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Individual Investigator Research Grant Awards
Targeted Request for Grant Application
Deadline: March 1, 2021

The RYR-1 Foundation expects to fund a limited number of Individual Investigator Research Grants, **to be awarded in mid-2021**. *Preference will be given to grant applications that address the "Research Priority Areas," as detailed below.*

You are invited to submit a grant application and short *curriculum vitae* (NIH Biosketch is preferred) to the RYR-1 Foundation by ***March 1, 2021.*** The total application, including the budget and bibliography, should not exceed 10 single spaced pages (using Arial 12 pt font), but may be less (see below for details).***Applications should be emailed to: Nicole Wallace, Program Director, at nicole@ryr1.org*.**

Summary of Application Format:

1. **Title of the RYR-1-Related Diseases Project (Face Page).**
2. **Personnel.**
3. **Abstract** (limit: ½ single-spaced page).
4. **Identify the Specific RYR-1 "Research Priority Area(s)"** *(see page 2 or www.ryr1.org/2021grant).*
5. **Explain the Impact on RYR-1-Related Diseases:** (limit: 1 single-spaced page). State why this research is important; and how it will make a significant difference in achieving the RYR-1 Foundation's mission of finding treatments and cures for RYR-1-related diseases.
6. **Specific Aims and Rationale** (limit: 1 single-spaced page).
7. **Preliminary/Supporting Data** (limit: 1 single-spaced page).
8. **Detailed Project Description:** (up to 4 single-spaced pages, but may be less). Key milestones and timelines for the proposed research must be included in this section. A chronological Gantt Chart to illustrate these events must be included. Bibliography should not exceed 10 items.
9. **Budget and Budget Justification:** Please use an NIH-style spreadsheet.
10. **Institutional Signatures and Related Considerations.**

Description:

Individual Investigator Research Grant Awards are designed to concentrate research in areas that will have the greatest potential to move towards treatments and cures for RYR-1-related diseases.

As appropriate, applicants are encouraged to use one or more of RYR-1 murine models currently available from commercial, corporate, academic, and other sources, including recently developed animal models.[1] **Recently developed murine models of RYR-1 myopathy demonstrate moderate-severe myopathy phenotypes, including mice with mutations on exons 34 and 96. Please see "Entry #1" and "Entry #2" on the spreadsheet entitled "Mouse Models of RYR-1-Related Diseases" at www.ryr1.org/mice.** For information on obtaining these mice, please contact Nicole Wallace, Program Director of the RYR-1 Foundation: nicole@ryr1.org.

The RYR-1 Foundation has identified Research Priority Areas (RPAs) that align with its mission; and the purpose of this targeted open call for applications is to address specific gaps in current research related to RYR-1-related diseases. While applications addressing the areas of particular interest (below) will be given priority consideration, ***the RYR-1 Foundation will also consider proposals for research that do not fit easily within these goals.***

RESEARCH PRIORITY AREAS (RPAs):

Priority will be given to research that has direct application to clinical therapies for RYR-1-related diseases. **Specific areas of research interest may include the following:**

A. **Novel therapeutic approaches to RYR-1-related diseases. All approaches will be considered, but potential interventions include:**
    a. Gene Editing (e.g., CRISPR/Cas9, Base editing, Prime editing, etc.).
    b. Gene replacement therapy (viral vectors and non-viral technologies).
    c. Therapeutic strategies utilizing protein and small-molecule binders.
    d. Therapeutic strategies utilizing nanotechnology/nanoparticles.
    e. Development of therapeutic interventions that modify RyR1 receptor activity,[2][3][4]

[1] The relationships/similarities between the animal models and human disease(s) should be clearly described, and the reasoning underlying the choice(s) of potential therapeutic agent(s) should be clearly explained. "Clinical endpoints" can include selections from a variety of tests, such as grip strength, voluntary wheel running, wire hang, in vitro contracture tests, peak twitch, tetanic specific force, body weight, weight of individual muscles, histopathologic changes of skeletal muscle, E-C coupling/uncoupling, dynamics of calcium metabolism, survival time, radiography of kyphoscoliosis, DHPR RT-PCR, and/or others.

[2] Murayama T, Kurebayashi N, Ishigami-Yuasa M, *et al* (2018): Efficient High-Throughput Screening by Endoplasmic Reticulum Ca2+ Measurement to Identify Inhibitors of Ryanodine Receptor Ca2+-Release Channels. *Mol Pharmacol* **94**:722-730.

[3] Rebbeck RT, Essaway MM, Nitu FR, *et al* (2017): High-throughput screens to discover small-molecule modulators of ryanodine receptor calcium release channels. *SLAS Discov* **22**:176-186.

[4] Andersson D, Betzenhauser M, Reiken S, *et al* (2011): Ryanodine receptor oxidation causes intracellular calcium leak and muscle weakness in aging. *Cell Metabolism* **14**: 196-207. https://docs.wixstatic.com/ugd/231519_a681f8a4699a439a973f293b1b9f408b.pdf

reduce muscle degradation, and/or increase regenerative capacity of skeletal muscle.[5]

B. Prevalence of RYR-1-Related Diseases

a. The most commonly cited prevalence of RYR-1-related myopathy is 1:90,000, and is based on a study from 10 years ago.[6] This is considered a marked underestimate of the true prevalence of this disease.
b. An updated prevalence study is needed and would exploit data from the numerous international patient registries/databases.

All grant applications related to RYR-1-related diseases that do not address the above RPAs will be reviewed, but may receive less priority. Other potential areas for support, include the following:

C. Cell and Molecular Mechanisms of RYR-1 Disease: Basic research designed to define the underlying pathogenic mechanisms of RYR-1-related diseases that identify potential new therapeutic targets.

D. Regenerative Medicine (RM): Development of strategies that provide functional rescue or replacement of degenerating and/or dead muscle cells that can lead to improvement of muscle function.

Eligibility:

Applicants must hold a Ph.D., M.D., D.V.M., D.O., or equivalent degree and have a faculty position or equivalent at a domestic or foreign nonprofit organization, or public or private institution, such as a university, college, medical school, hospital, research institute, or laboratory.

[5] Rogers RG, Fournier M, Sanchez L, *et al* (2019): Disease-modifying bioactivity of intravenous cardiosphere-derived cells and exosomes in *mdx* mice. *JCI Insight 2019 Apr 4; 4(7): e125754.* PMID: 30944252.
[6] Amburgey, K, McNamara N, Bennett LR, *et al* (2011): Prevalence of congenital myopathies in a representative pediatric united states population. *Annals of Neurology:* 70(4): 662-665. PMID: 22028225.

Award:

The total award will be up to **$90,000 USD** (up to **$45,000 USD per year for two years**).[7] Renewal is based on both documented progress and on availability of funds. The award may be used to support the salaries of research trainees (graduate students, postdoctoral or clinical fellows), technical staff; research animals; and research supplies. Partial support for the Principal Investigator's salary is permitted, but is not to exceed 20% of the total annual award.

Note: The RYR-1 Foundation and its trustees do not provide funds for indirect, administrative, or overhead costs. The RYR-1 Foundation does not provide funds for fringe benefits and annual "cost of living" increases. In addition, the RYR-1 Foundation does not pay for costs related to construction or renovation.

Purchase of capital equipment is generally not supported by the RYR-1 Foundation. Capital equipment is defined as a permanent or semi-permanent apparatus, device, or system costing more than $5,000 per device or system. Applicants must obtain prior approval from the RYR-1 Foundation President to submit an application proposing to purchase capital equipment. If approval is to be granted, all such equipment requests must be well justified in the budget section of the application and in the description of the proposed project. *A budget page is attached for your use.*

Letters of collaboration must be included. Consultation and collaboration with specialists in the following fields are encouraged: RYR-1 myopathy; pharmacotherapeutic agents; animal models of human RYR-1 myopathy; gene editing; gene replacement; and others.

If any of the investigators have either an active or pending grant on RYR-1-related matters, a list should be provided in this application, including the funding agency, title of the grant, names of investigators, percentage efforts, duration of the grant, and budget.

Institutional Considerations:

The budget page should end with a signature line for the senior financial officer of the host institution who is authorized to sign for the institution. That person's name, title, phone numbers, e-mail address, and street/mailing address should be included.

*Half of the first year's financial award will be delivered to the host institution upon activation of the project, and the remainder will be provided in follow-up tranches, dependent upon our receipt of an acceptable progress repor*t (up to 2 single spaced pages) at the end of the initial

[7] Research projects that are expected to exceed two years in duration will also be considered for funding. Please note, however, that total grant funding will not exceed $90,000 USD.

six months (or earlier if presented at a meeting of the RYR-1 Foundation SAB). Alternative payment mechanisms (e.g., reimbursement to the P.I., personally, rather than to the institution) may occasionally be acceptable under specified and well documented circumstances, but must be approved in writing, and in advance, by the President of the RYR-1 Foundation.

Please e-mail (in Microsoft Word or PDF format) the 1) Application, 2) Budget Page, and 3) Short CV of relevant personnel (NIH biosketch is preferred) to: *Nicole Wallace, Program Director of the RYR-1 Foundation, at nicole@ryr1.org. These materials must be received by* ***March 1, 2021 to be considered for funding.***

Please use your own e-mail address if possible when submitting the application so that we can inform you in a timely fashion if your application has been approved or not. In addition, please advise us as soon as possible of changes in e-mail addresses.

The RYR-1 Foundation uses the "Just in Time" concept. Applicants may defer the following items until completion of peer review and just prior to funding: certification of the Institutional Review Board (IRB) and Institutional Biosafety Committee (BC); approval of the application's proposed use of human subjects and proposed use of recombinant DNA; verification of the Institutional Animal Care and Use Committee (ACUC) approval of the proposed use of live vertebrate animals; Health Insurance Portability and Accountability Act (HIPAA) compliance; and evidence of compliance with the requirement for education in the protection of human research participants.

Evidence of these approvals must be documented by submission of a signed Institutional Agreement Form (IAF) at the time of the award. If approvals are pending at the time of the award, the RYR-1 Foundation funding cannot be expended for research involving human subjects, recombinant DNA, and live vertebrate animals until the signed forms are submitted to document that the appropriate approvals have been obtained.

DETAILED APPLICATION INSTRUCTIONS

SECTION I. TITLE/ APPLICATION FACE PAGE

The application Face Page must be signed by the Principal Investigator and the responsible institutional individual. Prior to submitting the application, print the Face Page and obtain the appropriate signatures.

SECTION II. PERSONNEL

Each individual Investigator Research Grant Application must be directed by a **single Principal Investigator** who is responsible for the conduct and management of the project. Co-Investigators are allowed, and must be identified and justified.

1. Identify all scientific and technical personnel involved in the proposed project. Identify all proposed collaborators in this section of the application and include letters of collaboration.

2. For all key personnel, include current and pending sources of ALL research support. For each source (federal, private, or commercial) provide: title, grant number, percent effort, funding amount, and budget period. This information should include total support for all current and proposed projects **AND** provide abbreviated one-page CVs for all key personnel, listing only **RELEVANT** publications from the last three years. **DO NOT** include free-standing Abstracts; NIH biosketch is preferred.

SECTION III. ABSTRACT (limit: ½ single-spaced page)

Provide an abstract of the proposed research project, written **in lay terms** for a non- scientific audience. The abstract should contain non-confidential material that can be posted on the RYR-1 Foundation's website if the application is funded.

SECTION IV. IDENTIFY SPECIFIC RYR-1 "RESEARCH PRIORITY AREA(S)"*(see above or www.ryr1.org/2021grant).*

SECTION V. EXPLAIN THE IMPACT ON RYR-1-RELATED DISEASES

State why this research is important; and how it will make a significant difference in achieving the Foundation's mission of finding a cure/effective treatment(s) for RYR-1-related diseases (limit: 1 single-spaced page).

SECTION VI. SPECIFIC AIMS AND RATIONALE (limit: 1 single-spaced page)

1. Describe the overall goal(s) and rationale for the proposed project. Numerically list the specific aims and correlate with Gantt Chart. Describe the anticipated results to be achieved in each three-month period of the project. Note that successful applicants will be required to submit regular Progress Reports that detail accomplishments for each of the specific aims identified in the application.

2. For clinical research projects, identify the specific disease(s) and patient population(s) to be studied. Include genomic diagnosis whenever possible.

SECTION VII. PRELIMINARY/SUPPORTING DATA (limit: 1 single-spaced page)

Describe existing experimental data or prior clinical research that support(s) the soundness and feasibility of the proposed experiments. Include evidence of in vitro and/or in vivo experiments, if applicable, that demonstrate the relevance of the proposed experiments for advancing therapeutic or preventive interventions.

SECTION VIII. DETAILED PROJECT DESCRIPTION (limit: 5 single-spaced pages)

1. **Experimental Plan and Methods:** For each specific aim, describe the experimental design procedures, and methods to be used. ***The level and amount of detail utilized in an NIH investigator-initiated research project grant application is not required by the RYR-1 Foundation*.** However, applicants must include sufficient information so that reviewers can understand the proposed experiment, its soundness, feasibility, and importance for advancing the knowledge of RYR-1-related diseases.

   Applications proposing **research using human samples** must provide the information delineated below.

   NOTE: If IRB approval is not required in order to conduct the proposed clinical study using human samples, then such projects are considered non-clinical, and applicants are not required to provide the information/materials listed below.

   Clinical Research Requirements:

   A. Study Description: A description of the proposed clinical study, including (a) hypothesis and study objectives; (b) study population(s) and relevance of the proposed study to clinical disease/patient outcome; (c) study design, methodologies, and the scientific rationale, including supporting data from completed basic, preclinical and clinical research, and the feasibility and appropriateness of applying such supporting data to the design and

execution of the proposed clinical study; (d) statistical analysis plan and, where applicable, including sample sizes power calculations; and (f) plan for receipt, storage and distribution of human, animal, or stem cell samples.

B. Human Samples: Documentation of the ability to acquire human samples prospectively or retrospectively, including obtaining samples from planned, ongoing or completed clinical studies/trials sponsored by any source. This should include written agreements between the applicant institution, the Investigational New Drug (IND), and clinical trial sponsor.
C. Informed Consent: Please submit a copy of the approved or proposed informed consent form to be used for collection of patient samples **(include in Appendix Materials; this information does not count against the 5-page proposal limit)**.

2. **Milestones and Timelines:** Delineate key milestones and timelines for the proposed research project. Milestones are intended to define the specific stages and/or steps involved in accomplishing the stated aims, and are to incorporate timelines for the initiation, execution and completion of each specific stage or step. The number or types of milestones will vary depending on the goals and intended outcomes of the proposed research project. This information should be shown in a Gantt Chart.

3. **Collaborative Plans:** *The RYR-1 Foundation wishes to foster the sharing of information.* Therefore, include specific plans for collaboration with other investigators to share research materials, methodologies/technologies, animal models, patient assessment tools and results, and both positive and negative findings.

4. **Future Relevance:** If the aims of the application are achieved, **describe how scientific knowledge or clinical practice will be advanced**. Include a brief discussion on the anticipated effects of the study on the concepts, methods, technologies, treatments, or services that drive the field of research on RYR-1-related diseases.

5. **References:** Provide a list of bibliographic references for: (a) up to **ten** publications, but only if relevant to support the science for the proposed research; and (b) up to **three** personal pertinent reprints representing the applicant's research (PDF format for each reprint). This information does **not** count against the page limits.

BUDGET PAGE

RYR-1 FOUNDATION		
Grant Title:		
Principal Investigator: (Family Name, First Name, Academic Degrees)		
Institution:		
Award Period:		
	Year 1	Year 2
Personnel (Itemize)		
Name & Position of the Person		
Salary (no fringe benefits allowed)		
TOTAL PERSONNEL		
Supplies		
Radioisotopes		
Biochemicals		
Tissue Culture		
Molecular Biology		
TOTAL SUPPLIES		
Travel Costs	up to $2,000 USD	up to $2,000 USD
Animal Costs (Itemize)		
Purchase		
Maintenance		
TOTAL ANIMAL COSTS		
Patient Costs (Itemize)		
Other (Itemize)		
TOTAL COSTS		
(Indirect costs not allowed)		