RYR-1 FOUNDATION

STRENGTH IN NUMBERS

# 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.


Photo Credit: Karen Martin, Highmark Health

# 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?

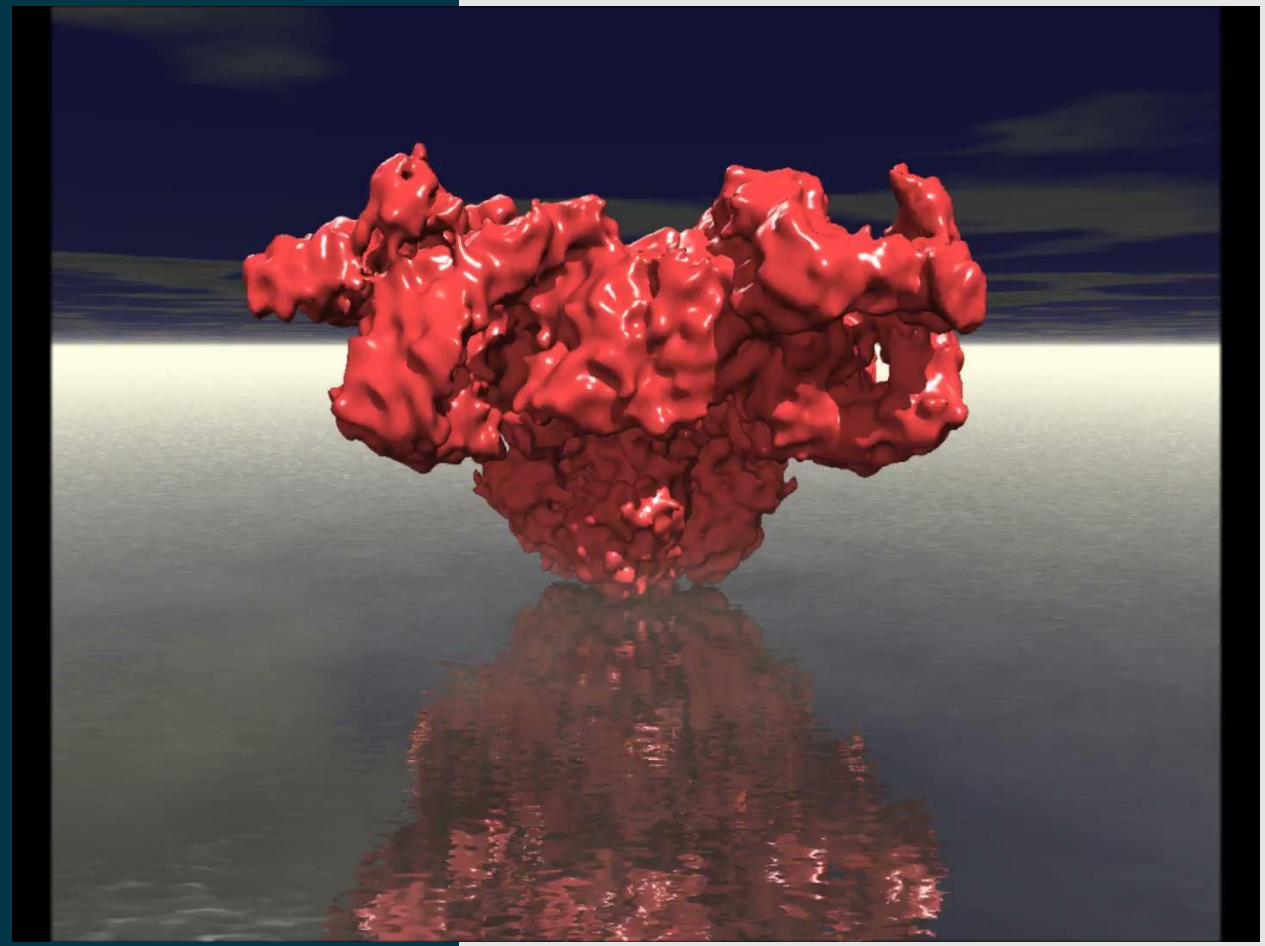
# RYR-1-Related Diseases are the MOST COMMON Congenital Myopathy

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

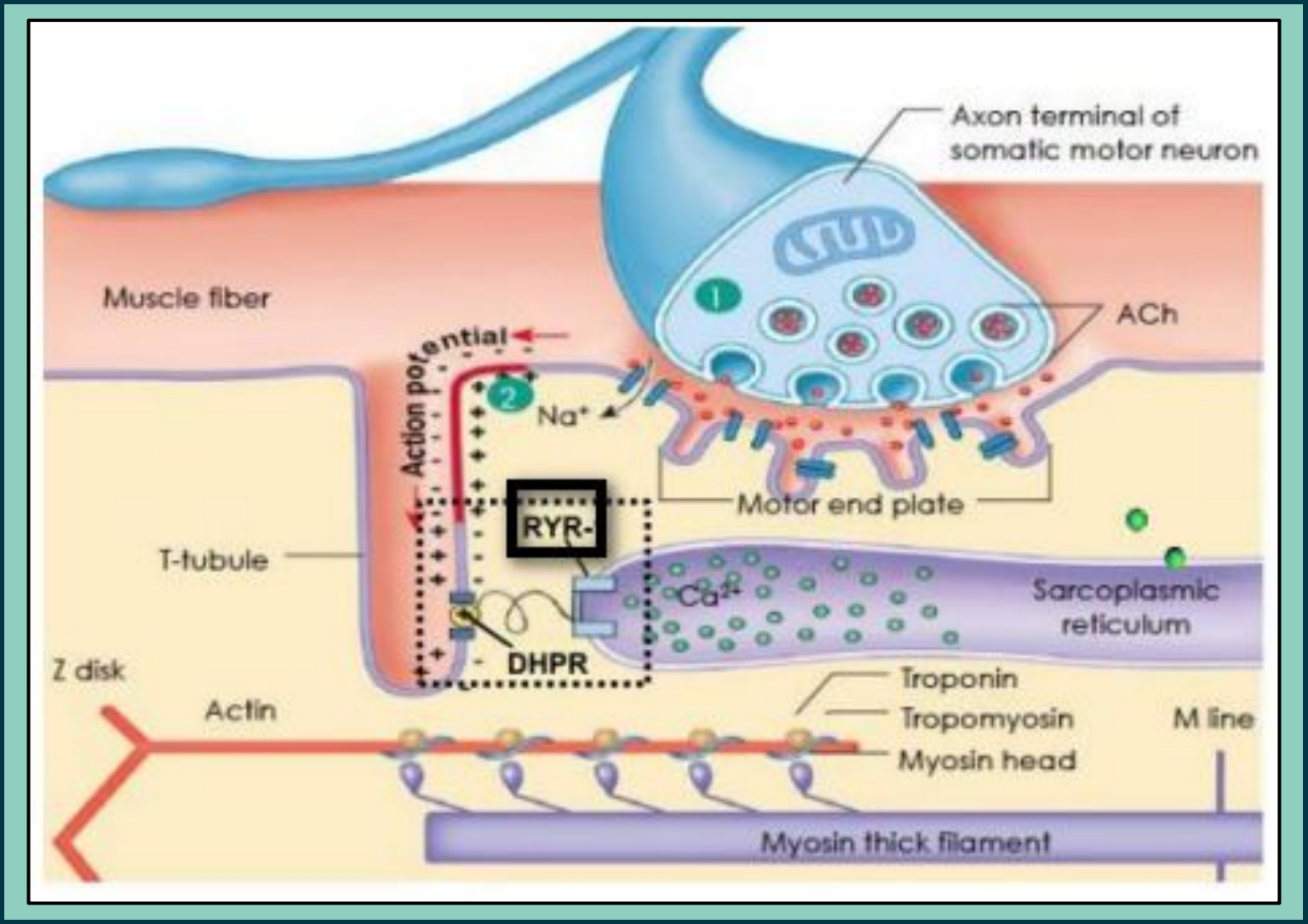
Common clinical features: Proximal muscle weakness, ophthalmoplegia, bulbar weakness, orthopedic deformities.

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

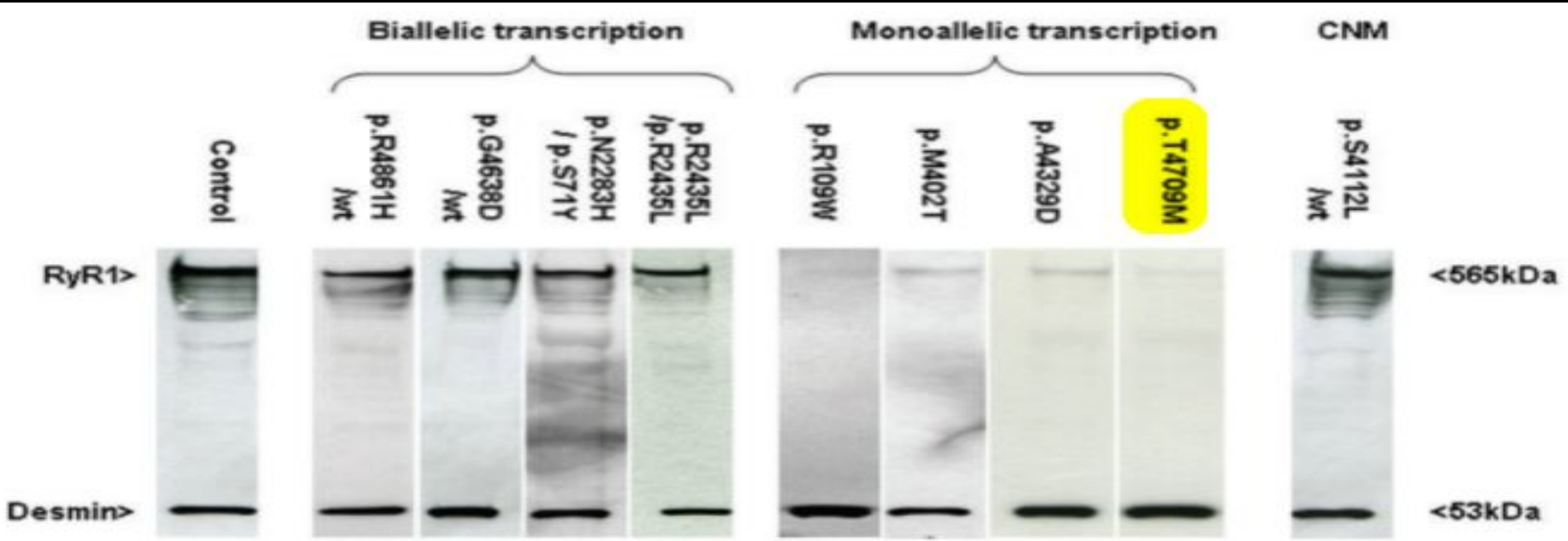
*Courtesy of Robert Dirksen, PhD*

# 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

# Mechanisms of Disease (continued)

4. **Dramatic reduction in RYR-1 channel expression (recessive)**
   - Nonsense mutations
   - Epigenetic Allelic silencing
     - *Increased* RYR1 gene hypermethylation
     - *Decreased* expression of of muscle-specific microRNAs (miRNA)
     - I*ncreased* histone modification from increased expression of class II histone deacetylases (HDACs)
   - Protein degradation due to channel instability




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.[23] 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

*Am. J. Hum. Genet.* 2006;79:859–868.

# 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...

**Pain**

**Functional Impairment**

**Quality of Life**

**Significant Fatigue**

[1] *Ruitenbeek et al. Functional impairments, fatigue and quality of life in RYR1-related myopathies: A questionnaire study.Neuromuscular Disorders. 2019 Jan;29(1):30-38. doi: 10.1016/j.nmd.2018.10.006.*

[2] *Capella-Peris et al. Mixed methods analysis of Health-Related Quality of Life in ambulant individuals affected with RYR1-related myopathies pre-post-N-acetylcysteine therapy. Quality of Life Research. Jan 2020 29:1641–1653. doi: 10.1007/s11136-020-02428-2.*

# 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


1. Witherspoon et al. 6-minute walk test as a measure of disease progression and fatigability in a cohort of individuals with RYR1-related myopathies. Orphanet Journal of Rare Diseases. 2018 Jul 3;13(1):105. doi: 0.1186/s13023-018-0848-9.

2. Witherspoon et al. Motor function performance in individuals with RYR1-related myopathies. Muscle Nerve 60:80-87, 2019.

# 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.ryr1.org/grants.


# Our research impact

**17** Total Number of Projects

**9** Current Research Projects

**2** International Research Workshops Hosted

**1** Major National Clinical Trial Facilitated

For details on research grants, please go to: www.ryr1.org/grants

# RYR-1-Related Diseases International Research Workshop: From Mechanisms to Treatments

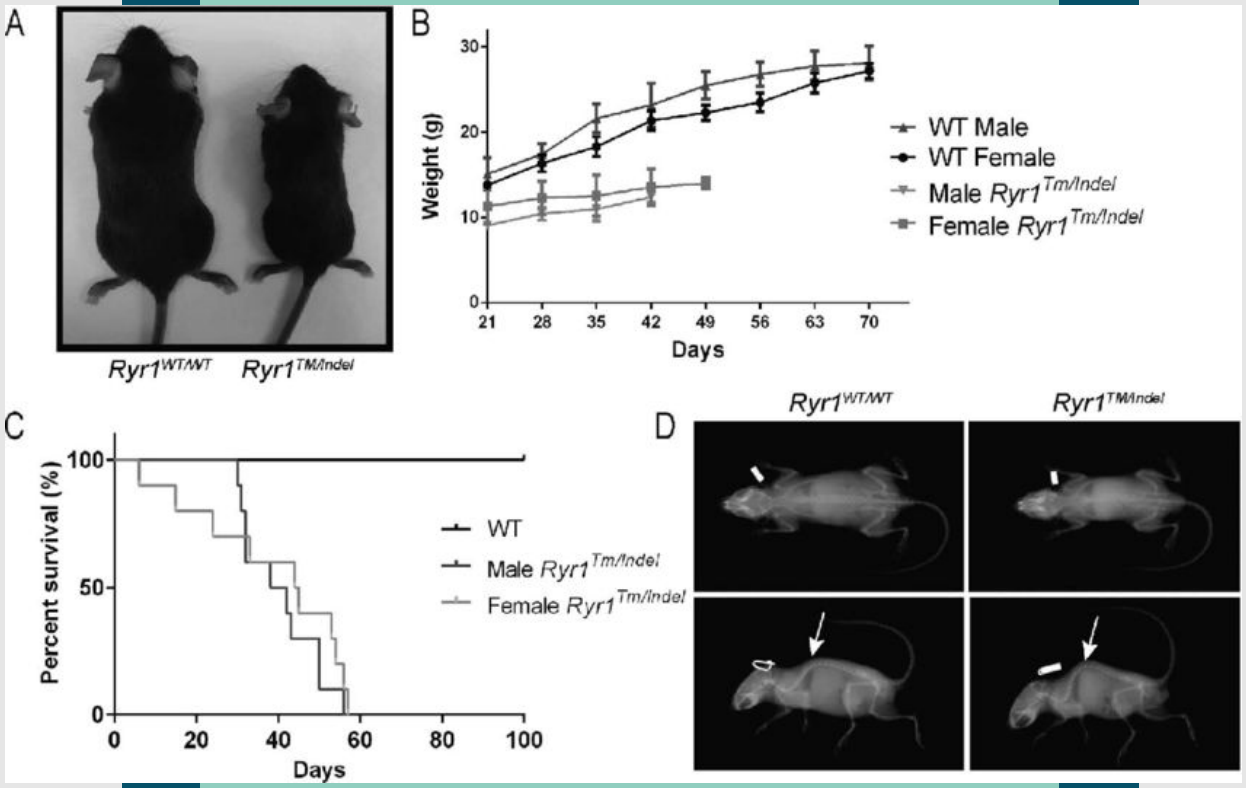
**Hyatt Regency Pittsburgh International Airport**
**Pittsburgh, PA, USA**
**July 21 - July 22, 2022**

**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



Laboratory of Dr. Bradley Launikonis
(The University of Queensland, Australia)

# Animal Preclinical Models of RYR-1

- Mice have been shipped to researchers around the world, including Australia

# Research Grant Success

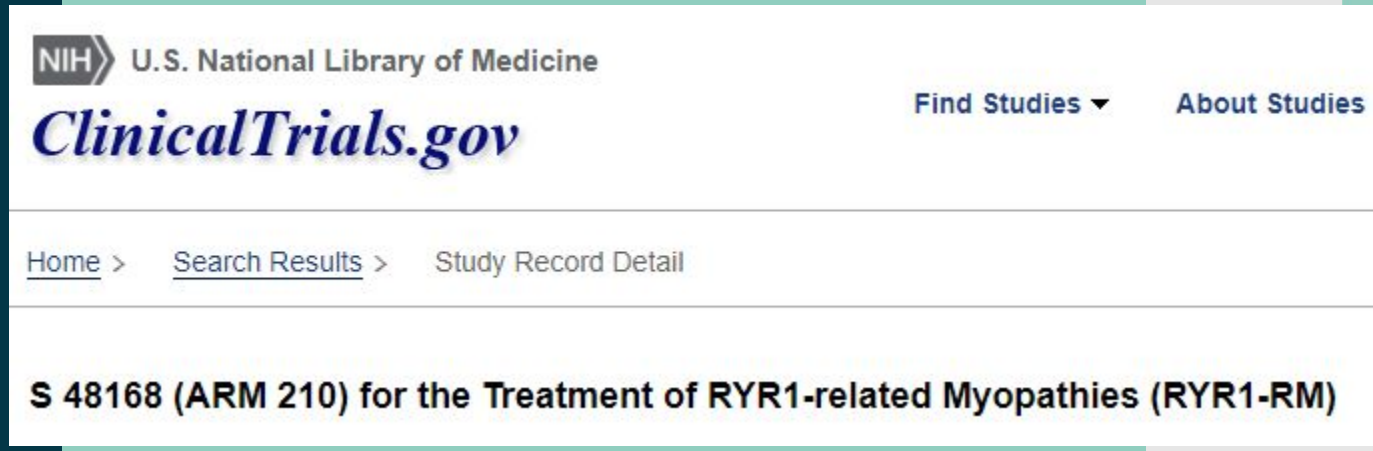
- Mechanism for leverage our resources to promising early-stage research, both in academia and biotech.
- As a small organization, we have a streamlined grant application process that is nimble and responsive to investigators.
- Successful track record in short period of time working with both academia, 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.

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### VC FUNDING

ARMGO receives $35 million investment from Forbion.

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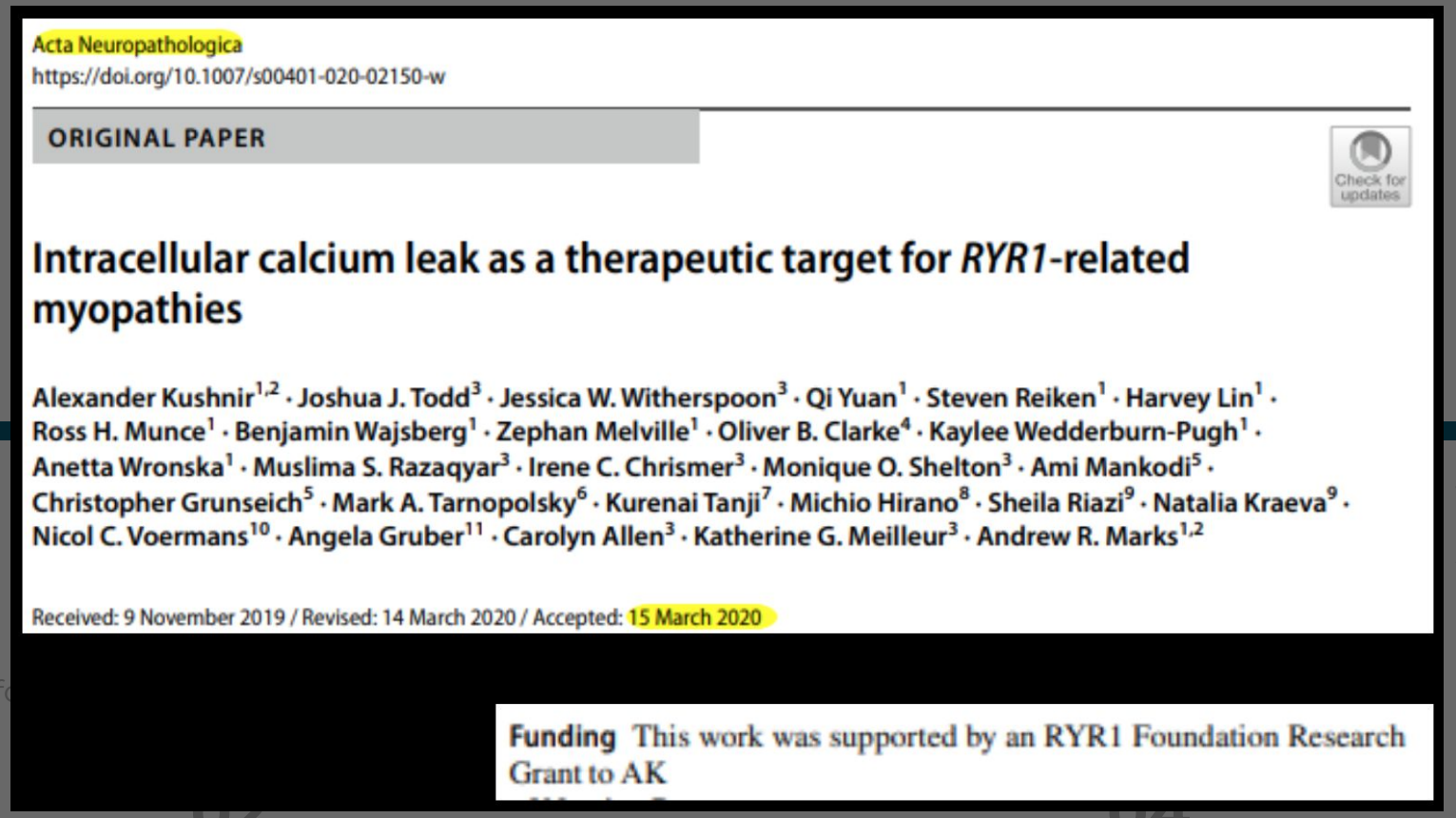

Acta Neuropathologica
https://doi.org/10.1007/s00401-020-02150-w

ORIGINAL PAPER

Check for updates

## Intracellular calcium leak as a therapeutic target for *RYR1*-related myopathies

Alexander Kushnir[1,2] · Joshua J. Todd[3] · Jessica W. Witherspoon[3] · Qi Yuan[1] · Steven Reiken[1] · Harvey Lin[1] · Ross H. Munce[1] · Benjamin Wajsberg[1] · Zephan Melville[1] · Oliver B. Clarke[4] · Kaylee Wedderburn-Pugh[1] · Anetta Wronska[1] · Muslima S. Razaqyar[3] · Irene C. Chrismer[3] · Monique O. Shelton[3] · Ami Mankodi[5] · Christopher Grunseich[5] · Mark A. Tarnopolsky[6] · Kurenai Tanji[7] · Michio Hirano[8] · Sheila Riazi[9] · Natalia Kraeva[9] · Nicol C. Voermans[10] · Angela Gruber[11] · Carolyn Allen[3] · Katherine G. Meilleur[3] · Andrew R. Marks[1,2]

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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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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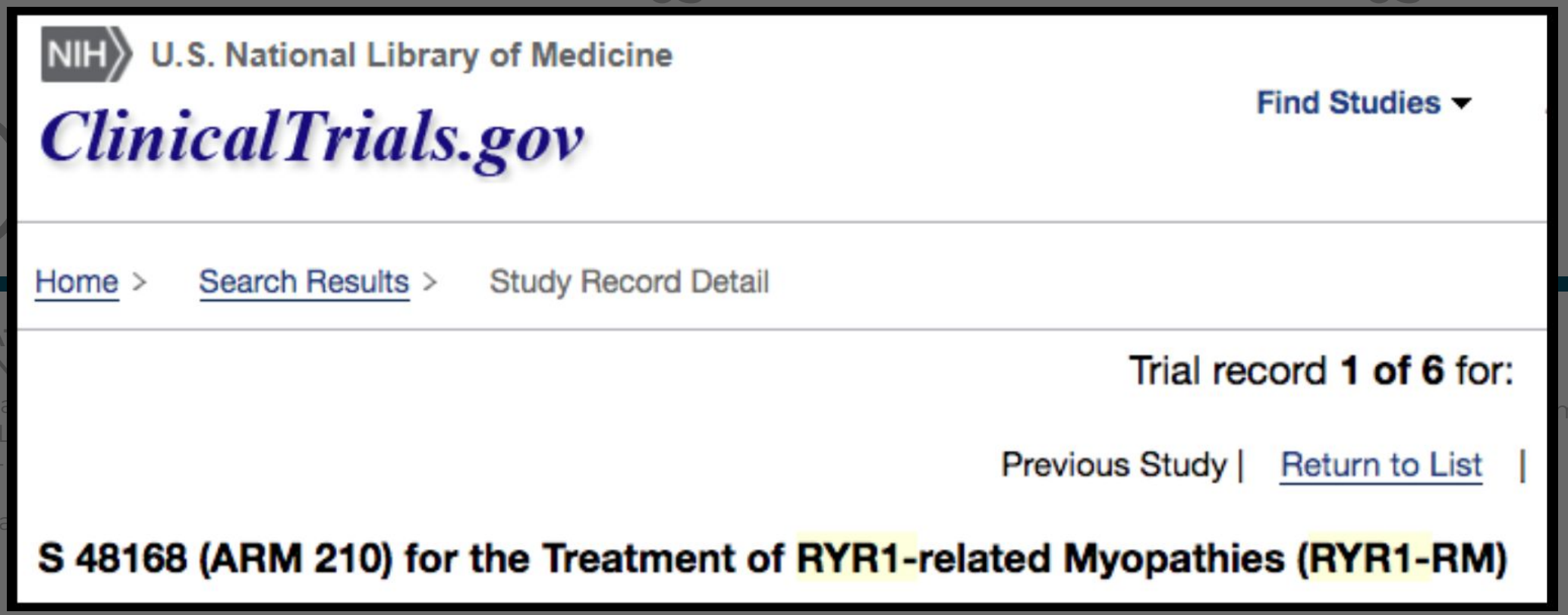
01 03 05



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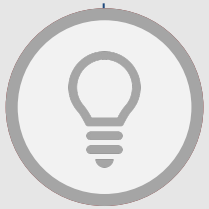

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## Safety, pharmacokinetics, and preliminary efficacy of Rycal S 48168 (ARM210) for *RYR1*-related myopathies: a phase one, open-label dose-escalation trial

P.532. J. J. Todd[1,2]; T. Lawal[2]; I. Chrismer[2]; A. Kokkinis[1]; C. Grunseich[1]; M. Jain[3]; M. Waite[3]; V. Biancavilla[3]; Milan Barnes[3]; S. Pocock[2]; K. Brooks[1]; M. Emile-Backer[2]; Y. Webb[4]; E. E. Marcantonio[4]; A.R. Foley[1]; K. Meilleur[2]; C. Bönnemann[1]; P. Mohassel[1]. [1] NINDS, NIH, Bethesda MD, USA; [2] NINR, NIH, Bethesda MD, USA; [3] National Institutes of Health Clinical Center, Bethesda MD, USA; [4] ARMGO Pharma Inc., Tarrytown NY, USA.

### Rationale

Ryanodine receptor 1 (RyR1) channel sub-conductance, aberrant SR $Ca^{2+}$ leak into the cytosol and oxidative stress often underlie the disease in *RYR1*-related myopathies (*RYR1*-RM)

Loss of RyR1-calstabin1 association was rescued with *ex vivo* Rycal treatment of *RYR1*-RM muscle[1]

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 FVC > 50% predicted
- No prior history of seizures

**Primary endpoint (safety and tolerability)**
TEAEs ≥ grade two in severity, SAEs and AESIs

**Exploratory endpoints**
S 48168 PK and muscle tissue concentrations

Δ in MFM-32 (% maximum score), hand grip and pinch strength (kg), timed functional tests (seconds)

Δ in PROMIS-fatigue (t-score)

Δ in plasma 15-F2t isoprostane and protein carbonyl concentrations

**Trial visit and design summary**

| Screening | NIH Clinical Center Visits 1 (Baseline) | 2 (Day 14) | 3 (Day 28) | Follow-up (Days 29-42) |
|---|---|---|---|---|

Low dose 120 mg/day N= 3 → DSMB interim analysis → High dose 200 mg/day N= 3

Age and sex-matched natural history data available from NCT02362425 [2]

### Participant Characteristics

Table 1. Demographics

| Measure | S 48168 dose group 120 mg/day (N= 3) | S 48168 dose group 200 mg/day (N= 3) | Natural history (N= 20) |
|---|---|---|---|
| Age, years | 38 ± 7 | 43 ± 5 | 39 ± 12 |
| MOI, dominant | 1 (33) | 3 (100) | 5 (33) |
| Sex, male | 2 (67) | 1 (33) | 13 (65) |
| Height, cm | 171 ± 20 | 167 ± 10 | 163 ± 12 |
| Weight, kg | 68 ± 10 | 91 ± 5 | 68 ± 18 |
| BMI, kg/m² | 24 ± 5 | 33 ± 4 | 26 ± 7 |

Data are n (%) or mean ± SD; Abbreviations: BMI, body mass index; MOI, mode of inheritance

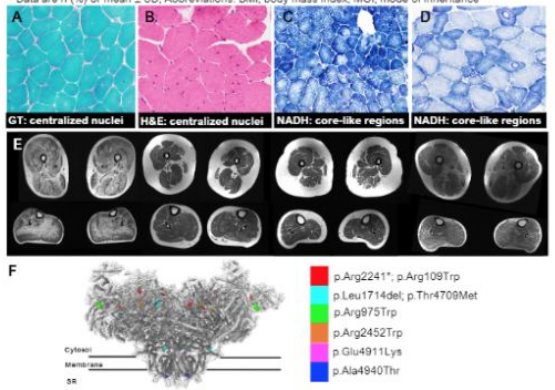


Fig 1. (A-D) Representative histology, (E) lower extremity MRI with variable degrees of fatty infiltration, the first with a clear pattern of muscle involvement characteristic of *RYR1*-RM (F) *RYR1* variants mapped to the 3D cryo-EM channel structure

### Safety and Tolerability

Table 2. Treatment-emergent adverse events

| Safety event | S 48168 dose group 120 mg/day (N= 3) | S 48168 dose group 200 mg/day (N= 3) |
|---|---|---|
| Total TEAE | 18 (100) | 9 (100) |
| TEAE ≥ grade 2 in severity [a] | 2 (11) | 1 (11) |
| AESI | 0 (0) | 0 (0) |
| SAE | 0 (0) | 0 (0) |
| Deaths | 0 (0) | 0 (0) |

Data are n (% total TEAEs); [a] Defined per CTCAE, V5.0

- 100% compliance was observed for both dose groups (pill count)

### Pharmacokinetics

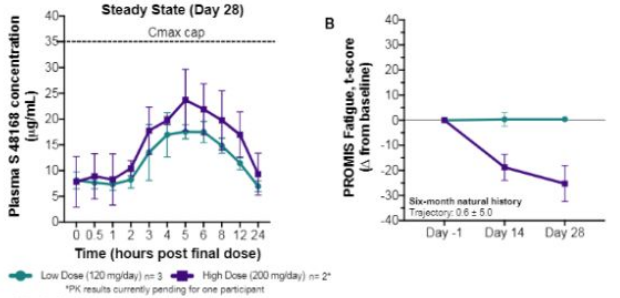


Fig 2. S48168 concentration-time curve

### Exploratory efficacy

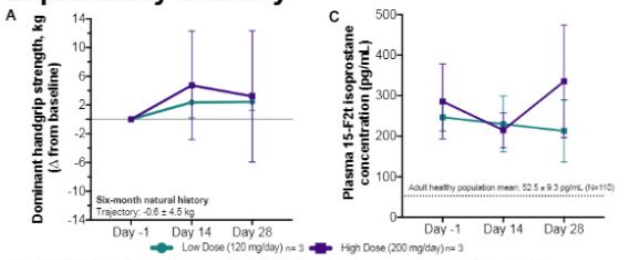


Fig 3. (A-C) Hand grip strength, PROMIS fatigue, and plasma isoprostane results

### Conclusions

- Clinical trials for rare myopathies are feasible as a collaborative endeavor between industry, academia, government, and patient advocacy (RYR-1 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 handgrip strength and fatigue warrant further investigation in a double-blind, randomized, placebo-controlled trial

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ARMGO Pharma, Inc.

## 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

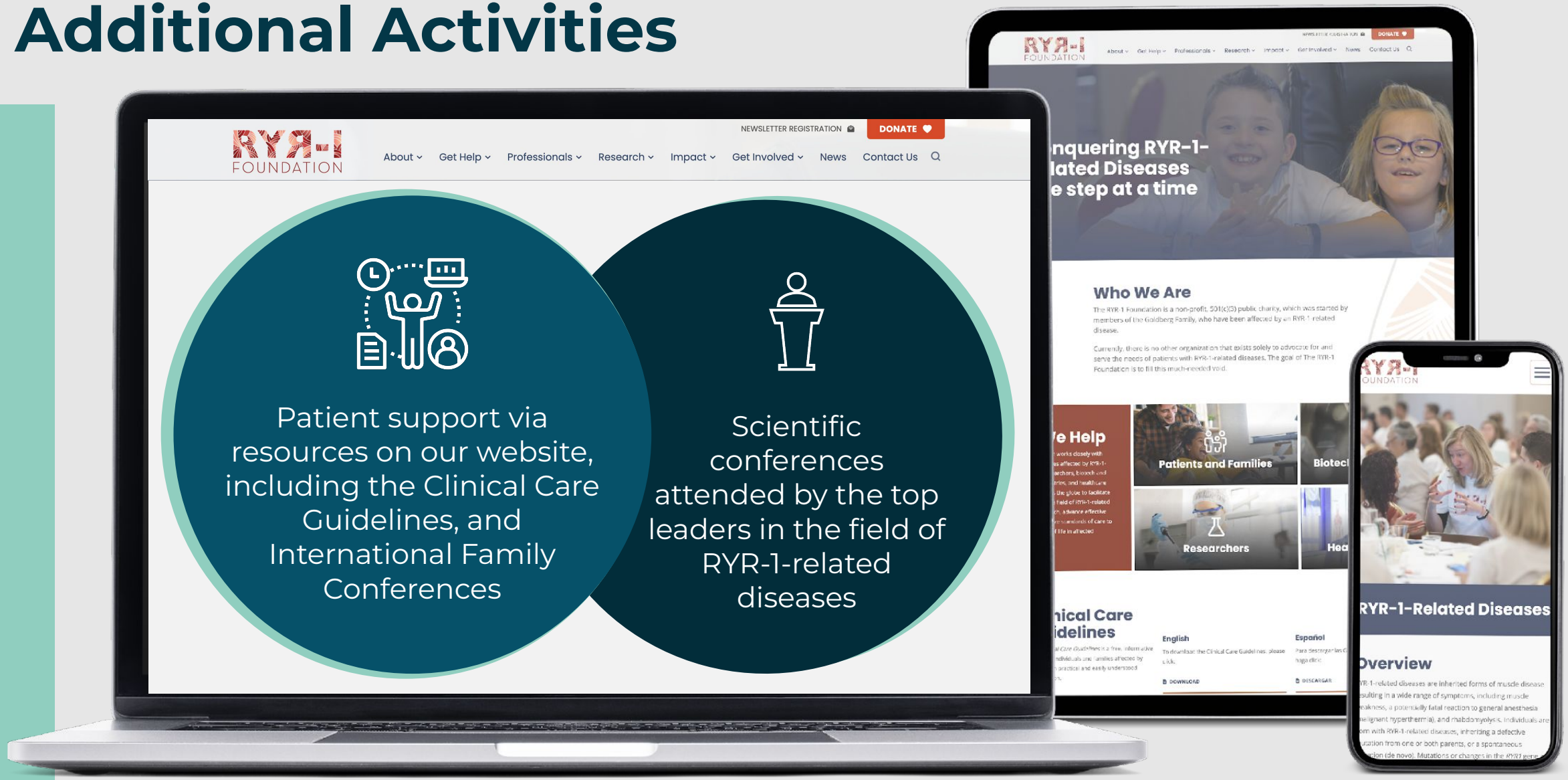
**ARMGO Pharma raises $35 million to progress clinical studies of lead molecule ARM210 in cardiac and skeletal muscle diseases**

- *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



# 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.

# Contact Information

**Phone:** (412) 529-1482

**Email:** nicole@ryr1.org

**Website:** www.ryr1.org

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www.ryr1.org