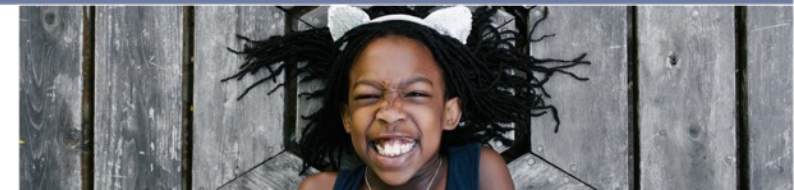


# Translational Research Program annual report

December 2022



# Introduction: A message from Director Mustafa Sahin, MD, PhD



## Momentum growing: The Translational Research Program

The last two years have put an enormous strain on the academic research community here in Boston, across the United States and around the world. The COVID-19 pandemic still presents myriad challenges to academic hospitals even as a growing sense of normalcy returns to much of society.

People still fall ill, breakthrough cases still occur and research labs still struggle with staffing and supply shortages. It is remarkable, then, that even with all these headwinds, the **Translational Research Program (TRP)** is excelling.

[LEARN MORE »](#)

## TIS awardees flourishing

Our Translational Investigator Services (TIS) awardees continue to bring exciting new therapies and therapeutic platforms to market. **Martha Murray, MD**, has secured vital Series A funding for her startup company, Miach Orthopaedics, to build the collagen scaffolds she designed that will revolutionize treating ACL tears. **Richard Malley, MD**, recently sold his startup company, Affinivax, to GSK plc (formerly GlaxoSmithKline), which promises to use his innovative vaccine development platform to fight treatment-resistant diseases across the globe.

The Boston Investment Conference continues to highlight the work of TIS members such as 2021 conference awardee **Ann Poduri, MD, MPH**. Dr. Poduri is focused on eliminating seizures in newborns and keeping children from developing epilepsy.

*Photo: Ann Poduri, MD, MPH*







## TIS awardees flourishing (continued)

This year the conference will support the pioneering work of **Roberto Chiarle, MD**, (pictured) who is developing new CAR-T therapies for neuroblastoma.

**Suneet Agarwal, MD, PhD**, a multiple TIS and pilot award winner himself, has now formally joined TRP leadership as associate director of the Translational Investigator Service program. In this role, Dr. Agarwal serves as a mentor to new and existing TIS awardees and helps to review and choose awardees.

We also continue to expand the range and types of awards we can offer to promising scientists. Generous members of the **Venture Philanthropy Network**, such as the Mooney Family and Ted and Erica Pappendick, have established exciting innovation and accelerator awards that truly move the needle of care by bringing even more exciting research closer to the clinic. We are eternally grateful for their steadfast support and are excited to announce a new class of Pappendick award winners in this report.



## A model of success

If it feels like these updates and milestones reflect a growing momentum within the program, that's because they do. The hospital's new chief scientific officer, **Nancy Andrews, MD, PhD**, recently told staff that one of her biggest surprises when she returned to Boston Children's was the strength of the translational research being done here. She singled out the TRP as a model of that success.

I believe we are at a transformative moment in time for the program, and we owe that to members of the VPN, without which there is no TRP. The commitment they've made will impact generations of children in Boston and around the world.

Sincerely,

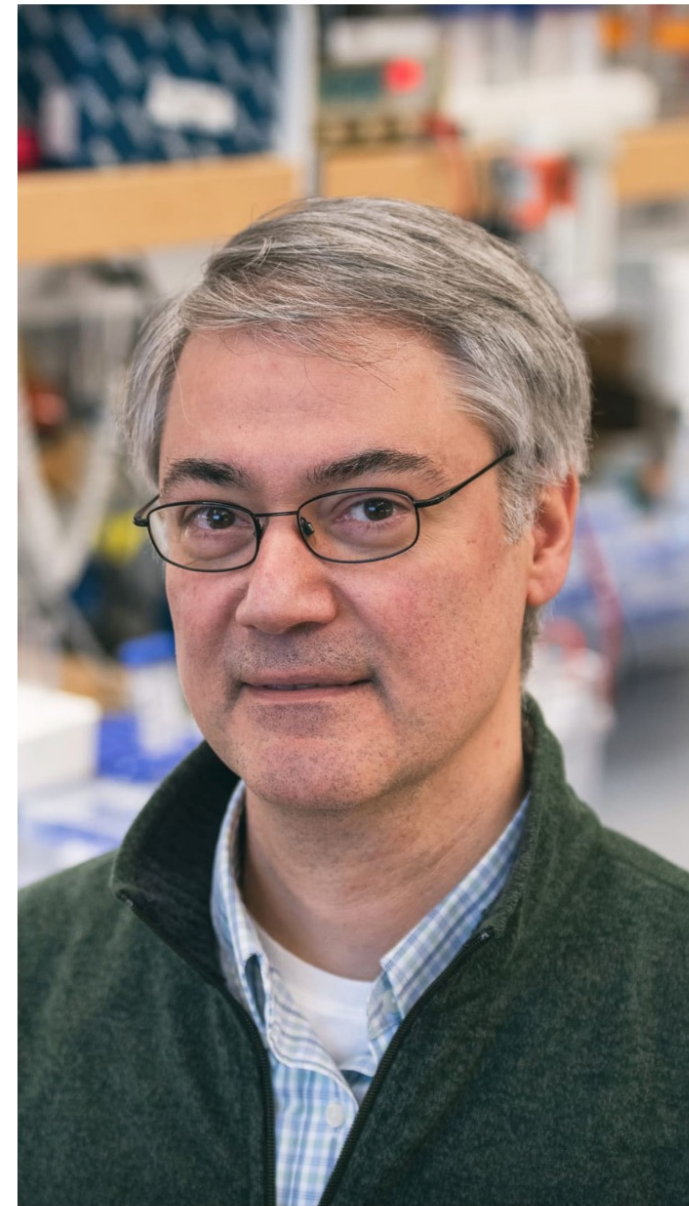
**Mustafa Sahin, MD, PhD**

Director, Translational Research Program;

Director, Translational Neuroscience Center;

Rosamund Stone Zander Chair, Boston Children's Hospital

Professor of Neurology, Harvard Medical School



# 2022 Impact





## Measuring the impact of the Translational Research Program: The 2022 TIS survey

How do we know the TRP is making a difference? For years we have surveyed TIS awardees about their research milestones, scientific publications, and other key indicators of success in translational science.

This important measure of our performance was unfortunately put on hold throughout the pandemic as researchers struggled to reopen shuttered labs and navigate personnel shortages.

We're pleased to report the return of the TIS survey this year and the critical insights it provides. Read on for the results.

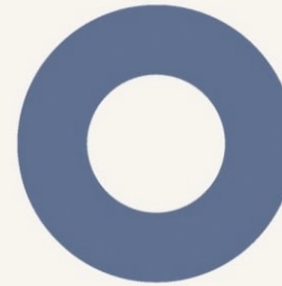




## Results showing the benefit of your support

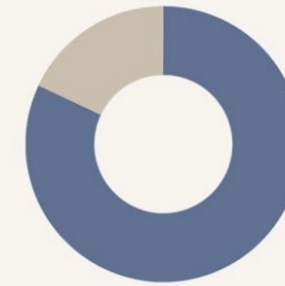
This year, 17 active and former TIS awardees completed the survey, providing a unique glimpse into the prowess of the program's translational research engine. Among the highlights: some of our highest-ever recorded results in the percentage of awardees filing patents for their work and changing the mortality or morbidity of a childhood disease. It's hard to think of better markers of translational science in action.

The percentage of those launching clinical trials is also up, showing our commitment to children's health. We expect these numbers to grow further still in the years ahead as our investment in junior faculty comes to fruition.



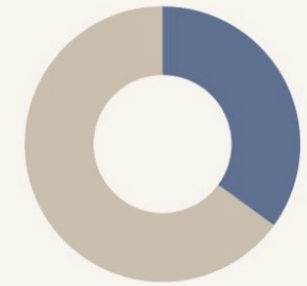
100%

of awardees used data from TRP-funded research in published manuscripts or professional presentations



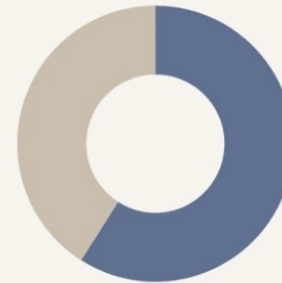
82%

of awardees used data from TRP-funded research to successfully submit for and receive external grant funding



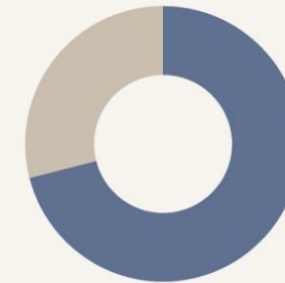
35%

of awardees launched a clinical trial that enrolled patients based on TRP-supported research



59%

of awardees filed patents based on TRP-supported research



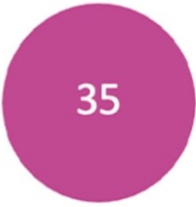
71%

of awardees reported a subsequent change in the morbidity or mortality of a serious childhood illness due to TRP-funded work



41%

of awardees said their TRP-supported work resulted in an enhancement of patient or family satisfaction



Clinical trials launched  
by TRP awardees



Over ½ of TRP awards  
resulted in breakthroughs  
that positively changed the  
morbidity of a serious  
childhood illness.



TRP investment of \$30  
million has resulted in more  
than \$360 million in outside  
funding.

## Better lives for children—a true measure of our success

Over the TRP's 14-year history, the success of our clinician-scientists in unlocking additional federal grant support, fostering medical breakthroughs and launching clinical trials has been nothing less than extraordinary.

What's most rewarding for us is the knowledge that behind these numbers lie the stories of countless patients and their families whose lives have been changed and often saved by the scientific acumen of TRP-funded researchers. This, then, is why we hold such a debt of gratitude for the support of the **Venture Philanthropy Network**, which makes it all possible. Changing clinical care at the bedside is the hallmark of our success.

*Graphic: TRP cumulative data points since our founding in 2008*



# 2022 Awardees

## Announcing the 2022 TIS and Pappendick Family awardees

The TIS awards serve as a critical foundation of the TRP. They allow our top scientific minds the flexibility to follow their research and conduct truly innovative science that bridges the gap between lab and clinic.

Established in 2020, the goal of the **Pappendick Family Therapeutic Acceleration Award** is to help investigators complete late preclinical and early clinical phase 1 studies so their research gets to patients more rapidly.

Read on for profiles of this year's awardees.



## Using MRI technology to unlock the mysteries of fetal development

Junior TIS awardee **Camilo Jaimes Cobos, MD**, is developing magnetic resonance imaging (MRI) methods and computational neuroimaging techniques that are optimized to evaluate the fetal brain. MRI technology is ideally suited to study fetal neurodevelopment because it is low risk and captures a wide range of essential information. The challenges of using MRI to study development *in utero* are significant, however, because movement of the fetus distorts MRI images.

Thankfully, Dr. Jaimes Cobos and his colleagues have developed new computational methods for overcoming these fetal-motion artifacts, and have tested the methods in a small clinical population. They are now ready to employ this technology more broadly to study and diagnose several neurodevelopmental disorders. Furthermore, the success of future fetal interventions will require these more robust and accurate imaging modalities.



**“Fetal life is the most dynamic stage in neurodevelopment and is crucial for lifelong behavioral and cognitive function. That’s why it’s critical to characterize normal and abnormal developmental trajectories.”**

*—Dr. Jaimes Cobos, MD*



Dr. Paolino will use the support of the mTIS award to study potential new combined therapies for acute lymphoblastic leukemia and acute myeloid leukemia, which are among the deadliest childhood cancers.

## Improving cancer treatment in children

A physician-scientist and cancer researcher with experience as a U.S. Army medic and in clinical trial operations, Jonathan Paolino, MD, is this year's mentored TIS (mTIS) awardee. Dr. Paolino studies childhood leukemia and ways to develop patient-specific treatment regimens that bolster the effectiveness of chemotherapy.

His research focuses on the use of innovative dynamic assays in patients' own living cancer cells to predict future response to therapy. This approach overcomes key barriers to personalized medicine and provides a path to optimize clinical outcomes while potentially reducing toxicity and the impact of treatment on quality of life for children with cancer.

## Developing a gene therapy for posthemorrhagic hydrocephalus

As many as a quarter of very low birth weight preterm babies experience intraventricular hemorrhage (IV), or bleeding into the brain's ventricles. What's worse, many neonates with IV go on to develop a condition called posthemorrhagic hydrocephalus (PHH), which can cause impaired neurodevelopment or even death.

**Maria Lehtinen, PhD**, whose basic and translational research has focused on conditions affecting cerebrospinal fluid, is developing a gene therapy for PHH. The treatment is based on her team's discovery that increasing expression of the NKCC1 gene reduces buildup of fluid in brain ventricles of very young mice with PHH-like symptoms. With support from the **Pappendick Family Therapeutic Acceleration Award**, Dr. Lehtinen and her team will set out to develop and test a gene therapy for PHH in animal models. If successful, the ultimate goal would be future clinical trials.



Posthemorrhagic hydrocephalus happens when small blood clots form in cerebrospinal fluid channels, impeding circulation and reabsorption and increasing pressure on the brain. Finding a treatment is critical.





"It is a great honor to receive the Pappendick Family Therapeutics Accelerator Award. It will allow us to bring together several research elements to create and then evaluate a new, multicomponent GBS vaccine."

—Dr. Zhang

## Using a new vaccine platform to create an effective Group B Streptococcus vaccine

Group B Streptococcus (GBS) is a bacterium that causes severe disease and even death in newborns. Current prevention methods struggle because they target only a small number of the antigens present on the bacterium's surface and often vary in effectiveness from patient to patient.

Thankfully, **Fan Zhang, PhD**, has helped develop a vaccine platform—called the Multiple Antigen Presenting System (MAPS)—that can induce robust immune responses to an array of bacterial components. Her lab has done preliminary work developing a MAPS-based GBS vaccine, and the 2022 Pappendick Family Therapeutic Acceleration Award will enable Dr. Zhang's team to take the next concrete steps toward bringing it to fruition. Their approach targets several novel surface proteins they've discovered and includes the protein SBD, which they found reduces the bacterium's naturally occurring defense against such vaccines.





# 2022 Grants



## 2022 Pilot Awards: The engine of innovation

In addition to the researcher-based TIS awards, the TRP also awards a number of project-based Pilot Awards every year, which help top researchers answer troubling scientific questions.

Pilot awards are critical in shaping the future of scientific study at Boston Children's. They often provide the necessary data gathering and proof-of-principle work that allows our clinician-scientists to apply for the essential federal funding that can bring their ideas to the patients that need them.

## Exploring the mechanism of neurocognitive dysfunction in CPVT

Children and young adults with the inherited cardiac arrhythmia called catecholaminergic polymorphic ventricular tachycardia (CPVT) can suffer sudden cardiac arrest while exercising or experiencing stress. Today's treatments are not very effective and the condition is life-threatening. CPVT is most often caused by mutations in the protein RYR2, which is highly expressed in the heart, but is also found in brain areas associated with learning and memory. In preliminary studies, **Vassilios J. Bezzerides, MD, PhD**, identified a specific defect in spatial learning in CPVT mouse models.

As Dr. Bezzerides's team investigates the function of RYR2 within the central nervous system, the researchers will identify protein binding sites that could serve as possible targets for therapeutic intervention. Their work also will strengthen the design of gene therapy for this devastating disorder.



This project will build on Dr. Bezzerides's findings to improve mechanistic understanding of the neurocognitive issues affecting CVPT patients.

## Initiating antisense oligonucleotide therapy for calmodulinopathy

Calmodulinopathies are rare genetic conditions that cause potentially lethal heart rhythm disorders. Current therapies are insufficient, with patients experiencing life-threatening arrhythmias. **William Pu, MD**, and his team will employ its human stem cell models and humanized mouse models of calmodulinopathy to develop a novel therapy based on antisense oligonucleotides (ASOs), a new class of therapeutic agent.

ASOs can prevent expression of deleterious mutated genes. Because of their relatively favorable and predictable toxicity profiles, ASOs are attractive for use in personalized medicine and rare diseases. Calmodulinopathy is an optimal disease target for ASOs. This study could open the door to a lifesaving therapy and provide proof-of-concept to stimulate development of ASOs for other cardiac disorders.



The planned experiments will assess the ability of ASOs to prevent disease and sudden death in calmodulinopathy models.



## Developing native promoter-directed SSADH restoration gene therapy

With fewer than 500 cases worldwide, succinic semialdehyde dehydrogenase deficiency (SSADHD) is a rare brain disorder caused by loss-of-function mutations of the ALDH5A1 gene. Lacking this gene, the brain cannot break down the neurotransmitter gamma-aminobutyric acid (GABA). The consequences are profound: Pathologic accumulation of GABA can cause neurodevelopmental delay, seizures and sudden unexpected death in epilepsy (SUDEP).

The dynamic team of **Alex Rotenberg, MD, PhD**, (pictured) and **Hing Cheong (Henry) Lee, PhD**, has made progress toward a practical and viable gene therapy approach to restore the ALDH5A1 gene. The research team now aims to construct an adeno-associated virus (AAV) viral vector specially designed to re-introduce the human ALDH5A1 gene in relevant brain cells. Gene restoration is a potential cure for SSADHD patients.



The lab's proof-of-concept study in SSADH mouse models demonstrated that brain-wide gene restoration via an AAV vector could reverse SSADHD symptoms and curb mortality.

Thank You



**Boston Children's**

Where the world comes for answers

