (a secure site with all the listings below)
2. PAYPAL (Our foundation's secure site)
3. CREDIT CARD (Network For Good credit card portal)
4. VENMO (@lgmd1d) Foundation Account
5. EVERY.ORG (ALL CRYPTO CURRENCIES)
6. SQUARE
7. If you are over 72 consider a Qualified Charitable Distribution (QCD) from a traditional IRA and lower that dreadful RMD and avoid that higher tax bracket. Also available to Roth IRA participants.

   RMD calculator HERE, medicare income bracket HERE. tax bracket for SS HERE.

Thank you for your support and all the best from us!

William Lowery MD