Novel Therapeutic Strategies for Congenital Myopathies

Update on RYR-1-Related Diseases, Models of RYR-1 Myopathy, and The RYR-1 Foundation
Our Leadership

**Michael F. Goldberg, MD, MPH**
Co-Founder, President, Co-Chair of Research, & Director

*RYR1* autosomal recessive mutations.

**Director of Neuroradiology**, Allegheny Health Network.

**Associate Professor**, Drexel University College of Medicine.

**MD/MPH** from Johns Hopkins University School of Medicine.
Overview

What are RYR-1 Related Diseases?

What impact do they have on the children and adults that have this disease?

Why did we create The RYR-1 Foundation?
RYR-1-Related Diseases are the MOST COMMON Congenital Myopathy

Congenital myopathy due to mutation(s) in RYR1 gene.

Common clinical features: Proximal muscle weakness, ophthalmoplegia, bulbar weakness, orthopedic deformities.

Rhabdomyolysis, heat stroke/intolerance, statin myopathy/myalgias.

Risk for fatal complication of anesthesia (malignant hyperthermia).

Courtesy of Filip Van Petegem, PhD
Schematic diagram illustrating the role of the RyR1 receptor in skeletal muscle function, including excitation-contraction coupling

*Courtesy of Robert Dirksen, PhD*
Mechanisms of Disease

1. **Increased sensitivity of RYR-1 channels to activators** (e.g., caffeine, halothane)
   - Dominant, associated with MH)
   - RYR-1 channels become hypersensitive to activation by electrical and pharmacological stimuli

2. **Enhanced RYR-1 calcium leak**
   - Dominant, associated with CCD, leaky channels leading to depletion of Ca++ SR stores

3. **Reduction in RYR1 Calcium permeation leading to reduced calcium release** (Dominant, CCD)
   - Process known as excitation-contraction UNcoupling
   - DHPR, is unable to cause Ca++ release from the SR
4. Dramatic reduction in RYR-1 channel expression (recessive)
   - Nonsense mutations
   - Epigenetic Allelic silencing
     - *Increased* RYR1 gene hypermethylation
     - *Decreased* expression of muscle-specific microRNAs (miRNA)
     - *Increased* histone modification from increased expression of class II histone deacetylases (HDACs)
   - Protein degradation due to channel instability
Biallelic transcription

Control

RyR1

Desmin

Monoallelic transcription

CNM

H. Zhou et al.

Brain (2007), 130, 2024–2036
Epigenetic Allele Silencing Unveils Recessive RYR1 Mutations in Core Myopathies

Haiyan Zhou, Martin Brockington, Heinz Jungbluth, David Monk, Philip Stanier, Caroline A. Sewry, Gudrun E. Moore, and Francesco Muntoni

regulation. However, during the RYR1-mutation analysis of a cohort of patients with recessive core myopathies, we discovered that 6 (55%) of 11 patients had monoallelic RYR1 transcription in skeletal muscle, despite being heterozygous at the genomic level. In families for which parental DNA was available, segregation studies showed that the nonexpressed allele was maternally inherited. Transcription analysis in patients' fibroblasts and lymphoblastoid cell lines indicated patients inherit a recessive allele from one parent only. Various lines of evidence suggest that the monoallelic RYR1 expression observed in the skeletal muscle of our patients is the result of epigenetic modification. We excluded changes in the nucleotide sequence of RYR1 in

Our studies of cultured myoblasts treated with the DNA methyltransferase inhibitor 5-azaC suggest that the monoallelic expression of RYR1 is associated with DNA methylation. Imprinted genes are usually associated with a CpG

We understand the impact that this disease has, and we believe we can change it. Let’s do this together!

Significant morbidity associated with RYR-1 myopathy presents an opportunity for therapeutic intervention\(^1,2\) in order to improve...


The Challenges to RYR-1 Gene Therapy

- *RYR1* gene (19q 13.2) encodes RyR1 protein
- Gene size >159 kb (106 exons)
- Exceeds packaging capacity of adeno-associated virus-mediated therapy
- 700 variants throughout *RYR1* coding region have been identified
We are the only organization working to improve the lives of individuals affected by RYR-1-related diseases.

- No treatments available...YET
- Care for RYR-1-related diseases is strictly supportive with no approved treatments for this group of debilitating disorders


The only organization in the world dedicated solely to RYR-1-related-diseases.

Our Mission:
To support research leading to an effective treatment or a cure for RYR-1-related diseases.

Our Goal:
To collaborate with researchers, clinicians, and biotechs to explore novel therapeutic strategies for RYR-1.

Why:
Over 80,000 people suffer with RYR-1 related diseases. We know we can help change the prognosis.
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We are Unique
An integrative approach that combines:

Patient Support

Biotech / Pharma

Research

Patient Advocacy
We know first-hand the challenges of RYR-1

Our objective is both professional and personal to:

Find Treatment: Work with the top researchers and companies in the world.

Patient Support: Created the only medical guides written specifically for patients (in eight languages).

Fund: Research required to find treatment.

Advocate: We make clinical trials happen.
World-Class
Scientific Advisory Board Members

Carsten G. Bönnemann, MD,
Chief, Neuromuscular and Neurogenetic Disorders of Childhood Section, NIH

James Dowling, MD, PhD,
Mogford Campbell Chair in Pediatric Clinical Neuroscience, Hospital for Sick Children

www.ryr1.org/scientificadvisoryboard
Yes, there are challenges to RYR-1 therapeutic development...

...But we’ve already accomplished more in eight years than we thought was possible.
Our Impact

- $4.2 million Raised in eight short years
- $1.7 million Research Projects Funded
- $850,000 Current committed research
- $200,000 Committed to scientific meetings

For details on research grants, please go to: www.ryrl.org/grants
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<thead>
<tr>
<th>Category</th>
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<tr>
<td>Major National Clinical Trial Facilitated</td>
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RYR-1-Related Diseases International Research Workshop: From Mechanisms to Treatments

Hyatt Regency Pittsburgh International Airport
Pittsburgh, PA, USA
July 21 - July 22, 2022

To access the workshop program, please click HERE.
Animal Preclinical Models of RYR-1

- We were able to create a new recessive compound heterozygous mice with a severe myopathy phenotype.

- Mice have undergone rigorous phenotype characterization by world’s leading RYR-1 experts.
Animal Preclinical Models of RYR-1

• Mice have been shipped to researchers around the world, including Australia
Research Grant Success

• Mechanism for leverage our resources to promising early-stage research, both in academia and biotech.

• As a small organization, we have a streamlined grant application process that is nimble and responsive to investigators.

• Successful track record in short period of time working with both academia, industry, and governmental regulatory agencies.
Clinical Trial Success

We facilitated a clinical trial of Rycals, which is a rare accomplishment.

- The RYR-1 Foundation funded preclinical research justifying a human clinical trial at NIH.

- Trial was at risk of being terminated. The RYR-1 Foundation, in its capacity as an advocacy organization, successfully lobbied Congress to intervene at NIH, thus resulting in the successful initiation of the trial.
Clinical Trials for Rare Myopathies are Feasible

**01**
IDEA THAT RYR-1 FUNDS
Funded basic research. Led to Bench-to-Bedside grant and approval for clinical trial.

**02**
ADVOCACY
Worked with corporate sponsor and NIH to identify PI.

**03**
CLINICAL TRIAL SUPPORT
Through our vast patient network, we raised awareness of trial and identified trial participants.

**04**
ONGOING ADVOCACY
Met with VC firm during their due diligence.

**05**
VC FUNDING
ARMGO receives $35 million investment from Forbion.

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July 2022
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Intracellular calcium leak as a therapeutic target for RYR1-related myopathies

Alexander Kushnir1,2, Joshua J. Todd3, Jessica W. Witherspoon3, Qi Yuan1, Steven Reiken1, Harvey Lin1, Ross H. Munce1, Benjamin Wajsberg1, Zephane Melville1, Oliver B. Clarke4, Kaylee Wedderburn-Pugh1, Anetta Wronda1, Muslimsa S. Razaqyar1, Irene C. Chrismer2, Monique O. Shelton3, Ami Mankodi5, Christopher Grunseich5, Mark A. Tarnopolsky6, Kurenai Tanji7, Michio Hirano8, Sheila Riaz9, Natalia Kraeva9, Nicol C. Voermans10, Angela Gruber11, Carolyn Allen13, Katherine G. Meilleur3, Andrew R. Marks1,2

Received: 9 November 2019 / Revised: 14 March 2020 / Accepted: 15 March 2020

Funding: This work was supported by an RYR1 Foundation Research Grant to AK
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www.ryr1.org
July 2022
January 29, 2019

Francis Collins, MD
Director
National Institutes of Health
collinsf@mail.nih.gov

Dear Dr. Collins:

I am writing to you as the President of a patient advocacy group the RYR-1 Foundation, which is working for treatments of RYR-1-related myopathy (RYR-1-RM), a rare, debilitating condition. Our website is: www.ryr1.org.

There is currently no treatment for RYR-1-RM; however, a new class of drugs known as Rycals has been developed to target RYR-1, and we think that these drugs offer tremendous potential as a therapy for this myopathy.

I am writing to you in order to ask for help with the start of a study using a Rycal (ARM210) in RYR-1-RM patients at NIH.
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Safety, pharmacokinetics, and preliminary efficacy of Rycal S 48168 (ARM210) for RYR1-related myopathies: a phase one, open-label dose-escalation trial

Rationale
Ryranolone receptor 1 (RyR1) channel sub-conductance, aberrant Ca2+ leak into the cytosol and oxidative stress often underlie the disease in RYR1-related myopathies (RYR1-RM).

Loss of RyR1-csatin1 association was rescued with ex vivo Ryranolone treatment of RYR1-RM muscle.

Rycal S48168 demonstrated a favorable safety profile in SAD and MAD male healthy volunteer studies (N=100).

Methods

**Key eligibility criteria**
- 18-65 years of age
- Genetic confirmation of RYR1-RM
- Supporting clinical phenotype
- Ambulatory and PVO2 ≥ 80 percent
- No prior history of seizures

**Primary endpoint (safety and tolerability)**
- TEAEs; 
- AICR in security, SADs and MADs

**Exploratory endpoints**
- S-48168 PK and muscle tissue concentrations
- Δ in M/MN(%) Maximum T-score; heart, grip and pinch strength (kg), time to functional steps (seconds)
- Δ in PROMIS fatigue (6 scores)
- Δ in plasma 15F2d integrin and protein carbonyl concentrations

**Trial and design summary**

**NIH Clinical Center visits**
- Screening (Day 0)
- Baseline (Day 14)
- End of treatment (Day 28)

**Follow-up visits (Days 42/56)**
- Low dose 125 mg
- N=3
- D0/8/16
- High dose 250 mg
- N=9
- D0/16/28

Age and sex-matched natural history data available from NCT02030423.

**Participant Characteristics**

<table>
<thead>
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<th>Mean</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
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<tr>
<td>MAD</td>
<td>1.50</td>
<td>1.50</td>
<td>0.50</td>
<td>2.50</td>
</tr>
<tr>
<td>SAD</td>
<td>2.00</td>
<td>2.00</td>
<td>1.50</td>
<td>3.00</td>
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</table>

**Pharmacokinetics**

**Steady State (Day 20)**

**Exploratory efficacy**

**Safety and Tolerability**

<table>
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<tr>
<th>Safety event</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Dizziness</td>
<td>10% (1/9)</td>
</tr>
<tr>
<td>Headache</td>
<td>11% (1/9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11% (1/9)</td>
</tr>
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**Conclusions**

- Clinical trials for rare myopathies are feasible as a collaborative endeavor between industry, academic, government, and patient advocacy (RYR1 Foundation).
- Favorable S48168 safety and tolerability profile in RyR1-RM affected individuals.
- Dose-dependent S48168 PK profile consistent with prior healthy volunteer studies.
- Positive trends in hand grip strength and fatigue warrant further investigation in a double-blind, randomized, placebo-controlled trial.

For more information, visit www.ryr1.org.

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ARMGO Pharma raises $35 million to progress clinical studies of lead molecule ARM210 in cardiac and skeletal muscle diseases

December 20, 2021 07:00 ET | Source: ARMGO

ARMGO Pharma raises $35 million to progress clinical studies of lead molecule ARM210 in cardiac and skeletal muscle diseases

- Series B investment led by Forbion and joined by Pontifax and Kurma Partners
- Investment will fund clinical studies of ARMGO’s lead molecule ARM210, an oral treatment, in development for cardiac and skeletal muscle diseases
Clinical Patient Database

- The RYR-1 Foundation Patient Registry (395 patients enrolled)

- Database with clinical and genotype correlations (work-in-progress)
Additional Activities

Scientific conferences attended by the top leaders in the field of RYR-1-related diseases

Patient support via resources on our website, including the Clinical Care Guidelines, and International Family Conferences
How we can work together

We seek to facilitate collaborations and partnerships between experts/academic RYR-1 researchers and organizations interested in novel therapeutic strategies.
Work with us to change the lives of people living with RYR-1-related diseases

• RYR-1-related diseases are the most common congenital myopathy.

• No treatments available. Tremendous opportunity to address unmet need.

• Highly motivated and organized patient population, eager for a therapy.

• The RYR-1 Foundation has a proven track record of working successfully with academic, industry, and governmental/regulatory stakeholders.

www.ryr1.org
July 2022
Contact Information

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Email: nicole@ryr1.org
Website: www.ryr1.org