



## American Heart Association and Additional Ventures

### Collaborative Sciences Awards in Single Ventricle Heart Disease

#### Request for Proposals

##### Timeline and Key Dates:

Request for Proposals Published	Thursday, September 7, 2023
Proposal Central System opens for applicants	Thursday, September 21, 2023
Pre-proposal Deadline	Tuesday, December 19, 2023 *before 3 PM CT
Pre-proposal Review	December 2023 / January 2024
Notify Applicants Invited to Submit Full Proposals	Mid-late January 2024
Invited Full Proposal Deadline	Thursday, March 21, 2024 *before 3 PM CT
AHA-AV Peer Review	April 2024
Invited Finalists Presentations (virtual)	Late May 2024
Notifications of Awards	Early June 2024
Awards Start Date	Monday, July 1, 2024
Public Announcement of Awardees:	Summer 2024

##### Opportunity:

Together, the American Heart Association (AHA) and Additional Ventures (AV) have established this jointly funded Request for Proposals (RFP) for the **AHA/AV Collaborative Sciences Awards in Single Ventricle Heart Disease (CSAs)**. The AHA and AV invite applications to the CSAs to support multidisciplinary, multi-institutional research teams to address key knowledge gaps in the clinical sequelae of single ventricle heart disease (SV) and its treatment paradigm (i.e., the Fontan circulation).

We encourage a forward-thinking approach to research that is not constrained by long-held hypotheses and dogma, and that is conducted in an environment of trust. As such, we seek to bring together investigators who are enthusiastic about working transparently in a highly collaborative network – one that includes field experts working with investigators with no previous record of SV research, who prioritize innovation over safe bets, and who are willing to risk testing unconventional ideas.

Each individual award seeks to support between two and four research groups, and totals \$2.25M in direct research costs, spanning up to three years. The 2 to 4 lead PIs collectively comprise the Core Leadership Team of each award. As part of this award program, we will create a “Network of Networks” in which all Core Leadership Teams are provided in-kind project management support in addition to all-expense paid bi-annual meetings and other networking opportunities. We anticipate approximately 8-20 total PIs to be part of this network. **We anticipate funding five AHA/AV Collaborative Sciences Awards, for approximately \$13.2M in total costs for our collective investment.**

## Funders

The AHA was founded in 1924 and its mission is to be a relentless force for a world of longer, healthier lives. The AHA has invested more than \$5.7 billion in research, making it the largest nonprofit funder of cardiovascular and cerebrovascular research outside the federal government.

Additional Ventures (AV) aims to accelerate research progress and improve clinical care for individuals born with single ventricle heart defects so that they have a normal duration and quality of life. For these individuals, there is no cure. To date, AV has invested over \$65M in single ventricle research.

## Purpose

The AHA/AV CSAs are intended to foster innovative collaborative approaches to research projects that propose novel pairings of research teams from at least two broadly disparate disciplines – **providing up to \$2.25M in direct costs for teams of 2 to 4 labs each for projects lasting up to three years.**

We believe that the recent appreciation of SV and its current treatment paradigm as a multisystem disease state encompassing cardiac and extra-cardiac deficiencies compels a collaborative and multidisciplinary approach to significantly increase our understanding of the complications and commodities that undermine the quality and duration of life of patients.

We seek to establish a multidisciplinary network of collaborating teams who will address high-priority SV-related questions – creating a team of teams all sharing related yet unique scientific goals to move the needle in this underserved field.

Further, we seek to:

- **Support** productive, meaningful collaborations to achieve goals that supersede the expertise or capabilities of any one lab
- **Attract** diverse talent from relevant fields outside of SV and cardiovascular researchers, as well as young investigators who will infuse fresh ideas and perspectives to SV research
- **Drive** intense focus to the selected research themes to accelerate discovery
- **Connect** teams across awards to embody our values of openness and transparency as a means of accelerating outcomes and impact of research findings

The goals of this CSA are to support individual research teams that span disciplines and institutions and the collective research network under the CSA. This “Network of Networks” is designed to encourage interaction and engagement with one another across awarded teams. In this spirit, each Core Leadership Group (the 2-4 PIs on the award) will be required to attend bi-annual in person meetings (all-expense paid) to share their science, as well as to conduct strategic planning. In addition, other to-be-defined networking opportunities will be offered.

## About Single Ventricle Heart Disease:

The human heart has four distinct chambers: two atria and two ventricles. In a healthy heart, the right ventricle pumps deoxygenated blood to the lungs and the left ventricle pumps the oxygenated blood to the rest of the body. Single ventricle hearts have just one functioning ventricle, and one ventricle that is

smaller, underdeveloped, or missing a valve, resulting in functional loss of that pumping chamber. Such conditions encompass a spectrum of diagnoses including, but not limited to:

- Hypoplastic Left Heart Syndrome
- Tricuspid Atresia
- Double Inlet Left Ventricle
- Double Outlet Right Ventricle
- Single Left Ventricle
- Pulmonary Atresia with Intact Ventricular Septum
- Unbalanced Atrioventricular Canal

Despite research efforts, little is known about the underlying etiology of SV heart disease, although mounting evidence suggests that the basis is multi-factorial and is comprised of genetic, epigenetic, and/or environmental contributions. However, beyond prenatal diagnosis from routine screening, nothing yet can be done to alter the course of disease *in utero* or to inform outcomes.

Clinically, the path for such patients has changed dramatically, as fifty years ago, a diagnosis of SV was considered universally fatal. Generally, single ventricle heart defects are treated through a multi-staged surgical intervention that ends in the Fontan procedure, in which the one functional ventricle pumps oxygenated blood to the body and deoxygenated blood passively returns to the lungs without a pump.

This palliative procedure is not a cure; the Fontan circulation is correlated with long-term end-organ damage that significantly decreases patients' quality and duration of life. Complications include, but are not limited to: myocardial dysfunction, pulmonary vascular dysfunction, arrhythmias, bleeding and stroke, AV valve regurgitation and dysfunction, protein-losing enteropathy, plastic bronchitis, lymphatic obstruction, liver disease, renal failure, neurodevelopmental defects, and psycho-social challenges.

These issues often worsen over time, resulting in Fontan failure or other organ failure. Currently, heart transplantation is the only option should SV patients fail. However, this procedure faces tremendous challenges that compromise overall quality and duration of life, which is further exacerbated by the fact that many Fontan patients are referred too late and are thus ineligible for a transplant. **The ability to better prognosticate, identify, and treat SV patients with impending failure before it is too late is paramount.**

### **Research Focus and Scope:**

The survival rate post-Fontan surgery is rising, with excellent transplantation-free outcomes in recent surgical history. Yet, these survival milestones are undermined by significant comorbidities and complications in individuals with the Fontan circulation, leading to premature morbidity and mortality, and a poor quality of life.

While efforts to understand the drivers of these complications are underway, they are limited in scope and scale, reducing the ability to draw relevant conclusions about the causes, treatments, and prevention. To some degree, many of the current knowledge gaps are rooted in an incomplete understanding of the disease etiology and epidemiology. Moreover, complications are further compounded by a lack of clinical tools, including a suboptimal detection timeline, limited diagnostics, a lack of treatment options, and an insufficient interdisciplinary research lens. These solvable challenges preclude the robust and timely identification of risk factors, hinder the potential to stratify this complex

population, and limit progress on development of improvements to disease management, treatment, and therapeutic development.

The AHA/AV Collaborative Sciences Awards in Single Ventricle Heart Disease are focused on the underlying biological mechanisms and clinical science related to complications and co-morbidities of single ventricle heart disease and the post-Fontan condition to improve the lives of patients. **Teams should focus their efforts on the below, in the context of single ventricle:**

- **Fontan-Associated Liver Disease**
- **Protein Losing Enteropathy and/or Lymphatic Perturbations**
- **Ventricular Failure and/or Arrhythmias**
- **Renal Failure**
- **Mental Health and/or Neurocognitive Delay**
- **Exercise Intolerance**

In addition to understanding the drivers of the above complications, important elements to explore are factors that lead to resilience (i.e., super-Fontans). Any other outstanding ideas into focus areas not included above will be considered on a case-by-case basis.

## **Award Details**

### **Budget:**

- Direct costs: Up to \$750,000 per year in direct costs for up to three (3) years (totaling \$2.25M in direct costs).
- Indirect Costs: Up to 10% institutional indirect costs (IDC) or up to \$75,000 per year **in addition to** the direct costs.
- Allowable costs:
  - Salary and fringe benefits of the co-PIs, collaborating investigators, consultants and other personnel with faculty appointments, commensurate with percent effort.
  - Project-related expenses such as salaries for technical personnel essential to conducting the project. Supplies, equipment, computers, travel (including international travel, if needed), human subjects' recruitment and reimbursement costs, data management costs, publication costs, including open access fees, etc.

**Award Duration:** Three years, with an option to request up to 12 months no-cost extension if there is a documented and approved need. Any no-cost extension request must be reviewed and approved in advance.

**CSA “Network of Networks”:** The goal of these CSAs is not only to support individual research teams that span disciplines and institutions – it is also to create a Network of Networks for the individually awarded teams to interact and engage with one another. In this spirit, all granted teams will be required to attend bi-annual in-person meetings (all-expense paid) to share their science, as well as conduct strategic planning. In addition, other to-be-defined networking opportunities will be offered.

**Project Management:** AHA and AV will provide project management support to the teams by supporting a full-time Project Manager (PM) at one of the awarded institutions. This PM will be embedded at the

institution and will support all the awarded teams (up to 5 teams). In addition, AV will provide additional program management support by a PhD-level staff member who will provide scientific and strategic support and event management.

### **Commitment to Diversity and Inclusion**

AHA and AV will form a dedicated peer review committee to include a diverse group of reviewers with a broad range of disciplines and scientific expertise in SV disease. Awards are open to all academic and health professionals. AHA and AV encourage inclusive and diverse applicants and proposals that include women and candidates from racial and ethnic groups underrepresented in science and medicine.

Before beginning a proposal, applicants should review the information on academic disciplines, eligibility and requirements that apply to all AHA research awards at AHA Application Resources.

### **Eligibility Requirements**

#### **Team Make-Up**

- The Core Leadership of each team should consist of two to four members, including a Coordinating Co-Principal Investigator and up to three additional Co-Principal Investigators (Co-PIs).
- Teams are required to consist of Co-PIs with expertise from at least two different disciplines:
  - At least one Co-PI must work in research directly related to SV as demonstrated by prior publications and/or biosketch.
  - At least one Co-PI must work in a divergent/disparate discipline (e.g., engineering, computer science, chemistry, mathematics, psychology, health law, etc.) and/or without prior focus in cardiovascular-related research.
- Co-PIs must be independent researchers (i.e., must meet their institution's eligibility to apply for independent awards). This award is not intended for individuals in research training or fellowship positions.
- Co-PIs should adequately convey that they are of equal stature in the project. Any additional personnel included, beyond the co-PIs, are to be included as collaborating investigators or consultants.
- While no minimum percentage effort is specified, the Co-PIs must demonstrate and document that adequate time will be devoted to ensuring the successful completion of the proposed project.
- AHA and AV have a strong commitment to supporting the next generation of scientists. While this award does not require early or mid-career investigators to be included as Core Leadership, we **strongly encourage** the inclusion of early or mid-career PIs as Core Leadership or as broader collaborators to the award.

#### **Credentials**

- Co-PIs must each hold a faculty/staff appointment.
- Co-PIs may be from the same institution, or from different institutions.
- Each Co-PI must hold an MD, PhD, DO, or equivalent post-baccalaureate terminal degree.

- One of the Co-PIs' institutions must be designated as the U.S. institution of record, agreeing to sponsor the application and accept award payments, and ensure that annual progress reports and expenditure reports are submitted to AHA and will be shared with AV.
  - Eligible Sponsoring Institution: Please refer to: <https://professional.heart.org/en/research-programs/application-resources> "*Is my institution eligible for AHA funding?*" under "General Guidelines."
- Citizenship: Please refer to: <https://professional.heart.org/en/research-programs/application-resources> "*Which visa types does the AHA accept?*" under "General Guidelines."

### Other Requirements

- All Co-PIs who are invited to submit a **full application** must be (or become) AHA Professional Members prior to submitting. (Note: this requirement does not apply to collaborating investigators, consultants, fellows or others who are not Co-PIs). Visit: <https://professional.heart.org/en/partners>
- Applicants may be a Co-PI on only one CSA proposal.

### Concurrent Funding

- CSA awardees may also apply for or hold another AHA or AV research award, if there is no overlap with this project (e.g., Established Investigator Award, Innovative Project Award, Transformational Project Award, AHA Institutional Research Enhancement Award, Career Development Award, EH direct award, EH-AHA Collaborative Sciences Award, Single Ventricle Research Fund, Catalyst to Independence Program, Expansion Award) and may be the program director or sponsor on an AHA Institutional Undergraduate Program award.
- AHA-funded awardees of a Strategically-focused Research Network or a Health Equity Research Network may hold individual AHA awards, including a CSA.
- Awards are not intended to supplement or duplicate currently funded work. Rather, it is expected that submitted applications will describe projects that are clearly distinct from ongoing research activities. Minor variations from existing research projects are not sufficient to constitute independent and distinct projects.

### Application Process

There are three stages for this funding opportunity: (1) pre-proposal (letter of intent), (2) invited full proposal, and (3) finalist presentation.

Pre-proposals are due no later than **Tuesday, December 19, 2023, before 3 p.m. Central Time**. Following evaluation, teams selected to submit full proposals will be notified in mid-late January, 2024. Invited full proposals are due no later than Thursday, March 21, 2024, before 3 p.m. Central Time. All submissions – pre-proposal and full proposal – require a signature from a designated institutional representative. Finalists will present virtually to AHA/AV selected reviewers in late-May 2024. Final funding decisions are anticipated by early June 2024 and awardees will be notified by June 30, 2024.

All applications must be completed and submitted through the Proposal Central online portal. We strongly recommend that applicants familiarize themselves with the online portal in advance of any deadlines. Exceptions will not be made for technical difficulties. For detailed application instructions, please visit the online portal for more information.

As a reminder, AHA and AV are collaborating to implement this RFP. As such, applicants may hear from AHA or AV staff with follow-up needs or questions pertaining to their submissions.

### **Pre-proposal Instructions**

A brief pre-proposal (referred to as Letter of Intent in Proposal Central) is required for funding consideration (no more than five [5] pages), to ensure responsiveness to the novel, collaborative nature of this program. Pre-proposals are to be prepared according to the template provided and submitted for review via Proposal Central.

The novel relationship and proposed collaboration of investigators from at least two widely disparate disciplines, alongside overall scientific fit, will be given the most weight in evaluating the pre-proposal to determine which teams will be invited to submit full applications.

Applicants must use the template available on the online portal. The pre-proposal consists of the following sections:

#### **Project Description**

- Project title
- Project summary (100 words maximum)
- Scientific goals and strategy (500 words maximum)
- Statement of impact and alignment with CSA Initiative goals (100 words maximum)

#### **Team Summary**

- List of Team investigators
- Description of each investigator's role on the project (100 words maximum per investigator)
- Description of the collective expertise and resources that the investigators bring to the Team
- Collaboration history of each investigator including reference to past intra-Team collaboration where relevant (review the pre-proposal template for specific parameters)

### **PRE-PROPOSAL (LETTERS OF INTENT) REQUIREMENTS AND INSTRUCTIONS:**

Please review the instructions, objectives, and requirements before you begin your Pre-proposal for submission in ProposalCentral. Please refer to general AHA Application Instructions for additional instructions on how to set up an account. **Applications will only be accepted through ProposalCentral.** All submissions require a signature from a designated institutional representative.

The initiating Co-PI will upload the pre-proposal (five pages max; see Pre-Proposal Template) describing an innovative, collaborative approach that incorporates a novel grouping of investigators from at least two widely disparate disciplines and/or areas of expertise. The pre-proposal must focus on the collaborative relationship of the investigators, such that the scientific objectives cannot be achieved without the efforts of at least two co-PIs and their respective disciplines and expertise. The combination and integration of studies may be inclusive of basic, clinical, population, and/or translational research.

Applicants to the Collaborative Sciences Award program will submit one application jointly.

- Applicants must determine which of their respective institutions will administer the project (if applicants are from more than one institution). A Co-PI from the selected institution is to be selected as the Coordinating Co-PI and should initiate the application process.
- The Co-PI who initiates the application in ProposalCentral must add the names of the other co-PI(s) in the application. The applicant team is limited to four co-PIs.
- Each Co-PI will receive an email invitation to join the application. This email is specific to the recipient and should not be shared. A co-PI who does not receive an email from ProposalCentral should call 214-360-6107 (option 1).
- Once joined to the application, each Co-PI must review and update their own Advanced Profile and upload a biosketch. Each biosketch has a 5-page limit.

Pre-proposals are due by **3 p.m. Central Time on Tuesday, December 19, 2023**. Note: The Proposal Central system will shut down at 3 p.m. Central Time. Early submission is encouraged. The applicant has the final responsibility for submitting the completed pre-proposal.

### **Full Proposal Instructions**

Full proposal submissions are **by invitation only**. The invited proposal must expand upon the pre-proposal, detailing how the research directly relates to complications and comorbidities of single ventricle heart disease, and must include the preliminary evidence supporting the proposal scientific objectives and specific aims.

Additional instructions for online submission will be provided to select applicants by mid-late January 2024. Full proposals are **due no later than Thursday, March 21, 2024**, before 3 p.m. Central Time.

The Proposal consists of the following sections:

#### **Project Overview (all PC fields)**

- Project title
- Lay summary
- Technical abstract
- Thematic Fit and Impact Statement
- List of all relevant Personnel

#### **Scientific Narrative (7 pg max - Upload)**

- Specific Aims (1 pg only)
- Rationale and Preliminary Data
- Research Tools, Models, and Resources
- Study Plan
- Power Calculations and Statistical Analysis Plan (if necessary)

#### **Literature Cited (upload)**

#### **Feasibility Narrative (1 upload)**



- Project Timeline and Milestones (1 pg)
- Workflow Schematic (1 pg)
- Team Communication Plan

**Budget Narrative (template provided)**

- Budget Justification
- Other Funding Sources

**Supporting Materials**

- Additional Figures (1 pg max)
- Relevant Articles (up to 4)

**Review and Selection Process**

We anticipate awarding five research teams an AHA/AV Collaborative Sciences Award, totaling approximately \$12M in direct costs for our collective investment. Decision-making will be guided by expert peer review; however, the joint AHA/AV Executive Leadership reserves the right to make ultimate final funding decisions on any application.

Pre-proposals to the CSA will be assigned to a group of multidisciplinary reviewers and may be reviewed by someone working in a related area and/or experts directly related to an applicant’s science area. The pre-proposal should be appropriate for reviewers who have a broad knowledge of the scientific area. To expedite the pre-proposal review process, written critiques will **not** be provided to applicants who are not invited to the full application stage.

Full proposals will be reviewed by external Peer Reviewers comprised of multidisciplinary scientists who are familiar with our program goals and have deep expertise in our program’s scientific focus areas, as well as methods proposed in the grant applications. As this RFP intends to bring diverse disciplines together, an equally diverse peer review committee will be essential to this process. Feedback will be provided for full proposals that are and are not selected for funding.

Selection of awardees will be based on the following criteria:

- **Quality** of the proposal, expertise, and capacity of the collaborative group for addressing the proposed project. There should be evidence of synergy and substantive contributions from all assembled members of the research team – i.e., not simply a collection of individual projects.
- **Potential impact** of the research questions being addressed in the application.
- **Focus on single ventricle** should be central, as the proposed work should have clear disease context to the complications and comorbidities of SV disease.
- **Degree** to which the proposed work brings in new ideas to the field and stimulates potential new avenues of investigation.
- **Demonstrated collaborative potential** of the proposed Team as evidenced by co-authorships, past collaborations among at least two (2) members of the Team, as well as relevant contributions to other successful research collaborations in the recent past.

- **Leadership capacity of the Coordinating Lead PI.** This investigator's vision, leadership qualities, willingness to collaborate, and demonstrated ability to bring together and lead a multidisciplinary team of experts to a successful conclusion will be a critical factor.

Note: Contacting peer reviewers concerning your proposal is deemed a form of scientific misconduct and will result in the removal of your proposal from funding consideration and institutional notification of ethical concerns.