RYR-1 FOUNDATION

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Novel Therapeutic Strategies for Congenital Myopathies

Introduction to RYR-1 Muscle Disease, RYR-1 Mutant Mouse Models, and the RYR-1 Foundation

Revised: October 2020

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What is RYR-1 Muscle Disease?

- Congenital myopathy due to mutation in *RYR1* gene
- ***Most common congenital myopathy***
- 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)

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What is RYR-1 Muscle Disease? (continued)

- ***No treatments available***
- Care for RYR-1 muscle disease is strictly supportive with no approved treatments for this group of debilitating disorders
- RYR-1 Foundation **Patient Registry**
  - *www.ryr1.org/registry*
- Natural history study has been performed, with assessment of outcome measurement[1]

[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.*

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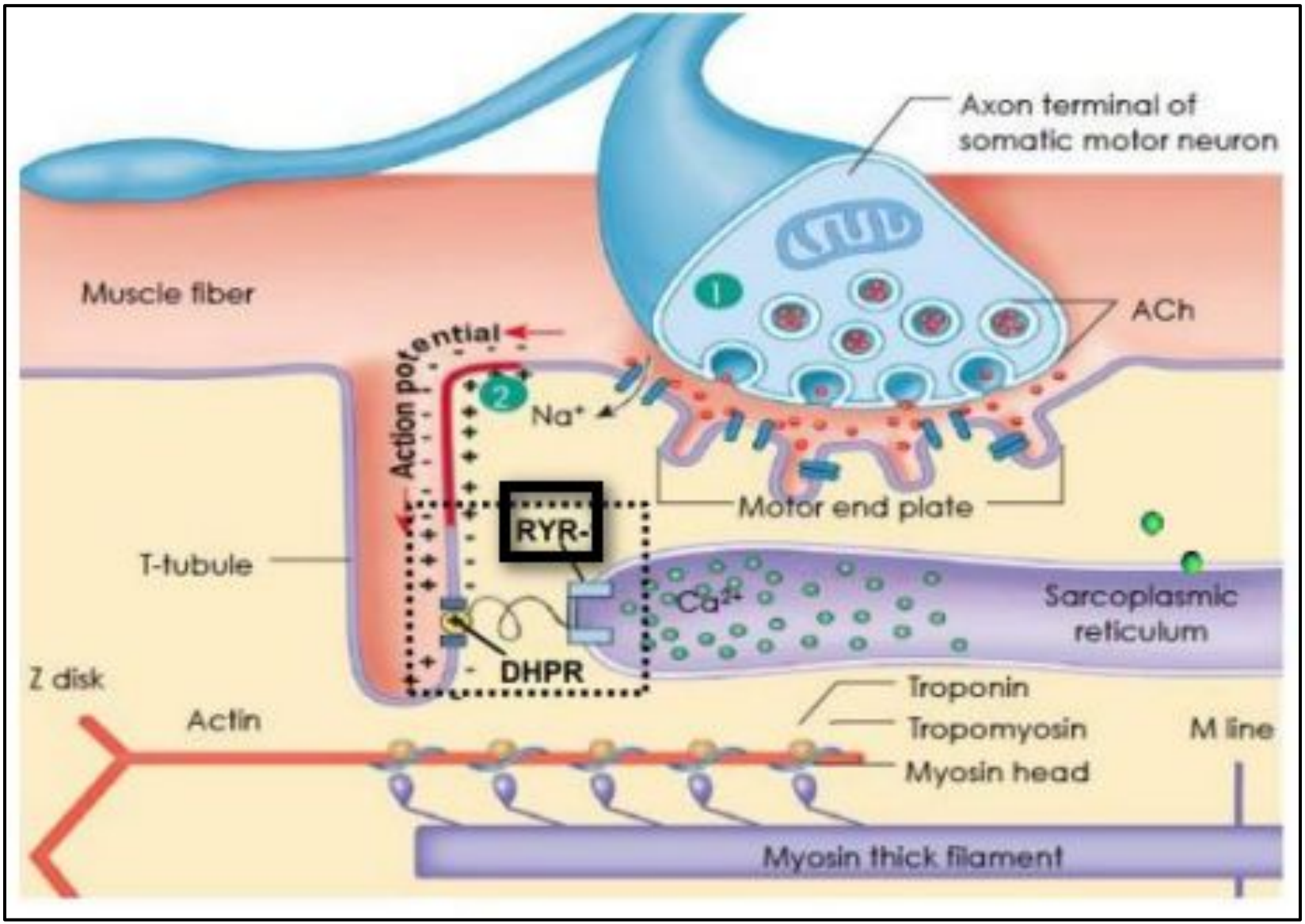
Unmet Need for Therapy

- ***No treatments available***
- No known group is researching gene-based therapies for RYR-1 muscle disease
- Significant morbidity associated with RYR-1 muscle disease presents an opportunity for therapeutic intervention:[1, 2]
  - Functional impairment
  - Significant fatigue
  - Pain
  - Reduced Quality of Life

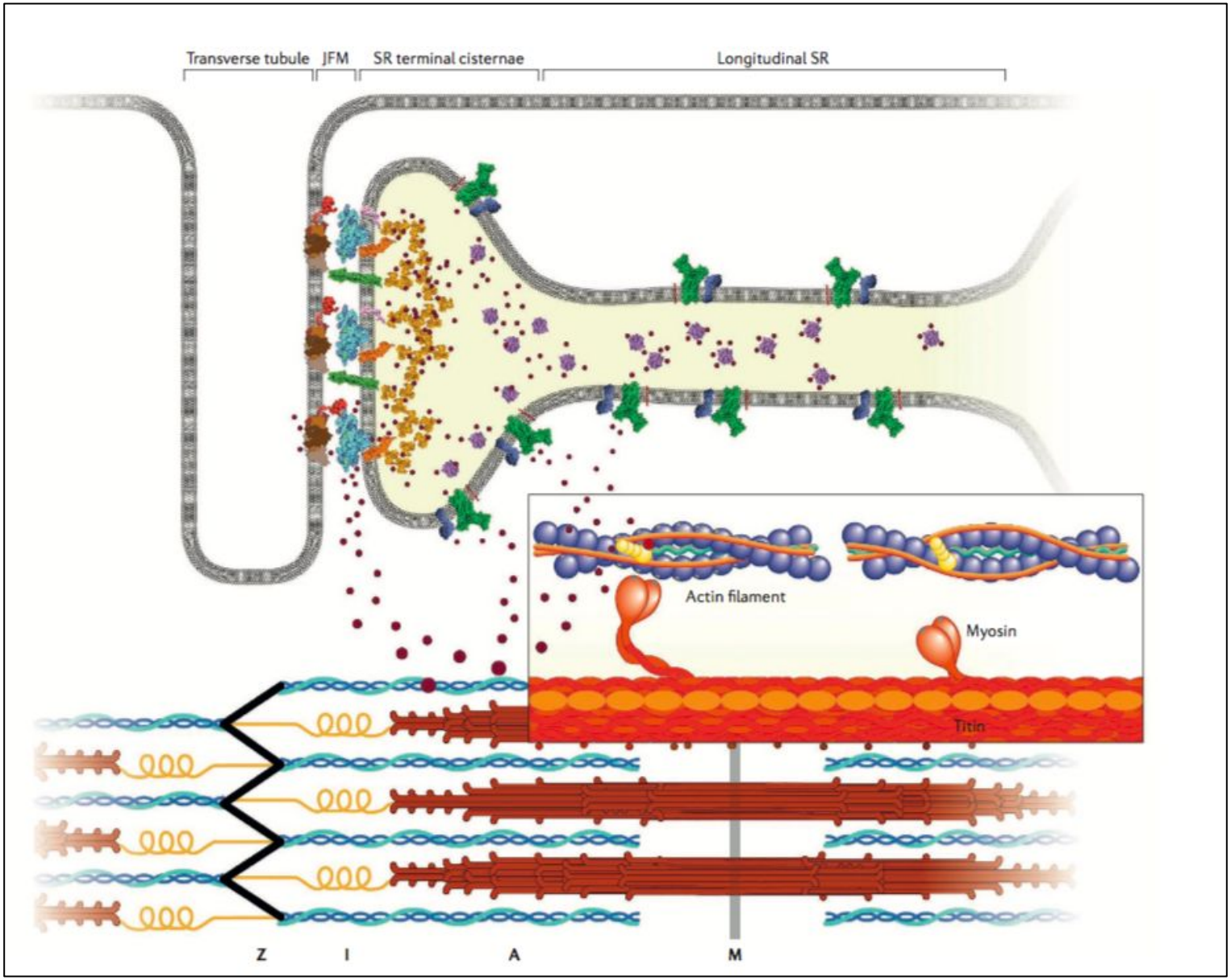
[1] *Ruitenbeek et al. Functional impairments, fatigue and quality of life in RYR1-related myopathies: A questionnaire study.Neuromuscular Disorders. 2019 Jan;29(1):30-38. doi: 10.1016/j.nmd.2018.10.006.*

[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.*



Schematic diagram illustrating the role of the RyR1 receptor in skeletal muscle function, including excitation-contraction coupling

Courtesy of Robert Dirksen, PhD



Source: Jungbluth, H., Treves, S., Zorzato, F. *et al*. Congenital myopathies: disorders of excitation–contraction coupling and muscle contraction. *Nat Rev Neurol* **14,** 151-167 (2018). https://doi.org/10.1038nrneurol.2017.191.

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To access a library of articles from the medical literature on RYR-1 muscle disease, please go to: www.ryr1.org/medical-literature.

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Challenges to Gene Therapy

- *RYR1* gene (19q 13.2) encodes RyR1 protein
- Gene size >159 kb (106 exons)
  - Coding sequence (15 kb)
- ***Exceeds packaging capacity of adeno-associated virus-mediated therapy***
- 700 variants throughout *RYR1* coding region have been identified

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RYR-1 Mouse Models

- Two new RYR-1 mouse models have been recently created which demonstrate a ***severe myopathy phenotype***
- Mice have undergone rigorous phenotype characterization by world's leading RYR-1 experts
  - Subject of ongoing research via a $2 million R01 NIH Grant
    - ***https://projectreporter.nih.gov/project_info_description.cfm?aid=10071615&icde=51096951***
- Ideal for testing of novel therapeutic strategies
- ***Freely available*** to researchers, biotech, pharma, etc.

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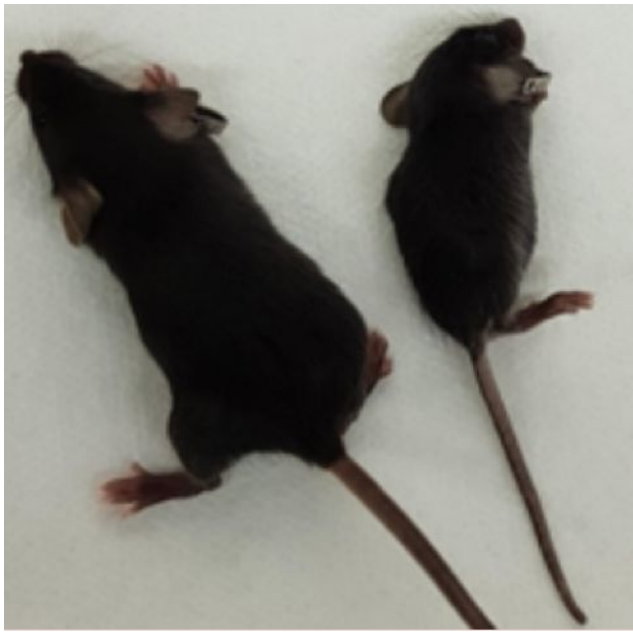
RYR-1 Foundation Grant

- ***"Toronto Mouse"***
  - Dr. James Dowling
  - Compound heterozygote:
    - T4709M missense mutation (exon 96)
    - 16 bp frameshift deletion on exon 96-->premature stop codon, resulting in null allele



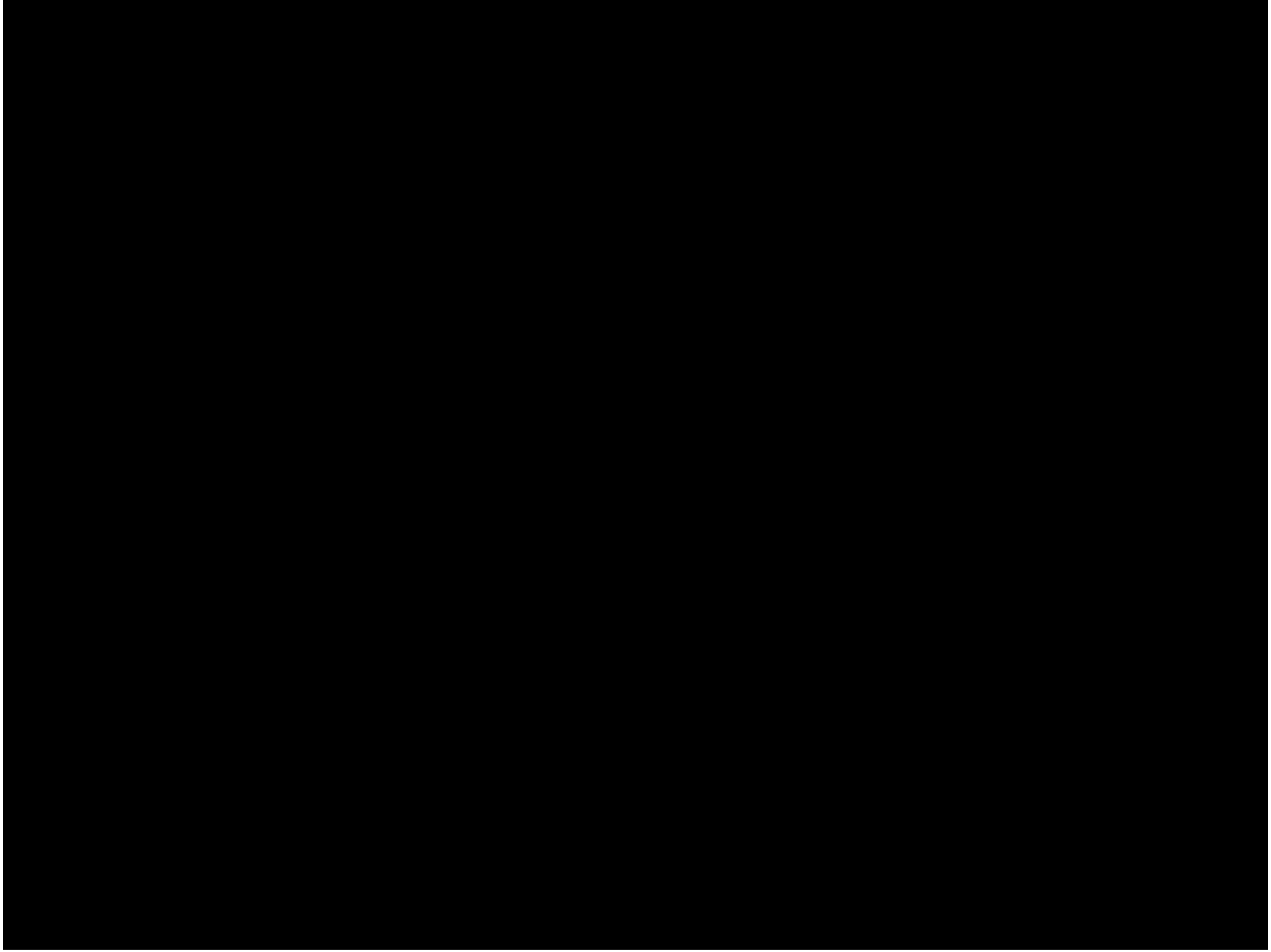
Mouse model of severe recessive RYR1-related myopathy

Stephanie Brennan[1,2], Maricela Garcia-Castañeda[3], Antonio Michelucci[3], Nesrin Sabha[1], Sundeep Malik[3], Linda Groom[3], Lan Wei LaPierre[3], James J. Dowling[1,2,4,†] and Robert T. Dirksen[3,†*]

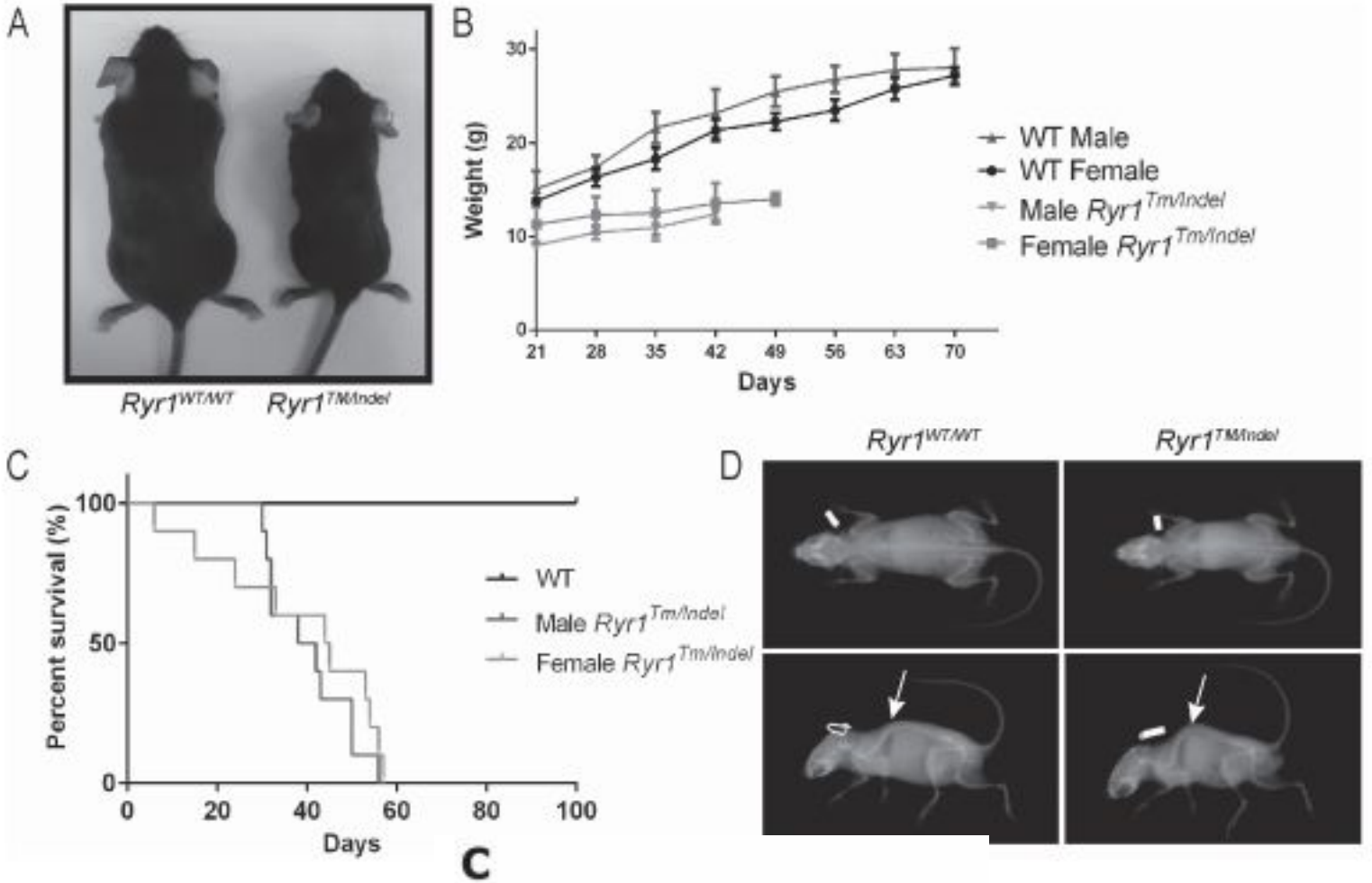
Human Molecular Genetics, 2019, Vol. 28, No. 18

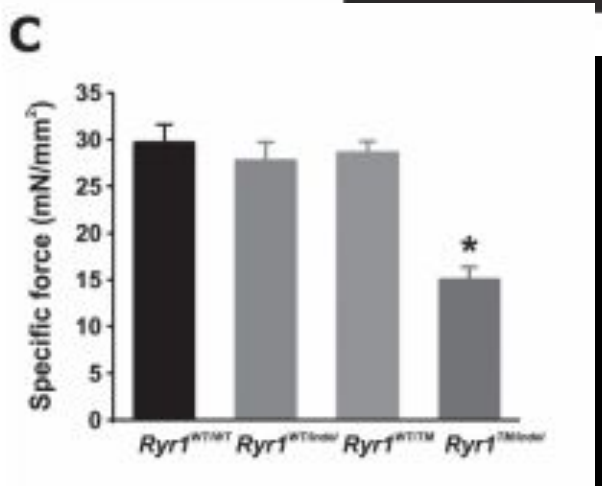
Funding

RYR-1 Foundation (to R.T.D. and J.J.D.);



Please click on the box above to play a video (video courtesy of James Dowling, MD, PhD)


A
Ryr1WT/WT
Ryr1TM/Indel
B
Weight (g)
Days
WT Male
WT Female
Male Ryr1Tm/Indel
Female Ryr1Tm/Indel
C
Percent survival (%)
Days
WT
Male Ryr1Tm/Indel
Female Ryr1Tm/Indel
D
Ryr1WT/WT
Ryr1TM/Indel


C
Specific force (mN/mm2)
*

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- ***"Rochester Mouse"***
  - Dr. Robert T. Dirksen
    - Lewis Pratt Ross Professor, University of Rochester
    - Chair of Pharmacology and Physiology, University of Rochester Medical Center
  - Genotype was based on mutations seen in an affected family
  - Demonstrates a moderate-severe phenotype, ideal for studying:
    - Pathophysiology
    - Therapeutic interventions

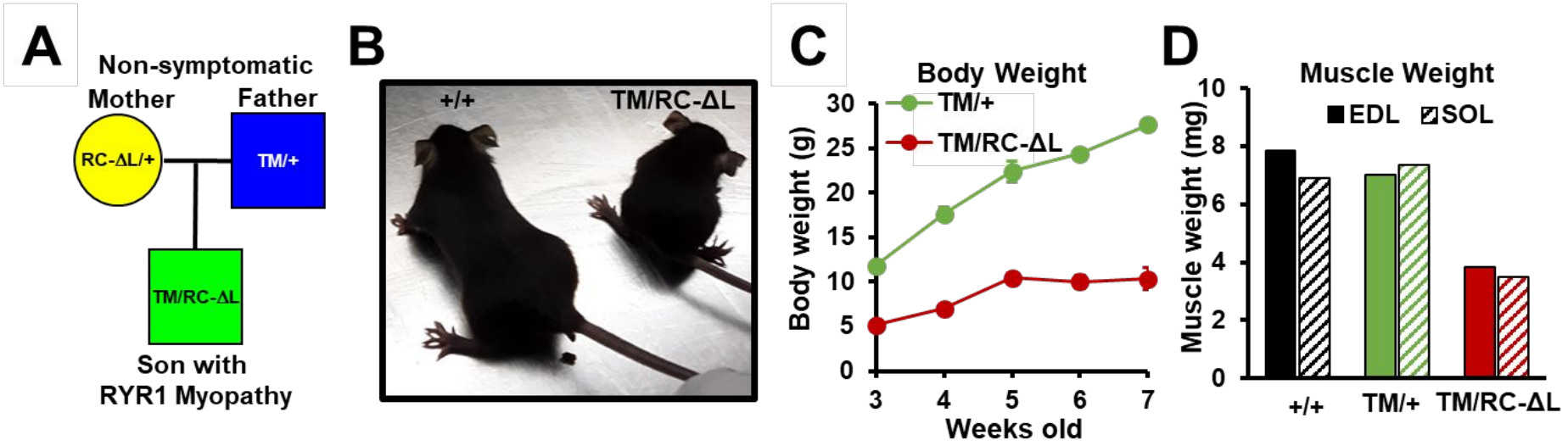
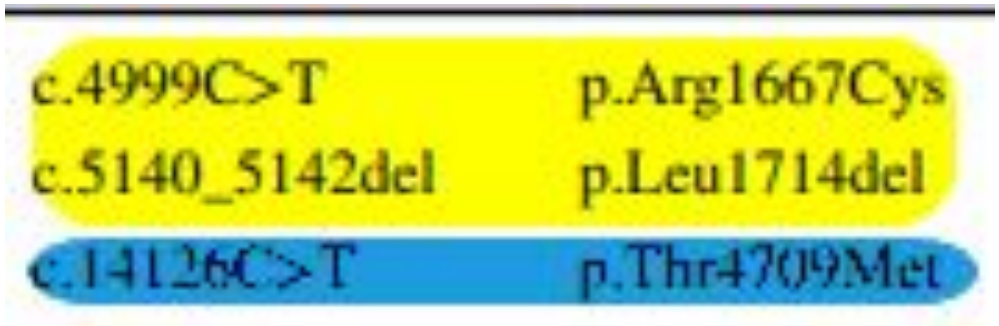
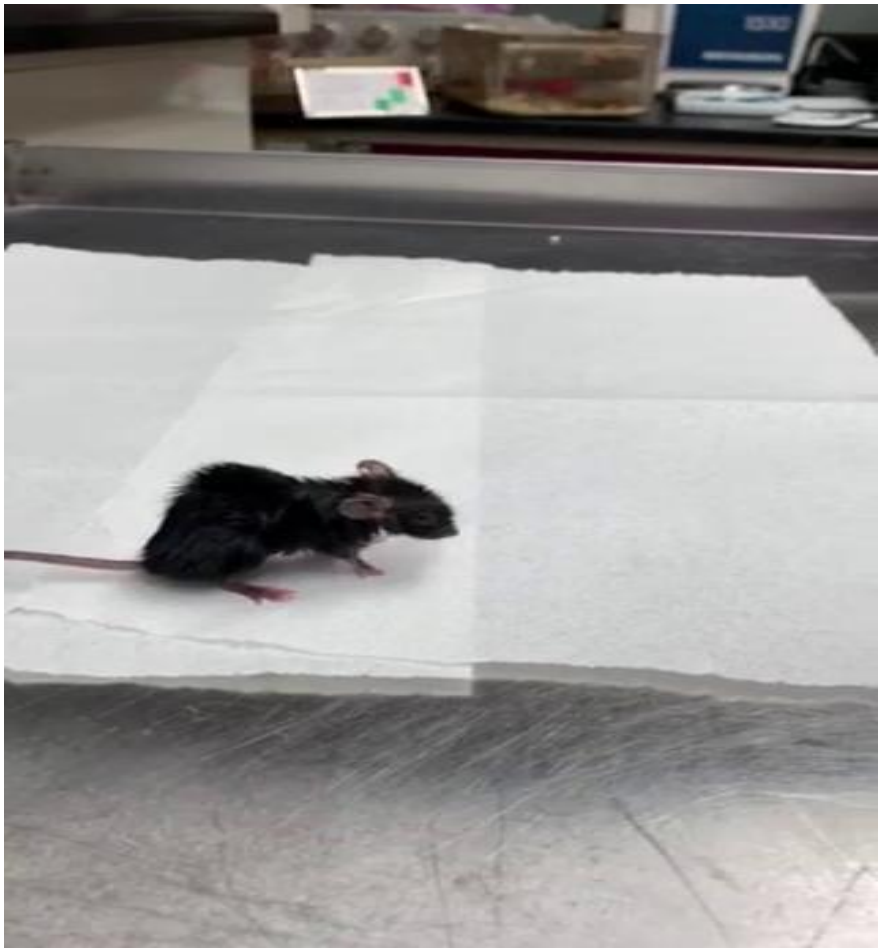


Figure. Reduced body and muscle weight of *Ryr1*$^{TM/RC\text{-}\Delta L}$ mice. A) Kindred schematic. B) 4 week old WT and *Ryr1*$^{TM/RC\text{-}\Delta L}$ mice. Body (C) and muscle (EDL and soleus) weight (D).



Courtesy of Robert Dirksen, PhD



Please click on the images above to play videos (videos courtesy of Robert Dirksen, PhD)

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RYR-1 Foundation Research Grants

www.ryr1.org/grants

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RYR-1 Foundation Research Grants

- Mechanism for leverage our resources to promising early-stage research
- As a small organization, we have a streamlined grant application process that is nimble and responsive to researchers
  - Evaluated by Scientific Advisory Board (SAB)
  - *Successful track record in short period of time*

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RYR-1 Foundation Research Grants: Proven Record of Success

- ***"Rycal Treatment in RYR-1-related myopathy muscle biopsies"***
  - Dr. Andrew Marks
    - Chairman of the Department of Physiology and Cellular Biophysics
    - The Clyde and Helen Wu Professor of Medicine and Pharmacology at Columbia University, New York City
  - Dr. Katy Meilleur
    - Biogen
    - NIH (2008-2019)

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

ORIGINAL PAPER

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]

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Funding This work was supported by an RYR1 Foundation Research Grant to AK

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies

Home > Search Results > Study Record Detail

Trial record **1 of 6** for:

Previous Study | Return to List |

S 48168 (ARM 210) for the Treatment of RYR1-related Myopathies (RYR1-RM)

ClinicalTrials.gov Identifier: NCT04141670

Recruitment Status : Recruiting
First Posted : October 28, 2019
Last Update Posted : July 8, 2020

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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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Future Research Plans

- To date, most research funding has been dedicated to development of animal models, high-throughput drug screens, and assessment of Rycals
- ***With several animal models now available, we are interested in exploring the feasibility of novel therapeutic strategies, including gene editing, gene replacement therapy, nanoparticle delivery, electroporation, as well as traditional pharmacologic agents***

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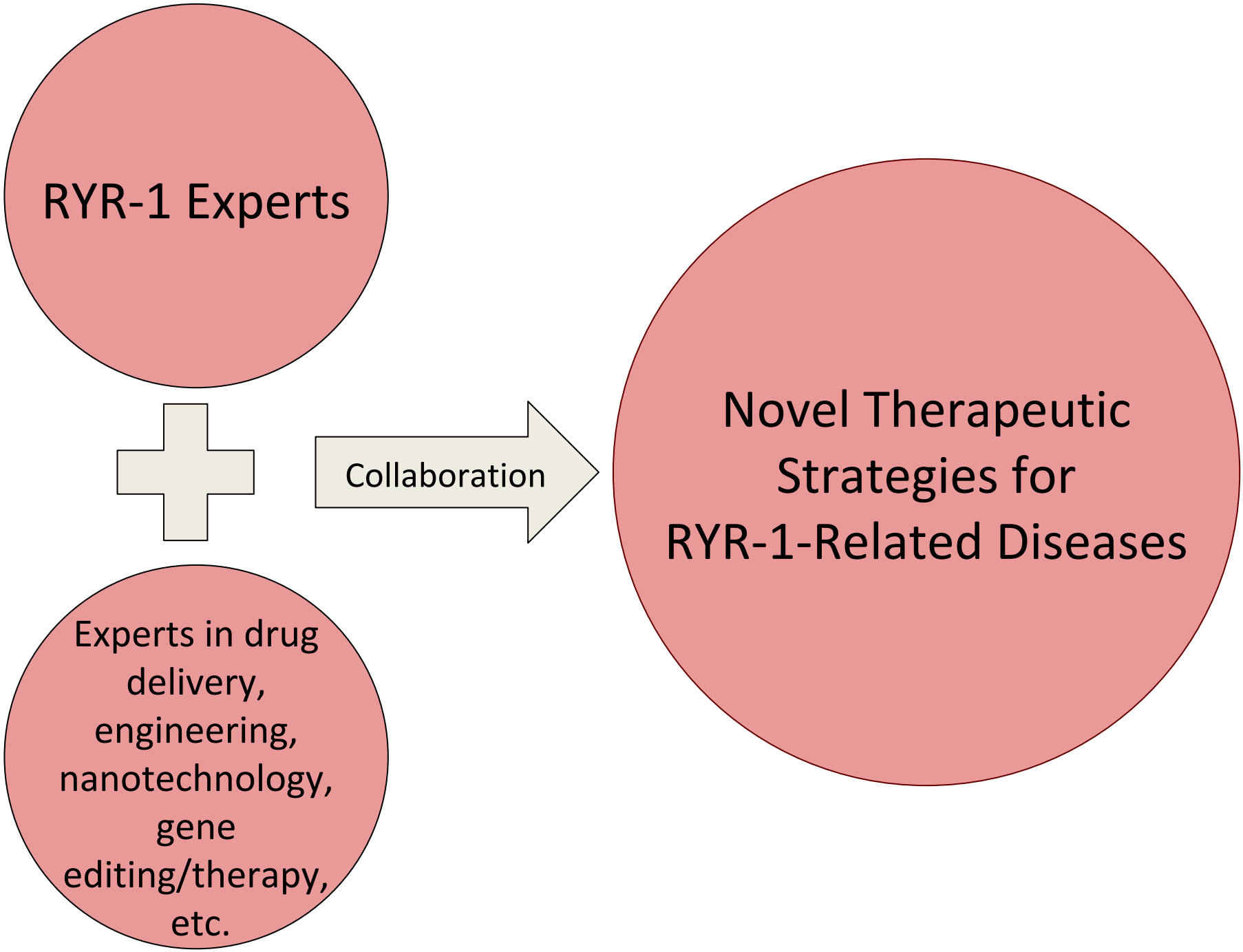
Future Research Plans (continued)

- We seek to facilitate collaborations and partnerships between expert/academic RYR-1 researchers and organizations interested in novel therapeutic strategies


RYR-1 Experts
Collaboration
Novel Therapeutic Strategies for RYR-1-Related Diseases
Experts in drug delivery, engineering, nanotechnology, gene editing/therapy, etc.

The RYR-1 Foundation

RYR-1 FOUNDATION

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Fast Facts

- 501(c)(3) public charity, based in Pittsburgh, PA, USA
- Total Fundraising since inception (2014): $ 3,600,000
- ***Total Research Funding to date:* $ 1,300,000**
- Total Number of Projects Funded: 14
- Current Committed Research Funding: $ 450,000
- Current Number of Research Projects: 6
- Total Cost of Scientific Conferences: $ 150,000

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

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Leadership

- Leadership is voluntary
  - World-Class Board of Trustees
    - ***www.ryr1.org/trustees***
  - World-Class Scientific Advisory Board
    - ***www.ryr1.org/scientificadvisoryboard***
  - Board of Advisors of affected individuals and family members
    - ***www.ryr1.org/advisors***

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Michael F. Goldberg, MD, MPH

Co-Founder, President, Co-Chair of Research, & Trustee

- *RYR1* autosomal recessive mutation
- Director of Neuroradiology, Allegheny Health Network
- Associate Professor, Drexel University College of Medicine

Photo Credit: Karen Martin, Highmark Health

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Morton F. Goldberg, MD, FACS, FAOS, FRACO

Co-Founder, Vice-President, Co-Chair of Research, & Trustee

- Ophthalmologist, specializing in retinal disease and genetics
- Former Chairman, Wilmer Eye Institute, Johns Hopkins School of Medicine
- Member, National Academy of Medicine, USA

Past RYR-1 Scientific Meetings

Pittsburgh, PA (June 2019)

Pittsburgh, PA (June 2019)

Baltimore, MD (June 2016)

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Patient Outreach

Group photo from the 2018 RYR-1 International Family Conference, Pittsburgh, PA, USA

2016 RYR-1 International Family Conference

Baltimore, MD, USA

2018 RYR-1 International Family Conference

Pittsburgh, PA, USA

2016 RYR-1 International Family Conference

Baltimore, MD, USA

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Conclusions

- RYR-1 muscle disease is the most common congenital myopathy
- No treatment available
- Facilitate collaborations and partnerships between expert/academic RYR-1 researchers and organizations interested in novel therapeutic strategies
- New murine models available for therapeutic research

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For more information, please contact:

Nicole Wallace
Program Director, RYR-1 Foundation
nicole@ryr1.org
(412) 529-1482