DEAR FRIENDS,

Although rare, RYR-1-related diseases are the most common form of "congenital myopathy" -- muscle disease caused by a genetic mutation. The most common manifestations include: mild-to-moderate muscle weakness (e.g., difficulty climbing stairs), severe weakness (e.g., requiring wheelchair assistance and breathing support), muscle cramping and pain, and a potentially fatal reaction to anesthesia, called malignant hyperthermia. Yet, despite the prevalence of this disease and the severity of these symptoms, the RYR-1 Foundation is the only organization that exists solely to support research on this disease. Further, the RYR-1 Foundation serves the needs of and advocates for individuals and families affected by RYR-1-related diseases.

In a very short period of time, the RYR-1 Foundation has become a leader in the field of RYR-1-related diseases.

Due to the support of our many generous benefactors, the Foundation's work has led to important breakthroughs in scientific knowledge. In addition, we have formed a worldwide community of affected individuals who can find comfort and support in the knowledge that they are not alone and that our organization now exists to help them.

The need for treatments or a cure is urgent. With your support, the RYR-1 Foundation can continue to fund world-renowned scientists, expand the RYR-1 community, and make our slogan, "Strength in Numbers," a reality.

Sincerely yours,

Michael F. Goldberg, MD, MPH
President & Co-Chair of Research
RYR-1 Foundation

RYR-1 FOUNDATION
STRENGTH IN NUMBERS

To learn more about the story of the RYR-1 Foundation and the work we are doing, please view our documentary at: **www.ryr1.org/documentary**.

SUPPORTING RESEARCH

The Foundation exists to raise funds that support both basic science and clinical research of RYR-1-related diseases. Funding research gives us the best chance to find a treatment or a cure.

As of 2020, the RYR-1 Foundation has funded/committed over **$1.3 million** in RYR-1-related research. This has already led to important advances in knowledge and potential therapies. RYR-1 Foundation grant recipients include:

JÁNOS ALMÁSSY, PhD, UNIVERSITY OF DEBRECEN (HUNGARY): *"Functional and Pharmacological Characterization of the T4709M Mutant Ryanodine Receptor at Single-Channel Level"*

ALAN BEGGS, PhD, HARVARD UNIVERSITY (UNITED STATES): *"Drug Discovery for RYR-1 Myopathies Using Zebrafish Models"*

RAZVAN L. CORNEA, PhD, UNIVERSITY OF MINNESOTA (UNITED STATES): *"High-Throughput Screens to Discover Novel Modulators of Dysfunctional RYR-1 Channels for Therapeutic Development"*

JAMES DOWLING, MD, PhD, UNIVERSITY OF TORONTO (CANADA): *"Cas9-Mediated Point Mutagenesis of RYR-1"*

JAMES DOWLING, MD, PhD, UNIVERSITY OF TORONTO (CANADA) AND ROBERT DIRKSEN, PhD, UNIVERSITY OF ROCHESTER (UNITED STATES): *"Drug Discovery and Validation for RYR-1-Related Myopathies"*

ANGELA DULHUNTY, MD, PhD, AUSTRALIAN NATIONAL UNIVERSITY (AUSTRALIA): *"Developing Animal Models with an RYR-1 Mutation and Clinical Phenotype for the Purpose of Evaluating Cell and Molecular Mechanisms of RYR-1 Disease"*

ALEXANDER KUSHNIR, MD, PhD, COLUMBIA UNIVERSITY (UNITED STATES): *"RYR-1 Myopathy Database"*

WILLIAM R. LAGOR, PhD, BAYLOR COLLEGE OF MEDICINE (UNITED STATES): *"Targeted Removal of Pathogenic RYR-1 Alleles"*

BRADLEY S. LAUNIKONIS, PhD, THE UNIVERSITY OF QUEENSLAND (AUSTRALIA): *"Assessment of the Ability of Small Molecule RYR-1 Modulators to Correct the Ca2+ Fluxes in Skeletal Muscle Fibers with RYR-1 Myopathy"*

ANDREW MARKS, MD, COLUMBIA UNIVERSITY (UNITED STATES) AND KATHERINE MEILLEUR, PhD, CRNP, NATIONAL INSTITUTES OF HEALTH (UNITED STATES): *"Rycal Treatment in RYR-1-Related Myopathy Muscle Biopsies"*

VINCENZO SORRENTINO, MD, UNIVERSITY OF SIENA (ITALY): *"Endoplasmic Reticulum Stress in Skeletal Muscles of Patients with Central Core Disease and other RYR-1-Related Myopathies: A Potential Mechanism of Disease and a Druggable Target"*

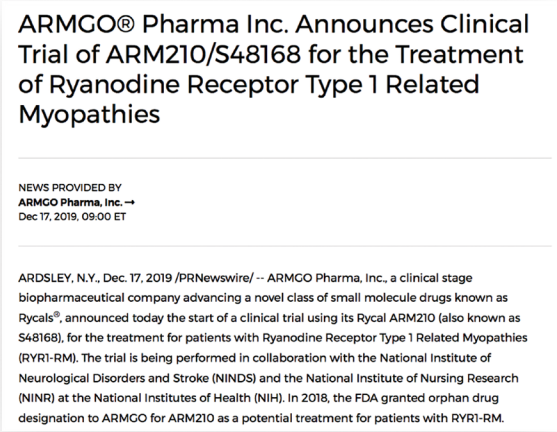
JOSHUA J. TODD, PHD, CCRP, NIH (UNITED STATES): *"Mitoquinol Mesylate and N-3 Polyunsaturated Fatty Acids: A Novel Therapeutic Approach for RYR-1 Related Myopathy"*

FILIP VAN PETEGEM, PhD, UNIVERSITY OF BRITISH COLUMBIA (CANADA): *"Structural Investigation of Disease-Associated Mutations in the Ryanodine Receptor Pore and EF Hand Region"*

RYCAL TREATMENT IN RYR-1-RELATED MYOPATHY MUSCLE BIOPSIES

In 2016, the RYR-1 Foundation awarded a grant of $80,000 to Dr. Andrew Marks, Chairman of the Department of Physiology and Cellular Biophysics at Columbia University, and Dr. Katherine Meilleur, former Assistant Clinical Investigator at the National Institute of Nursing Research, for their research project entitled "Rycal Treatment in RYR-1-Related Myopathy Muscle Biopsies."

Dr. Marks discovered Rycals, a class of drugs that reverses the calcium "leak" in muscle cells with RYR-1 mutations. The grant from the RYR-1 Foundation allowed researchers to assess the effect of Rycals on samples of muscle biopsies taken from actual RYR-1 patients. The results of their study showed that Rycals not only reversed the calcium leak in those human muscle biopsies, but also repaired muscle damage and improved the muscle function.



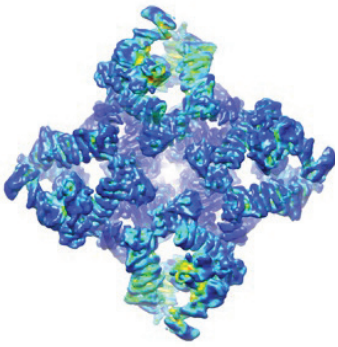
ARMGO® Pharma Inc. Announces Clinical Trial of ARM210/S48168 for the Treatment of Ryanodine Receptor Type 1 Related Myopathies

NEWS PROVIDED BY
ARMGO Pharma, Inc. →
Dec 17, 2019, 09:00 ET

ARDSLEY, N.Y., Dec. 17, 2019 /PRNewswire/ -- ARMGO Pharma, Inc., a clinical stage biopharmaceutical company advancing a novel class of small molecule drugs known as Rycals®, announced today the start of a clinical trial using its Rycal ARM210 (also known as S48168), for the treatment for patients with Ryanodine Receptor Type 1 Related Myopathies (RYR1-RM). The trial is being performed in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Nursing Research (NINR) at the National Institutes of Health (NIH). In 2018, the FDA granted orphan drug designation to ARMGO for ARM210 as a potential treatment for patients with RYR1-RM.

ARMGO Press Release, dated December 17, 2019, announcing Clinical Trial of ARM210/S48168 for the Treatment of Ryanodine Receptor Type 1 Related Myopathies.

The data from this project served as the basis for and justification of a human clinical trial that is currently ongoing at the National Institutes of Health (NIH), and several patients have already received a course of this experimental drug. In addition to funding Rycal research, the RYR-1 Foundation has played an important role in advocating for the initiation of this trial. In 2019, the Rycal trial was at risk of being permanently terminated due to a personnel problem at NIH. Working closely with the Rycal vendor and our contacts at NIH, the RYR-1 Foundation immediately initiated a phone call and letter writing campaign, ultimately soliciting the invaluable assistance of members of the United States Senate and House of Representatives. It is clear that were it not for the successful advocacy efforts of the RYR-1 Foundation, this trial would not have been initiated. For more information on the vital role the RYR-1 Foundation played in this clinical trial, please go to: **www.ryr1.org/rycals**.



3D schematic molecular structure of the ryanodine receptor developed by Dr. Andrew Marks.

SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board (SAB) of the RYR-1 Foundation is a group of the world's leading authorities in RYR-1-related diseases. The SAB determines the research priorities of the RYR-1 Foundation. Meetings of the SAB occur on a biannual basis to evaluate grant applications, evaluate ongoing funded research, and discuss future research strategies.

Attendees of a meeting of the RYR-1 Foundation's Scientific Advisory Board. Participants included representatives from academia, the pharmaceutical industry, NIH, and patient advocacy organizations.

ANDREW R. MARKS, MD (CHAIR)

Dr. Marks is Chairman of the Department of Physiology and Cellular Biophysics and The Clyde and Helen Wu Professor of Medicine and Pharmacology at Columbia University in New York City. He is the former Editor-in-Chief of the prestigious Journal of Clinical Investigation. He is also a member of the National Academy of Medicine. Additional honors include the Established Investigatorship Award and the Basic Research Prize from the American Heart Association, the Distinguished Clinical Scientist Award of the Doris Duke Charitable Foundation, and memberships in the American Society of Clinical Investigation, the American Association of Physicians, the American Academy of Arts and Sciences, and the National Academy of Sciences.

Dr. Andrew Marks giving a lecture at an RYR-1 International Family Conference.

Dr. Marks discovered that "leaky" intracellular calcium release channels (ryanodine receptors) contribute to heart failure and impaired exercise capacity, particularly in muscular dystrophy. His

research has provided groundbreaking insight into RYR-1-related diseases for over 25 years, including the cloning of RYR-1 DNA in 1989 and the discovery in 2014 of the high-resolution structure of the RYR-1 receptor.

Based on fixing the "leak" in the ryanodine receptor/calcium release channels, Dr. Marks's research is in clinical trials for the treatment of heart failure, cardiac arrhythmias, and muscular dystrophy. He is the chair of the SAB for ARMGO Pharma, Inc., a company he founded in 2006 to develop novel therapeutics for diseases related to the ryanodine receptor, and he is the inventor on six U.S. patents for these new treatments.

CARSTEN G. BÖNNEMANN, MD

Dr. Bönnemann is a pediatric neurologist specializing in neuromuscular disorders and neurogenetics. He is a Senior Investigator in the Neurogenetics Branch and Chief of the Neuromuscular and Neurogenetic Disorders of the Childhood Section of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health in Bethesda, MD.

Dr. Bönnemann is also Adjunct Professor of Neurology at the University of Pennsylvania and the Children's Hospital of Philadelphia (CHOP). He is a member of the Executive Board of the World Muscle Society as well as Co-Editor-in-Chief of the Journal of Neuromuscular Disease. Dr. Bönnemann is an internationally recognized expert in the diagnosis of neuromuscular diseases. His research is dedicated to understanding the molecular genetics and cell biology of muscular dystrophies and early onset myopathies in order to develop molecular-based treatments. Dr. Bönnemann was a Pew Scholar in the Biomedical Sciences, and received the Derek Denny-Brown Neurological Scholar Award of the American Neurological Association.

ROBERT T. DIRKSEN, PhD

Dr. Dirksen is the Lewis Pratt Ross Professor and Chair of Pharmacology and Physiology at the University of Rochester Medical Center. Dr. Dirksen obtained his BS in Biology and Chemistry from the University of Notre Dame, and MS and PhD in Pharmacology from the University of Rochester. Dr. Dirksen has focused much of his scientific efforts on understanding the underlying defects of skeletal muscle in patients with Myotonic Dystrophy, malignant hyperthermia, Central Core Disease, and other RYR-1-related diseases. His particular focus has been on understanding the control of calcium movements in muscle and the complex relationship between altered calcium movements and abnormal muscle function. His work has shown that dysfunction in calcium flow through RYR-1 calcium channels is the underlying cause of muscle weakness in patients with RYR-1-related diseases.

Dr. Robert Dirksen giving a lecture at an RYR-1 International Family Conference.

His work has been funded by the National Institutes of Health and the Muscular Dystrophy Association, among others. He has published over 80 original research articles in leading scientific journals. Dr. Dirksen is currently the Past-President of the Society of General Physiologists and serves on the editorial boards of several journals, including the Journal of General Physiology, Skeletal Muscle, and Frontiers in Skeletal Muscle Physiology. He was Chair of the 2015 Gordon Research Conference on "Muscle: Excitation-Contraction Coupling," and has served on several NIH Study Sections related to muscle biology and disease.

"Dr. Dirksen is so important to the RYR-1 Foundation—his discoveries on how muscle cells with RYR-1 mutations function have helped many other scientists around the world!"

RYR-1 FAMILY CONFERENCE ATTENDEE

JAMES DOWLING, MD, PhD

Dr. Dowling is a clinician-scientist who is focused on gene discovery and therapy for childhood muscle diseases. He is a Professor of Neurology at the University of Toronto and a neurologist at the Hospital for Sick Children in Toronto. He is also the inaugural Mogford Campbell Chair in Pediatric Clinical Neuroscience at Toronto's Hospital for Sick Children. In addition, he is a member of the Executive Board of the World Muscle Society and the Vice-Chair of TREAT-NMD.

Dr. Dowling is considered one of the world's leading experts in RYR-1-related diseases. His research spans the continuum from new gene discovery to disease pathogenesis in genetically modified organisms. He is also engaged in targeted drug discovery for RYR-1-related diseases. His laboratory employs both the zebrafish and mouse model systems, along with complementary *in vitro* analyses. Dr. Dowling is the recipient of numerous NIH and private foundation research grants. Recently, in conjunction with the Toronto Centre for Phenogenomics, he has developed a transgenic mouse line carrying a human RYR-1 mutation.

SUSAN HAMILTON, PhD

Dr. Hamilton is the Chair of the Department of Molecular Physiology and Biophysics at the Baylor College of Medicine, and also serves as Professor in that department. For over 30 years, she has studied excitation-contraction (E-C) coupling in skeletal muscle and the molecular mechanisms of human diseases related to E-C coupling. In doing so, she has become one of the world's leading experts in the mechanisms underlying the disease processes of malignant hyperthermia (MH) and Central Core Disease (CCD), both of which are related to mutations in the RYR-1 gene. This has led to research for possible therapeutic interventions. Her lab created the first mouse model (a knock-in mutation into the RYR-1 gene) of malignant hyperthermia and has also created a mouse model of human CCD.

Dr. Hamilton has been the senior author on numerous peer-reviewed publications, and her research has been funded continuously by NIH grants. She is the former Senior Vice President and Dean of Research at the Baylor College of Medicine. She is also the recipient of numerous

honors, including membership on the Board of Trustees of the Gordon Research Conference. She was also the recipient of the 2010 Mayerson-DiLuzio Award from Tulane University.

Dr. Hamilton is the senior author of a groundbreaking article entitled "A chemical chaperone improves muscle function in mice with a RyR1 mutation." The article discusses the potential role of 4-phenylbutyrate (4PBA) as a treatment in improving muscle function in mice carrying the I4895T mutation in the RYR-1 gene. To read this article, please visit: **www.ryr1.org/medical-literature**.

LIVIJA MEDNE, MS, CGC

Ms. Medne is a senior genetic counselor in the Divisions of Human Genetics and Neurology and a co-director of the Roberts Individualized Medical Genetics Center (RIMGC) at the Children's Hospital of Philadelphia (CHOP). For the last 15 years, she has specialized in neuromuscular and neurogenetic disorders and served as a CHOP co-investigator for several clinical research trials and patient registries. As a genetic counselor, her goal is to facilitate accurate and genetically confirmed diagnoses for all children with suspected neuromuscular disorders and other diagnoses. More recently, she has developed expertise in large-scale genomic testing and played a critical role in developing the RIMGC program at CHOP to allow incorporation of genomic testing into clinical practice. With increasing numbers of testing options and modalities, it is critically important that each and every individual gets access to the right test at the right time. Ms. Medne has developed significant expertise in interpreting genetic testing results for neuromuscular disorders, including RYR-1-related diseases. While many genetic neuromuscular diagnoses still lack targeted therapies, they can be better managed and treated when the exact molecular diagnosis is known.

Ms. Livija Mende giving a lecture at an RYR-1 International Family Conference.

PAYAM MOHASSEL, MD

Dr. Mohassel is an adult neurologist and neuromuscular specialist at the National Institutes of Health (NIH). After his clinical training at Johns Hopkins University, Dr. Mohassel joined the NIH in 2014 to continue research training in muscle disease with Dr. Carsten Bönnemann, who is also a member of the RYR-1 Foundation's Scientific Advisory Board. His research focus in neuromuscular neurogenetic disorders spans gene discovery efforts, pre-clinical studies in cellular and animal models, and early-stage clinical trials. As a clinical neurologist trained in myopathies and muscular dystrophies and experienced in translational research, Dr. Mohassel is passionate about bringing new therapies to individuals with muscle disease such as RYR-1-related diseases. Dr. Mohassel is currently the principal investigator of a phase I clinical trial for RYR-1-related diseases (please see page three for additional details) and was awarded the Young Myologist of the Year award by the World Muscle Society in 2020.

Dr. Sheila Riazi giving a lecture at an RYR-1 International Family Conference.

SHEILA RIAZI, MSc, MD, FRCPC

Dr. Riazi is an Associate Professor in the Department of Anesthesia, and Adjunct Professor at the Department of Kinesiology at the University of Toronto, and a staff anesthesiologist at the University Health Network (Toronto Western Hospital). Dr. Riazi also directs the only Canadian diagnostic center for malignant hyperthermia (MH), where she assesses at-risk individuals and provides genetic testing and the caffeine-halothane contracture test (CHCT). Her research interests include pathophysiology of MH, exertional heat illnesses, and phenotypic variability in MH susceptible patients.

Dr. Riazi has received several teaching and research awards and has secured funding from several Canadian and American grant agencies. She is also a member of the MH International Professional Advisory Council, the board of directors of MH Association of the United States (MHAUS), and a member of the editorial board of the Canadian Journal of Anesthesia.

SUSAN TREVES, PhD

The main focus of Dr. Treves's laboratory at the University of Basel in Switzerland is to study intracellular calcium homeostasis in mammalian cells under normal and pathological conditions, with particular emphasis on skeletal muscle excitation-contraction coupling. One of the models she uses to study calcium dysregulation in skeletal muscle is unique to her laboratory, because she uses biopsy-derived human skeletal muscle cells differentiated into myotubes *in vitro*. As a result of her PhD work in the laboratory of Professor Tullio Pozzan, one of the pioneers in the development of fluorescent Ca^{2+} indicators, she has a broad understanding on the use, pitfalls, and advantages of the available methods to study calcium homeostasis with fluorescent calcium indicators. This expertise has allowed her laboratory to directly assess the effect of mutations in the human ryanodine receptor calcium channel in muscles obtained from patients affected by neuromuscular disorders. Her laboratory applies a broad range of techniques, including cell and tissue culture, molecular biology, cell biology, biochemistry, microscopy, imaging, and fluorescence measurements of intracellular $[Ca^{2+}]$.

RYR-1 Foundation President Dr. Michael Goldberg is joined by members of the RYR-1 Foundation Scientific Advisory Board in Naarden, Netherlands at the RYR-1 Workshop of the European Neuromuscular Centre. This workshop was co-sponsored by the RYR-1 Foundation.

From left to right: Dr. Robert Dirksen, Dr. James Dowling, Dr. Susan Hamilton, Dr. Michael Goldberg, and Dr. Andrew Marks.

FILIP VAN PETEGEM, PhD

Dr. Van Petegem is a Professor in the Department of Biochemistry and Molecular Biology at the University of British Columbia (UBC) in Vancouver, Canada. Born in Belgium, he obtained his PhD in Biochemistry at Ghent University in 2002 and performed postdoctoral studies at the University of California San Francisco (UCSF).

Dr. Van Petegem leads a research lab at UBC, where he studies the structure and function of ion channels, with a focus on cardiac and skeletal muscle. This includes the Ryanodine Receptor (RyR) and voltage-gated calcium channels (CaV), two types of ion channels that have intimate communications inside muscle cells. Mutations in the genes that encode these channels cause malignant hyperthermia, Central Core Disease, cardiac arrhythmia, and much more. A major approach consists of determining very detailed 3D ultra-structures of these channels, allowing his lab to peer into the direct effects of the disease mutations on these structures.

Dr. Van Petegem has received New Investigator Awards from the Canadian Institutes of Health Research (CIHR) (2008) and the Michael Smith Foundation for Health Research (2008) as well as a UBC Faculty of Medicine Award for excellence in basic science (2013). He received a new investigator award from the Canadian Society for Molecular Biosciences (CSMB) in 2016, and a Killam Research Fellowship in 2017. He serves on the Macromolecular Beam team committee at the Canadian Light Source and frequently consults with industry.

NICOL C. VOERMANS, MD, PhD

Dr. Voermans's research at the Radboud University Medical Centre in The Netherlands focuses around genotype-phenotype comparisons and trial-readiness of rare inherited myopathies. As a clinical neurologist trained in neuromyology and experienced in translational research, she is well prepared to bridge the gap between the neuromuscular bench and bedside. Her passion for supporting patients with rare genetic disorders and her enthusiasm for interdisciplinary work are what drove her to this research field.

Dr. Voermans has focused on congenital myopathies, with a special interest in the clinical presentations and pathophysiology of RYR-1-related diseases. In 2014, Dr. Voermans gained experience in functional analysis of the RYR-1 channel in the lab of Dr. Susan Treves in Switzerland. Dr. Voermans has focused on the wide spectrum of RYR-1-related diseases throughout life, including intermittent phenotypes such as exertional rhabdomyolysis. She is a medical advisor to the congenital myopathies group of the Dutch patient organization for neuromuscular disorders.

Recently, Dr. Voermans has extended her scope to include other congenital myopathies (centronuclear myopathies, nemaline myopathies, SEPN1-related myopathies, and facioscapulohumeral muscular dystrophy (FSHD)). Her research in these myopathies has increased the knowledge of genotypes and phenotypes, natural history, and outcome measures, all of which are crucial for future trials.

Dr. Ronald Litman, Vice President of the Malignant Hyperthermia Association of the United States, speaking at a patient "Q & A" session at the 2016 RYR-1 International Family Conference.

Dr. Sheila Riazi (center), member of the RYR-1 Foundation Scientific Advisory Board, at an RYR-1 International Family Conference.

ONGOING ACTIVITIES

PATIENT REGISTRY:

Developing a list of patients with RYR-1-related diseases is critical for research, as it allows physicians to learn about the natural history of these disorders. Furthermore, as any potential therapy must be tested in a clinical trial prior to FDA approval, having a patient database is essential in encouraging pharmaceutical companies to develop therapies for this "orphan disease."

FUNDING OF RYR-1 RESEARCH MEETINGS:

International research meetings are essential for the dissemination of new scientific discoveries. They are also important for networking and the sharing of ideas among clinicians, basic science researchers, and the pharmaceutical industry. The RYR-1 Foundation has sponsored various meetings, including: Gordon Research Conference, World Muscle Society, International Congress on Neuromuscular Diseases, and European Muscle Conference. The Foundation has also co-hosted and sponsored a meeting at the European Neuromuscular Centre, specifically on RYR-1-related diseases.

In addition, the RYR-1 Foundation hosts biannual meetings of the Scientific Advisory Board (SAB). These are critically important forums for the world's leading RYR-1 researchers and clinicians to share research, to collaborate, and, ultimately, to advance the field of RYR-1-related diseases. Hosting these meetings is a costly endeavor; however, the RYR-1 Foundation has been awarded $85,000 in grants to support these meetings.

FUNDING BASIC AND CLINICAL RESEARCH:

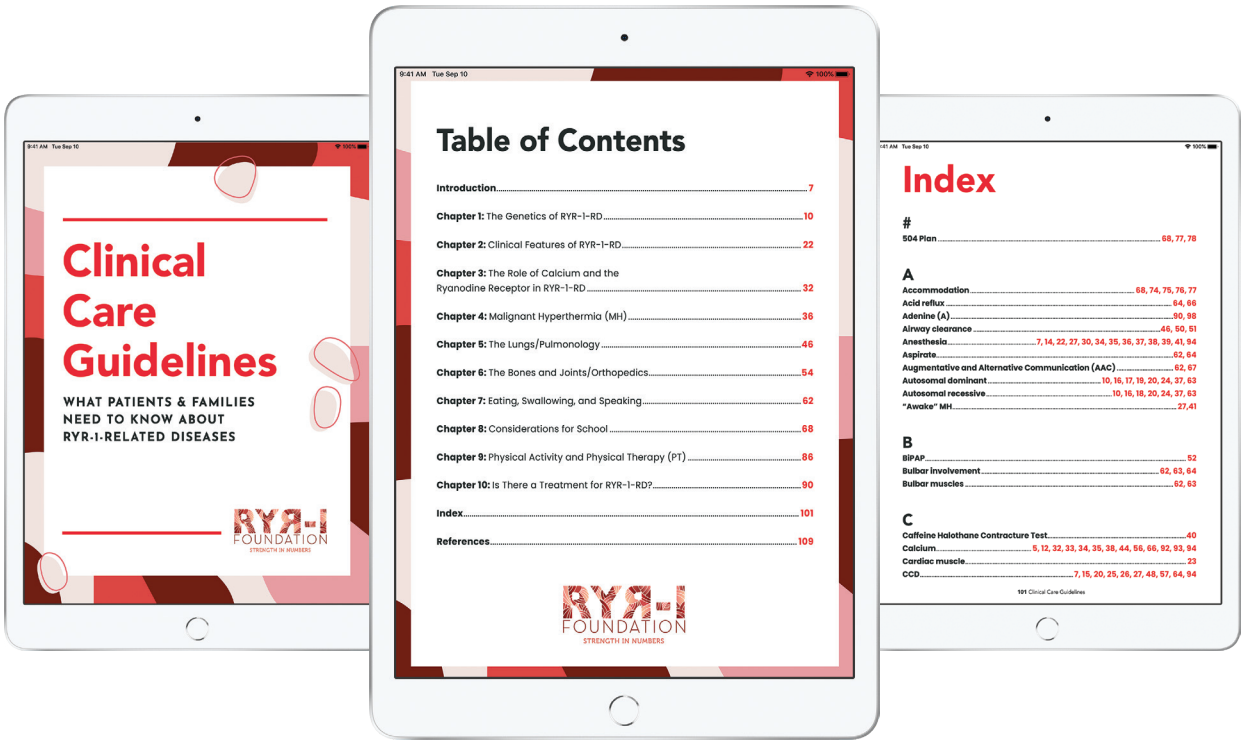
Acquiring funding for clinical research for a rare disease can be challenging for clinicians and scientists. As a relatively small organization focusing on a single group of conditions, the RYR-1 Foundation has worked successfully with researchers to obtain funding for the translation of basic research to future clinical trials.

CLINICAL CARE GUIDELINES: WHAT PATIENTS AND FAMILIES NEED TO KNOW ABOUT RYR-1-RELATED DISEASES

In September 2020, the RYR-1 Foundation published the long-awaited *Clinical Care Guidelines (CCG)*, made possible by a $50,000 grant from The Oscar and Elsa Mayer Family Foundation. This is a handbook written exclusively for individuals and families affected by RYR-1-related diseases. The CCG has over 100 pages of original content that will help the RYR-1 community better understand RYR-1-related diseases. This free online handbook utilizes numerous educational graphics and illustrations. Many topics are covered, including the role of calcium in RYR-1-related diseases, modes of genetic inheritance, and potential therapies. Each chapter contains a link to extensive online resources that the RYR-1 Foundation has provided. **A copy of the *CCG* is freely available and easily downloadable at www.ryr1.org/ccg**. On this webpage, there is also a brief video that introduces the CCG. To maximize the impact of the CCG on the international RYR-1 community, it will be translated into numerous languages.

"I've found the site so informative - the most informative information I've found... I've read the Clinical Care Guidelines and have been digging into all the resources on your website. I plan on providing the guidelines and a number of other resources to our primary care providers so they can be more knowledgeable."

INDIVIDUAL AFFECTED BY AN RYR-1-RELATED DISEASE




RELAXED MUSCLE
Chapter 3 - Calcium and the Ryanodine Receptor
A.
Muscle Cell
B.
Cytoplasm
SR
C.
SR
Calcium
Cytoplasm
RyR1
DHPR
Channel
CLOSED
MUSCLE CONTRACTION
A.
Muscle Cell
B.
Cytoplasm
SR
C.
SR
Calcium
Cytoplasm
RyR1
DHPR
Channel
OPEN
Figure 3.1 - A. Muscle in its relaxed, non-contracted state. B. In a magnified view of a muscle cell in its relaxed state, there are calcium ions within the sarcoplasmic reticulum (SR), but not in the cytoplasm. C. In a magnified view of the wall of the SR, the DHPR has not been activated and the RyR1 receptor is closed, preventing calcium from exiting the SR and entering the cytoplasm.
Figure 3.2 - A. Muscle in its contracted state. B. In a magnified view of a muscle cell in its contracted state, calcium ions have exited the SR and are now in the cytoplasm. C. In a magnified view of the wall of the SR, the DHPR has been activated and the RyR1 receptor goes from closed to open. This allows calcium ions to exit the SR and enter the cytoplasm. By entering the cytoplasm, the calcium can then continue on to the next stage of muscle contraction.
22 Clinical Care Guidelines
This process is analogous to the flushing of a toilet. In this analo
Inside of the cell (cytoplasm), the tank is the SR calcium storage
ter represents the calcium (Ca^{2+}) ions. The act of flushing the toil
ions) from the storage tank (SR) into the bowl (cell interior or
controlled by the toilet handle (DHPR) pulling on the
for water to flow from the storage tank to the toil
al who pulls on the handle is analogous to
RyR1 gatekeeper channel. When the
release water (calcium) from the
flush represents the flow of
needed for muscle co


Chapter 1 - Genetics
AUTOSOMAL DOMINANT
Parents
Mutation
Affected
Unaffected
Children
Affected
Affected
Unaffected
Unaffected
50% affected
Some RYR1 mutations are passed on through autosomal dominant inheritance. That means one mutant copy of the RYR1 gene is enough for someone to have RYR-1-RD. If one parent with autosomal dominant RYR-1-RD conceives a child with a parent who does not have RYR-1-RD (and is not a carrier of a recessive mutation of RYR1), there is a 50% chance that the child will have RYR-1-RD.
Source - ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns
17 Clinical Care Guidelines

FAMILY CONFERENCES

Since its inception, the RYR-1 Foundation has hosted biennial international family conferences. These conferences are unique opportunities for affected individuals and families to meet, form friendships, gain knowledge, and develop a true RYR-1 community. Combined, these events have hosted 388 attendees, representing 75 RYR-1-affected families from 31 states and eight countries.

Although the COVID-19 pandemic has precluded the ability to have in-person meetings, the RYR-1 Foundation has hosted numerous online events to help the RYR-1 community stay informed and to create social connections amongst its members.

For rare conditions like RYR-1-related diseases, providing a forum for affected individuals and families to meet others like them has significant psychological value. When an affected individual or their family members seek to find someone else who understands what they are experiencing, a family conference becomes an invaluable and necessary resource. It is a goal of the Foundation to enhance and enrich these relationships within the RYR-1 community by hosting events on a regular, recurring basis.

To view a documentary about the RYR-1 International Family Conferences, please go to: **www.ryr1.org/conferences**.

Below: Photos from prior family conferences.

Group photograph of attendees of the 2018 RYR-1 International Family Conference, July 13–15, 2018, in Pittsburgh, PA.

> To meet a whole staff of doctoral level scientists spending their lives researching the disease that impacts our families' lives so drastically was so powerful!

RYR-1 INTERNATIONAL FAMILY CONFERENCE ATTENDEE

If not for attending the conference, there is no telling how long these concerns would have gone unchecked. I can't thank y'all enough for all that we have learned from the conference!

RYR-1 INTERNATIONAL FAMILY CONFERENCE ATTENDEE

Peter L. Saltonstall, President and CEO of the National Organization for Rare Disorders (center), receiving an award after delivering the keynote address at the 2018 RYR-1 International Family Conference. He is joined by Nicole Wallace, Program Director of the RYR-1 Foundation (left), and Dr. Michael F. Goldberg, President of the RYR-1 Foundation (right).

SUPPORT AND ADVOCACY FOR AFFECTED INDIVIDUALS AND FAMILIES

Due to the rarity of RYR-1-related diseases, the diagnosis can be anxiety-provoking and isolating for individuals and their families. The Foundation serves as a resource, primarily through our website (**www.ryr1.org**) and Facebook page (**www.facebook.com/ryr1foundation**), in which individuals can access a wealth of information.

Educational videos about RYR-1-related diseases can be viewed directly on the RYR-1 Foundation's website: **www.ryr1.org/videos**.

ROLE OF CALCIUM IN RYR-1 MYOPATHY:
Dr. Robert Dirksen

MALIGNANT HYPERTHERMIA:
Dr. Ronald Litman

INTRODUCTION TO RYR-1 MYOPATHY:
Dr. James Dowling

WHAT ARE RYCALS:
Dr. Andrew Marks

NOLAN'S STORY

Nolan's doctors noticed there was something wrong the moment he was born. His weakness at birth was so profound that it took Nolan several weeks to even open his eyes or move a finger. Nolan spent the first two months of his life in the hospital. Mandy, Nolan's mother, recalled grieving for the loss of the typical mother-newborn bonding experience, as she was unable to take Nolan home to simply "cuddle on the couch."

Nolan is a young boy who is affected with an RYR-1-related disease. Although Nolan's strength has improved somewhat since birth, he currently cannot sit independently, lift his head, eat, or clear his oral secretions. This puts him at risk for numerous medical complications, including life-threatening infections.

When Nolan's parents learned of the RYR-1 Foundation, they were shocked that an organization existed specifically to help individuals with Nolan's rare disease. When asked about the RYR-1 Foundation's mission to support research for RYR-1-related diseases, Mandy said, "It is everything--the most important thing. If we only get one thing in life, it would be to have a treatment or a cure for Nolan."

Eager to accelerate the pace of research, Lindsey, Nolan's aunt, organized a fundraiser, "Hike for Team Nolan," which raised over $11,000 for the RYR-1 Foundation. In reference to the RYR-1 Foundation and the "Hike for Team Nolan," Mandy says, "When we got Nolan's diagnosis, we never dreamed that a cure was even possible. Recent developments in gene therapy make us believe that it is more than possible, and **we are hopeful that through the work of the RYR-1 Foundation, Nolan will someday be able to complete this hike alongside his Aunt Lindsey."**

To watch a video on "Nolan's Story," please go to: **www.ryr1.org/nolan**.

JACKSON'S STORY

Jackson is a young boy with an RYR-1-related disease. He is currently unable to walk without assistance and is forced to alternate between a wheelchair and walker.

Jackson's mother, Marcie, noticed problems with Jackson at three days after birth, when he was unable to breastfeed due to weakness in his facial muscles. At six months of age, he had hip surgery--this would be the first of many surgeries, which often required prolonged inpatient stays and intensive outpatient therapy.

Currently, he sees numerous specialists to deal with complications related to his RYR-1-related disease, including neurologists, orthopedists, and pulmonologists. In addition, he must use a walker, orthotic braces, a gait trainer, forearm crutches, and a wheelchair. His family's home has had to be adapted to include a ramp and stairlift.

"The RYR-1 Foundation will change so many lives, and I am excited about its impact on ours."

MARCIE, JACKSON'S MOTHER

In addition to the physical toll this disease has taken on Jackson, there is a significant psychological component as well. Marcie wrote to the Foundation: "Jackson is very aware that he is different from other children. Around age 5, he was very angry and upset about his disability....He cries easily if he thinks someone is staring at or making fun of him."

Despite all of this, Jackson is outgoing, friendly, and intelligent. He plays sled hockey, the viola in his school orchestra, and the cornet in his school band.

To watch a video on "Jackson's Story," please go to: **www.ryr1.org/jackson**.

BRENTNEY'S STORY

When Brentney was born in 1993, her parents noticed something was wrong right from birth. Doctors told her family that they did not think she would ever be able to walk or talk. Nevertheless, each and every day, Brentney has continued to exceed everyone's expectations.

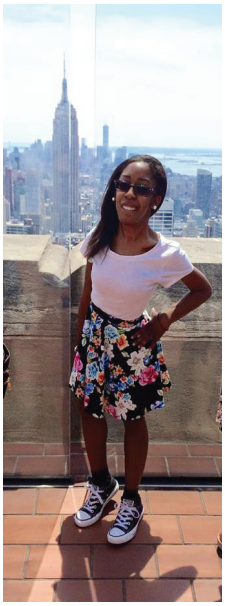
Like many other individuals with RYR-1-related diseases, Brentney was initially misdiagnosed. Due to her rapid health decline in 2015, she and her family became skeptical about her initial diagnosis, which led to genetic testing. It was not until January 2016, at the age of 22, that Brentney received her true diagnosis – an RYR-1-related disease.

Despite unanswered questions and countless doctor appointments, Brentney and her family continue to remain optimistic, hopeful, and inspirational. On May 6, 2016, Brentney graduated with her associate's degree from Trident Technical College. Although there were some serious health roadblocks along the way, Brentney never felt defeated. She accomplished a milestone in her life that no one can ever take away from her.

> "Up until meeting other individuals of the RYR-1 community, no one else could fully understand what I have been going through...for that, I am forever grateful."
>
> **BRENTNEY, AFFECTED WITH AN RYR-1-RELATED DISEASE**

As an attendee of the first RYR-1 International Family Conference in 2016, Brentney personally experienced the value of the RYR-1 Foundation. "After discovering the RYR-1 Foundation, I was finally able to interact with and meet people who could identify with the same things I was going through," Brentney explains.

To watch a video on "Brentney's Story," please go to: **www.ryr1.org/brentney**.



CODY'S STORY

As the 10th overall pick in the 2008 NHL Draft, Cody Hodgson had a bright career ahead of him in the NHL. Cody played for the Vancouver Canucks, Buffalo Sabres, and Nashville Predators over the course of a six-year career. Although Cody had experienced muscle cramps his entire life, he dismissed them as a regular part of being a competitive athlete. As his symptoms became more severe during his professional playing days, he recalled, "I knew I had to get medical help." He experienced many distressing signs and symptoms, including: trouble breathing, heart arrhythmias, severely low blood pressure resulting in "blacking out," and tea-colored urine. The severity of these symptoms culminated in a hospitalization in 2015, when doctors diagnosed him with rhabdomyolysis, a severe and potentially fatal condition related to abnormal muscle breakdown.

Cody (right) at an RYR-1 International Family Conference with Lindsay Goldberg (left) and Cody's brother, Clayton (middle).

During the 2015-2016 season with the Predators, Cody was referred to Dr. Sheila Riazi, an anesthesiologist and one of the world's leading experts on malignant hyperthermia, a muscle condition most commonly due to a mutation in the RYR-1 gene. Dr. Riazi, a member of the RYR-1 Foundation's Scientific Advisory Board, quickly realized that Cody's numerous injuries, severe symptoms, and episodes of rhabdomyolysis were all likely due to RYR-1-related malignant hyperthermia. She ordered genetic testing and a muscle biopsy, which confirmed the diagnosis.

Receiving this diagnosis from Dr. Riazi was a source of tremendous relief for Cody. "You put up with a lot of injuries, and it takes a physical toll when you play hockey," Cody said "but it really scares you when you are not sure what is going on with you."

Dr. Riazi informed Cody of the RYR-1 Foundation and put him in touch with its President, Dr. Michael Goldberg. After meeting with Dr. Goldberg in early 2018 and learning more about the work of the RYR-1 Foundation, Cody said, **"Hopefully, the RYR-1 Foundation and I can help to not only push for a cure, but also help the parents, patients, and families affected by it now so that they can better understand their condition, take the appropriate precautions, and have a treatment available to them."**

To watch a video on "Cody's Story" and an interview with Dr. Michael Goldberg, President of the RYR-1 Foundation, and Cody Hodgson, please go to: **www.ryr1.org/cody**.

HOW A GIFT TO THE RYR-1 FOUNDATION CAN HELP

Costs of Research:

$500:
Supports the purchase of lab supplies.

$2,000:
Partial salary support for lab technicians.

$60,000:
The cost of developing each mouse model with a mutation in the RYR-1 gene.

$120,000–$150,000:
The annual cost of a basic science research project (lab equipment, staff salaries, supplies, etc.).

$750,000–$1,000,000:
Cost of a Phase I clinical trial to assess safety of a drug.

$2,000,000–$3,000,000:
Cost of a Phase II clinical trial to assess effectiveness of a drug.

To make a donation to the RYR-1 Foundation, please go to: **www.ryr1.org/donate**.

For questions about making a donation, please contact **Nicole Wallace, Program Director**, at **nicole@ryr1.org** or **(412) 529-1482.**

WHO WE ARE

RYR-1 Foundation President, Dr. Michael Goldberg (right) and Vice President, Dr. Morton Goldberg (left).

MICHAEL F. GOLDBERG, MD, MPH, PRESIDENT, CO-CHAIR OF RESEARCH, TRUSTEE

Mike is President and Co-Chair of Research of the RYR-1 Foundation. He is a neuroradiologist and is the Director of Neuroradiology at the Allegheny Health Network in Pennsylvania. He is an Associate Professor at Drexel University College of Medicine. He can be reached at mike@ryr1.org.

MORTON F. GOLDBERG, MD, FACS, VICE PRESIDENT, CO-CHAIR OF RESEARCH, TRUSTEE

Along with Mike, Mort is the Co-Chair of Research. He is also an ophthalmologist specializing in inherited retinal diseases. He is the Joseph Green Professor of Ophthalmology at the Johns Hopkins School of Medicine and the Director Emeritus of the Wilmer Eye Institute at Johns Hopkins University. He is a member of the National Academy of Medicine of the National Academies of Science of the United States.

LINDSAY GOLDBERG, RN, SECRETARY, TREASURER, PATIENT LIAISON, BUSINESS MANAGER, TRUSTEE

Lindsay acts as a liaison between affected individuals and their families along with physicians, genetic testing companies, and scientists. She has a BSN from the University of Michigan and is a registered nurse who worked for 10 years specializing in pediatric cardiac intensive care. She can be reached at lindsay@ryr1.org.

MICHAEL LEGUM, ASSISTANT TREASURER, TRUSTEE

Mike is a senior portfolio manager for Park Circle Investments, a Baltimore-based private investment company. Prior to Park Circle, he worked in the film business, spending five years at New Line Cinema. He is a graduate of the University of Pennsylvania with a BA in English.

RYR-1 Foundation Trustees and Program Director.

ALLISON GARROTT BRASWELL, MS, EDS, TRUSTEE

Allison attended Vanderbilt University, and then, earned her Educational Specialist degree in School Psychology from the University of Memphis. She and her husband, Bo, have raised three children in Memphis, Tennessee, and she has worked as a trustee and volunteer for several community organizations. Allison has a dominant RYR-1 mutation.

MYRNA GOLDBERG, MSW, TRUSTEE

Myrna is a retired social worker, having previously worked in hospitals, protective services, and school social work settings. She serves on the Board of Advisors of the University of Maryland School of Social Work, is an active member of the Baltimore Women's Giving Circle, and is a docent at the Baltimore Museum of Art.

JUSTIN C. McARTHUR, MBBS, MPH, FAAN, TRUSTEE

Dr. Justin McArthur is the Neurologist-in-Chief at the Johns Hopkins Hospital and John W. Griffin Professor of Neurology at the Johns Hopkins University School of Medicine. He is also a Professor of Pathology, Medicine, and Epidemiology. He has become nationally and internationally recognized for his work in the epidemiology and treatment of HIV infection, multiple sclerosis, and other neurological infections and immune-mediated neurological disorders.

MICHAEL J. ORSECK, MD, FACS, TRUSTEE

Michael is a plastic surgeon, specializing in aesthetic surgery and reconstructive microsurgery. Dr. Orseck also serves as a Trustee of the Board of Directors of Spartanburg Regional Healthcare System. His daughter, Gabby, has an RYR-1-related disease.

EMILY PEDERSEN, TRUSTEE

Emily worked as a Recreation Therapist and Child Life Specialist at Weisman Children's Rehabilitation Hospital in Marlton, New Jersey for eight years. She has participated in and organized fundraising runs to support research for RYR-1-related diseases. Emily has a daughter who was diagnosed with Central Core Disease, a form of an RYR-1-related disease.

Emily Pedersen (right) with Jackson (left), a boy affected by RYR-1.

RANDOLPH PEPPER, CPA, TRUSTEE

Randy is recently retired as the Director of Finance & Accounting for Central Processing Services, LLC, a privately held company in suburban Detroit. He has a BA degree from the University of Michigan, and a MBA from Wayne State University. He has over 30 years experience in a variety of Controller/CFO positions for mid-size privately held companies.

JENNIFER RYAN, MBA, TRUSTEE

Jeni is also a trustee of the Schooner Foundation and has an MBA in Operational Management from Simmons College. She is the former COO of Integral Resources, a telemarketing firm specializing in small donor acquisition for nonprofits. Both she and her daughter have Central Core Disease, a form of an RYR-1-related disease.

DONALD J. ZACK, MD, PhD, TRUSTEE

Dr. Donald Zack is the Guerrieri Family Professor of Genetic Engineering and Molecular Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University School of Medicine. His research concerns the mechanisms of retinal degenerative disease and glaucoma, and efforts to develop new drug and stem cell-based therapeutic approaches.

NICOLE WALLACE, PROGRAM DIRECTOR

Nicole joined the RYR-1 Foundation team in January 2017 as the Program Director. She coordinates daily operations and works closely with the Officers and Trustees of the RYR-1 Foundation. She is a graduate of the University of Pittsburgh with a BS in Psychology. She can be reached at nicole@ryr1.org and (412) 529-1482.

RYR-1 Foundation President and Co-Chair of Research Dr. Michael Goldberg and Secretary, Treasurer, Patient Liaison, and Business Manager Lindsay Goldberg.

RYR-1 Foundation Assistant Treasurer Michael Legum (left) and Vice President and Co-Chair of Research Dr. Morton Goldberg (right).

RYR-1 Foundation Secretary, Treasurer, Patient Liaison, and Business Manager Lindsay Goldberg (left) and Program Director Nicole Wallace (right).

ADVISORS

MARCIE EPSTEIN
Wife of Steve and Mother of Jackson, who are both affected by RYR-1

MATTHEW GOLDBERG, JD
Reliability and Operations Compliance at a public utility company

CODY HODGSON
Director of Alumni Hockey Relations, Nashville Predators

JACQUELINE HOFFMAN-ANDERMAN, RN, BSN
Mother of Maddie, affected by RYR-1

DREW HUSETH, AICP
Individual Affected by RYR-1 and Land Entitlement Manager for Woodside Homes

SOFIA LEON
Mother of Tommie, member of a large family with more than 20 members affected by Central Core Disease

JEREMY NATHANS, MD, PHD
Professor in the Departments of Molecular Biology and Genetics, Neuroscience, and Ophthalmology, Johns Hopkins Medical School

AMY A. PERRIN, MS, FNP-C
Mother of Courtney, affected by RYR-1

BRENTNEY SIMON
Individual affected by RYR-1 (recessive minicore)

AVI SWERDLOW
Product Manager, Google

YAEL SWERDLOW
Special Education Consultant

RYR-1 Foundation Advisors, Marcie Epstein (left), Yael Swerdlow (second from left), and RYR-1 Foundation President Dr. Michael Goldberg (right) with a conference attendee.

We are in awe of the strides the foundation has made and your devotion to the RYR-1 population!

ATTENDEE, RYR-1 INTERNATIONAL FAMILY CONFERENCE

RYR-1 FOUNDATION

STRENGTH IN NUMBERS

www.ryr1.org

The mission of the RYR-1 Foundation is to:

1) Support research leading to an effective treatment or a cure for RYR-1-related diseases; 2) Bring awareness and serve as a resource for medical professionals; and 3) Provide education, outreach, and advocacy for individuals and families affected by RYR-1-related diseases.