Vol 3 / Issue 3

LGMD News

Uniting the Limb-Girdle Muscular Dystrophy Community

GENE THERAPY 101

Part Three of Sarepta Therapeutics' Educational Series

THE SMALL4RARE GROUP

A Small Molecule-Based Approach for Sarcoglycanopathies

Living a Fulfilling Life

Mélanie Bordes shares her story of hope, challenges, adjustments, goodbyes, and new beginnings

A COMMUNITY FOR DYSFERLINOPATHY PATIENTS IN KOREA

Introducing the Korea Dysferlinopathy Patient Association

ML BIO SOLUTIONS

Evaluating the Clinical Trial Option

fortify

Fortify is a Phase 3 clinical trial evaluating if an investigational oral therapy (BBP-418) is safe and effective for treating Limb Girdle Muscular Dystrophy type 2I / R9, FKRP-related (LGMD2I/R9)

About Fortify

Fortify is a randomized, double-blind, placebo-controlled trial for individuals with genetically confirmed LGMD2I/R9 measuring patient response to treatment by measuring both biomarkers and clinical assessments. For every three study participants, two will receive BBP-418 treatment and one will receive placebo.

About the Therapy

In patients with LGMD2I, the enzyme FKRP does not work properly. FKRP is responsible for a critical step in a process called "glycosylation," whereby a crucial string of sugars are added to the alpha dystroglycan (α-DG). Without this string, α-DG does not work correctly in its role as a "shock absorber" for muscle fibers. BBP-418's theoretical mechanism of action supplements the FKRP enzyme by adding more of the molecule that FKRP normally reacts with to drive residual activity of FKRP and helping it to stabilize muscle cells and act as a shock absorber. BBP-418 is an investigational therapy and is not yet approved by any health authorities for the treatment of LGMD2I/R9.

Who Can Participate

You may be eligible to participate in Fortify if you:

- Have a genetically confirmed diagnosis of LGMD2I/R9
- Are 12 to 60 years of age
- Have not used ribose or systemic corticosteroids prescribed for the treatment of LGMD or other investigational therapies for the treatment of LGMD within 90 days of screening

There are other requirements to participate in Fortify. A physician or study team member will help determine if you are eligible to participate and if this study is a good fit for you. Speak with your physician about your ability to participate in Fortify.

Fortify Locations:

The trial will be conducted at clinical sites in the United States and Europe.

Additional information about our BBP-418 study is available at **www.clinicaltrials.gov** and at **www.mlbsolutions.com**.

Scan to visit our website

ML Bio Solutions

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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 personally. The Speak Foundation helps our voices to be heard.

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Exciting Plans for the 2023 LGMD Conference

It's because of your support that we're able to organize events like the International LGMD Conference and resources such as LGMD News magazine.

Connect with Us

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TheSpeakFoundation.com

This is a very exciting time. We've been busy organizing the International LGMD Conference, which will take place in Washington, D.C. in October. It is a challenge to cover everything that's happening in LGMD research, clinical trials, and drug development in just three days — but it's a good problem to have! There's just so much to talk about and so much progress to share. We'll have updates on several clinical trials covering different LGMD subtypes, and on new treatment approaches.

In addition, we'll hear about natural history studies, and how they're making LGMDs ready for successful clinical trials, and (taking advantage of the DC location) hear about advocacy initiatives, as well as presenters from government agencies, including our keynote speaker, Dr. Peter Marks of the FDA.

Beyond providing these updates, the Conference creates a spirit of community among the attendees. At the first Conference, held in Chicago in 2019, we heard from so many people how they'd never met another person living with LGMD, and that suddenly they felt less alone in living with this disease.

The 2021 Conference was held virtually due to the COVID pandemic. We were happy with how it turned out, and how our community adapted to this unprecedented situation. But there's just something about meeting in person with others who share experiences that can't really be replicated virtually. Be sure to read through the comments from patients, clinicians, and industry partners in this issue (Article: *The Value of Connecting in Person*) about how much they gained from attending in 2019. We're so happy to be able to meet up in person again this year. We hope you will join us!

It's because of your support that we're able to organize events like the International LGMD Conference and resources such as *LGMD News* magazine. To donate to our foundation, please reach out to one of our coordinators at ***ContactUs@TheSpeakFoundation.com***. Your help is needed for us to continue our work! ▪

Kat Bryant Knudson

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

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 R1/2A 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 R19/2S
CamronsCure.com

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

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

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

LGMD Awareness Foundation
Raising awareness of and advocating for the LGMD community
LGMD-Info.org

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

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

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

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

Team Titin
Strengthening the titin community: LGMD R10/2J
TitinMyopathy.com

The Jain Foundation
Funding research for LGMD R2/2B 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 R1/2A 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 D2/1F
ConquistandoEscalones.org

"GFB ONLUS"/ Family Group of Beta-Sarcoglycanopathy
Representing the LGMD R5/2C Gamma Sarcoglycan-related, LGMD R3/2D Alpha Sarcoglycan-related, LGMD R4/2E Bèta-Sarcoglycan-related, and LGMD R6/2F 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 R1/2A Calpain 3-related community
AICA3.org

Japan

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

Netherlands

Stichting Spierkracht
Raising awareness and supporting the LGMD R3/2D Alpha Sarcoglycan-related community
StichtingSpierkracht.com

South Korea

Korean Dysferlinopathy Patients Association
Providing patients with LGMD R2/2B information and research updates
Cafe.Naver.com/UniteDsyferlinopathy

Spain

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

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

Katherine Mathews, MD, FAAN

University of Iowa

Meet the Expert

Katherine Mathews MD, FAAN is a neurologist and pediatrics specialist affiliated with the University of Iowa. Dr. Mathews has been practicing medicine for more than 30 years. Her current positions include Professor of Pediatrics and Neurology; Director, Iowa Neuromuscular Program; Co-Director, Muscular Dystrophy Clinic; and Vice Chair for Clinical Investigation, Department of Pediatrics. Dr. Mathews directs an ongoing natural history and outcome measure study of the dystroglycanopathies, is the site PI for a number of industry-sponsored clinical trials for neuromuscular diseases, and is active in the clinic, caring for patients with all types of neuromuscular diseases.

Q

What protein and supplements are best for LGMDs? Can I safely combine supplements for calcium hydroxymethylbutyrate (HMB), Coenzyme Q10, Creatine, Chondroitin, and Glucosamine?

A

Different doctors have different recommendations regarding supplements. I generally encourage a healthy diet with lots of colorful fruits and vegetables instead of supplements. Be aware of a few points when taking supplements. Supplements are not regulated by the FDA so the ingredients in the pill might not match what is on the label. This has been well documented in chemical testing. This becomes particularly problematic when taking several supplements. Second, many supplements have side effects or toxicity if taken in excess. Creatine, for example, can cause kidney injury. Third, some supplements have drug interactions — with each other and/or with prescription medications. Be sure to let your doctors know all the supplements you are taking, and you might also talk with a trusted pharmacist about the combinations.

Q

I read an article published in the *Molecular Therapy Nucleic Acids* journal, which says that scientists in Germany used CRISPR-Cas9 technology to correct a CAPN3 mutation (LGMD R1/2A).[1] Is this promising and if so, when might we see this application in the United States?

A

CRISPR technology is very powerful and has advanced research in many diseases. It can be used to create animal models of human diseases or to correct a mutation in isolated cells grown in culture, for example. The genetic therapies (exon skipping or gene transfer therapy) that are currently used in human diseases don't change our DNA — the recipe that is identical in every cell of the body. CRISPR does target the DNA. Thus, a mistake (such as accidently turning on a cancer-causing gene) could have serious and irreversible consequences. Many groups are working diligently to bring CRISPR and related technology safely to human diseases, but we aren't there yet.

[1] https://musculardystrophynews.com/news/lgmd-type-2a-mutation-corrected-by-crispr-cas9-gene-editing/

Q

If testosterone helps create bigger, stronger muscles in healthy people, are there any benefits/risks of taking small, regular doses of testosterone for males after age 40, when the level of testosterone produced by the body starts to decline? I know there have been some studies for Duchenne patients taking testosterone, but are you aware of any studies on individuals affected by less severe types of muscular dystrophy such as LGMD R12/2L?

A

I do not recommend taking testosterone unless you have a diagnosed deficiency. If you are concerned about this, it is something that your doctor can check.

Q

Could you share any progress that is being made regarding the autosomal dominant LGMDs, and when we might see clinical applications? Are there any clinical trials for dominant LGMDs?

A

I am not aware of any clinical trials open for the dominant LGMDs. However, there are excellent scientists working to better understand these diseases, which is a critical step for developing therapies. In addition, registries and natural history studies collect data that is needed for planning future trials. To make sure you are aware of clinical research options for a specific disease, I generally recommend checking the website **ClinicalTrials.gov** every 3-6 months.

Q

How do you recommend preventing and managing muscle soreness?

A

If you have significant muscle soreness (or brown urine*) after activity, recognize that you overdid it and modulate your activity in the future. Muscle soreness that is not directly related to activity can be more difficult to manage. Treatment often takes some experimentation and the use of several different approaches for the best result. Sometimes you can change things in the environment: for example, can you position your arm in a way that eliminates gravity and is more comfortable? Meeting with an occupational therapist might be helpful to explore strategies for modifying your activities or environment. Regular stretching or limited exercise/activity can both prevent and treat some muscle pain. Physical therapy can be helpful in managing muscle pain. People sometimes find heat, cold, or gentle massage to be helpful. Over-the-counter creams or pain medications (like ibuprofen or naproxen) can help. If someone is experiencing depression, anxiety, or sleep disturbance along with pain, these should be discussed with your doctor since they can all make pain worse. Finally, prescription medications can be helpful for some people.

* Brown urine following exercise is often a sign of rhabdomyolysis (breakdown of muscle fibers), which requires immediate medical attention.

I am not aware of any clinical trials open for the dominant LGMDs. However, there are excellent scientists working to better understand these diseases, which is a critical step for developing therapies. In addition, registries and natural history studies collect data that is needed for planning future trials.

Question

If proven to be effective and if there are limited side effects, some of these non-gene-specific treatments might be helpful for a wider range of people.

Q

What is the status of progress for treatments for LGMD R2/2B?

A

Like many other types of LGMD, studies of potential treatments are in the pre-clinical (animal and cells) stages. Because this is one of the more common types of LGMD, there are many groups working on it. I found at least five papers published in the past year directly related to exploring treatment options for dysferlinopathies. As I discussed previously, monitoring **ClinicalTrials.gov** is a good way to make sure you are aware of new trials.

Q

Is there any thought of expanding the use of stem cells with more sub-types of limb-girdle muscular dystrophy? Some of the subtypes are very rare. Both of our children have type R19/2S, and we would like to help them maintain their strength or gain more.

A

Stem cells are not approved for use in any muscular dystrophy currently. Many years ago, cell transfer was attempted to treat Duchenne muscular dystrophy and was not found to be beneficial. Technology has changed since then and cell-based therapies are still being explored in muscular dystrophies, primarily in animal models.

It is often hard to know how best to treat people with very rare types of muscular dystrophy. Some therapies being evaluated for different types of muscular dystrophy (such as Duchenne MD) have mechanisms of action that are not specific to just one gene. If proven to be effective and if there are limited side effects, some of these non-gene-specific treatments might be helpful for a wider range of people. Therefore, it is good to be aware of developments across diseases and to cheer any progress for any muscular dystrophy treatment.

Q

Can LGMDs cause digestive issues? What advice do you have for patients that struggle with constipation?

A

Constipation is common among people with neuromuscular diseases, perhaps in part related to decreased physical activity. In addition, the type of muscle found in most of the gastrointestinal tract, smooth muscle, might be affected by the protein deficiency affecting skeletal muscles in some cases. Treatment usually involves fiber supplements and dietary fiber, or medicines like Glycolax. Making sure your diet contains fiber along with fresh fruits and vegetables, and that you stay adequately hydrated, can also be helpful. Your doctor can help you find the best approach for you. If constipation is a problem, I do recommend staying ahead of it with a regular (usually daily) program rather than only treating constipation when it gets bad. Gastroenterologists generally recommend a soft, formed stool daily. ▪

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TheSpeakFoundation.com
ClinicalTrials.gov

Have a Question for Our Experts?

Send Questions To:
ContactUs@TheSpeakFoundation.com

My Way of Living
A Fulfilling Life

How do I begin writing my story about life with LGMD? A story full of hope, challenges, adjustments, goodbyes, and new beginnings. A story that began more than 30 years ago and, hopefully, is far from being over.

In 1991, at the age of four, I was diagnosed with early-onset muscular dystrophy (MD). As a toddler, I couldn't crawl. When I started walking, I often fell and hit my head when I tried to climb the stairs. I was never able to run or jump. My legs were weak, and I couldn't get up from the floor. Due to hypertrophy, my calves were like those of a football player, and I walked like a duck.

Sadly, inexperienced doctors assumed I was lazy and slow, and failed to pursue other causes of my symptoms. Finally, after countless appointments, a pediatrist checked for elevated creatine kinase and discovered my levels were extremely high. He sent me to a center specializing in neuromuscular diseases in Munich, Germany. There, the specialists did two muscle biopsies and determined I had MD.

Shortly after receiving the diagnosis, I remember crying angrily for hours and asking my Mum repeatedly why I had to have this disease. I desperately wanted to be able to run, jump, and move like other kids. That was the painful start to my journey of accepting this disease as a part of me.

My parents didn't give me any privileges and never treated me any differently than my younger brother who is unaffected by MD. Education has always been important in our family, so my mother fought to

Below: World traveler and blogger Mélanie Bordes takes time to enjoy a beautiful beach sunset in France.

ensure I could attend a regular school. Having a disability was never an excuse my parents would accept for my not doing my best. Therefore, as I grew up, I quickly learned how to manage my life as independently as possible.

Like some other forms of LGMD, LGMD R9/2i can affect the heart. When I was 15, my heart started racing every day without my doing anything strenuous. My resting pulse rate was 120 bpm, and I could even hear my heart beating. Sometimes I felt like my heart wanted to jump out of my body, so my mother and I saw a cardiologist. Several examinations, including a heart MRI, showed that I had heart failure, and I began to receive heart medication. After a few rough months of adaptation, the treatment quickly stabilized my symptoms. Today, many years later, my heart function is still relatively good except for arrhythmias that first occurred in my mid-twenties.

Below: Mélanie with her husband at a library in France.

"Having a disability was never an excuse my parents would accept for my not doing my best. Therefore, as I grew up, I quickly learned how to manage my life as independently as possible."

In 2009, I transitioned from pediatric to adult care. My new neurologist immediately asked why genetic testing hadn't been done previously. Blood was drawn, and just six months later, the results showed a compound-heterozygous mutation in the FKRP gene, which means I have LGMD R9/2i. Finally, I had an official diagnosis and a name for my disease.

Despite having LGMD, I live a fulfilling life. I studied English and French (business-focused), completed an additional apprenticeship, worked for nearly 10 years, met my husband, and moved to a foreign country. The disease helped me become resilient and persevering. Still, the most challenging part of living with LGMD R9/2i is seeing my body deteriorate more and more without my being able to do anything about it. As a result, I have no choice but to accept the loss of abilities and independence and find creative solutions to adapt to new situations.

Meeting my husband in 2012 completely changed my life. At the time, I was gradually losing the ability to walk and therefore, was using a manual wheelchair most of the time. However, I was still working two jobs and could drive independently. I lived in Bavaria/Germany while my husband lived in France, so he and I traveled at least every two weeks to see each other on weekends. Traveling on my own by plane was quite an adventure as I couldn't stand and transfer by myself and was completely dependent on the airport's assistance service.

Around that time, my neuromuscular disease (NMD) specialist recommended I quit working, as it took a tremendous toll on my

Left: Mélanie at the Eiffel Tower, Paris, France.

body and considerably limited my energy. This change made it possible for me to move to France to live with my husband. We traveled for pleasure whenever we could. Unfortunately, finding precise information about the accessibility of places was difficult to obtain most of the time. Therefore, I thought it would be a good idea to share my travel experiences with other disabled travelers. This inspired me to create the *Little Miss Turtle* wheelchair travel blog.

We've been to many places around the world that left me speechless. Some of my favorite travel destinations as a wheelchair user are Cape Town/South Africa, which is incredibly beautiful, and Banff National Park in British Columbia/Canada. But the country that I love most is Japan. The mix of modernity, high-tech, cultural rigor, and century-old ancient traditions is fascinating. In addition, it is easy to get around as a wheelchair user in Japan. I had the most memorable experiences in Tokyo (where I've been many times) and on a high-speed train trip across the country. Another country I love is the US because of its great accessibility and the sheer vastness and natural diversity it offers. Traveling was an essential part of our lives — until the COVID-19 outbreak changed everything.

Above: Mélanie visiting the Louvre in Paris, France.

In 2020 I canceled all planned health check-ups because I was too scared of catching the virus. My husband and I shielded ourselves from others, and a year went by. Then in early 2021, I suddenly started suffering from digestive problems that progressively worsened. The portions I could eat got smaller and smaller. My general practitioner dismissed the symptoms, saying the condition would improve on its own. It didn't. Towards the end of the year, I grew increasingly tired; I even fell asleep in my wheelchair. The nights were difficult for my husband and me, as I often woke up 10 or more times to drink or use the restroom. I felt exhausted, had severe muscle tremors, and could hardly concentrate.

When we went to my annual checkup in February 2022, we were shocked to find that I had lost almost 12 kg (or 26 lbs) in a few months. My neurologist sent me for a CT scan, and I endured many different gastroenterological tests only to be told everything was fine. But my instincts told me otherwise.

Below, Left: Wheelchair hiking in the Bavarian Alps, Germany.

Below, Center: Mélanie visiting Antibes, France.

Below, Right: Exploring Tenerife Island, Spain.

Above: Mélanie using a CoughAssist device.

I emailed my pulmonologist about the situation. A day later, his secretary called, and I was admitted to the hospital. It turned out that I was in respiratory decompensation. My CO_2 level was so high that I was close to a coma. My body had done everything physiologically possible to compensate, but this only worked for a period of time. After a week's hospital stay, I returned home with a new ventilator setup, mouthpiece ventilation during the daytime, and noninvasive ventilation (NIV) at night. My pulmonologist predicted that I would automatically regain weight and feel much better with the new equipment and settings. That's exactly what happened — along with the restoration of my digestive health.

Today I am increasingly dependent on ventilation. Mouthpiece ventilation is no longer enough for me during the day; therefore, I use my nasal mask more often. Traveling by plane has become impossible as I can no longer fly. From now on, we will travel by car and train across Europe. I can't tell you how happy and grateful I am to have visited so many beautiful places when I could still do so. My heart is filled with memories from our travels, and these memories give me joy and strength whenever I'm unwell. It is challenging to accept that I have so little energy compared to how it used to be. My path of acceptance is ongoing. It is a steady process where I occasionally encounter new hurdles, and hurdles are meant to be overcome. ■

Written by Mélanie Bordes

A Small Molecule-Based Approach for Sarcoglycanopathies

From Cystic Fibrosis to Muscular Dystrophy

Sarcoglycanopathies (LGMDR3-6) are one of the most common categories of LGMDs. They are also among the most severe forms of LGMD, even though the spectrum of the diseases is heterogeneous. Some cases have onset, symptoms, and progression close to those of Duchenne muscular dystrophy, while others are characterized by late onset and slow progression. The reason of this heterogeneity resides mainly in the type of mutations in the sarcoglycan genes carried by the patients, although the person's genetic background may also play a role. This leads to a different residual amount of the sarcoglycan (SG) complex present at the sarcolemma (the plasma membrane of striated muscle), with the most severe cases being those in which sarcoglycans are totally absent.

The sarcoglycan complex (composed of four proteins, alpha-, beta-, gamma-, and delta-sarcoglycan, which are bound together in a group) is a key element of the dystrophin-associated protein complex (DAPC) whose primary role is to preserve sarcolemma integrity during muscle contraction. Mutations in any of the sarcoglycan genes disturb the formation of the SG-complex resulting in destabilization of DAPC. Being more fragile, the sarcolemma undergoes repeated damage as a result of muscle contraction stress, eventually leading to muscle wasting.

Figure 1 shows the sarcolemma structure of either healthy subjects where the SG-complex and the DAPC are fully functional (a), sarcoglycanopathy patients where it is possible to observe the complete loss (b) or the strong reduction (c) of the SG-complex. Large gene deletions, defects affecting the splicing process, null or frameshift mutations result in the complete loss of one of the SG proteins, impairing the formation of the complex (panel b). Together, they account for approximately 33% of the genetic mutations observed in the four sarcoglycans genes.

On the other hand, the majority (67%) of sarcoglycan defects are missense mutations, resulting in a full-length SG carrying just a single amino acid substitution. However, this minimal variation has an impact on the

We observed that 1-2 days of treatment with the small molecules was sufficient to reveal a clear and strong signal of the mutated sarcoglycans at the plasma membrane, in comparison to cells treated with vehicle alone.

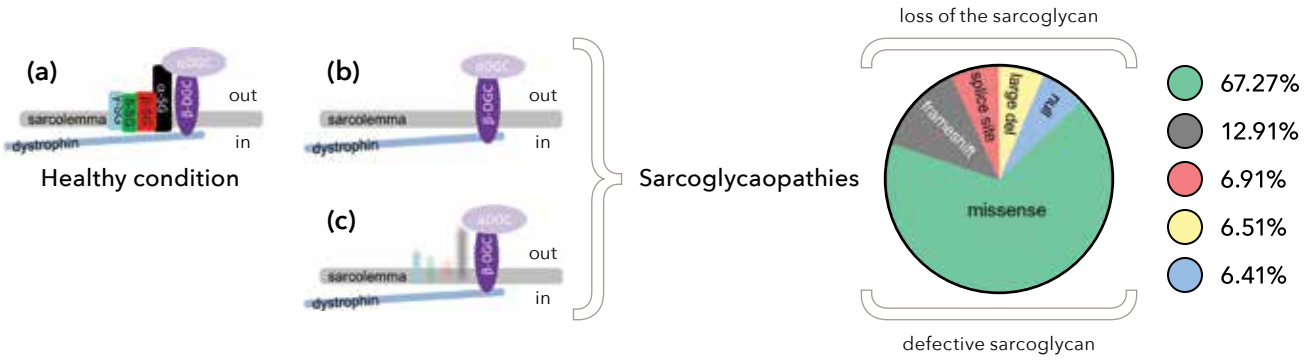

Figure 1: Consequences of sarcoglycan mutations Source: NIH ClinVar

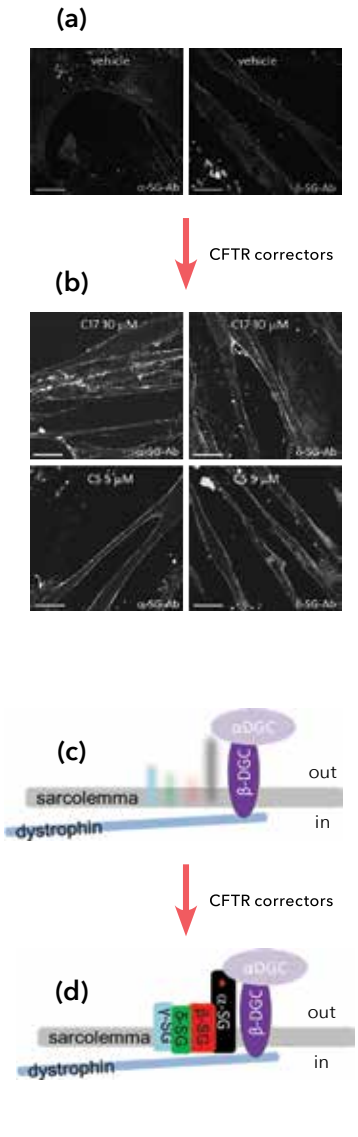

Figure 2:
CFTR correctors induce the recovery of the sarcoglycan complex at the sarcolemma of LGMD2D/R3-derived cells

Modified from Carotti M. et al HMG 2018

three-dimensional structure of the sarcoglycan which, as defective, is recognized by the cell's quality control and marked for degradation. Some of the defective sarcoglycan (depending on the mutation) can escape elimination and form the SG complex, which reaches the sarcolemma in small amounts, often only traces (as in c). Our group has shown that sarcoglycans with missense mutations are often discarded even if potentially functional.

This finding prompted us to search for small molecules that can help the defective protein to evade degradation, allowing a sufficient amount of the sarcoglycan complex to be expressed so as to protect the sarcolemma. We have been helped in this by the vast work being done researching cystic fibrosis (CF). In CF, a number of mutants of the cystic fibrosis transmembrane regulator (CFTR), the protein responsible for the disease are marked for degradation, sharing a similar fate with the mutant sarcoglycans. Fortunately, a large number of small molecules which are able to modulate mutant CFTR proteins have been identified. Among these are the "CFTR correctors" which, by avoiding the degradation of the defective CFTR, allow it to reach the plasma membrane. Therefore, we wondered whether these molecules could also be effective in treating sarcoglycanopathies. At first, we tested CFTR correctors in a human cell line forced to produce different mutants of α-sarcoglycan. We observed that 1-2 days of treatment with the small molecules was sufficient to reveal a clear and strong signal of the mutated sarcoglycans at the plasma membrane, in comparison to cells treated with vehicle alone.

The next step was to test the most effective compounds in skeletal muscle cells isolated from a subject with LGMD2D/R3 carrying the L31P/V247M mutations on the SGCA alleles (Figure 2a), which showed just traces of the SG complex at the sarcolemma (as depicted in c). It was really exciting to observe, 3-4 days after the treatment, the sarcolemma of these precious cells becoming positive for the sarcoglycan complex (b). Furthermore, we verified the increased sarcolemma stability of treated myotubes. Indeed, we measured a reduced release of the creatine phosphokinase (CpK) enzyme from treated LGMD2D/R3 cells compared to control cells, after the application of a stressful condition. Similar positive results were collected with LGMD2E/R4 patient-derived cells carrying the mutation I92T on the SGCB gene. Altogether, these data suggested that when recovered at the sarcolemma, the sarcoglycan complex is working, even though it contains a mutated subunit (as represented in Figure 2d).

To definitively prove that the rescued SG complex is working, i.e. able to protect skeletal muscle from degeneration, we tested in vivo the CFTR corrector which performed the best in the in vitro test, C17. This was one of the hardest tasks we faced, primarily due to the lack of suitable animal models recapitulating the features observed in human patients with missense mutations. To overcome this problem, we induced the expression of the human α-sarcoglycan sequence, wild type or mutated, in the hindlimbs of new-born mice lacking the endogenous α-sarcoglycan. As adults, the animals transduced with the wild type α-sarcoglycan had humanized hindlimbs practically indistinguishable from those of a wild type mouse. Conversely, those transduced with the R98H mutant of α-sarcoglycan have humanized hindlimbs with a clear dystrophic phenotype, characterized by traces of the sarcoglycan complex at the sarcolemma and poor muscle strength (Figure 3a). When the

humanized mice were treated for up to five weeks with a daily administration of C17, we observed the rescue of the muscle strength to values close to those of the wild type and a strong localization of the sarcoglycan complex at the sarcolemma of the hindlimb muscles (Figure 3b).

The chronic treatments of mice (5 weeks of daily administration) highlighted no signs of toxicity, but further experiments are needed because we have to exclude any possible side effects for humans. Furthermore, we are studying the pharmacological properties of C17, which is the most effective corrector for sarcoglycanopathies, but not fully developed for treating CF. Further experiments are also planned to evaluate the duration of the rescue. In other words, we want to understand how long the sarcoglycan complex recovered at the sarcolemma is stable, because this will allow us to determine the required frequency of administration of the small molecule. Last but not least, we intend to verify whether oral administration, easier for patients, has the same efficacy as injection.

In these years, enormous effort has been devoted to finding therapeutic solutions for sarcoglycanopathies. Among them, gene replacement therapy has reached the most advanced stage of development, with the ongoing clinical trials for LGMD2E/R4 showing very promising data. Our group has also been engaged in searching for a cure for sarcoglycanopathies for many years. However, our strategy, as above described, does not aim to introduce a healthy copy of the gene, but intends to recover the endogenous, mutated sarcoglycan. Because it is potentially applicable in nearly two thirds of sarcoglycanopathy cases, this approach could become a valuable complement to gene therapy.

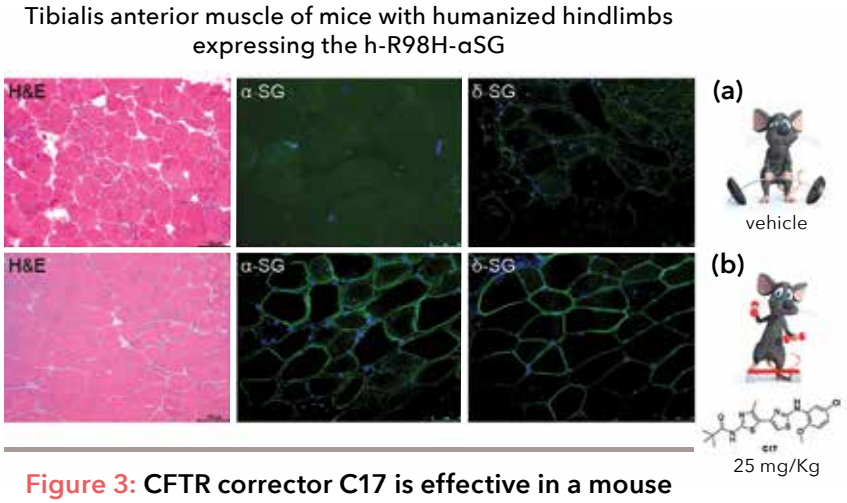

Figure 3: CFTR corrector C17 is effective in a mouse model of sarcoglycanopathy Modified from Scano M. et al HMG 2022

Above: The small4rare group (top row, left to right): Marcello Carotti, Francesco Dalla Barba, Paola Caccin, and Alberto Benetollo. (Bottom row, left to right): Martina Scano, Dorianna Sandoná, and Mario Tarantini. Not pictured: Chiara Fecchio, Elisa Bianchini, Roberta Sacchetto, and Leonardo Nogara.

We are aware that more effort and money will be needed to further preclinical studies about the use of CFTR correctors in sarcoglycanopathies. However, tenacity, resilience, and commitment have never been lacking in our small4rare group. Here I would like to mention in particular Martina Scano, Alberto Benetollo, and Marcello Carotti; Elisa Bianchini and Chiara Fecchio among the former members; Roberta Sacchetto and Leonardo Nogara among our collaborators. These results were possible thanks to their work, but also thanks to the generosity and vision of patients with sarcoglycanopathy (and their parents) who donated their cells to research. ■

Written by Dorianna Sandoná, PhD
Associate Professor of Molecular Biology
Department of Biomedical Sciences, University of Padova

Patient-Student Interactions Improve Rare Disease Recognition and Care

Interacting with patients with rare disorders not only builds awareness of these diseases among future doctors but also counters intrinsic bias and stigma associated with disability.

Three years ago, I became an associate neurology clerkship director at the Johns Hopkins University School of Medicine. Part of the role involves making sure students are prepared for their board exams, and re-engaging in the world of test prep has been eye-opening. As a student, I had no way of gauging the quality of the study aids and medical texts I was using. However, as a subspecialist, I recognize that content on rare diseases, like muscular dystrophy, is frequently oversimplified, outdated, or even incorrect. Considering how many new LGMD genes have been discovered and how much new research has emerged on these conditions, it is not surprising that exams and study aids addressing them just cannot keep up to date.

One of the consequences of practitioners in training having little exposure to patients with muscular dystrophy is that the condition often remains unrecognized by trained professionals. My patients frequently describe a yearslong diagnostic process, and unfortunately, patients with limited access to care may never be diagnosed. As new therapies are developed for muscular dystrophy, this diagnostic gap may result in patients not receiving treatments that can prevent the progression of their disease.

With this as an immediate concern, I do not think that simply adding more content to the curricula is the solution. The medical school curriculum is supposed to encompass all human illnesses, and focusing too much on any one disease is impractical. Furthermore, much of the information about diseases that students consume through exam review is quickly forgotten. What ensures retention is engaging with real patients. Many muscular dystrophy clinics are affiliated with medical schools, so I would encourage patients with MD to invite students to participate in their visits. Actually, many medical schools already recruit patients to train students about how to perform physical examinations. I advocate for this also. Interacting with patients with rare disorders not only builds awareness of these diseases among future doctors but also counters intrinsic bias and stigma associated with disability.

Finally, I offer my deepest thanks to my patients who have shared their experiences with the medical, physical therapy, and genetic counseling trainees in our clinic. The time patients spend with medical personnel now truly improves the care future patients will receive. ■

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

UPDATED: JULY 1, 2023

GRASP-LGMD Natural History Studies

Recruiting Defining Clinical Endpoints in Limb-Girdle Muscular Dystrophy (LGMD) (GRASP-01-001)

Inclusion Criteria

- Ages 4–65
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern or in a distal extremity)
- Genetic confirmation of one of the LGMD subtypes listed below

Exclusion Criteria

- Any other illness that interferes with subject safety or data integrity
- Positive pregnancy test at any timepoint of the study

Note: Each subtype will enroll 80% of subjects who are able to walk 10m independently in 12 seconds or less. Twenty percent will be subjects who ambulate more slowly or not at all.

Subtypes

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

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

Inclusion Criteria

- Ages 8 and older
- Clinically affected (defined as weakness on bedside evaluation consistent with BMD)
- Genetic confirmation of a dystrophin mutation

Exclusion Criteria

- >16 hours of ventilatory support
- Any other illness that interferes with subject safety or data integrity

Note: Subjects ages 8-16 must be ambulatory and their dystrophin mutation must be in-frame.

Note: Subjects 17 and older may be non-ambulatory, but must not have lost ambulation prior to the age of 16.

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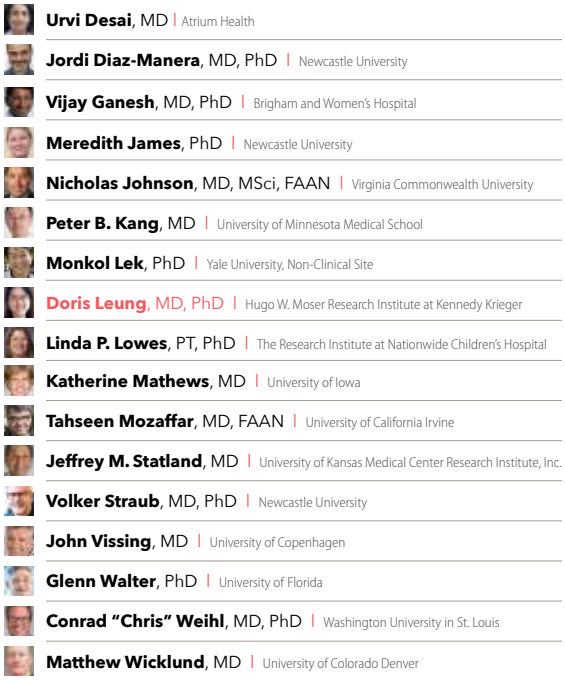
GRASP-LGMD Consortium Members



- **Urvi Desai**, MD | Atrium Health
- **Jordi Diaz-Manera**, MD, PhD | Newcastle University
- **Vijay Ganesh**, MD, PhD | Brigham and Women's Hospital
- **Meredith James**, PhD | 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
- **Linda P. Lowes**, PT, PhD | The Research Institute at Nationwide Children's Hospital
- **Katherine Mathews**, MD | University of Iowa
- **Tahseen Mozaffar**, MD, FAAN | University of California Irvine
- **Jeffrey M. Statland**, MD | University of Kansas Medical Center Research Institute, Inc.
- **Volker Straub**, MD, PhD | Newcastle University
- **John Vissing**, MD | University of Copenhagen
- **Glenn Walter**, PhD | University of Florida
- **Conrad "Chris" Weihl**, MD, PhD | Washington University in St. Louis
- **Matthew Wicklund**, MD | University of Colorado Denver

Spotlight: Dr. Doris Leung

Hugo W. Moser Research Institute at Kenedy Krieger

Dr. Doris Leung is the Director of the Center for Genetic Muscle Disorders at Kennedy Krieger Institute and an associate professor in the Department of Neurology at the Johns Hopkins University School of Medicine. She obtained her undergraduate degree in biochemical sciences from Harvard University and her medical degree from Duke University School of Medicine. She completed her neurology training at the Stanford University Medical Center. Dr. Leung joined the Center for Genetic Muscle Disorders as a translational research fellow in 2010. Since then, she has earned a PhD from the Graduate Training Program in Clinical Investigation at the Johns Hopkins Bloomberg School of Public Health. Dr. Leung's multidisciplinary clinic focuses on the diagnosis and management of hereditary muscle diseases, and her research is centered on the development of biomarkers for muscle disease. She has also served as a site principal investigator for multiple clinical trials and natural history studies in muscular dystrophy.

SPONSORED CONTENT

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.

DISCOVERY

Development begins with years of research, with scientists designing and testing the proposed gene therapy—the vector, promoter, and transgene—that aims to determine the best way to deliver a functional gene to the right cells.

MANUFACTURING

Manufacturing is a key part of gene therapy development and regulatory review and approval. In the US, the regulatory body is the Food and Drug Administration (FDA).

CLINICAL TRIALS

Studies focus on the safety of the gene therapy and test to see if it addresses the disease it is meant to treat.

Trials can take years to collect and analyze enough data to meet regulatory requirements.

PRE-CLINICAL STUDIES

The potential gene therapy is tested to see if it works as intended in the laboratory.

The FDA generally requires the manufacturing process to be in place prior to starting clinical trials. This process is comprised of several complex steps and components.

CHAPTER 1 CHAPTER 2

Sarepta is committed to providing gene therapy educational resources to rare disease communities

Check out more GT 101 in the previous 2023 issues of the *LGMD News Magazine* or email Advocacy@Sarepta.com

How is a gene therapy developed?

CHAPTER 3 OF A FOUR-PART SERIES

As part of the FDA's review, they may also perform inspections of the manufacturing facility and processes to help ensure a high-quality product.

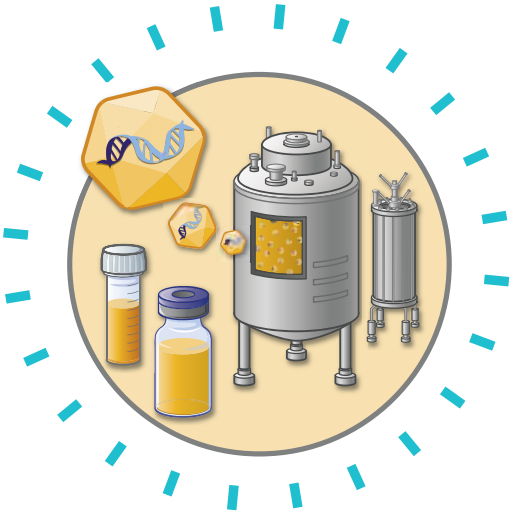
CONTINUING STUDIES

Additional follow-up studies may be required to collect more information on the gene therapy even though the gene therapy is available on the market.

REGULATORY REVIEW & APPROVAL

Once the clinical trials are complete, an application is submitted to the FDA for the gene therapy to be approved for commercial use in patients.

The FDA review process can typically take up to one year.



What can I do?

→ Learn about trials by talking to your doctor and knowing your genetic subtype

→ Join advocacy groups, registries and natural history studies

SAREPTA THERAPEUTICS

More on manufacturing gene therapy vectors

Once the manufacturing process is defined, making a single batch of gene therapy vector can take several months.

Gene therapy vectors containing the promoter and the transgene are made in living cells. Many vectors are needed when targeting a disease that affects cells throughout the body, such as a neuromuscular condition.

Gene therapy manufacturing involves multiple phases with dozens of steps, each of which must meet the strictest quality measures and involve:

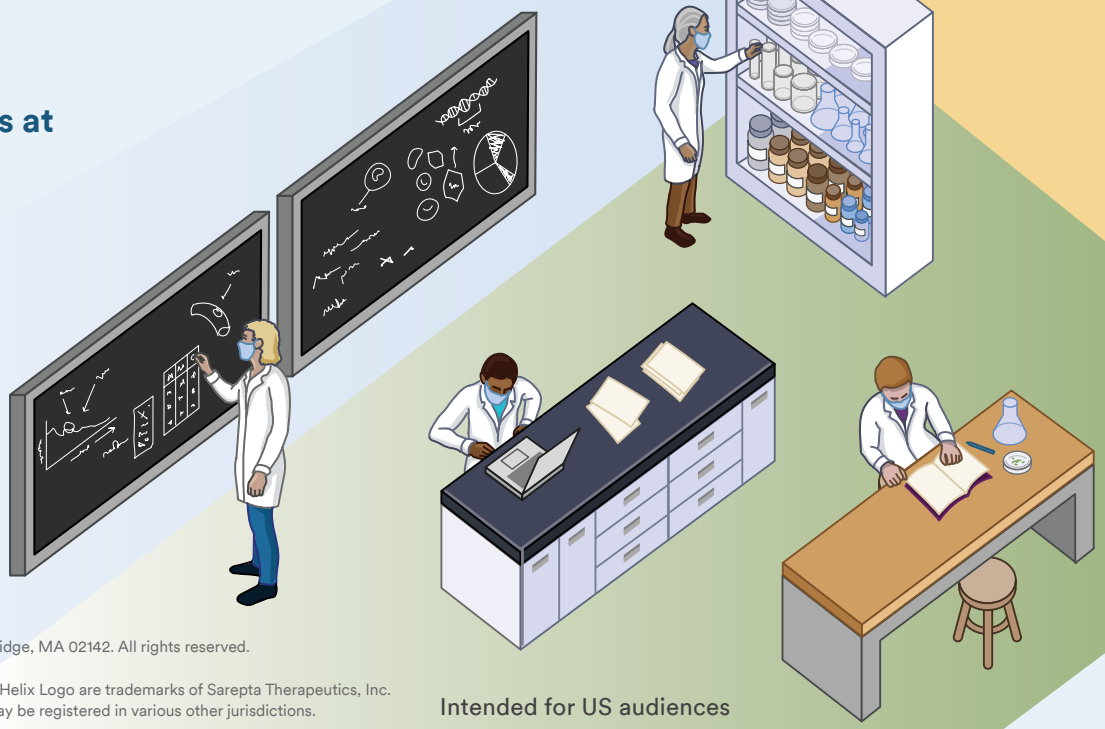
- Growing living cells into sufficient quantities to produce the gene therapy vector
- Multiple purification steps to remove impurities
- Numerous tests to help ensure the quality and safety of the product

Once a batch is complete, the product is packaged, stored and shipped to where it's needed.

Want to test your knowledge?

Scan the QR code to take a short gene therapy quiz on limbgirdle.com

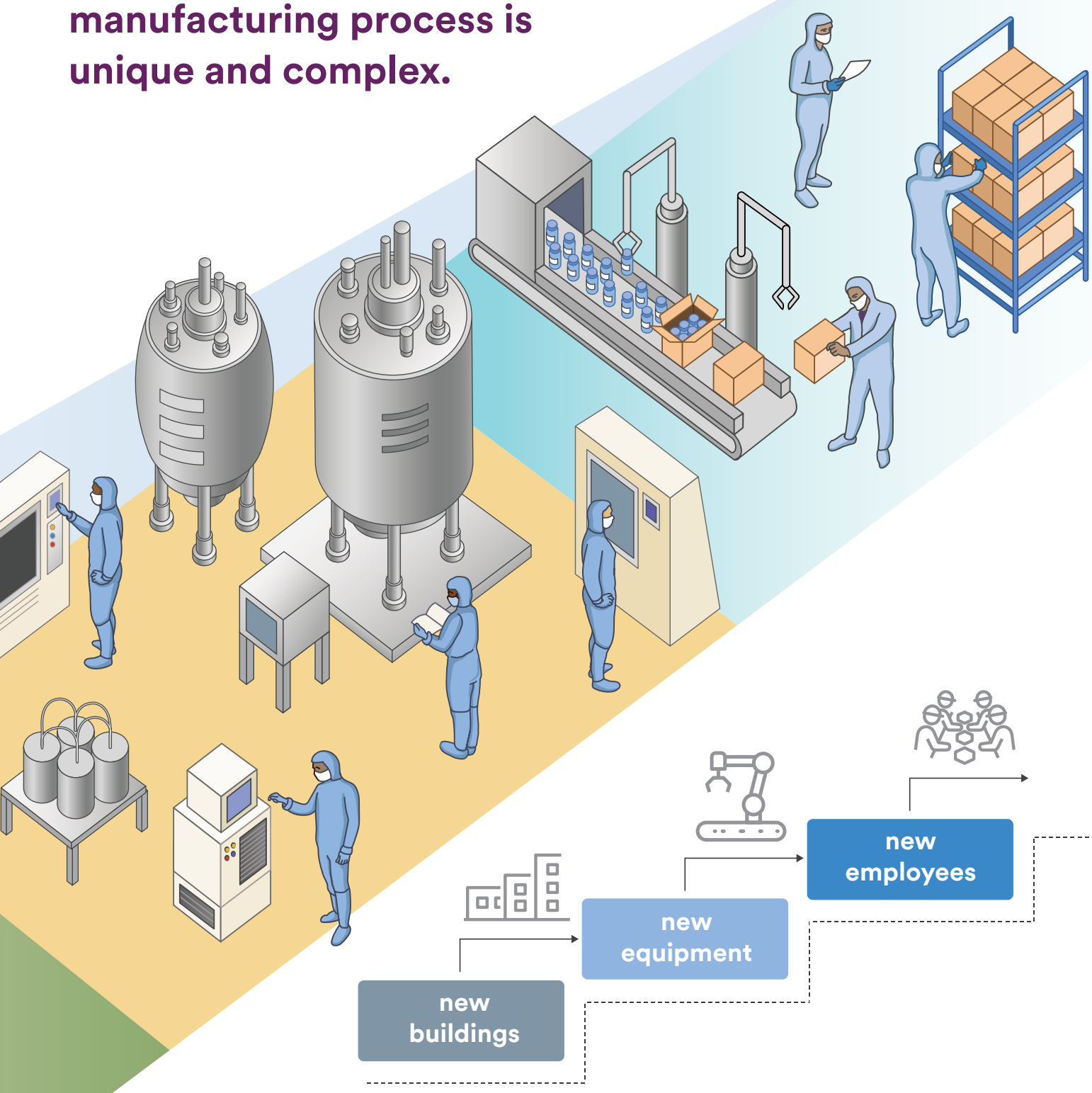
If you have questions or comments for us, email us at Advocacy@Sarepta.com



SAREPTA THERAPEUTICS

Intended for US audiences

The gene therapy manufacturing process is unique and complex.



Scientists and engineers may have to design, test and build new equipment, instruments and processes. This may mean adding new buildings and hundreds of specially trained employees.

THE VALUE OF CONNECTING IN PERSON

Why Should You Attend the 2023 International LGMD Conference in Washington, D.C., in Person?

Read what some of the professionals and those living with LGMDs (and their family members) have to say about attending the 2019 International LGMD Conference in Chicago

Nicholas Johnson, MD, M.Sci., FAAN

Virginia Commonwealth University, Richmond, Virginia, USA
Vice Chair for Research

"The International LGMD Conference is a key milestone for our community. It provides a unique place for all the stakeholders to meet. I am hopeful this meeting will catalyze progress toward treatments for these conditions. I am certainly looking forward to attending."

Louise R. Rodino-Klapac, PhD

Sarepta Therapeutics
Executive Vice President, Head of R&D, Chief Scientific Officer

"We hope that families who attend this conference will benefit from connection to one another, to the advocacy organizations that have formed to represent them, and to the research that is growing to upend this unmet medical need. As sponsors of the event over multiple years, it has been wonderful to see this community increasingly come together to improve the futures of people living with LGMD. Thank you to every volunteer and organizer involved in this important effort."

Katherine Mathews, MD, FAAN

University of Iowa, Iowa City, Iowa, USA
Professor of Neurology
Director, Muscular Dystrophy Clinic
Vice Chair for Clinical Investigation, Dept of Pediatrics

"Often, people with LGMD don't know others with LGMD and feel they are alone in the experiences they are having and problem-solving. Attending the International LGMD is a wonderful opportunity for people with LGMD and their families to interact and share knowledge, lessons learned, and experiences. Having a forum focused on LGMD is also an opportunity for clinicians, researchers, and those with LGMD to catch up on recent advances in science across the different genetic types of LGMD."

SCAN ME

REGISTER TODAY!

Cyndy Baxter

Villanova, PA

LGMD R9/2i ■ Age: 56

Chris Carroll

East Norriton, PA

LGMD R3/2D ■ Age: 39

What was your experience like attending the 2019 International Limb-Girdle Muscular Dystrophy Conference in person?

"My main reason for coming to the conference is the people. I most enjoyed the welcome reception where I got to mingle with all the people I have met on a Facebook group and put a face and a voice to the names, reconnecting and catching up with a friend with LGMD whom I had met before, meeting new people from other countries, and visiting the 2L booth to find out what is new and talk to people that may have the same problems I am having. Even our CEO and main researcher for Muscular Dystrophy Canada were there to support LGMDs." ***– Chuck Joosten***

"Upon arriving at the 2019 international LGMD Conference, I was almost brought to tears when I saw all my peers because for me this was the first time I had ever seen another person with my disease face to face. Overall, the conference was one of the best experiences of my life! I gained many new friendships and connections as well as so much priceless advice and education." ***– Cassidy Nilles***

"Meeting the LGMD community in person and connecting with them felt amazing because at the end of the day, they 'get me.' We are on this journey of living with LGMD together and that made me feel at ease. I came with my caregiver, and it was a fun-filled weekend; we laughed, met new people, and ate great food while also seeing the great city of Chicago" ***– Keisha Greaves***

"We enjoyed our experience at the 2019 International LGMD Conference. It was nice to meet people with LGMD and share experiences. We enjoyed learning the latest information about LGMD." ***– Jessica Gerardo & Camron Lawrence***

"The biggest value of attending in person for me was to be around so many like-minded people. Although everyone there is affected by LGMD in some way, we all had a different story to share!" ***– Chris Carroll***

"When I attended the 2019 International LGMD Conference, I was an (almost) brand-new member of the LGMD community. Only six months before the conference, I was finally diagnosed with LGMD after searching for a diagnosis for almost 30 years. Attending the conference in person as a newly-diagnosed member of the LGMD community gave me a sense of belonging and support that I had never felt before!" ***– Cyndy Baxter***

"I loved meeting other people in person who have LGMD just like me. For the very first time, I met someone my age who has exactly the subtype I have. Even when I go to MDA camp each summer, no one there has limb-girdle, so this was extra special." ***– Brooklyn Garza***

"Being at the international LGMD conference in Chicago was an awesome experience." ***– Kaya Leijenhorst***

"It is truly amazing hearing other people's stories. I got to learn a lot from others and share our experiences." ***– Julianna Rodrigues***

"I loved attending the conference in Chicago, which I consider a high point in my life as a person with an LGMD. The ability to meet others with various subtypes, together with their spouses, children, parents, and other friends and family members, was extremely moving and joyful." ***– Josh Thayer***

Brooklyn Garza

Pflugerville, TX

LGMD R1/2A ■ Age: 16

Keisha Greaves

Cambridge, MA

LGMD, subtype unknown ■ Age: 37

What was the greatest thing that you learned?

"You can make friends everywhere, but going to the conference is being together with people that understand and know how to live with LGMD. Virtual attending is not the same!" ***– Kaya Leijenhorst***

"I learned about the current state of clinical trials in the pipeline for LGMD2i and how to get involved in those trials. I gained hope and belief in the possibility of treatments and potential cures for LGMD2i." ***– Cyndy Baxter***

"The greatest thing we learned was the advancements in gene therapy. It was amazing to see all the work being done for the future of the LGMD community. It provides hope that there will be a cure for LGMD in the future!" ***– Jessica Gerardo & Camron Lawrence***

"The greatest thing I learned from the conference was information about the ongoing trials being run by Sarepta and listening to Dr. Mendell and the rest of the medical panel speak about their experiences working firsthand in these trials." ***– Chris Carroll***

"My wife, Dagmar, and I were able to have supper with people from Sarepta Therapeutics to share ideas and pick each others' brains. Sarepta is a huge company doing research focusing on LGMDs, and to be able to rub shoulders with them was a privilege." ***– Chuck Joosten***

"I gained a lot of new friends, and honestly, every moment was a learning experience! In addition to all the updates on research and drug development, I was excited to learn that natural history studies were ongoing or being launched for various other subtypes. And I learned 'life hacks' on traveling and other recreational activities." ***– Josh Thayer***

Chuck Joosten
Sarnia, Ontario, Canada
LGMD R12/2L ■ Age: 57

Jessica Gerardo (Mother)
Camron Lawrence (Patient)
Lynn, MA ■ **LGMD R19/2S** ■ Age: 20

Kaya Leijenhorst
Netherlands
LGMD R3/2D ■ Age: 21

Cassidy Nilles
Lisle, IL
LGMD R10/2J ■ Age: 33

"I learned that as alone as I feel having this rare disease, I am not actually alone, and there is an entire community going through so many of the same things. I also gained many friendships and relationships, with not only fellow LGMD warriors but with their families as well." ***– Cassidy Nilles***

"I learned there are a lot of scientific things happening and a lot of people working on my disease. I got a lot of information from the booths and signed up for a natural history study. My mom also received so much useful information from the breakout sessions." ***– Brooklyn Garza***

"Attending the 2019 conference was amazing and an experience I will never forget. I got to learn from doctors and hear about upcoming clinical trials." ***– Keisha Greaves***

"The greatest thing I learned at the conference was about all the different adaptations that people with LGMD have developed in order to live independently. I gained a family. The LGMD community is a tight-knit one where we always support one another. The opportunity to meet this family in person was just priceless." ***– Julianna Rodrigues***

How did it help improve your quality of life?

"My biggest memory of the conference was the video of the babies with SMA that had gene therapy and were now playing normally with other children. This gave me faith that someone is working on a cure instead of me just reading about progress in bulletins and flyers." ***– Chuck Joosten***

"I gained a better understanding of clinical trials. Especially with my subtype being unknown, I am not sure if I will ever get answers, but that is OK, and I have come to terms with that after attending the LGMD conference." ***– Keisha Greaves***

SCAN ME

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"There were different conference topics to learn about at various times. The topic of adaptive equipment was the most useful to me. I learned new ideas and equipment that helped me with my daily life." ***– Jessica Gerardo & Camron Lawrence***

"After the conference, I felt less isolated and lonely than before. I already had a valued group of friends with my subtype, but now I am part of a broader community that also shares so many aspirations and goals." ***– Josh Thayer***

"The best thing for me was the relationships that my wife and I gained from the conference, which have grown and blossomed since then. I have honestly met some lifelong friends who have given me the confidence to share my story and be an advocate for this disease." ***– Chris Carroll***

"I am currently enrolled in a clinical trial with a potentially life-altering treatment for LGMD2i." ***– Cyndy Baxter***

"It gave me hope that a treatment/cure is coming soon and that I am not alone." ***– Brooklyn Garza***

"Being a part of this dynamic conference brought on a new sense of confidence in me. Being surrounded by hundreds of others with LGMD and hearing their stories along with learning about the newest revelations in therapies and treatments gave me so much hope for our future!" ***– Cassidy Nilles***

"Just being together. We need each other." ***– Kaya Leijenhorst***

"The conference has helped me to improve my quality of life by incorporating all the information I learned into my daily living. It also taught me to be more proactive about my own health care and search for clinical trials in my area." ***– Julianna Rodrigues***

If you could share anything with someone who is considering coming to the 2023 Conference, what would it be?

"Be open and talk to as many people as possible. I went into the conference wanting to get as much as I could from it, and it made a world of difference." ***– Chris Carroll***

"Come meet your LGMD family in person! This experience is a life-changing one that allows you to gain so much knowledge not only about LGMD but about yourself as well. I have made some lifelong memories and friends that I will carry with me forever" ***– Julianna Rodrigues***

"At the conference, we had the unique experience of meeting other people with LGMD. Meeting and spending time with people who share the same triumphs and struggles as you provides a sense of support that you rarely find anywhere else. We left with a support system and friendships that we have maintained to this day." ***– Jessica Gerardo & Camron Lawrence***

"There are a lot of reasons to come to the conference, including the great speakers and events that are set up." ***– Chuck Joosten***

"If you are physically able to attend the conference, it will be worth the trip! You will leave the conference with special memories and new connections in a community that is committed to supporting each other." ***– Cyndy Baxter***

"Attending the International LGMD Conference will be a life-changing experience. There is so much hope to be gained from hearing others' personal stories of success and happiness through many different avenues of life. With almost any question you've ever had regarding LGMD, there is sure to be someone at the conference who is able to answer it!" ***– Cassidy Nilles***

"Come if you can, you will not regret it. Watching online is good, but there is just something different about meeting people who are like you in person." ***– Brooklyn Garza***

"Know that you will feel welcomed and that you will find a friendly group of people to learn from and share with. Know that it is about inclusion and that it is fun." ***– Josh Thayer***

"You will learn a lot about the LGMD community, connect with awesome people, have a great time, and have friends for life!" ***– Keisha Greaves***

"I hope to meet you in person in Washington. Together we are stronger, and the landscape is changing! Take the chance to get all the reliable updates." ***– Kaya Leijenhorst***

Julianna Rodrigues
Allentown, PA
LGMD R2/2B ■ Age: 32

Josh Thayer
Brookline, MA
LGMD R2/2B ■ Age: 58

Written By Igor Ferreira da Silva

A Diagnosis Turned Into a Mission

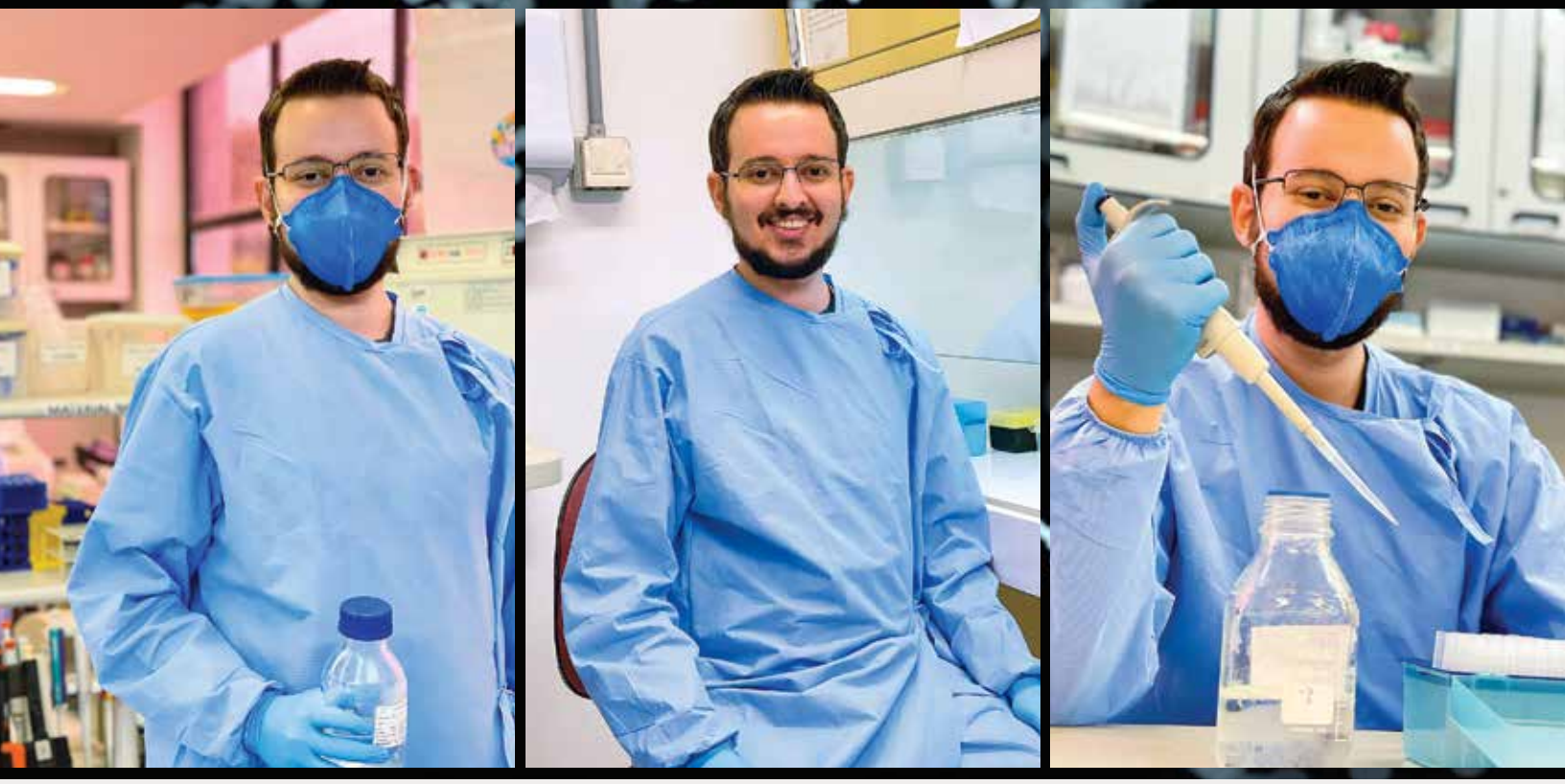
I have always been fascinated with scientific discovery. The year 2018 looked as if it was going to be a very good year, but I would soon discover something that would change my life.

My name is Igor Ferreira da Silva and I am 24 years old. Growing up in Rio de Janeiro, I was a dedicated student. In high school, I devoted myself to studies and extracurricular projects focused on environmental education and science. When two other students and I developed a project that won third place in the biological and health sciences category for the main science fair in Rio de Janeiro, my passion for biology continued to grow. In 2016, at the age of 18, I started my college path, specializing in biological sciences.

College was a time of ups and downs in my life. While I was happy to pursue my passion, I was growing both mentally and physically tired. Every day was a journey of almost 100 km round trip by train to and from the university. One day in 2018, while on my way home, I began to notice that at just 20 years old, I was having more difficulty climbing stairs at the train station than others who were elderly or overweight. Until this time, I thought that my trouble was a result of my sedentary lifestyle, but at that moment, I realized that my mobility issues were not normal.

The year that muscular dystrophy came into my life had started on such a high note, being selected as an intern

"I am very excited and motivated to continue researching and doing my best in the area of muscle biology. Although not every day is easy, I am motivated to go far and leave my contribution to this world."



in a microbiology laboratory and learning all about health research. After seeing the doctor regarding my mounting concerns, I was referred to a neurologist who quickly suspected that I might have muscular dystrophy. A series of tests, including CPK, electroneuromyography, and an aldolase blood test, all indicated that I had a myopathy. As time went on, I gradually experienced more difficulty with balancing, climbing stairs, and standing up from seated positions, among other symptoms that continued to worsen.

These experiences led me to study more about muscular dystrophy and consider leaving my microbiology internship to pursue working in the area of muscle biology research. In 2020, I finally received genetic confirmation of my diagnosis of LGMD R1/2A. That same year, I finished college and became a biologist at the age of 22.

In 2021, I started a master's program in cellular and molecular biology at the Oswaldo Cruz Foundation (FIOCRUZ), with muscle biology as a research area. Currently, I am developing a research project in which I will evaluate a promising biological molecule with the potential to improve the muscle regeneration process. Although my current project does not directly involve muscular dystrophy, I hope to gain knowledge that I can apply to a future PhD project involving MD. I am very excited and motivated to continue researching and doing my best in the area of muscle biology. Although not every day is easy, I am motivated to go far and leave my contribution to this world.

Living with LGMD is very difficult, as we all know, but we can still achieve our dreams, make a difference, and find happiness. Who knows where our journeys of discovery might take us? ▪

Photos courtesy of Rafaella Reis

CLINICAL TRIALS 101

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

Evaluating the Clinical Trial Option

It's a dynamic time for the LGMD community as multiple companies are planning or launching clinical trials. It's important to have as much information as possible when considering whether to enroll in a clinical trial. Ask many questions as you work through your decision-making process. Choosing to participate in a clinical trial is a major commitment made on behalf of a trial and the broader LGMD2I community. It is also important to remember that participation in a clinical trial is always voluntary, and you may decide to stop participation in a trial for any reason, at any time.

Before deciding to participate in a clinical trial it is important to:

- Approach the prospect of clinical trial with a better sense of what is involved
- Reflect on what is important to you and your family and how participating in a clinical trial will impact you

ML Bio Solutions

Being a Participant in a Clinical Trial

Individuals in a clinical trial are voluntary participants in research studies. Only the individual and their family members should decide if participating is the right thing for them. Participating in a clinical trial means that you are making a commitment to fulfill the requirements of the study. It takes time and effort — and it's important to have the support of your family.

Understand the Clinical Trial Protocol

Each clinical trial has a unique protocol or study design/plan. The study protocol is determined by the company sponsoring the clinical trial (often referred to as "the Sponsor"). The protocol is reviewed by the FDA and other local health authorities before the clinical trial can begin. It is important to understand the protocol and know what will be asked of you as a clinical trial participant.

Consult Your Doctor

Speak to your doctor. It may be necessary to stop taking certain medications while participating in a clinical trial. Plan to work with the study's principal investigator and your doctor to plan.

Genetic Testing

Why is a record of genetic testing a requirement for clinical trial participation? It is critical that only patients who have the disease the investigational therapy is attempting to treat enroll in the clinical trial. The only way to truly confirm that a patient has LGMD2I, the disease potentially addressable by an investigational therapy, is to have confirmed genetic testing.

Medical History

In advance of a clinical site screening appointment gather your medical records. This should include printed copies of your genetic testing and any other medical history relevant to your diagnosis and participation in a clinical trial.

ICF (Informed Consent Form)

Informed consent is the process of telling potential study participants about the key elements of a protocol. Informed consent means that you understand the clinical trial protocol, the risks and benefits of participation, what will be required to participate, the logistics of the clinical trial and that you agree to participate in the trial. A study participant's informed consent is documented through the signing of the Informed Consent Form (ICF). After reading the Informed Consent documents, ask yourself if you understand the study and feel comfortable asking the study doctor additional questions.

Each assessment, such as a biopsy, is another piece of data that is evaluated to determine if the investigational therapy is working as planned. In case you missed it, check out ML Bio's articles:

- ***Why are Biopsies Important in Clinical Trials?*** in the Winter 2023 Volume 3, Issue 1 of the LGMD News Magazine.
- ***What is Substrate Supplementation Therapy and How Could it Work as a Treatment for LGMD2I?*** in the Spring 2023 Volume 3, Issue 2 of the LGMD News Magazine.

Written By Mina Kim
Representative of the Korea Dysferlinopathy Patient Association (KDPA)

A Community for Dysferlinopathy Patients in Korea

I live in Busan, Korea, with my husband, son, and daughter, and I've been living with dysferlinopathy (LGMD R2/2B) for 17 years.

Before the disease started, I wasn't worried about using my body. I used to enjoy running and outdoor sports during every season. When I reached the top of a mountain, I felt very satisfied. Although my younger sister and brother already had symptoms, I didn't worry about the disease because I thought I could do anything.

Then in 2006, at the age of 27, I was diagnosed with LGMD R2/2B not long after giving birth. One day, when I was going home with my baby, I got out of the car and went up the stairs. What I felt was noticeably different from muscle weakness caused by lack of stamina or physical fatigue. I felt like I was a lump of soft clay made in art class at school. I knew what that meant: this muscle disease that my younger sister and brother had suffered with for over ten years had now shown up in me. My heart sank terribly. It is so challenging to have LGMD as they do. Thankfully, I am going through this with my family who always cheer me up and support me.

After receiving genetic testing through Busan National University Hospital in Yangsan, which confirmed the diagnosis, my attending physician, Dr. Zinhong Shin, suggested that I might want to start an association for dysferlinopathy patients in Korea. He told me about ten other patients with whom he had contact. At that time, I'd never met anyone else with this disease except my siblings. I was very interested in talking to other patients about fighting this disease, so I said "okay" and decided to create a patient group.

It was lucky that I met Dr. Shin and that he encouraged me to connect with other patients. Since then, I've been working to accept the disease and live positively. Sometimes I meet a situation that I cannot handle, which makes me feel depressed. Nevertheless, I am not alone! There are those who can understand us, even without any words being spoken. I am really thankful for this community!

Introducing the Korea Dysferlinopathy Patient Association (KDPA)

KDPA was established in 2020, starting with just ten patients. That year, we held our first annual meeting with Dr. Shin at Busan National University with the purpose of informing the public about dysferlinopathy. Patients shared their stories about how they live with this disease. In 2021 we held our meeting in Sejong. Last year, we held

Opposite: Mina Kim and her husband.

meetings in both Yangsan and Seoul, and we were grateful to have Professor Volker Straub of Newcastle University, UK, join us to give a lecture about dysferlinopathy. Afterwards, professors and patients had a valuable Q&A session that lasted more than an hour.

Ten Korean patients are participating in COS2 (Clinical Outcome Study 2), which is funded by the Jain Foundation and led by Newcastle University. The participants in COS2 are very pleased that they can have their overall body function evaluated in detail apart from their regular medical visits. Also, through surveys included in the study, they are more aware of the emotional impact of living with this disease.

KDPA helps patients to understand the cause of this disease. In addition, we share information about proper rehabilitation, assistive devices, hospitals, institutional benefits, and employment for improving our lives. When important news is announced, it can be shared and studied by doctors and patients in our community. The patients also actively support and encourage one another,

Above: Mina's daugher, father, son, Mina, her sister, mother, and brother.

which can be so helpful in coping with the daily experiences of LGMD.

The number of KDPA members has reached approximately 100 within three years; in addition to patients, over 200 family members, friends, and other people interested in the disease have joined our online community. We hope KDPA can develop as part of the global patient community and share in a friendship exchange program. We would love to share our experiences for improving life with others. Together we shall dream of the big celebration we will have when treatments for LGMD are launched! ■

Written By Hilda Bih

Growing Up Disabled In Cameroon

Above: Hilda and family, 1986.

> *A culture that considers being born with a disability as a bad omen or a curse for the family, as well as the lack of government investment in basic accommodations, has contributed to keeping those with disabilities on the fringes of society.*

Disability can be one of the hardest things to deal with in a developing country such as Cameroon, West Africa, where I grew up. My family's love and sacrifices shielded me from some of the harsh realities that children living with disabilities face daily. As I grew older and ventured out more, I was shocked by the number of people with disabilities who were left to their own devices, some of whom ended up on the streets and survived by begging or peddling goods on the motorways. A culture that considers being born with a disability as a bad omen or a curse for the family, as well as the lack of government investment in basic accommodations, has contributed to keeping those with disabilities on the fringes of society.

When I was around the age of four or five, my family noticed that during playtime I walked and held things differently from my friends. My parents became more concerned when the weakness I experienced led to constant falls and difficulties walking. When several visits to local hospitals did nothing to provide answers, my parents' next step was turning to traditional healers known as medicine men, who claimed to have ancestral and spiritual powers to unlock the mystery that was causing my body to deteriorate. Much of my childhood was spent going from one healer to another, each one claiming I was either bewitched by some relative or I was a spirit-being from another world who needed to be cleansed to fit into human society.

Every other person living with a disability in my community has a similar story, complete with razor-cut scars on their bodies from the treatment received from medicine men. The result, unfortunately, is the same — a broken and

Hilda Bih

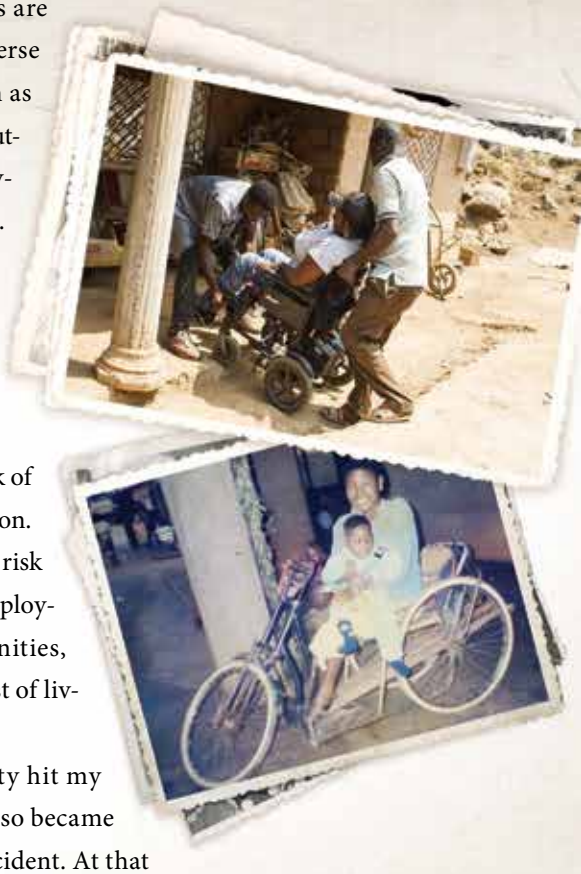
traumatized person left to an impoverished family that has run out of options. For those with more severe disabilities, the result could be abandonment or worse still, being killed as a means of returning them to the spirit world. A very small number of persons with disabilities are fortunate enough to go through the typical milestones of life, like receiving an education, securing employment, and starting a family of their own.

I am one of the fortunate ones. Blessed with parents who believed in the power of education, my hospital stays and traditional doctor visits only interrupted but never halted my academic journey. With a resolve to keep moving, without understanding the cause of my disability, life felt like groping in darkness. As my weakness progressed and I lost mobility, my family sacrificed to keep me in school. We had little access to cars and had long distances to cover, so for many years, they carried me on their backs to and from school every day, as well as to other places I needed to go. School campuses and classrooms were not accessible, but we kept going. Even after receiving a donated wheelchair, I still had to either follow lessons from outside the room or be carried into classrooms by my classmates.

Lack of access is a daunting hurdle for those with disabilities in developing countries. There has been a slight improvement since I was growing up some 30 years ago, thanks to advocacy by civil society and faith-based organizations. However, the World Bank in 2022 reported many barriers to full social and economic inclusion of persons with disabilities[1]: inaccessible physical environments and transportation, unavailability of assistive devices and technologies, non-adapted means of communication, gaps in service delivery, and discriminatory prejudice and stigma in society. The report goes on to describe the link between poverty and disability, stating that "persons with disabilities are more likely to experience adverse socioeconomic outcomes such as less education, poorer health outcomes, lower levels of employment, and higher poverty rates. Poverty may increase the risk of disability through malnutrition, inadequate access to education and health care, unsafe working conditions, a polluted environment, and lack of access to safe water and sanitation. Disability may also increase the risk of poverty, through lack of employment and education opportunities, lower wages, and increased cost of living with a disability."

The harsh reality of poverty hit my family hard when my father also became disabled as a result of a car accident. At that time, the cause of my progressive weakness remained unknown. I had reached an age where I needed to move away from my family to stay in school. This engendered a new crisis of identity that almost cost my life. It was difficult to find hope in a society where every move seemed like a fight for survival. I had been infused with enough reason from my optimistic family and from stories I read to convince me the future would be bright despite my challenges. However, in high school, I tried to take my life because I never wanted to experience the same misery that I thought everyone with a disability lived in.

Below: Hilda visiting a village and first mobility device



If You Need Support

National Suicide Prevention Lifeline
English: **1-800-273-8255** (TALK)
Spanish: **1-888-628-9454**
Live Online Chat:
SuicidePreventionLifeline.org/Chat

International Association for Suicide Prevention
FindaHelpline.com/i/iasp

[1] The World Bank, https://www.worldbank.org/en/topic/disability, Accessed 6 April 2023.

Above: Hilda painting a beautiful landscape.

What saved me was the faith that I developed over many years. As a child, I went to church many times with my family, but as I lost mobility, I was able to attend less often. I felt isolated spiritually when I couldn't attend church, so that was one of the first places I was excited to visit after getting a mobility device. Unfortunately, like my school and other places, I could not access the church building. It was heartbreaking to see that even the church lacked key accessibility features. There were days I insisted on going to church, only to end up following along with the service while sitting outside in the sun because I found no one to carry my wheelchair up the stairs. This was hard to bear as I believed the church should be the example of caring for others. People with disabilities in all countries need better access to their spiritual communities.

Barriers did not deter me from seeking to grow in faith, however. I moved to different denominations seeking acceptance and spiritual fulfillment, but in most churches, the leaders saw a greater need to pray to heal my disability than teach me the tenets of the faith. Feeling hurt and rejected, I stayed away from church even more, only returning when I felt safe and strong enough to avert the offers of unsolicited healing sessions.

After accepting my disability, the next big challenge was to find a diagnosis. Renewed visits to hospitals yielded very little and even made me wonder if those who attributed my disability to witchcraft were right. I began to do my own research, and after asking a doctor about muscular dystrophy, the best answer I could get was that I probably had a neuromuscular condition. The paucity of specialists in this field is another major concern in Cameroon. I found out about a neurologist, one of the very few in the country, based in Yaounde, the capital. Due to the expense and the distance to get there, I was not able to book an appointment to see him.

Thankfully, in 2015, I was offered the chance to travel to the United States to be a speaker at the Speak Foundation's patient support conference held, at that time, annually in Atlanta, Georgia. As fate would have it, The Speak Foundation partnered with the Jain Foundation to offer genetic testing kits for muscular dystrophy (Next Generation Sequencing through Emory University) to patients in attendance, and I was able to take advantage of this momentous opportunity. The results confirmed that I had a form of muscular dystrophy. At the age of 35, I finally received an answer to the question I had been asking all my life.

I consider myself very blessed to have resilient parents who continued to love, support, and educate me despite all the difficulties we have faced. Education has not only given me an opportunity to be employed but to explore the world, learn, share my story, and offer hope. It is encouraging to see the strides that other countries like the United States have made in granting access to persons with disabilities. In 2018, I moved to the United States where I currently live, hoping and working towards a day when the same level of access will be afforded to those with disabilities in Cameroon and other countries in Africa.

More important, my parents passed on their faith to me and my siblings, a faith that assures us that we are all created in the image of God, disabled or not, and that someday the Lord Jesus Christ will remove disability and give us perfect bodies. My faith remains my greatest resource and strength to this day. ▪

In 2018, I moved to the United States where I currently live, hoping and working towards a day when the same level of access will be afforded to those with disabilities in Cameroon and other countries in Africa.

Do you or does someone you know have LGMD2I/R9?

AskBio will be conducting a clinical study of an investigational gene therapy for individuals with a confirmed genetic diagnosis of LGMD2I/R9.

- This is a one-time intravenous infusion of gene therapy designed to produce fukutin-related protein (FKRP) in the body, primarily in muscle.
- Part 1 of the study will assess the safety of LION-101 only in adults (ages 18 and 65 years).
- This is a randomized, placebo controlled, double-blind study.
- The study is designed to investigate at least two different doses of LION-101 versus placebo.
- The initial phase of this first-in-human dose-finding study will be conducted in the US.
- Travel to study sites may be reimbursed; local and home-based testing will be used when possible.
- Information on the clinical trial can be found on clinicaltrials.gov.

To learn more, please visit AskBio.com, email AskFirst@AskBio.com or go to clinicaltrials.gov (NCT05230459)

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