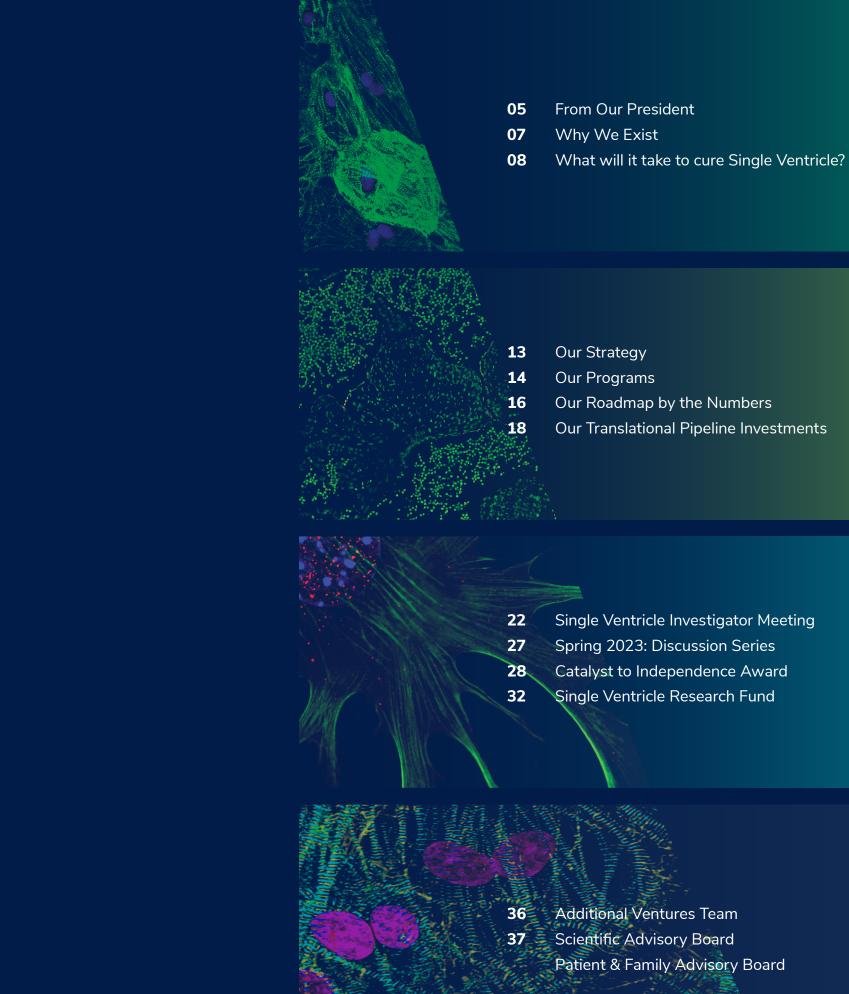


**Connecting the Dots:** Impactful Initiatives and Investments in Single Ventricle Research

Biomedical Research Annual Report July 2022 - June 2023



### Why Single Ventricle?

How are we Solving Single Ventricle?

Highlights July 2022 – June 2023



Image: Troponin staining of cardiac cells, captured by Adam Feinberg's Lab at Carnegie Mellon University

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# Why Single Ventricle?

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# "

Through coordinated strategic and interdisciplinary work, we're connecting the dots, creating new junctions, and activating novel pathways to strengthen community in this space."

#### WHY SINGLE VENTRICLE?

## **From Our President**

By connecting the right people, projects, and processes, we can accelerate scientific progress – amplifying our impact and expediting our path towards curative solutions for single ventricle heart disease.

When we started our venture in the single ventricle space over three years ago, we observed a nascent field in its infancy, deserving of robust resource development and investment aimed at tackling critical gaps in our understanding of single ventricle causes, risks, and outcomes. In order to accelerate progress towards better treatments and functional cures, it was clear that this space required a driving force to unify segmented disciplines, forge connections between siloed investigators, and streamline processes to enable scientific discovery in single ventricle research.

These concerted efforts are changing the trajectory of the space, with moments that exceeded expectations Through coordinated strategic and interdisciplinary work, we're connecting the dots, creating new junctions, and and results that surpassed our greatest imaginings. I'm incredibly proud of the progress that our community has activating novel pathways to strengthen community in this space. In the past year, we have reached new made so far and immensely grateful for the individuals that milestones, engaged with new partners, and deepened our devote their time, resources, and expertise in service of commitment to advancing scientific and clinical research our shared mission. Together, we are affecting meaningful centered around single ventricle heart disease. change for the patients and families impacted by single ventricle heart disease - and we can't thank you enough Our third full year as a foundation brought many for going on this journey with us.

Our third full year as a foundation brought many opportunities for firsts – convening our first in-person Single Ventricle Investigator Meeting with over 170 attendees; hosting our first investigator-driven open call for the Single Ventricle Research Fund with 15 newly awarded teams; and supporting the next generation of scientists with the first cohort of the Catalyst to Independence Award recipients. We're inspired to aim even higher, and we will continue to chase bold ideas with creative, nimble, and innovative programs that push the envelope of venture philanthropy. In our next year, we're launching new initiatives that will generate foundational resources to scaffold our understanding of single ventricle origins and outcomes, support collaborative team science projects anchored in establishing predictive and preventative care, and galvanize our scientific community with opportunities for engagement, intersection, and connection.

Sincerely,

Erin Hoffmann President and Co-Founder, Additional Ventures



Zachary, 7 years old, PA-IVS,



Holsten, 19 months old, HLHS with ostium primum ASD





Parker, 20 months old, HLHS



Bryce, 14 months old, Tricuspid atresia, hypoplastic

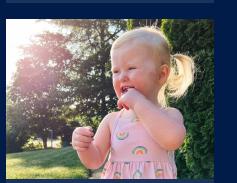


Tricuspid atresia, hypoplastic right heart





Dieter, 4 years old, HLHS



Palmer, 2 years old, PA-IVS

WHY SINGLE VENTRICLE?

## Why We Exist

### We are on a singular mission to accelerate research and clinical discovery in single ventricle heart disease.

Single ventricle heart disease includes a spectrum of complex congenital heart defects characterized by structural or functional loss of one ventricle, including hypoplastic left heart syndrome (HLHS), tricuspid atresia, and pulmonary atresia with an intact ventricular system (PA-IVS). These defects require invasive interventions and long-term care, with staggering financial and economic impacts.



#### There is no cure for single ventricle heart defects.

Most individuals born with single ventricle heart defects undergo two to three palliative surgeries within the first years of life, culminating in the Fontan operation. In 2017, there were an estimated 70,000 individuals worldwide living with Fontan circulation, which uses one functional ventricle to pump oxygenated blood to the body and relies on passive exchange to return deoxygenated blood to the lungs. While lifesaving, the Fontan circulation does not create a "normal" heart or circulatory system and thus is not considered a cure.



#### The current treatment paradigm is not enough.

While current care paradigm has drastically improved life expectancy for many single ventricle patients, most still experience significant co-morbidities and complications that worsen over time and lead to reduced quality and duration of life. Overworked single ventricles in Fontan circulation are often compounded by abnormalities in other organs that have an increased likelihood of failure, ultimately leading to Fontan Failure, heart transplant, or death. Currently, it is not possible to predict which complications will occur or when, nor identify who is at risk of developing each complication.







#### **Curative solutions are** achievable when the right catalysts come together.

Patients and families deserve more. As an impact-focused organization, we're uniquely positioned to accelerate progress in single ventricle and pediatric cardiology broadly through hands-on, holistic support like investing in foundational resources and high-risk studies across a broad portfolio, and developing creative environments fueled by integrated multidisciplinary and team-based approaches. We're disrupting the traditional research space by re-imagining how science is done and funded - and we believe we can illuminate a functional cure for single ventricle.

WHY SINGLE VENTRICLE?

## What will it take to cure Single Ventricle?

Single ventricle heart disease includes a spectrum of complex congenital heart defects with unknown causes and disparate outcomes. This complex challenge requires a comprehensive solution. Our living Research Roadmap summarizes four interconnected thematic areas critical to improving our understanding and treatment of single ventricle heart disease.

With a scientific community poised to act and a defined roadmap for action, curative solutions for single ventricle are achievable.

#### **Understand Single Ventricle Origins**

- Deep Phenotype-Genotype Analysis
- Biological Mechanisms Underlying Single Ventricle
- Environmental Risk Factors of Single Ventricle

Origins

Cures

#### Introduce **Functional Cures**

- Bionic & Mechanical Approaches
- In Utero Intervention
- Transplant Availability & Decision Making

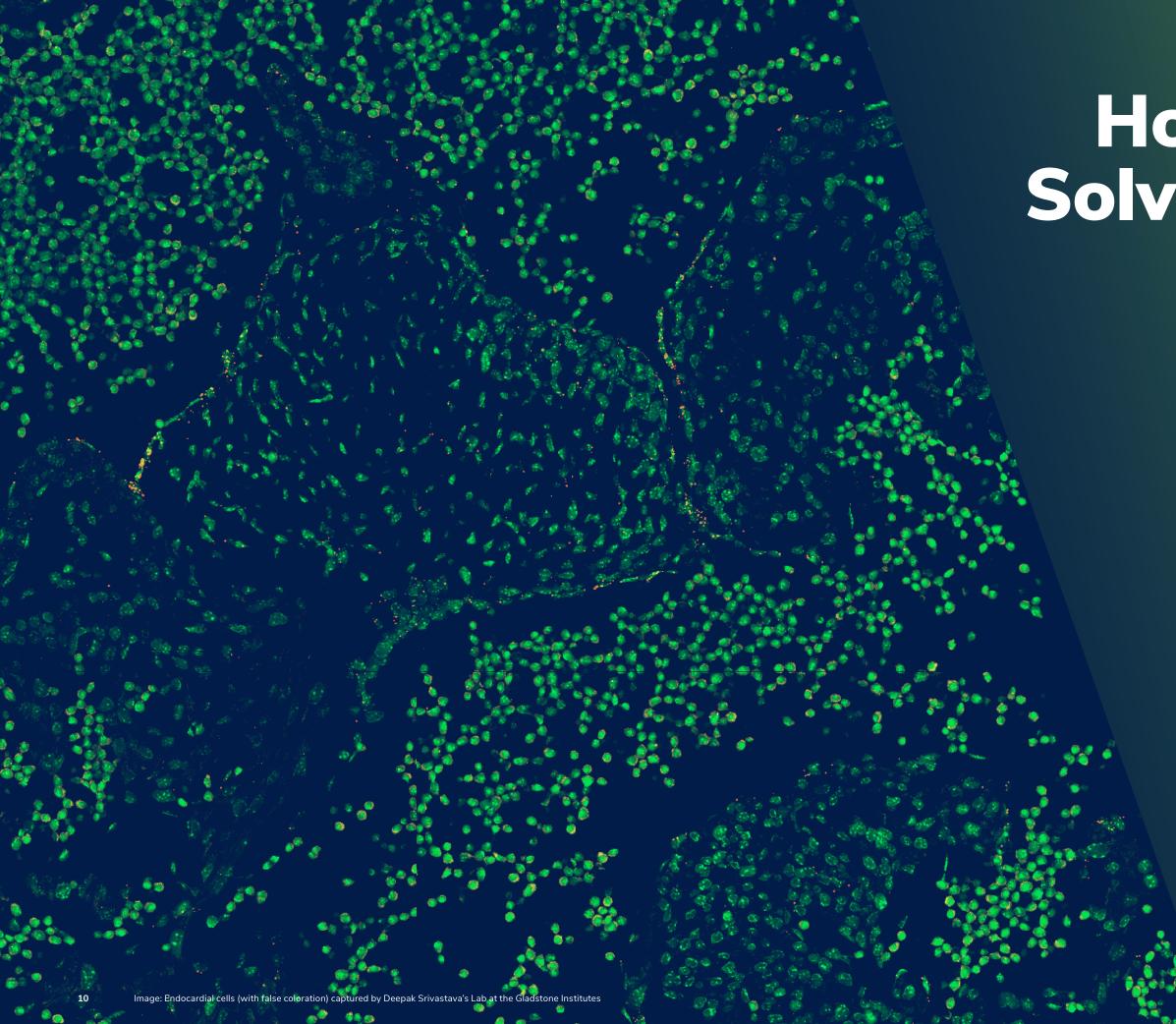
### **Define Biological Mechanisms of Outcomes**

- Etiology of Outcomes
- Factors Leading to Resilience
- Risk Factors of Outcomes: Modifiable & Non-Genetic



#### **Establish Predictive** and Preventative Care

- Biomarkers of End-Organ Function
- Therapeutics for Sequelae
- Non-Invasive Interventions



# How are We Solving Single Ventricle?

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## **Our Strategy**

We believe strategy should befit the challenge at hand: single ventricle is a complex, multi-dimensional series of conditions, requiring a complementary multi-pronged approach. Our work is grounded by an integrated 4-part strategy to drive research and clinical innovation in single ventricle heart disease so that all patients, regardless of their age, stage, or anatomy, live a long and healthy life.

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I always said when she was born that the chance of further advances in care for single ventricles patients occurring during her lifetime, that could add to her longevity, is great. I hope medical advances will give her the opportunity to live a long and fulfilling life."

- DEBRA, MOTHER TO A SINGLE VENTRICLE DAUGHTER

#### **Making Targeted** Investments

We support academic and clinical investigators through impactfocused grant programs and invest in innovative companies developing new technologies.

#### Supporting **Team Science**

We employ creative models of coordinated team science that combine expertise, skills, and most importantly, vision to create a sum that is greater than its parts.

#### **Building Foundational** Resources

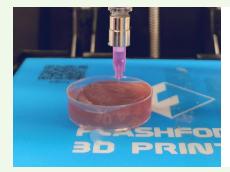
We generate comprehensive, openaccess resources for our scientific and clinical communities by supporting, building, and integrating datasets.

### Creating Community

We convene a series of events that enable learning, collaboration, and innovation across disciplines, fields, and networks in the single ventricle research space.

### **Our Strategy in Action: Our Programs**

Our team leads several key initiatives that are fueled by our strategy and in service of our mission.



#### **Cures Collaborative**

A multidisciplinary 9-person team working together to develop a regenerative medicine solution that can improve cardiac function and reduce poor outcomes associated with single ventricle heart disease.



#### **Project Singular**

A comprehensive genetic and phenotypic repository launching in 2024 that aims to identify and understand causes of single ventricle heart defects and related sequelae.



#### **Single Ventricle Investigator Meeting**

A biennial scientific conference open to researchers investigating single ventricle origins, outcomes, care, and cures. This year, we hosted our first in-person conference with over 170 attendees, and 120 speakers.



#### **Speaker Series**

A virtual platform that connects investigators across diverse topics and fosters creative new avenues of thinking and discovery through dynamic research presentations and interactive discussion.









#### **Single Ventricle Research Fund**

A 3-year, \$600k annual research award program that provides foundational support for research with relevance to single ventricle. This year, we awarded 15 teams, with a total investment of \$10M.

#### **Expansion Award**

A 1-year, \$50k annual research award program that enables teams to explore bold, new single ventricle-focused approaches and directions inspired by their current work. This year, we funded 12 projects, with a total investment of \$600k.

#### **Catalyst to Independence Award**

A 6-year, \$1.2M annual research award program supporting senior-level postdocs through transition to early career faculty. This year, we supported 3 investigators, with a total investment of \$1.5M.

#### **Strategic Partnerships**

A series of opportunities to expand, integrate, and bolster the single ventricle research ecosystem through engagement with partner organizations with complementary expertise, and resources.

## **Our Progress: Roadmap by the Numbers**

We take a targeted approach to seed research and development across our portfolio and bring our scientific community closer to finding curative solutions for single ventricle. Since the inception of Additional Ventures in 2020, we have committed over \$62M in funding, all guided by our Research Roadmap.



## "

The research that is going on gives us hope - there are some pretty exciting studies that seem to be right on the cusp of huge breakthroughs. This focus on improving longevity is exciting and we monitor it constantly, hoping to see those breakthroughs come to fruition!"

- MORGAN, MOTHER TO A SINGLE VENTRICLE SON

## **Our Investments Across** the Translational Pipeline

Moving discoveries from the bench to the bedside is essential to achieving better outcomes for individuals with single ventricle physiology. Over the last year, we've supported the translation of discoveries in single ventricle research by funding projects focused on bringing products to the next stage of development.



HOW ARE WE SOLVING SINGLE VENTRICLE?

### Where are we now?

From prognostic biomarkers and therapeutics to Fontan assist devices and 3D printing technologies, we are dedicated to improving and expanding treatment options for single ventricle patients.

#### Here are six examples of our investments across the translational pipeline.

#### **Discovery**

#### **1. Prognostic Biomarkers**

Dr. Ari Cedar's group at Johns Hopkins University is investigating biological pathways involved in Fontan Failure, including discovery of biomarkers to assess risk stratification, predict treatment response, and enable individualized care for patients with Fontan circulation.

#### **Proof-of-Concept**

#### 3. Fontan Assist Devices

We're supporting efforts to create two novel Fontan Assist Devices: 1. Our Cures Collaborative team is developing an external self-powered pump made of human cells. 2. Dr. Iki Adachi's group at Texas Children's Hospital is developing a subpulmonary assist device with a magnetically levitated pump.

#### **Preclinical & Clinical Trials**

#### 5. Donor Heart Availability

Drs. Jennifer Conway and Darren Freed at Stollery Children's Hospital are developing ex situ heart perfusion devices to increase the quantity and quality of donor hearts used in pediatric populations.

#### 2. Druggable Targets

Dr. Sushma Reddy's group at Stanford University identified circulating biomarker profiles in single ventricle patients that can be used to predict heart failure. Now, they're developing novel therapies for druggable targets that will preserve heart function.

#### 4. 3D Bioprinting Technologies

FluidForm is a regenerative medicine company that uses proprietary Freeform Reversible Embedding of Suspended Hydrogels (FRESH) technology to create human tissue for drug discovery, surgical repair, and organ transplant. In 2023, we invested \$1.5M to kickstart their efforts.

#### 6. Noninvasive Interventions

Dr. Kenneth Brady at Lurie Children's Hospital is testing a novel, noninvasive methodology to measure and proactively manage cerebral hypotension exposure during surgery and improve neurodevelopmental outcomes in single ventricle patients.

Image: Beige fibroblast captured by Chris Breuer's Lab at Nationwide Children's Hospital

# Highlights July 2022 June 2023

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HIGHLIGHTS

### **Single Ventricle Investigator Meeting**

At our first in-person, open event, we convened over 170 attendees across disciplines and connected diverse investigators across single ventricle research. With 50+ plenary presentations, 40+ poster presentations, and 16 breakout sessions, the Single Ventricle Investigator Meeting enabled researchers to exchange ideas, discuss challenges, and catalyze cross-cutting approaches. And the outcome was electric.



## ADDITIONAL VENTURES SINGLE VENTRICLE ESTIGATOR MEETING 2022

#### HIGHLIGHTS

### SVIM 2022: Galvanizing the Single Ventricle Community

The 2022 Single Ventricle Investigator Meeting (SVIM) focused on fundamental scientific discoveries that address critical knowledge gaps and lay the foundation for the development of functional cures for single ventricle heart disease.







At SVIM 2022, we illuminated the essential role of basic research, a discipline that explores underlying principles of developmental biology, pathophysiology, modeling, bioengineering, clinical medicine, and more to create a bedrock for scientific progress.



170+ Attendees **120+ Speakers Across Disciplines** 





### SVIM 2022: Key Topic Areas





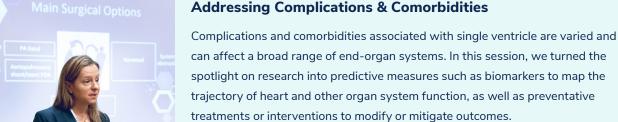
#### Understanding Single Ventricle Etiology

The genetic basis of single ventricle heart disease is mostly unknown, and molecular mechanisms underlying single ventricle heart defects are not well understood. In this session, we heard from researchers investigating origins of single ventricle defects, including genetic and non-genetic elements such as epigenetic, hemodynamic, and environmental factors that impact development.

#### **Defining Biological Mechanisms of Outcomes**

Many guestions remain about what drives onset of various complications and comorbidities in single ventricle patients. Here, we took a deeper dive into what's known about the etiology of outcomes, along with modifiable and nongenetic risk factors of outcomes.





### **Developing Functional Cures**

Here, we discussed progress and challenges in novel approaches to functionally cure patients prior to palliation or after the Fontan procedure, including regenerative medicine solutions to heal or repair an injured heart, mechanical and biological devices to serve as a conduit for flow, and tissue engineering approaches to create de novo tissues, ventricles, and even entire organs.



#### **Optimizing Transplant Outcomes**

Currently, heart transplantation is the closest option to a functional cure for single ventricle; however, this procedure faces tremendous challenges that limit feasibility and compromise the overall quality and duration of life. We partnered with Enduring Hearts to shed light on challenges and insights into transplant availability, longevity, and timing.

#### HIGHLIGHTS

### **SVIM 2022: Highlighting Patient & Family Perspectives**

SVIM 2022 was tailored specifically for researchers but we made sure that the faces and voices of the single ventricle patient and family communities were not only heard, but highlighted throughout the conference.





We were honored to have over 50+ single ventricle patients and their family members generously share their photos and testimonials with us for use in posters and slides, which served as an important reminder of the gravity and urgency of our collective work in this space, and an incredible inspiration for our investigators.

"I dream of the day they can live healthier lives filled with more quality than ever thought possible" Karissa, Mom Maci Forever 5 years old, complex HLHS



#### HIGHLIGHTS

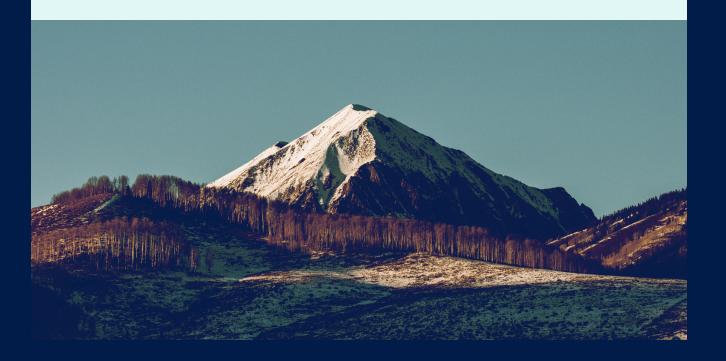
### What's Next for SVIM?

It's impossible to quantitate the full scope of outcomes that will stem from SVIM 2022, but it's clear that opportunities for interdisciplinary connection enlighten and strengthen our growing community.

The Single Ventricle Investigator Meeting will reconvene in Denver, CO on October 17-19, 2024.



Denver, CO Oct 17-19

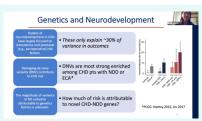


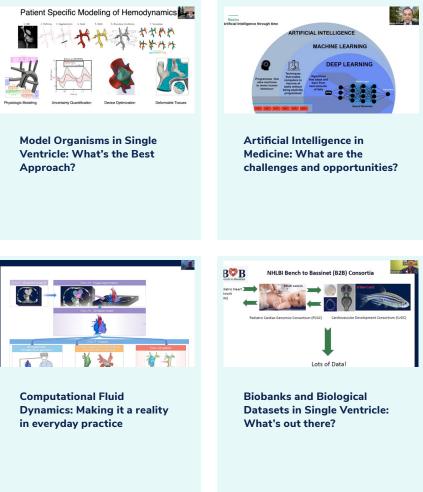
#### **HIGHLIGHTS**

## **Spring 2023: Discussion Series on** Single Ventricle Biology, Care, and Cures

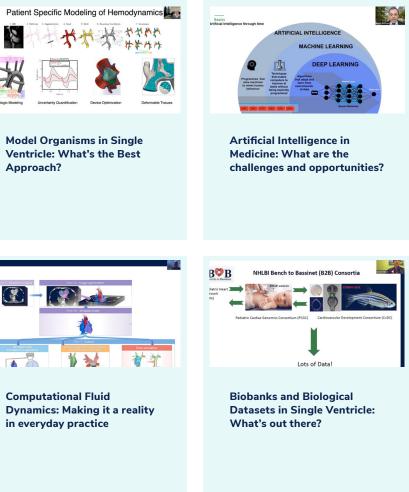
On the heels of SVIM 2022, we hosted a 6-week virtual Discussion Series on Single Ventricle Biology, Care, and Cures that built upon the topics and conversations that were started at SVIM – and brought these discussions to an even larger audience.

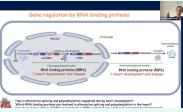
### **Discussion Series Topics:**





**Brain Health Outcomes** Among Individuals with Single Ventricle Heart **Disease Across the Lifespan** 





**New Frontiers in Single** 

Ventricle Gene Regulation



HIGHLIGHTS

### **Catalyst to Independence Award**

The future of scientific research depends on engaging, supporting, and promoting the next generation of early career scientists, and the single ventricle field is no exception.

The Catalyst to Independence Award is like a shortcut through a forest – without it, the journey to tenure-track faculty is unmapped and full of pitfalls.

The transition from postdoctoral fellow to tenure-track faculty is a bottleneck where less than a quarter of postdocs ultimately go on to lead their own research labs. Thus, we created a new pathway to address this critical career juncture, foster creative, talented, and promising single ventricle postdoctoral researchers, and jumpstart their career transition to independent faculty researchers.

The Catalyst to Independence Award is the only program of its type dedicated to advancing early career single ventricle scientists and creating new labs focused in this field. Through a combination of support in professional development, community building, and networking, as well as generous research funds, our Catalyst Awardees are addressing some of the biggest questions in the single ventricle field.

The inaugural Catalyst to Independence Award cycle received 26 applicants, from which **3 stellar postdoctoral researchers were selected as the first class of Catalyst Award Fellows.** Each award recipient will receive up to \$1.2M USD covering up to 3 years of support during postdoctoral training and an additional 3 years of support as new independent tenure-track faculty establishing their own research labs.



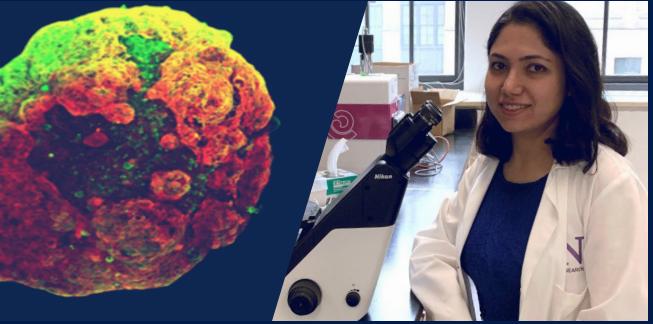
### Lay Teng Ang, PhD

Catalyst to Independence Award Recipient (2022)

Dr. Lay Teng Ang is a Siebel Scholar and Instructor for the Institute for Stem Cell Biology and Regenerative Medicine at Stanford University. As the mentee of Dr. Philip Beachy, her research seeks to overcome major challenges associated with utilizing regenerative tissue as a clinical therapy for single ventricle heart disease. Here, she will create a co-culture of endothelial, smooth muscle, and myocardial cells to build a vascularized heart organoid model. This platform will overcome a big bottleneck in cardiovascular tissue engineering by enhancing cell viability, further advancing our ability to manufacture cardiac tissues.

Engineered 3D heart tissues have the potential to provide "functional cures" for children with Single Ventricle Disease. However, a major obstacle is the difficulty of ensuring that nutrients reach cells deep within these engineered heart tissues. .... The Catalyst Award will also be instrumental in my transition to a faculty position. As a Catalyst Award fellow, I am excited to contribute scientifically and professionally to the Single Ventricle Disease community."

#### ) Recipient (2022)



#### Hananeh Fonoudi, PhD

**Catalyst to Independence Award Recipient (2022)** 

Dr. Hananeh Fonoudi is a Postdoctoral Research Fellow at Northwestern University. Under the mentorship of Dr. Paul Burridge, Dr. Fonoudi will expand our understanding of Hypoplastic Left Heart Syndrome (HLHS) pathology. She will use HLHS patient-derived induced pluripotent stem cells to create 3D organoids. By interrogating these organoids through imaging, genetic and cellular analyses, and high throughput drug screening, she will transform our ability to model HLHS and at the same time generate a new platform for target-based drug discovery.

Moreover, receiving this award has enabled me to join a larger team dedicated to addressing the challenges surrounding single ventricle disease, fostering tremendous collaboration and discussion with field experts. Ultimately, this recognition provides a unique platform for me to make lasting contributions in the field of single ventricle disease, paving the way for a successful and impactful career trajectory."



**Catalyst to Independence Award Recipient (2022)** 

Dr. Sanjeev Ranade is currently a Staff Research Scientist at the Gladstone Institute, but will be starting his own independent lab at Sanford Burnham Prebys in January, 2024. As the mentee of Dr. Deepak Srivastava, Dr. Ranade will investigate how the misregulation of neural crest cells contributes to single ventricle etiology. Leveraging novel mouse models and human pluripotent stem cells, his work will uncover gene regulatory programs and spatiotemporal origins of impaired outflow tract development – ultimately adding to our understanding of regulatory mechanisms governing progenitor cell differentiation in normal cardiogenesis and in single ventricle.

I have directly experienced how the Catalyst Award can provide a turbo-charge boost during the transition to independent research phase. I recently finished an exhausting but exhilarating winter of faculty applications and interviews and saw how the Catalyst Award was a tangible way to de-risk aspects of my application.



HIGHLIGHTS

### **Single Ventricle Research Fund**

Our flagship SVRF award program supports fundamental research critical for moving the field forwards and improving care for those with single ventricle.

In our third cycle of SVRF, we hosted an open call and welcomed any research efforts aligned within the focus areas of our Research Roadmap, allowing us to select from the most promising, additive projects, regardless of field or scientific discipline.

Our 15 newly funded teams span fields, focus areas, expertise, career stages, and geography: our most diverse cohort yet! Through this year's SVRF program, we've invested \$3.9M in early career faculty and \$2.6M in principal investigators that identify as historically underrepresented, seeding a vibrant and dynamic collective primed to accelerate scientific progress in the single ventricle space.

This group of SVRF awardees joins a larger community of over 50 teams that are dedicated to solving some of the most pressing questions in single ventricle causes, care, and cures. With an investment of nearly \$9.9M this year alone, and a total investment of over \$30M since the program's inception, the SVRF program is our largest research award program to date – and a driving force in supporting foundational research in single ventricle heart disease.





We aim to be true partners with our investigators - offering hightouch, personalized, and responsive feedback throughout the award processes. Our SVRF post-award management process features progress report discussions wherein our awardees meet (virtually!) with our Scientific Advisory Board and members of our research community to share progress and annual updates on their awards. In lieu of collecting traditional written reports, we host these lab meeting-style calls to build community, inspire new avenues of thinking, provide support, and stay abreast of research in the field in real time.

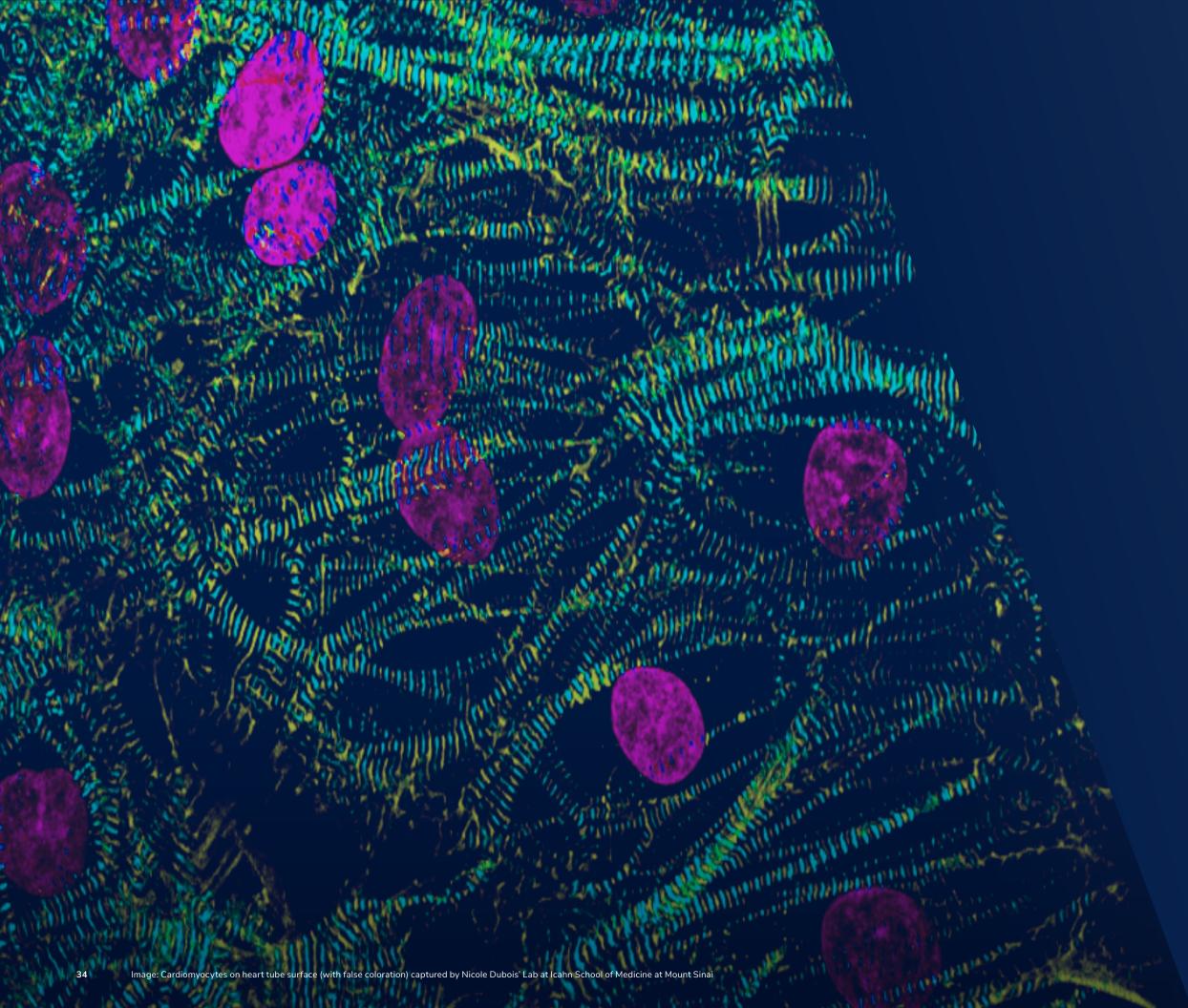






captured by Sean Wu's Lab at Stanford University, Vasanth Vedantham's Lab at UCSF

Clockwise from top left: Vasanth Vedantham's Lab at UCSF, Developing heart mouse embryo captured by Neil Chi's Lab at UCSD, Jian Shu Lab at MGH and Harvard Medical School, Matthew Alonzo of Mingtao Zhao's Lab at Nationwide Children's Hospital, Conduction system in the developing heart



# Our Team

### **Additional Ventures Team**



Erin Hoffmann President and Founder



Mike Schroepfer Founder



Kaitlin Davis, PhD Senior Program Manager, Research and Grants



**Taylor MacLean** Program Manager, Project Singular



**Diane Pickles** Program Director, Project Singular



Elizabeth Ewen, PhD Senior Program Manager, Project Singular

## "

With the right people, structure, and support, we can work together collaboratively to make unprecedented advances in single ventricle research. We're so grateful to the dedicated scientists and clinicians that share our mission and devote their work to this space."

- ERIN HOFFMANN, PRESIDENT & CO-FOUNDER OF ADDITIONAL VENTURES



Kirstie Keller, PhD Vice President of Programs



Courtney Steger, PhD Program Manager, Scientific and Community Engagement



Daniel Radecki, PhD Program Officer, Research and Grants







Anthony B. Firulli, PhD

Endowed Professor of Pediatrics, Indiana University School of Medicine

Alison Marsden, PhD



Anthony Philippakis, MD, PhD



Rahul Rathod, MD, MBA

Chief Data Officer, Institute Scientist, Broad Institute of MIT and Harvard

Medical School

### **Patient & Family Advisory Board**





B. Arman Aksoy, PhD Father to a Single Ventricle Daughter

Computational Biologist

Writer and Filmmaker

**Bi-Ventricular Repair** 

Post-Fontan Single Ventricle,

Jameson Rich





Professor of Pediatrics – Cardiology and Bioengineering, Stanford University



#### Shelley Miyamoto, MD

Jack Cooper Millisor Chair in Pediatric Heart Disease. Professor of Pediatrics. Director. Cardiomyopathy Program, University of Colorado and Children's Hospital Colorado



Associate Cardiologist-in-Chief and Director of the Single Ventricle Program and the Fontan Clinic at Boston Clinic at Boston Children's Hospital, Associate Professor at Harvard



#### Deepak Srivastava, MD

President, Gladstone Institutes Professor, University of California, San Francisco



Tawanna Williams, CPC Mother to a Post-Heart Transplant Single Ventricle Daughter

Owner/Lead DEI Consultant, Race Equity Solutions, Podcast Creator/ Host, Broken Open



Taylor Houlihan, MD Single Ventricle Fontan Patient

Pediatric Resident



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