Vol 3 / Issue 1

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

Advances in Stem Cell Therapies for Muscular Dystrophies at the University of Minnesota

Dr. Rita Perlingeiro Leads a Research Team Developing Stem Cell-Based Therapies for Patients with Skeletal Muscle Diseases

GENE THERAPY 101

Sarepta Therapeutics Kicks Off a Four-Part Educational Series

A DIAGNOSIS TURNED INTO A MISSION

Dr. Vovanti Jones, Living with LGMD2B/R2, has a Unique Perspective Treating Patients Living with Neuromuscular Diseases

A Novel Approach to Protect Muscle from Damage

Edgewise Therapeutics is Taking a New Approach to Developing Therapies for Patients with Muscular Dystrophy

ML BIO SOLUTIONS

Why are Biopsies Important in Clinical Trials?

Are you living with LGMD?

This masterclass is for your clinical care team; encourage them to register today!

Calling all healthcare professionals!

Virtual LGMD Masterclass: USA Edition

9th and 10th March 2023

Register & find out more

The TREAT-NMD limb girdle muscular dystrophy (LGMD) masterclass is a 2-day event aimed at healthcare professionals based in the USA.

It will be a fantastic opportunity for clinicians to learn all the latest in diagnosis, management and care of patients with LGMD.

- ✓ Interactive workshops
- ✓ Q&A sessions
- ✓ Expert speakers
- ✓ Free to attend

TREAT-NMD Neuromuscular Network

TREAT-NMD Alliance Limited, a registered charity in England & Wales (No. 1200765). Address: The Catalyst, 3, Helix, Newcastle upon Tyne NE4 5TG

LGMD News

Vol 3 / Issue 1

Contents

How To Donate

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Thank you for your support!

The Speak Foundation
Uniting the entire LGMD community to make a difference together in future treatments for this rare disease.

The origin of The Speak Foundation's name comes from Proverbs 31:8. It is, "Speak up for those who have no voice." Living with a rare disease means many of us wait years to have a voice in areas that impact our daily lives. The Speak Foundation helps our voices to be heard.

Departments

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Looking Ahead to 2023

In 2023, advocacy will be one of our most important tasks.

As we look ahead to 2023, we are excited to embark on our third International LGMD Conference, which will be held in Washington, DC! Registration for the conference will open in April, so be sure to follow our social media and see the Spring issue of *LGMD News* for more details.

Back in person for the first time since 2019, we will celebrate together as we hear from the best researchers in the world on LGMD. There will also be updates from industry partners on the status of drug development for gene therapy and other novel treatment strategies for LGMDs. There are now five companies in the LGMD landscape, with many more expressing interest.

As we look to the future with hope, what can our community actively do? In 2023, advocacy will be one of our most important tasks. We need to keep our momentum and build on the progress that has been made. We recently held the first ever Externally-Led Patient-Focused Drug Development (EL-PFDD) Meeting with the FDA for LGMD subtypes 2A/R1, 2C/R5, 2D/R3, 2E/R4, 2F/R6, and 2I/R9. We will publish the Voice of the Patient (VOP) Report summarizing the PFDD in the next few months, which will highlight our learnings from this monumental event. You can watch a replay of the EL-PFDD and find more information about the VOP once it is released at **lgmdpfdd.com**.

Stay tuned and connected to us through our website and *LGMD News* magazine, as there are more advocacy opportunities coming up that you can be involved in. We encourage you to read each issue to stay informed! ▪

Kat Bryant Knudson

Kathryn Bryant Knudson
Editor In Chief
Founder & CEO, The Speak Foundation

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lgmdpfdd.com

Our Mission

The Speak Foundation was based on the principle of "Speak up for those who have no voice." *Speak up for those who cannot speak for themselves.* —Proverbs 31:8

LGMD News is a program of the Speak Foundation. In order to help individuals and families living with limb-girdle muscular dystrophy receive critical and life-saving information, the Speak Foundation began publishing this resource in 2021.

International Consortium of LGMD Organizations

United States

The Speak Foundation
Uniting the entire LGMD community
TheSpeakFoundation.com

Beyond Labels & Limitations
Funding research for LGMD 2A/R1 and educating on its disease course
BeyondLabelsLimitations.com

Breathe with MD
Educating and raising awareness about breathing muscle weakness in neuromuscular disease
BreatheWithMD.org

CamronsCure
Funding research for LGMD 2S/R18
CamronsCure.com

Coalition to Cure Calpain 3
Funding research for LGMD 2A/R1
CureCalpain3.org

Cure LGMD2I
Funding research for LGMD 2I/R9
CureLGMD2I.org

Kurt + Peter Foundation
Funding research for LGMD 2C/R5
KurtPeterFoundation.org

LGMD Awareness Foundation
Join us for LGMD Awareness Day
LGMD-Info.org

LGMD-1D DNAJB6 Foundation
Representing LGMD 1D/D1 and DNAJB6 subgroup
LGMD1D.org

LGMD2D Foundation
Funding research for LGMD 2D/R3 and educating patients and physicians
LGMD2D.org

LGMD2I Research Fund
Funding research for LGMD 2I/R9 and educating the patient community
LGMD2IFund.org

LGMD2L Foundation
Representing the LGMD 2L/R12 Anoctamin5-related community
LGMD2L-Foundation.org

Team Titin
A consortium of scientists and affected community members for LGMD2J/R10 Titin-related
TitinMyopathy.com

The Jain Foundation
Funding research for LGMD 2B/R2 and educating the patient community
Jain-Foundation.org

Argentina

ADM Argentina Muscular Dystrophy LGMD Group
Funding research for neuromuscular diseases
ADM.org.ar

Australia

Daniel Ferguson LGMD2A Foundation
Funding research for LGMD 2A/R1 and educating the patient community
DFFoundation.com.au

France

"GI LGMD"/LGMD Patient Group of AFM-Telethon
Focusing on all subtypes of LGMD, supporting research and educating the patient community
LGMD.AFM-Telethon.fr

Italy

Conquistando Escalones Association
Funding research for LGMD 1F/D2
ConquistandoEscalones.org

"GFB ONLUS"/ Family Group of Beta-Sarcoglycanopathy
Representing the LGMD 2C/R5 Gamma Sarcoglycan-related, LGMD 2D/R3 Alpha Sarcoglycan-related, LGMD 2E/R4 Bèta-Sarcoglycan-related, and LGMD 2F/R6 Delta-Sarcoglycan-related communities
Beta-Sarcoglicanopathy.org

Gruppo Cingoli of UILDM – Unione Italiana Lotta alla Distrofia Muscolare
Focusing on all subtypes of LGMD, raising awareness and providing support for the entire Italian community
UILDM.org

Italian Association Calpain 3
Funding research for the LGMD 2A/R1 Calpain 3-related community
AICA3.org

Japan

Patients' Association for Dysferlinopathy Japan
Representing the Japanese and International LGMD 2B/R2 Dysferlin-related and Miyoshi Muscular Dystrophy 1 (MMD) communities
PADJ.jp/index.html

Netherlands

Stichting Spierkracht
Raising awareness and supporting the LGMD2D/R3 Alpha Sarcoglycan-related community
StichtingSpierkracht.com

Spain

Conquistando Escalones Association
Funding research for LGMD 1F/D2
ConquistandoEscalones.org

Proyecto Alpha
Funding research for LGMD 2C/R5 Gamma Sarcoglycan-related, LGMD 2D/R3 Alpha Sarcoglycan-related, LGMD 2E/R4 Bèta-Sarcoglycan-related, and LGMD 2F/R6 Delta-Sarcoglycan-related
ProyectoAlpha.org

Dr. Meredith James

Clinical Specialist Neuromuscular Physiotherapist,
John Walton Muscular Dystrophy Research Centre,
Newcastle University, Newcastle upon Tyne, UK

Jordi Diaz-Manera, MD, PhD

Professor of Neuromuscular Diseases and Consultant Neurologist
John Walton Muscular Dystrophy Research Centre,
Newcastle University, Newcastle upon Tyne, UK

Meet the Experts

Meredith James is a Clinical Specialist Neuromuscular Physiotherapist at the John Walton Centre for Muscular Dystrophy Research at Newcastle University, where she is involved in clinical and research activity for children and adults with neuromuscular disorders. In her research capacity, Meredith is responsible for the evaluation of children and adults involved in natural history and clinical trials, as well as the development of clinically meaningful, reliable and sensitive outcome measures for NMD.

Jordi Diaz-Manera, MD, PhD is Professor of Neuromuscular diseases and Consultant Neurologist at John Walton Centre for Muscular Dystrophy Research at Newcastle University and Newcastle Hospitals NHS Foundation Trust. Jordi has been working on the implementation of muscle MRI for the diagnosis and follow-up of patients with neuromuscular diseases. In terms of basic research, he has been working in unravelling the molecular pathways leading to muscle fibrosis and fat replacement. Jordi has been involved in several clinical studies related to different types of limb-girdle such as dysferlinopathies, sarcoglycanopathies, and laminopathies.

Q

Each year, as the weather gets colder, tasks become noticeably more difficult. For example, my legs actually ache and ambulation is more difficult in the cold. Can you share why this happens and what we can do to help, other than the obvious, such as dressing warmer?

A

The weakness of the muscles, especially in the lower legs, can also affect the efficiency of your circulation. Dressing warmer is important, particularly ensuring you use layers such as thermals or warm socks. Try to keep moving regularly. Talk to your local muscle team, physical therapist (PT), or occupational therapist for further advice.

Q

Is "dry needling" okay or contraindicated for LGMD (muscle pain, knots)? My physical therapist recommended this, but I want to be sure it is safe for those with muscle diseases.

A

There are no contraindications we are aware of for the use of dry needling or acupuncture for LGMD. It is utilized by many PTs for pain relief.

Q

What are some of the most commonly-used orthotics for different stages of progression in LGMDs? I want to plan ahead as my progression continues, and I keep buying items that often are not long-term planning solutions.

A

The LGMDs have differing patterns of muscle weakness, so unfortunately there is not a one-size-fits-all approach to selecting orthoses. The choice of orthoses is a team approach between yourself, your PT, and the local orthotics service. Some individuals find off-the-shelf ankle supports useful for very mild foot drop and other individuals use carbon fiber ankle foot orthoses. There are many options that can be prescribed. It is likely the type of orthoses you need will change over time.

Q

Is there any indication of gene therapy treatments having an adverse effect on fertility?

A

As far as we know, there is not.

Q

What is the best place to keep up to date on what clinical trials are happening for forms of LGMD? How can we keep up to date on the current results of ongoing gene therapy trials (whether they are showing positive results and what kind)?

A

The Speak Foundation's *LGMD News* magazine! This free resource provides great updates on research in the field. Additionally, your local neuromuscular specialist clinic should be able to provide you with up-to-date information. You can also look at other NMD patient groups and advocacy websites. Most clinical trials are listed on the **ClinicalTrials.gov** website.

Q

Are there resources for free genetic testing in the United Kingdom?

A

The genetic tests are covered by the National Health Service (NHS) and are free.

Q

Do you see more treatment options becoming available for LGMD2D patients in the near future?

A

Yes, we are convinced that gene therapy trials for LGMD2D/R3 will start very soon. Moreover, there are Italian researchers working on a series of drugs that reduce the process of sarcoglycan protein degeneration in the cells of patients with missense mutations.

Q

What should I do if I want to participate in a clinical trial? Is there anything I can do now, in terms of readiness, to prepare for the possibility of gene therapy or other treatments becoming available? What is most important for us as patients to focus on or do while we wait for treatments?

A

Stay informed, ensure you are on a patient registry, and have a local specialist neuromuscular team follow you.

Q

I am 45 years old and was recently diagnosed with LGMD2B. I was a very active person and now, with the loss of mobility, I can no longer run. I can cycle, swim, and walk. I have researched LGMD and hear that I should not do too much physical activity. At the same time, I cannot stop exercising entirely. What is the recommendation? Is it okay for me to cycle or walk for more than an hour?

A

Exercise prescription is specific to the individual, like medication. Regular exercise that you enjoy is important. If you can cycle or walk for an hour and you do not experience extreme fatigue or muscle ache the next day or two that limits your activities, then that should be safe. It is important to discuss your exercise prescription with your local neuromuscular PT, and if appropriate, other team members such as the neuromuscular neurologist. ■

Stay informed, ensure you are on a patient registry, and have a local specialist neuromuscular team follow you.

Have a Question for Our Experts?

Send Questions To:
ContactUs@TheSpeakFoundation.com

A Novel Approach to Protect Muscle from Damage

Edgewise is developing a novel approach that aims to protect muscle and prevent muscle damage. This focus on muscle protection is intended to lead to therapies for multiple types of muscular dystrophy, including certain types of limb-girdle muscular dystrophy (LGMD).

Edgewise Therapeutics, a company focused on creating novel precision medicines for the treatment of rare muscle disorders, is taking a new approach to developing therapies for patients with muscular dystrophy. Protecting and sustaining muscle health is critical in allowing individuals living with muscular dystrophies to maintain functional independence to carry out daily activities like walking, hugging loved ones, and beyond. With this in mind, Edgewise is developing a novel approach that aims to protect muscle and prevent muscle damage. This focus on *muscle protection* is intended to lead to therapies for multiple types of muscular dystrophy, including certain types of limb-girdle muscular dystrophy (LGMD).

How Does Muscle Function?

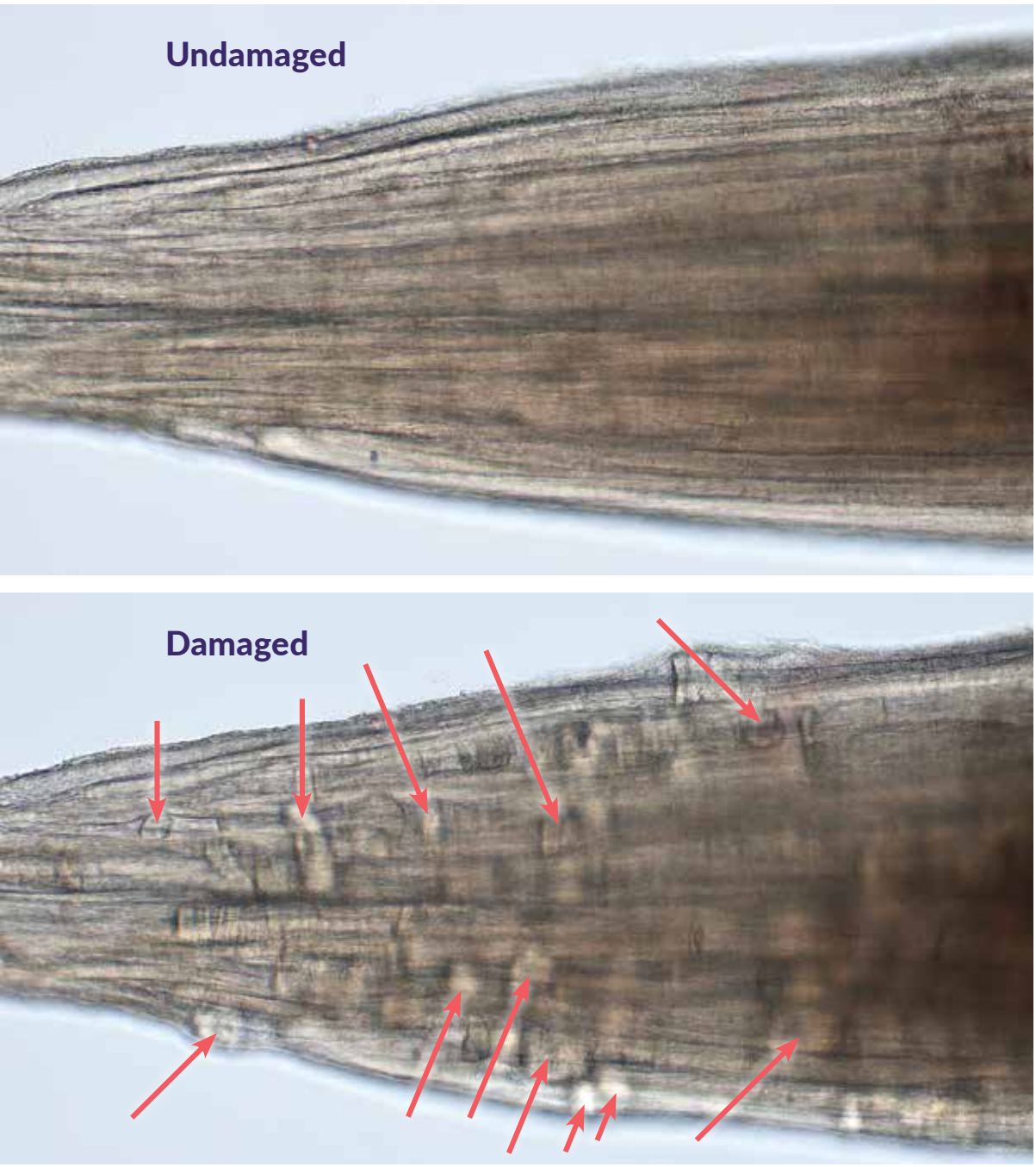
Skeletal muscles are made up of bundles of different types of fibers, called slow- and fast-type, that convert chemical energy into mechanical force, otherwise known as a muscle contraction. Slow and fast fibers behave differently to allow muscle performance over a wide range of activity levels. In both slow and fast fibers, the proteins that cause muscle contraction are myosin and actin.

How Does Muscle Damage Occur in Certain Types of Muscular Dystrophy?

In healthy muscle fibers, several structural proteins form a complex called the dystroglycan complex that connects muscle fibers to each other and to the contractile elements, myosin and actin. This enables muscle fibers to contract together as a unit and distribute force across fibers. In Duchenne (DMD) and Becker muscular dystrophy (BMD) and certain types of LGMD, one or more of these structural proteins does not function properly. In these instances, force is not distributed efficiently during contraction. Inefficient distribution of force during contraction leads to muscle fiber instability, increased injury, and breakdown. It does not matter which structural protein of the dystroglycan complex does not function properly; the resulting muscle breakdown process is the same.

This breakdown can be visualized microscopically in small muscles from mice with mutations in the dystrophin gene (which cause DMD and BMD).

In healthy muscle, fibers repair themselves through a regenerative process where new muscle fibers are regrown to replace the damaged ones. Muscle fiber regeneration occurs in



Images courtesy of Yu Su in collaboration with Sue Brooks and Dennis Claflin, University of Michigan

Left: DMD muscle (mdx mouse) suffers extensive contraction-induced injuries. Red arrows point to fibers which have succumbed to stress.

In muscular dystrophy, muscle tissue breaks down in response to daily activity and leaks out proteins into the bloodstream.

individuals with muscular dystrophy, but the elevated level of damage found in dystrophic muscle can overwhelm or even exhaust the repair process. The net result is a breakdown of the muscle, which is replaced by fibrotic (scar) and fatty tissues, leading to muscle loss and progressive loss of function.

What are Biomarkers and How Do they Help Us Understand Muscle Damage?

In muscular dystrophy, muscle tissue breaks down in response to daily activity and leaks out proteins into the bloodstream. Because muscle-specific proteins are not ordinarily

present in blood unless muscle damage has occurred, they can be used as indicators, or biomarkers, of muscle damage. By measuring and evaluating these biomarkers, we can tell a lot about how much damage is occurring. Two examples are creatine kinase (CK) and myoglobin, which are present in all muscle fibers and leak out of muscle with injury. Other proteins are specific to fast and slow muscle fibers and can be used to gauge which particular muscle fiber types are being damaged. In BMD, DMD, and specific types of LGMD, a biomarker specifically associated with fast muscle fibers is elevated, whereas biomarkers associated with slow muscle fibers are not. This suggests that fast muscle fibers incur injury and leak proteins at a greater rate than do slow muscle fibers. At Edgewise, our goal is to protect and preserve the fast muscle fibers, which are more susceptible to injury. By protecting fast muscle fibers, we hope to reduce overall damage to the muscle.

At Edgewise, our goal is to protect and preserve the fast muscle fibers, which are more susceptible to injury. By protecting fast muscle fibers, we hope to reduce overall damage to the muscle.

What is the Edgewise Approach?

Edgewise's approach focuses on protecting fast muscle fibers through modulation of the type of myosin that is present in fast fibers. Modulation of this myosin is intended to limit, but not prevent, contraction of fast fibers and allow them to contribute to muscle movement while preventing them from breaking down with use. In muscle diseases in which the dystroglycan complex does not form properly, everyday muscle use leads to ongoing injury; these diseases may benefit from myosin modulation. This includes forms of muscular dystrophy like DMD, BMD, and some forms of LGMD. In animal models of DMD, modulating fast muscle myosin stabilized and protected muscle fibers without affecting strength or coordination. In longer-term animal studies, modulating fast muscle myosin prevented muscle fibrosis and loss of strength.

What Stage is this Approach in Clinical Development?

The effects of myosin modulation have been evaluated in Phase 1 trials that included adults living with BMD. In these trials, when a novel myosin modulating compound was given by mouth once a day, biomarkers that indicate muscle damage, including CK and myoglobin, were improved. Based on these data, Phase 2 studies in individuals living with BMD and DMD to further study myosin modulation have been initiated.

Path Forward for LGMD?

We believe that myosin modulation may also be a possible therapeutic approach for the treatment of certain types of LGMD and are working toward a clinical development program to study myosin modulation in these types of LGMD. Myosin modulation is intended to stop the damage where it begins, and it has the potential to be used alone or in combination with other therapeutic approaches. By protecting muscles from damage, we intend to preserve and potentially improve muscle function. Our goal is to dramatically enhance the lives of people living with progressive muscle disorders. ■

Written by Abby Bronson
VP Patient Advocacy and External Innovation, Edgewise Therapeutics

Katherine Krieger,
Associate Director, Patient Advocacy, Edgewise Therapeutics

Breanne Stamper,
Senior Scientist, Edgewise Therapeutics

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LGMD ICD-10 Diagnosis Codes are Active and Ready to Use

After several years of advocacy led by LGMD organizations, leading clinicians, and researchers, new ICD-10 diagnostic codes are finally available and ready to use! What does this mean for the LGMD community?

First, the new codes, which became available October 1, 2022, allow individuals with any form of LGMD to have a more precise diagnostic ICD-10 code. For some, including those with LGMDs 2A/R1, 2B/R2, 2D/R3, 2E/R4, and 2L/R12, new ICD-10 diagnostic codes specific to their genetic subtype are now available. An ICD-10 code for the remaining sarcoglycanopathies (2C/R5 and 2F/R6) is also available, as is a code for all autosomal dominant LGMDs, a code for all other genetically-defined autosomal recessive LGMDs, and a code for all clinically diagnosed LGMDs without a genetic subtype identified as of yet. The advocacy organizations involved had hoped to receive subtype-specific codes for all LGMDs, particularly LGMD 2I/R9, but unfortunately this request was declined and we will need to reapply with another nomination.

Second, what benefits do these new ICD-10 diagnostic codes offer? If used widely and correctly, as discussed below, these codes can advance disease understanding by facilitating better tracking, surveillance, and understanding of the natural history of the condition. These codes should make subtype-specific treatments and care more accessible by making the genetic diagnosis more readily available within coverage and reimbursement systems. These codes will also better connect eligible patients to clinical trials for subtype-specific treatments.

Finally, what can you do to help? If you or your loved one is diagnosed with LGMD, please ensure that your providers are using the correct ICD-10 diagnostic codes in their medical records. Encourage your clinicians or medical providers to note the genetic subtype of your LGMD so that the medical coder can use the correct ICD-10 code. If your medical providers are unaware of the new ICD-10 codes, inform them! The benefits of these new codes will only extend as far as the clinical community is willing to use them and use them accurately.

The arrival of ICD-10 diagnostic codes for the LGMDs could usher in a season of progress in disease surveillance, understanding, and care. It is now incumbent on the entire stakeholder community to spread the word to ensure they reach their full promise. ■

Written by Paul Melmeyer
VP, Public Policy & Advocacy, MDA

These codes should make subtype-specific treatments and care more accessible by making the genetic diagnosis more readily available within coverage and reimbursement systems. These codes will also better connect eligible patients to clinical trials for subtype-specific treatments.

Measuring Motor Function in LGMD

This measure is of great benefit to our community, as it will facilitate clinical trials in LGMDs, and aid in monitoring patients.

Outcome measures are measurements that describe or reflect how an individual functions or feels. Functional outcome measures, where physical therapists assess movements such as getting on/off a chair or walking, are used to inform diagnosis, monitor the impact of disease on function, and guide clinical care decisions such as physical therapy programs or proactive prescription of mobility aids. Functional outcome measures are also used in natural history studies to allow us to compare individuals around the world and to determine the impact of new treatments in clinical trials.

In the past, the lack of a functional outcome measure specific to LGMD has limited the understanding of the patterns of disease progression and how to best measure the response to a new drug treatment. As part of the Jain Foundation Clinical Outcome Study of Dysferlinopathy (COS), an international cohort of 193 participants from COS were assessed six times over three years and a new outcome measure, the North Star Assessment for limb-girdle type muscular Dystrophies (NSAD) was developed. The NSAD included tasks such as rolling over, sitting up from lying down, reaching when sitting, standing, and running. The scores on the NSAD closely correlated with how participants rated how much difficulty they experienced performing activities of daily living.

To ensure the NSAD was suitable across other types of LGMD, the physical therapy teams at the John Walton Muscular Dystrophy Research Centre in Newcastle, UK and Nationwide Children's Hospital, Columbus, Ohio, collaborated and tested the scale in over 130 individuals with 14 different subtypes of LGMD. The results confirmed that the scale was appropriate for all of the LGMD subtypes. The NSAD is the first outcome measure of motor performance specifically designed for LGMD and is suitable for use in clinics and research. This measure is of great benefit to our community, as it will facilitate clinical trials in LGMDs and aid in monitoring patients. ■

Written by Meredith James, Physiotherapist
John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK

UPDATED: JANUARY 1, 2023

GRASP-LGMD Clinical Trials

Recruiting Defining Endpoints in Becker Muscular Dystrophy (GRASP-01-002)

Inclusion Criteria

Ages 8 and older:

- Clinically affected (defined as weakness during evaluation consistent with Becker Muscular Dystrophy)
- Genetic confirmation of an in-frame dystrophin mutation
- Willing and able to give informed consent and follow all protocol instructions

Ages 8–16:

- All of the above and must be ambulatory

Exclusion Criteria

Ages 8–16:

- Out-of-frame dystrophin mutation
- Inability to walk 10 meters without assistive devices
- >16 hours of ventilatory support
- Other illness that would interfere with participation or results

Ages 17 and older:

- Loss of ambulation prior to age 16
- >16 hours of ventilatory support

Recruiting Defining Clinical Endpoints in Limb-Girdle Muscular Dystrophy (LGMD) (GRASP)

Inclusion Criteria

- Age between 4–65 at enrollment
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern, or in a distal extremity)
- A genetically or functionally confirmed mutation in ANO5, CAPN3, DYSF, DNAJB6, or SGCA-G
- Ambulatory

Exclusion Criteria

- Non-ambulatory at the time of enrollment
- Any other illness that would interfere with the ability to undergo safe testing or would interfere with interpretation of the results in the opinion of the site investigator

Subtypes

- CAPN3 (LGMD 2A/R1)
- DYSF (LGMD 2B/R2)
- ANO5 (LGMD 2L/R12)
- DNAJB6 (LGMD 1D/D1)
- Sarcoglycan (LGMD 2D/R3, LGMD 2E/R4, LGMD 2C/R5, LGMD 2F/R6)

Contact: **Jessica St. Romain** | Project Manager, Grasp-LGMD Consortium | (804) 828-7887 | *Jessica.Stromain@vcuhealth.org*

GRASP-LGMD Consortium Members


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Jordi Diaz-Manera, MD, PhD | Newcastle University


Vijay Ganesh, MD, PhD | Brigham and Women's Hospital


Meredith James | Newcastle University


Nicholas Johnson, MD, MSci, FAAN | Virginia Commonwealth University


Peter B. Kang, MD | University of Minnesota Medical School


Monkol Lek, PhD | Yale University, Non-Clinical Site


Doris Leung, MD, PhD | Hugo W. Moser Research Institute at Kennedy Krieger


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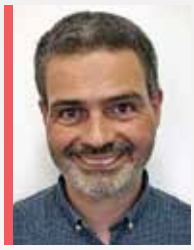
John Vissing, MD | University of Copenhagen


Conrad "Chris" Weihl, MD, PhD | Washington University in St. Louis


Matthew Wicklund, MD | University of Colorado Denver

Spotlight: GRASP-LGMD Researchers


Dr. Meredith James


Dr. Jordi Diaz-Manera

Our GRASP-LGMD experts are from the John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK. **Dr. Meredith James** is a neuromuscular physiotherapist (often referred to as a physical therapist in the US) with long experience in the assessment of LGMD patients and **Dr. Jordi Diaz-Manera** is a neurologist specialized in neuromuscular diseases.

Gene Therapy 101

Produced by
Sarepta Therapeutics

Sarepta Therapeutics is a biotech company headquartered in Cambridge, Massachusetts. We have over 20 gene therapy programs in development, including for limb-girdle muscular dystrophy types 2E/R4, 2D/R3, 2C/R5, 2B/R2, 2L/R12, and 2A/R1.

The science of gene therapy is complicated—Sarepta is committed to providing educational resources for rare disease communities to improve understanding of this investigational treatment approach. To do this, we're kicking off a four-part educational series, where we'll delve into questions and topics the community has asked about, such as:

What is the goal of gene therapy?

Why is gene therapy currently a one-time treatment?

How is gene therapy evaluated in clinical trials?

How long are the therapeutic effects of gene therapy expected to last?

Look for more Gene Therapy 101 in the next few issues.

If you're interested in learning more, here are a few additional ways to connect with us:

TEST YOUR KNOWLEDGE

Scan the QR code to visit limbgirdle.com and quiz yourself on the topics featured in this article

FIND MORE INFORMATION

Visit our YouTube channel to watch our GT-FAQ series, featuring short videos on gene therapy science

ASK A QUESTION

Have more gene therapy science questions? Have comments, or just want to connect? Email us at Advocacy@Sarepta.com

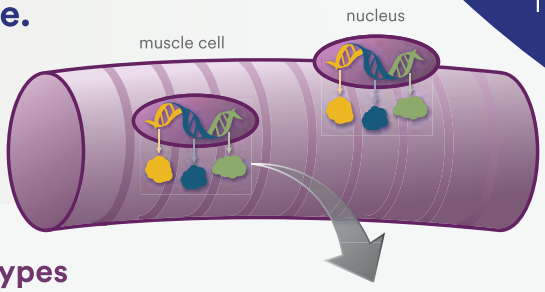
SAREPTA THERAPEUTICS

Intended for US audiences

What is the goal of gene therapy?

Gene therapy aims to slow or stop progression of a specific genetic disease.

HOW? To begin, let's first look at what may cause a genetic disease.

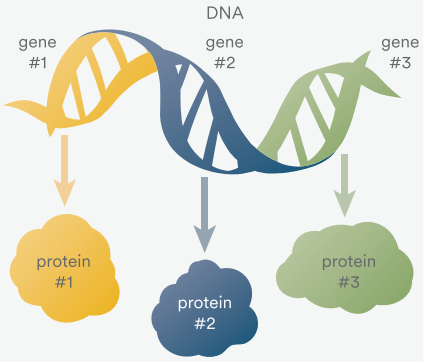


A person's body is made up of different types of cells, like muscle cells.

"DNA at Work"

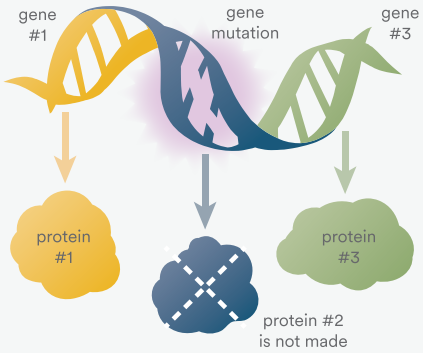
Inside the nucleus of muscle cells is a set of the person's own DNA. DNA is divided into segments called genes, which provide the instructions for making proteins.

Proteins are considered the building blocks for how the body functions. Simply put, they do important jobs that help keep cells, and therefore a person's body, healthy.



Genetic Disease

Sometimes a person may have a gene mutation, or change, which can result in not enough of an important muscle protein being made. If this happens, there may not be enough protein to do its job correctly. A person's muscles may not function properly as a result, and a person may be diagnosed with a genetic disease through genetic testing.

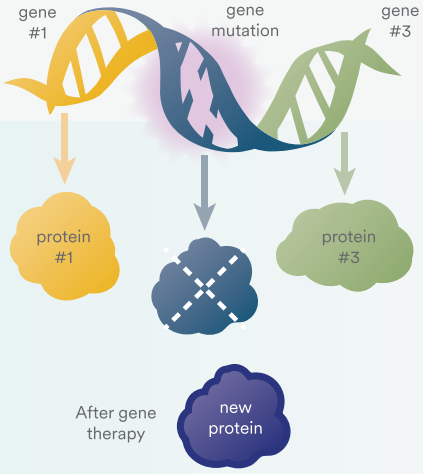


So, how does gene therapy aim to slow or stop progression of a disease?

After Gene Therapy

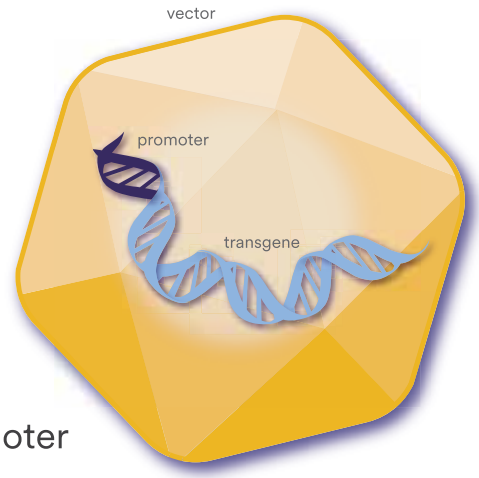
Gene therapy has the potential to help the cell to make a new protein, which is designed to do the job of the missing protein.

With the new protein now doing the important job in the cell, the hope is that the disease's progression would be slowed or stopped.



What are the key components of gene therapy?

There are three main components of gene therapy:



1. **Vector** – the vector aims to deliver the promoter and transgene to the disease-impacted cells
2. **Promoter** – the promoter aims to tell the cell to begin making the new protein if it's been delivered to the right place in the body
3. **Transgene** – the transgene is a functioning copy of a gene that aims to give the cell instructions to make a new, therapeutic protein

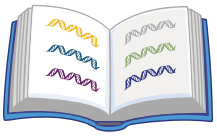
Not all gene therapies are the same.

The vector, promoter, and transgene may differ across investigational gene therapies, even if they are being developed to treat the same disease.

SAREPTA THERAPEUTICS

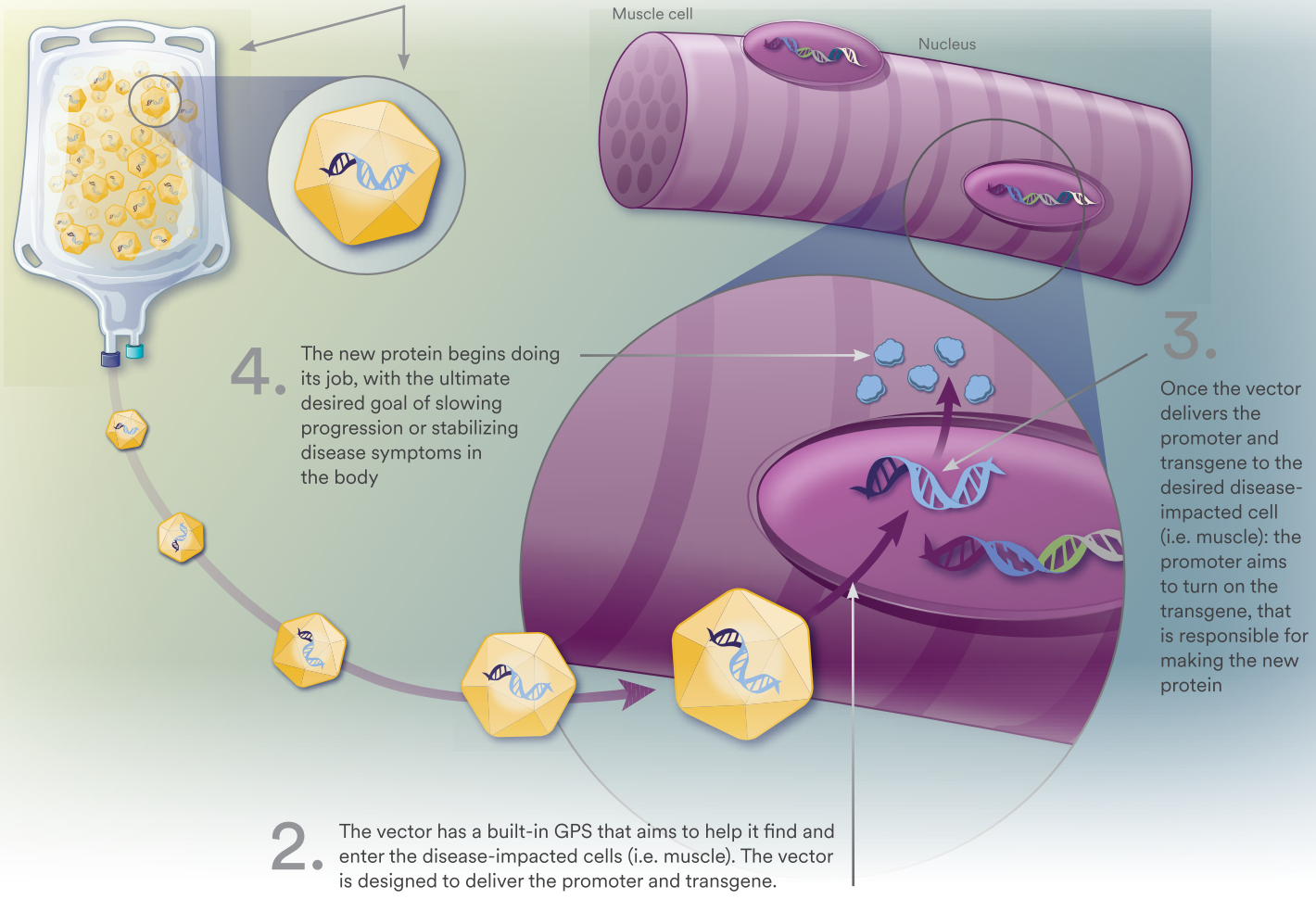
Intended for US audiences

How does gene therapy work?



Gene therapy aims to deliver the right instructions to cells so that they can make the new protein.

The vector, promoter, and transgene work together to help accomplish the intended goal:



Want to test your knowledge?

Scan the QR code to take a short gene therapy quiz on limbgirdle.com.
If you have questions or comments for us, email us at Advocacy@Sarepta.com.

Written By Hannah Oosterlinck
Executive Director, Muscular Dystrophy Family Foundation

Helping Drivers with Muscular Dystrophy

For over 60 years, the Muscular Dystrophy Family Foundation (MDFF) has provided support to help people with muscular dystrophy.

MDFF was founded in 1958 by four fathers of sons with Duchenne muscular dystrophy determined to help Indiana families struggling with MD. In the future, our hope is to extend beyond the state of Indiana into other states, since most states do not have an organization focused on muscular dystrophy and providing direct financial support.

MDFF is a small, but strong and mighty organization led by Tim Doyle, President of MDFF. Tim is the last surviving member of the five siblings in his family who had muscular dystrophy. He lives with limb-girdle muscular dystrophy and has been a wheelchair-user for over 30 years. His experience and extensive knowledge of business, accounting, and fundraising has led to MDFF being the thriving nonprofit it is today.

While advancements and treatments for the disease provide hope, our immediate goal continues to be to provide families with equipment, home modifications, and services they need to eliminate some of the day-to-day challenges that come with living with a neuromuscular disease. We also provide events, such as our Zoo Day, Expo, Children's Museum Day, and Holiday Party to bring families together and connect them with resources. In addition to events and direct financial assistance,

Meet MDFF's Previous Van Recipients

Maddox
2021 Accessible Van Giveaway Recipient

Elliott
2021 Accessible Van Giveaway Recipient

DaMarri & Dairrean
2020 Accessible Van Giveaway Recipients

MDFF also does an annual accessible van giveaway. This program involves an application process for Hoosier families to apply for consideration to receive a fully funded, accessible van customized to suit their specific needs.

Thanks to the generosity of the community, MDFF is giving away four accessible vans in 2022, which marks a record of the most vans we have given away in a year's time. MDFF is paying the cost for three of the vans, and the fourth comes to MDFF through a generous, anonymous donor who wished to bless a family in Fort Wayne. This brings the total to 12 accessible vans given away over the past seven years. Apart from the van donated to MDFF, the organization pays for the vans, conversion costs, and updates, while mobility dealer Superior Van & Mobility works to customize the van for each family.

In 2022 alone, MDFF has given away over $240,000 in equipment, vehicles, and resources that families have needed to improve their day-to-day lives with MD. While we do not have a cure for the many forms of MD, MDFF hopes that lifting some of the burdens from our families will make these diseases a little easier to live with.

To learn more or support the work of MDFF, please visit **MDFF.org** ▪

Kamaria
2020 Accessible Van Giveaway Recipient

Van Baren Family
2019 Accessible Van Giveaway Recipient

Jacobs Family
2018 Accessible Van Giveaway Recipient

Patients Who Have Gone Into Science Series

PART 4 Dr. Vovanti Jones, MD

LGMD2B/R2

Written By Brad Williams, PhD
Director of Research, Jain Foundation
and John Faver

A Diagnosis Turned Into a Mission

As a young child, Vovanti Jones was fascinated with medicine. "Since age four, as my dad tells it, I would wonder about how one goes from being a tiny baby to an elderly adult." Vovanti's mother was an elementary school educator. "She dedicated her life to opening the minds of children and supporting them," Vovanti continues. "This made me want to help those who have medical problems."

Today, Dr. Vovanti Jones is the Medical Director of the Stroke Inpatient Rehabilitation Unit at Rusk Rehabilitation Hospital in Columbia, Missouri, and the Co-Director of the MDA and ALS clinics at the University of Missouri. She also lives with LGMD2B/R2, giving her a unique perspective as she treats patients adapting to physical challenges and living with neuromuscular diseases.

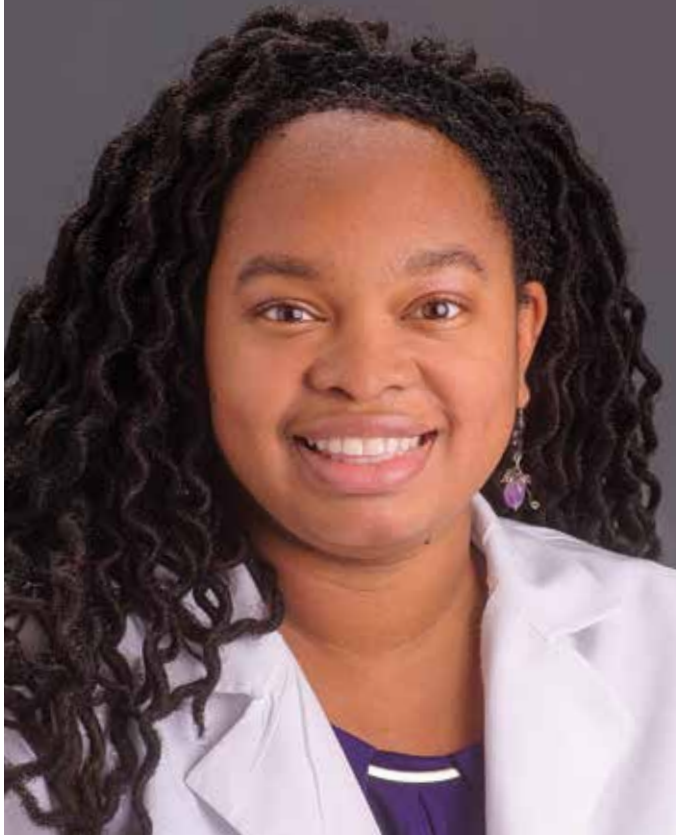
"Being a person with a disability, I feel that sometimes my connection with patients is different; more understanding than they might have with other physicians." Dr. Jones feels that patients can sometimes be more straightforward with her about their physical challenges, compared to able-bodied physicians. She observes that "We need people with disabilities in medicine."

"We need people with disabilities in medicine."

Being diagnosed with LGMD shortly before she was about to apply to medical school added a major challenge to Vovanti's goal of a career in medicine. "After my diagnosis, there was a short period where I doubted whether I would be able to handle the physical challenges that medical school presented. My family and several mentors encouraged me to continue applying to programs, so I did, and well… I got in!"

Nevertheless, the progression of LGMD impacted Vovanti's experience of medical school. While she had always envisioned herself being an obstetrician, she realized that the long hours and physical demands of obstetrics made it an impractical choice for her.

Also, she was initially admitted to an MD-PhD program, which involves a research component before clinical rotations. Vovanti was worried that the progression of LGMD would make the rotations more difficult the longer she had to wait to complete them. Therefore, she made the difficult decision to transition to an MD-only track.



Left: Despite difficulties, Dr. Vovanti Jones is compelled to play a pioneering role as a person with a disability in medicine.

"Going into medicine is hard, even for able-bodied students. It will take dedication and some ingenuity to get through it, but the reward can be sweet."

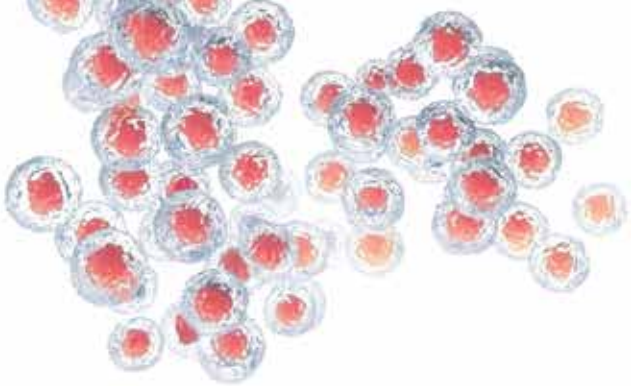
However, as Vovanti observes, "With the loss of one dream came the rise of another." She was introduced to the field of physical medicine and rehabilitation (PM&R) somewhat randomly during a rotation in medical school—and loved it. After spending the next two years of medical school exploring different aspects of PM&R, she decided this was the field for her.

Dr. Jones acknowledges that LGMD has posed numerous challenges during her medical career: "The first one that comes to mind is trying to avoid a slip on the formaldehyde in the anatomy lab while I navigated it with a cane." Despite difficulties, she was compelled to play a pioneering role as a person with a disability in medicine. "My medical school never really had someone with my level of disability, so I had to forge a path on my own."

This not only involved physical adaptations but also influencing the mindsets of co-workers. On one occasion, a rotation supervisor made assumptions about Vovanti's limitations—without asking her. "She had it in her mind that I had limited function, and decided to limit me without even discussing my capabilities." Ultimately, Dr. Jones was able to resolve the situation "by advocating for myself and my disability." Other supervisors were much more helpful and took the time to work with her to find the best ways to make accommodations.

Dr. Jones recommends that people with disabilities pursuing medical careers utilize the disability services office in their medical school or hospital, as they may be able to suggest and offer a variety of accommodations. "Going into medicine is hard, even for able-bodied students. It will take dedication and some ingenuity to get through it, but the reward can be sweet," states Dr. Jones.

Having the benefit of a dual perspective, Dr. Jones shares some final thoughts on how the doctor-patient relationship can be improved for people living with limb-girdle muscular dystrophy. "To the patient community, I will say that medicine is a diverse field. Not all physicians will have heard of LGMD. Be patient with your doctors as they try to learn with you. Educate them about your experiences. To clinicians, I would say don't make assumptions. Talk to your patients and don't automatically limit them based on your preconceived notions on disability. Sometimes small modifications can be the difference between an independent life and isolation." ■



Written By **Rita Perlingeiro, PhD**
Professor of Medicine, University of Minnesota

Advances in Stem Cell Therapies for Muscular Dystrophies at the University of Minnesota

The major focus of the research group led by Dr. Rita Perlingeiro at the University of Minnesota is the development of stem cell-based therapies for patients with skeletal muscle disease, including and especially muscular dystrophies.

When muscle is damaged, the resident muscle stem cells, called satellite cells, are called into action. They proliferate and regenerate muscle fibers lost to the damage. At the same time, in order to maintain the long-term regenerative ability of the muscle, some of the cells need to be held in reserve, to repopulate the stem cell pool, rather than generate new muscle fibers. The premise of Dr. Perlingeiro's research program is that a cell therapy needs to be able to regenerate new, healthy

Dr. Perlingeiro and collaborators are optimistic they are putting together a strong pre-IND package and are hopeful that, in the near future, stem cell-based interventions will represent a therapeutic option for patients with muscular dystrophies.

Dr. Rita Perlingeiro

muscle fibers, but also to repopulate the stem cell pool with healthy stem cells. Such a therapy provides both short-term repair to damaged muscle and long-term capacity to replace fibers as they are lost and repair future damage. The approach the laboratory has taken to generate such cells is to derive them in vitro from pluripotent stem cells. The laboratory has used this approach in preclinical studies evaluating long-term therapeutic effects in animal models of Duchenne muscular dystrophy (DMD), limb-girdle muscular dystrophies (LGMD), and facioscapulohumeral muscular dystrophy (FSHD), among others.

Pluripotent stem cells (i.e., embryonic or adult reprogrammed stem cells, referred to as iPS cells) are an attractive source for cell-based therapeutics because they have unlimited proliferative potential but can also be coaxed to differentiate into all cell types of the body. The Perlingeiro group developed an approach focused on the use of natural regulators of muscle development, the Pax3 or Pax7 genes, to recapitulate muscle development from pluripotent stem cells in the tissue culture dish, which leads to the production of large numbers of mouse and human skeletal muscle progenitor cells. Once transplanted into mouse models of DMD, LGMD2I/R9, and FSHD, these cells can ameliorate the disease phenotype by restoring functional muscle. Importantly, a portion of the transplanted cells seeds the muscle stem cell compartment, and accordingly, the presence of donor-derived muscle is persistent (>12 months). With grant support from the National Institutes of Health (NIH) and advocacy organizations such as the LGMD2i Fund and the Coalition to Cure Calpain 3, the Perlingeiro research team has also combined this approach with CRISPR/Cas9 gene-editing techniques, which enabled the genetic correction of fukutin-related protein (FKRP) and Calpain 3 (CAPN3) in iPS cells from patients with LGMD2I/R9 and LGMD2A/R1, respectively. Importantly, besides in vitro validation of gene correction in iPSC-derived generated myotubes, the investigators demonstrated in vivo rescue of dystrophic phenotypes using relevant mouse models for LGMD2I/R9 and LGMD2A/R1. For this, the Perlingeiro lab collaborated with Dr. Qi Lu from the Carolinas Healthcare System and Dr. Melissa Spencer from UCLA, who provided FKRP^{P448L} and CAPN3-KO mice, respectively. The Perlingeiro team then generated immunodeficient counterparts of these mouse models of LGMD, thus providing a receptive environment for the engraftment of human myogenic progenitors. Of note, for FKRP, the developed gene correction approach is universal, as it replaces the entire mutant open-reading frame with the wild-type sequence, thus it is able to correct all FKRP mutations. In the case of CAPN3, the developed strategy corrects all mutations downstream of exon 15. These studies provide proof-of-principle for the future development of autologous cell transplantation for FKRP and CAPN3-associated muscular dystrophies.

For muscular dystrophies, either autologous (donor cells are from the patient themselves) or allogeneic (donor cells are from another individual), cell transplantations have the potential to lead to an effective treatment. For allogeneic transplantation, one would utilize iPS cell-derived myogenic progenitors obtained from a healthy donor, which following transplantation would give rise to donor-derived, new, healthy myofibers and muscle stem cells. As mentioned above, the autologous approach would require in vitro genetic correction of dystrophic iPS cells prior to transplantation. This would allow for personalized medicine, and thus it would circumvent the issue of immune rejection. Although exciting, the autologous route may not be the most feasible option at this time due to the high cost for the manufacturing of a cell product that is suitable for only one patient. One of the major limiting factors is the length of time it takes to generate, to genetically correct, to screen, as well as to characterize properly-corrected selected clones that are in accordance with Food and Drug Administration (FDA) regulations, which further significantly augments the cost. To bypass this feasibility issue, there has been significant investment by several institutions worldwide in the establishment of universal donor iPS cell banks, also referred to as the HLA haplobank model, which allows for the selection of matched donors to generate graft material that will require only limited induction immunosuppression. In this scenario, the same iPS cell line may be used for multiple patients in addition to multiple indications (several types of muscular dystrophies). Thus, an allogeneic iPS cell-based therapy is a practical option in the first instance since it eliminates a number of the constraints associated with the autologous setting. At the same time, manufacturing, scalability, and safety studies of an allogeneic product will also support feasibility for eventual application of autologous products.

With this in mind, and triggered by the robust proof-of-concept studies acquired in the last decade, together with a team of experts at the University of Minnesota, the Perlingeiro team began working on the roadmap to develop a stem cell-based treatment for muscular dystrophies. With Dr. David McKenna, director of the Molecular Cellular Therapeutics (MCT) Facility, the Perlingeiro laboratory adapted culture methodologies in accordance with current good manufacturing practices (cGMP), and optimized purification and expansion. These efforts resulted in the successful production of several cGMP runs of iPS cell-derived myogenic progenitors, referred as MyoPAXon. These cells are frozen and can be used off-the-shelf; thus the team has the materials necessary for a near-future clinical trial. With Dr. Robert Schumacher, director for the Center for Translational Medicine, the group designed and is currently performing preclinical studies on the cGMP cells in preparation for an investigational new drug (IND) submission to the FDA. Optimization and preclinical studies were funded by grants from the Department of Defense and Duchenne UK.

The planned clinical trial will be led by Dr. Peter Kang, director of the Muscular Dystrophy Center at the University of Minnesota. In preparation for the trial, another member of the team, Dr. Peter Karachunski, is using ultrasound and MRI imaging approaches to evaluate the suitability of muscles to be targeted, in view of the desire to deliver muscle stem cells into an environment that is still conducive to new muscle formation. Dr. John Wagner, director of the Institute for Cell, Gene, and Immunotherapies at the University of Minnesota, is playing a pivotal advisory role by sharing his expertise with clinical trial design, FDA interaction, and clinical trial execution. Finally, as part of the effort to raise funds to support the clinical development of this cell therapy, Dr. Perlingeiro, together with collaborator Dr. Michael Kyba and entrepreneur Al Hawkins, have cofounded the startup company, Myogenica.

Having had positive feedback as well as valuable suggestions from the TREAT-NMD Advisory Committee for Therapeutics and the FDA through a pre-IND interaction, Dr. Perlingeiro and collaborators are optimistic they are putting together a strong pre-IND package and are hopeful that, in the near future, stem cell-based interventions will represent a therapeutic option for patients with muscular dystrophies. ■

By Douglas Sproule, MD, MSc
Chief Medical Officer, ML Bio Solutions

Why are Biopsies Important in Clinical Trials?

How Do Healthy Muscles Work?

Just like cooks have a cookbook full of different recipes, our bodies use our genetic code to determine how our bodies are made and how each part functions. For example, there is a recipe that dictates how a healthy muscle cell is made and how it works. Ingredients such as enzymes, sugars, and proteins, among other additions, make up healthy muscle cells. When these muscle ingredients work together, the muscle cells can expand and contract. This contracting and expanding makes the whole muscle, and hence our bodies, move.

The fukutin-related protein (FKRP) gene makes an important enzyme that works with another important ingredient, a protein called "alpha-dystroglycan" (aDG). In healthy muscles, aDG, along with other muscle ingredients, acts as a shock absorber that stabilizes the moving muscles to prevent damage when used. However, to work properly and stabilize the moving muscle, aDG must go through a process called "glycosylation." The FKRP enzyme helps aDG go through the glycosylation process. During this process, the FKRP enzyme and other enzymes on the surface of muscle cells attach long chains of sugars called "glycans" to aDG. These glycan chains then attach aDG to the muscle cell structure in order to soften the shock of muscle cell contractions. Glycan chains help anchor aDG in place to support its role as a shock absorber for the muscle cells.

What Causes Limb-Girdle Muscular Dystrophy Type 2i (LGMD2i)?

LGMD2i is caused by mutations in the FKRP gene. In muscles affected by LGMD2i, the FKRP enzyme does not work well, and as a result, aDG is not properly glycosylated. When aDG is not properly glycosylated, it is not able

Healthy muscle cells are designed to absorb the shock of movement to prevent damage when used.

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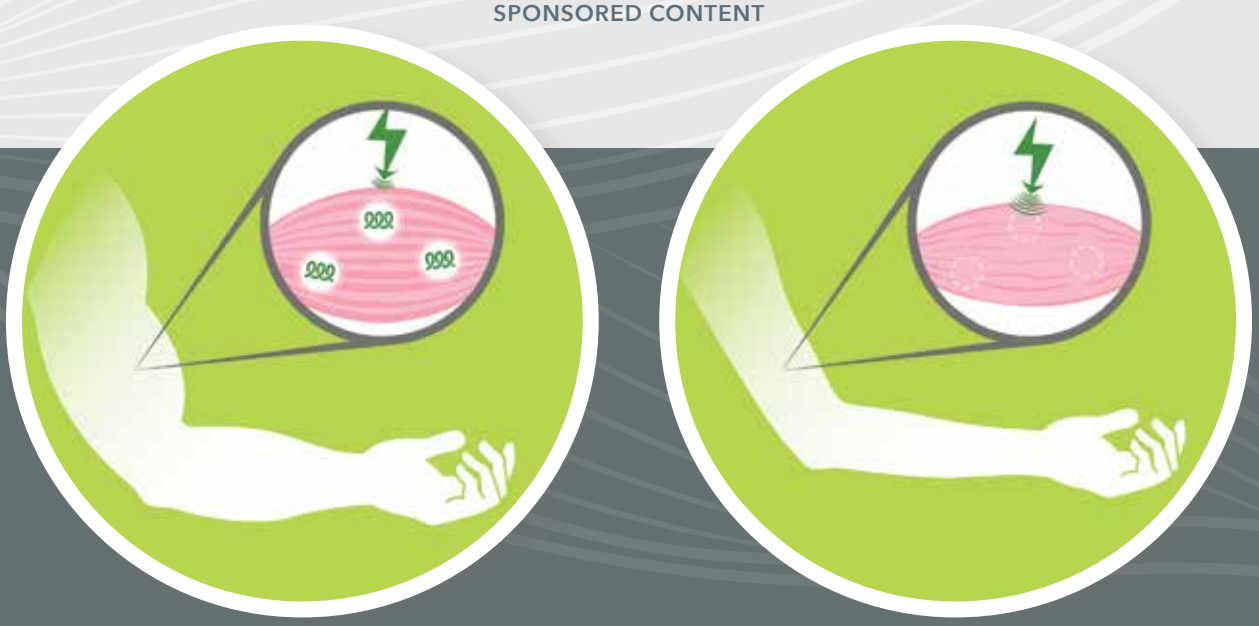
a bridgebio company



A protein called "alpha-dystroglycan" (aDG) acts as a shock absorber that stabilizes and prevents damage in healthy muscles as they contract.

In muscles affected by LGMD2i, the shock absorber function does not work well, which leaves muscles fragile and susceptible to damage.

to anchor to the muscle cell, making the muscle fragile and prone to damage—even with normal, everyday use. Simply walking can damage the muscle of someone with LGMD2i about as much as a marathon run damages healthy muscle. Even healthy muscle could not survive several marathons every day, 365 days a year; the muscle would continually break down and be replaced by scar tissue. This is because repair mechanisms in our body cannot keep up when the muscle damage is simply too much and too frequent. At some point, there is so much scar tissue and so little muscle that the muscle can no longer do its job.

Can We Measure the Amount of Glycosylated Alpha-Dystroglycan in Muscles?

Individuals with LGMD2i have reduced levels of glycosylated aDG. Unfortunately, we cannot yet measure the glycosylation of aDG with a simple blood test. The good news is that ML Bio Solutions has developed a test using a tiny piece of muscle, which allows us to measure the glycosylation of aDG or, in other words, the amount of glycan chains attached to aDG. This piece of muscle can be obtained using a fine needle biopsy, for example, in the shin area.

How Might a Therapy Help LGMD2i Muscles?

One way to make an LGMD2i muscle less fragile is to help restore the shock absorbing capabilities of aDG by adding glycan chain attachments between aDG and the muscle cell structure. Fine needle biopsies, before and during treatment, can be used to see whether a potential treatment for LGMD2i has been able to impact the muscles at the cellular level. It is possible that a therapy that could help increase the amount of glycosylated aDG may improve muscle function by increasing the shock absorbing mechanism in muscle cells.

Biopsies before and during treatment can be used to see whether a potential treatment for LGMD2i has been able to impact the muscles at the cellular level.

Written By Dale Short

Engineering Pathways to Access

They do double takes as I pass on my three-wheeled, adaptive mountain bike (aMTB). The electric motor whirs as they murmur 'Oh, that's so cool…'

Scanning the trail ahead, I see no option but to go over the watermelon-sized rock jutting out from the middle of the path. I ease the throttle and place my right front wheel against it.

"Spot my roll hoop in case I tip too far," I say to my friend Pat as he lays down his mountain bike.

Pat stands beside me with one hand on the metal tube that loops over my head, bracing it. I punch the throttle and the rear tire skids for a second, then bites the ground beneath me, and the bike lurches over the rock.

"You're clear!" Pat shouts.

I'm already bouncing down the trail ten feet past the rock. Jesse, the trail builder, mutters, "We'll have to sledgehammer that rock," as I pass by.

We're a mountain bike caravan of four riders a mile into the woods, well beyond the parking lot with its painted blue handicap spots. The dog walkers hiking the trail pay little attention to my three companions other than to step aside to let them pass by on their normal bikes. However, they do double takes as I pass on my three-wheeled, adaptive mountain bike (aMTB). The electric motor whirs as they murmur "Oh, that's so cool…"

Our destination is the start of New Jersey's first adaptive rated mountain bike trail. The organizations building it, the Jersey Off-Road Bicycle Association, the New York-New Jersey Trail Conference, and Marty's Reliable Cycle, all want me — an adaptive-rider — to test their progress. I swoop down the wide, packed dirt turns of the newly-built trail. For a quarter mile, I'm thrilled to feel the pull of gravity, the dust in my eyes, the smell of dead leaves, and just a little fear of a skinned elbow if I crash. At the bottom, I skid to a stop and the trail-building crew looks to me for a verdict.

"It's amazing!" I say with a huge grin as I start to turn around to go for a second pass.

I biked thousands of miles growing up, but as I got older, hills became harder to manage. In 2013, at the age of 22, I was diagnosed with limb-girdle muscular dystrophy type 2A/R1. When I received my diagnosis, I wished that I had gone to college for biology or medicine so that I could do something to change my disease. Instead, with a degree in mechanical engineering, I swore to build myself whatever I needed to stay active.

Inspire

When I received my diagnosis, I wished that I had gone to college for biology or medicine so that I could do something to change my disease. Instead, with a degree in mechanical engineering, I swore to build myself whatever I needed to stay active. I've now turned my garage into a machine shop that operates as my personal laboratory to conceptualize, design, and build adaptive equipment.

I've now turned my garage into a machine shop that operates as my personal laboratory to conceptualize, design, and build adaptive equipment. When crossing the sandy dunes at the Jersey Shore started to feel too difficult, I built a carbon fiber sand-scooter. It's a combination of golf cart, ebike, and tuk-tuk parts that allows me to join my family on the beach. When I began to need a scooter to go on errands, I made a folding trunk crane from an ATV winch that picks my scooter up and lowers it into the back of my car. Even less ambitious projects like custom grab bars and railings for friends' houses make a big difference in my ability to access spaces.

My latest creations have opened up the world of adaptive mountain biking to me. When I saw Instagram videos produced by Bowhead, an aMTB manufacturer, showing paraplegic riders tearing through the woods, I instantly knew I had to own one. Actually, it would be more accurate to say, "I needed to find a way to get off of one!" As anyone with LGMD knows, rising from a seated position only a few inches off the ground is nearly impossible! To get around this barrier, I designed a hitch-mounted lift that fits onto the back of my car. I drive the bike onto the lift and activate a hydraulic ram, which elevates me and the bike to standing height so that I can independently get off the bike.

More and more groups, such as Rocky Mountain Adaptive and Kootenay Adaptive Sports, are offering accessible recreation experiences. I encourage you to find or start one in your own community. You do not need to be an engineer to create a simple piece of equipment that will make a meaningful difference in your life. I think almost everyone with a disability has created at least one device of their own, whether a plywood scrap to serve as a transfer board or a rope to close a door behind a wheelchair. Remember, when you are faced with watermelon-sized rocks in your trail, skinned elbows don't have to be the outcome! With some innovation, friends, and the right bike, you can traverse any bumps in the road. ▪

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