



## **Request for Proposals for Novel Approaches to Improve Post-Transplant longevity for Children with Complex Congenital Heart Diseases**

**Full Proposal Deadline:** October 23rd, 2020

**About Enduring Hearts:** Enduring Hearts launched in 2013 with a mission to fund research to increase the longevity of, and improve the quality of life for pediatric heart transplant recipients.

**About Additional Ventures:** Additional Ventures is a nonprofit foundation that aims to accelerate research progress and improve clinical care for children born with complex congenital heart defects so that they have a normal duration and quality of life. Although one in one hundred children are born with a congenital heart defect, there are limited options for those with the most complex forms, including single ventricle (SV) heart defects. For these children, there is no cure. With rapid advances in areas like genomics, single-cell technologies, and tissue engineering, now is the time to coordinate concerted efforts to understand how to overcome this devastating, complex disease.

**Goal:** Enduring Hearts in partnership with **Additional Ventures** is announcing new funding to stimulate innovative research focusing on identifying, reducing and eliminating pre and post-transplant risk factors that affect outcomes of children born with complex congenital heart disease including single ventricle heart defects.

**Background:** Heart transplantation has been lifesaving for many infants and children born with congenital heart defects (CHD) that are not able to be corrected with cardiovascular surgery. Between 2005 and 2018, ~40% of children requiring a heart transplantation had CHD.<sup>1</sup> Children born with hearts having only one functional ventricle (complex CHD; cCHD) have undergone heart transplantation since 1985.<sup>2</sup> However, both early and late post-transplant survival of children with cCHD is “inferior to cardiomyopathy”, with prior Fontan procedure being a major risk factor.<sup>2</sup> Children born with cCHD and transplanted are at increased risks for rejection caused by antibodies (antibody-mediated rejection; AMR) and cardiac allograft vasculopathy. In one recent report, over 90% of children with treated AMR had CHD as their indication for transplantation.<sup>3</sup> The pathophysiologic mechanisms (injury, innate-immune and/or alloimmune)<sup>4</sup> by which these risk factors adversely modify the responses of recipients who had ccCHD is not known. Based in part on this evidence, better identification of mechanisms and methods to modify/eliminate the higher risk factors.

**Grant Opportunity:** In this grant series, we are seeking proposals which identify, reduce and eliminate pre- and post-heart transplant risk factors that affect long-term outcomes of children born with cCHD, in particular, those with single ventricle heart defects and surgical palliation.

The Enduring Hearts Scientific Advisory Committee will select projects of up to 2 years and no greater than \$300,000 in total costs that have a combination of the best science, innovation, and potential for clinical impact. Specific areas of research requested for the current proposal include:

- Identification of the complex interplay of multiple risk factors that better predict the need and timing of transplantation or affect outcomes (e.g. modelling algorithms, quantitative cardiac functional analyses, biomarkers/digital biomarkers, psycho-social influences, continuity of care), that will lead to resiliency in children with cCHD pre- and/or-post heart transplant.
- Development of more robust risk-reduction strategies (e.g. technologies, therapeutics, alternative interventions) to improve outcomes in pediatric heart transplant patients, including those that improve neurodevelopment, psychosocial, or behavioral (e.g. compliance) outcomes.
- Development of novel risk-reduction strategies leading to early detection of, and interventions/therapies for, Antibody-Mediated Rejection (AMR) and Cardiac Allograft Microvasculopathy (CAM) to improve longevity of pediatric heart transplant recipients, including those with cCHD.

### **Eligibility**

1. Each applicant organization must be a non-profit academic or research institution, including domestic and non-U.S. non-profit organizations, domestic and non-U.S. public/private academic universities or institutions of higher learning (including colleges, universities, medical schools, and other related academic research institutions); certain qualified governmental agencies with active biomedical research programs may also apply.
2. All proposed research projects must be led by a Principal Investigator (PI) who holds a doctorate (e.g., Ph.D., M.D.) or related research degree. PIs must be an independent investigator.
3. Applicants may apply to multiple grants but can only be the PI on one application.
4. Eligible Institutions: Academic or research institution, including, but not limited to domestic non-profit organizations, public/private institutions, and certain US federal agencies.

### **Priority**

Priority will be given to proposals that include one or more of the following:

- ◆ Collaborative projects led by PIs across institutions, disciplines, or scientific arc (e.g. collaboration between clinical and basic research scientists)
- ◆ Proposals from women and underrepresented minorities

**Application Process:** A full proposal should be submitted to Enduring Hearts no later than October 23 2020. Applicants must include a complete application and a proposed budget.

Applications must be submitted to: [Grants@enduringhearts.org](mailto:Grants@enduringhearts.org)

## What will be required for the full proposal?

### Requirements for proposal's application (*font & Layout: 1 inch margins, single spaced, Arial, 11 pt*)

- Page 1. **Cover page** including:
  - Project title (title identifying the project and its intended area of focus)
  - Short running title
  - The Primary Investigator's (PI) name, email, and the applicant organization's name
  - Structured technical abstract (250 words maximum) formatted as follows:
    - Rationale as related to priority, or priorities, of the Pediatric Heart Transplant Risk Reduction Initiative.
    - Aim(s) (summary of what the project aims to accomplish)
    - Anticipated Methods addressing specific aims
    - Major milestones and anticipated timeline that the PI anticipates in addressing the stated aims of the project and the priority, or priorities, of the Pediatric Heart Transplant Risk Reduction Initiative.
  
- Page 2 – 8. **Complete Research Proposal** (7 pages maximum) structured as follows:
  - Rationale and Alignment with stated Pediatric Heart Transplant Risk Reduction priorities
  - Approach and Specific Aims with major milestones that should include an estimated timeframe of completion.
  - Innovation and significance to include a detailed description of how achieving the aims of the proposed project the priority, or priorities, of the Pediatric Heart Transplant Risk Reduction Initiative.
  - Regular Language or Lay Summary (250 word) describing the project's aims, goals, and how it will benefit the pediatric heart transplant candidates and/or recipients
  
- Page 9. **Team and Team Capabilities.** Provide a statement outlining the research group's ability to address the research question, support the research, and manage patients, if applicable. Identification of any key personnel in addition to the PI and what role they will play in this study. Specify the time commitment of the PI to the project. Include any relevant citations from the Team on the Key Reference list (page 10) below. By submitting this proposal, the Principal

Investigator is agreeing to submit at least one abstract and/or manuscript relating to the work resulting from this grant.

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- **Key References** cited.
- **Additional documentation including**
  - Information about the applicant organization and the lead investigator it has selected
  - Contact information (email and phone) for the lead investigator and the authorized representative of the applicant organization which will receive the grant correspondence and funds

Page 12. **Budget and Justification.** The maximum total grant budget permissible is \$300,000 for a grant period of up to 2 years. Justified expenditures include partial PI salary support, equipment, software, patient recruitment, fringe benefits, salary for hired personnel, project specific travel, publication costs, and up to 10% indirect expenses that are included in the total grant budget. Include a narrative summary and justification for each major item. Enduring Hearts budget form must be used. Please request the BUDGET form, and study-specific budget questions by emailing [grants@enduringhearts.org](mailto:grants@enduringhearts.org).

**Appendices:**

- NIH bio sketch of the Principal Investigator is required. You may include other CV's of key personnel.
- Institution letter of commitment stating that the applicant organization will be able to support the research led by the PI.
- A statement addressing the policy that no awards will be made for projects that receive overlapping funding from other sources (unless supplementary in nature) or that duplicate other projects already funded.
- A statement from the PI that as a requirement to receive this award over its duration, the Primary Investigator agrees to the following:
  - To provide Enduring Hearts biannual scientific progress reports with an accompanying lay summary, notification of presentations and a copy of any

publications to be sent to our grant's administrators via e-mail:  
([grants@enduringhearts.org](mailto:grants@enduringhearts.org)).

- To acknowledge Enduring Hearts/Additional Venture support in any publication or presentation resulting from this award, with logo as appropriate. Acknowledgement should read as follows: "This work was supported by an Award from Additional Venture and Enduring Hearts Transplant Risk-Reduction Initiative"
- That Enduring Hearts may publish your professional title, your project title, and your institutional affiliation except in any purchased media advertising.

Applications will be confidentially reviewed by members of the Enduring Hearts Scientific Advisory Committee and selected Expert Reviewers. All institutional conflicts of interest will be observed. Should a member of the Enduring Hearts Scientific Advisory Committee become materially involved with proposed research, your institution should provide an acceptable conflict of interest mitigation plan for review to Enduring Hearts. This plan should address whether the doctor(s) involved with Enduring Hearts that are also participating in the research will receive any other non-monetary benefits because from their participation in the research; it should address the process or procedure the institution will use in overseeing the proposed conflict of interest mitigation plan, if applicable.

### **COVID-19 POLICY AND SUPPORT**

*Our organizations are deeply committed to supporting our scientific communities. We are sensitive to how COVID-19 is affecting the wellbeing of our grantees, and are dedicated to supporting scientists, clinicians, and academics through these unprecedented times.*

*We anticipate that COVID-19 will cause delays and changes to planned research activities, through the introduction of both professional and personal difficulties. Our team is cognizant that no standard plan will work for all grantees or apply to all situations; as such, we are willing to work with our grantees on a personal basis to discuss options and find appropriate solutions. These may include, and are not limited to: budgeting revisions, revisions to timelines and due dates of deliverables, personnel changes, shifts to remote work (e.g. computational approaches), allowances for child/dependent care or transportation, and mental health support. Please contact [grants@enduringhearts.org](mailto:grants@enduringhearts.org) to discuss how we can help with specific challenges to this RFP and [kaitlin@additionalventures.org](mailto:kaitlin@additionalventures.org) with questions for Additional Ventures ; we know that allowing flexibility means a greater chance of success.*

## REFERENCE LIST

1. Rossano JW, Singh TP, Cherikh WS, Chambers DC, Harhay MO, Hayes D, Jr., Hsich E, Khush KK, Meiser B, Potena L, Toll AE, Sadavarte A, Zuckermann A and Stehlik J. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-second pediatric heart transplantation report - 2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant*. 2019;38:1028-1041.
2. Kirklin JK. Current challenges in pediatric heart transplantation for congenital heart disease. *Curr Opin Organ Transplant*. 2015;20:577-83.
3. Vaughn GR, Jorgensen NW, Law YM, Albers EL, Hong BJ, Friedland-Little JM and Kemna MS. Outcome of antibody-mediated rejection compared to acute cellular rejection after pediatric heart transplantation. *Pediatr Transplant*. 2018;22.
4. Halloran PF, Reeve J, Aliabadi AZ, Cadeiras M, Crespo-Leiro MG, Deng M, Depasquale EC, Goekler J, Jouven X, Kim DH, Kobashigawa J, Loupy A, Macdonald P, Potena L, Zuckermann A and Parkes MD. Exploring the cardiac response to injury in heart transplant biopsies. *JCI insight*. 2018;3.