Into the Clinic
The Translational Research Program
Progress Report to the Venture Philanthropy Network
August 2016
Translational Research Program

Progress Report to the Venture Philanthropy Network

August 2016

1. Overview
Letter from Director ................................................................. 3
Research Highlights ................................................................. 5
Program Highlights ................................................................. 11

2. Performance ................................................................. 13

3. Projects: Seed and Core Grants 2014 to 2015
2014 ............................................................................................ 21
2015 ............................................................................................ 26

4. Translational Investigator Service Awardees
   and Translational Innovator Awards
From theory to therapy .................................................. 27
TIS 2015:
   Arin Greene ................................................................. 29
   Alejandro Gutierrez ......................................................... 29
TIS 2014:
   John Kheir ......................................................................... 31
   Martha Murray ................................................................. 31
TIS 2013:
   Ann Poduri ................................................................. 33
   Scott Snapper ................................................................. 33
TIS 2012:
   Suneet Agarwal ............................................................... 35
   Rachel Rosen ................................................................. 35
TIS 2011:
   Rick Malley ................................................................. 37
   Alex Rotenberg ............................................................... 37
5. History and Leadership
TRP History and Mission .................................................. 43
TRP Leadership
   David A Williams .......................................................... 45
   Judy Fleming ............................................................... 47
Review Committee ......................................................... 49

6. Appendix ........................................................................ 59

On the cover: Emir Seyrek
traveled to Boston Children’s
from Turkey to take part in a gene
therapy trial. He is now an active,
healthy four-year-old.
Letter from the Director

Filling the translational pipeline

Janet Soul, MD, won one of the very first Translational Research Program (TRP) seed grants in 2009 by proposing a new way to treat seizures in newborns. Now, some seven years later, she is wrapping up a groundbreaking clinical trial to evaluate whether a commercially available drug, bumetanide, can be repurposed as a treatment for newborn seizures. Thanks to that early TRP award—and the visionary support of the Venture Philanthropy Network (VPN)—Soul was able to secure major funding (including more than $4 million from the NIH) to launch the first randomized, double-blind controlled trial of a new seizure medicine to be tested in newborns in nearly 20 years.

Soul’s work has reverberated globally. Following her lead, groups in Europe, the U.S. and New Zealand have initiated clinical trials of new treatments for neonatal seizures. Soul is now leading an international team of academics, drug experts and regulators to create a blueprint for future trials of seizure treatments in newborns. After the results of her own trial are completed, Soul hopes to begin a large, multicenter trial to evaluate bumetanide’s effectiveness. This research is poised to transform lives. Seizures occur more commonly in the newborn period than at any other age—in 2 to 4 babies per 1,000 births. Since neonatal seizures often lead to later epilepsy, effective treatments are urgently needed.

The movement of innovations out of the lab and into the clinic is evident throughout the multiple projects supported by the TRP and the VPN. As you’ll read, TRP investigators are bringing powerful innovations to patients—from cancer vaccines and gene therapy to improved methods for bone marrow transplant and knee surgery. And as we witness remarkable impact in the clinic, the TRP continues to drive research in the pipeline, ensuring a steady march of translational successes.

The TRP’s newest initiative, for example, promises to amp up the wave of neuroscience discoveries being made at Boston Children’s. In the next year, some
TRP awards will focus on traumatic brain injuries (TBIs). Our program and the Brain Injury Center at Boston Children’s will jointly fund the 2016 Translational Innovator Award (TIA) in Traumatic Brain Injury. This two-year award is designed to propel high-risk, high-reward innovative research. Investigators across the hospital, not solely within fields directly related to TBI, submitted excellent ideas. Of the nine letters of intent (LOIs) received, all were promising enough to invite full proposals. The winner of the 2016 TIA award is Benoit Scherrer, PhD, from the Radiology Department. He is an expert on imaging for traumatic brain injury.

We are proud of the TRP’s role as an engine of translation of our basic discovery research, and grateful to the VPN, whose members share our deep commitment to fund transformative science and scientists. Thank you for your continued investment in life-changing work at Boston Children’s Hospital.

Thank you,

David A. Williams, MD
Director, Clinical and Translational Research Program, Boston Children’s Hospital
Leland Fikes Professor of Pediatrics, Harvard Medical School
Research Highlights

First-in-human trials of an ALK cancer vaccine

In recent years, scientists, clinicians, patients, and the public have shown extraordinary interest in cancer therapies that seek to rev up a patient’s immune system to fight disease. Such immunotherapies represent an important new frontier in cancer treatment. In 2013, Roberto Chiarle, MD, received TRP seed funding to advance innovative cancer vaccines that target a key cancer gene called ALK. ALK drives tumor growth in deadly cancers, including lymphoma and lung cancer, and in neuroblastoma—tumors that account for 7 percent of all childhood cancers yet cause 15 percent of child cancer deaths.

Earlier this year Dr. Chiarle and his colleagues received a highly competitive grant from Dana-Farber/Harvard Cancer Center and the Koch Institute at MIT to bring these landmark studies closer to clinical use. The Chiarle team is about to open the first-in-human clinical trial of an ALK cancer vaccine in adults whose lung cancer tumors are “ALK-positive” (ALK+). The results obtained from the ALK vaccine trial in adults are expected to help advance Chiarle’s pre-clinical neuroblastoma studies, which are currently being tested in mouse models.
Kinder, gentler and safer bone marrow transplants

Suneet Agarwal, MD, PhD, is one of the champions of rare disease. He has dedicated his career to developing cures for rare, nonmalignant bone marrow failure syndromes—blood disorders that affect roughly ten children in a million. Bone marrow (or "stem cell") transplants are often too difficult to endure for young patients. Typically, before infusing donor blood cells, doctors must destroy the patients’ own bone marrow, using radiation and chemotherapy in a “conditioning” process. These harsh treatments can damage other organs, further weakening often fragile patients. “Because the conditioning process is so difficult, we usually only give stem cell transplants to treat life-threatening disease,” says Agarwal. That leaves some patients with no real therapeutic options. “Reducing or eliminating the toxicity would let us offer stem cell transplantation for many more children and adults with blood or immune diseases.”

With help from the TRP’s multi-year TIS funding, Agarwal has developed a new, gentler, safer conditioning process. His approach avoids chemotherapy and radiation altogether, and instead relies on immunosuppression to dampen down patients’ immune systems while the healthy transplanted cells move in and displace the dysfunctional cells. This revolutionary method was recently tested in a Phase II clinical trial in children with dyskeratosis congenita (DC), a rare genetic syndrome.

Agarwal’s gentler conditioning method has proven remarkably successful. All seven patients who received the treatment survived the procedure, bone marrow transplant, as well as the post-treatment period (a median follow-up time of 29
Riley’s story

Riley seemed perfectly healthy until age 11—when his body became covered with bruises and a mosquito bite turned into a hematoma. Testing in his home state of Idaho revealed a critically low level of platelets, red blood cells and white blood cells—a sign of bone marrow failure. After a series of wrong guesses, Riley was diagnosed with dyskeratosis congenita (DC). He would eventually need a bone marrow transplant, and that usually meant a brutal pre-transplant “conditioning” regimen of chemotherapy and radiation.

Then Riley and his mom, Katie, met Dr. Suneet Agarwal at a Maine camp for DC patients. Dr. Agarwal told Katie about the gentler conditioning he had devised to prepare children for bone marrow transplants. By the summer of July 2015, when Riley was 14, every other therapy had failed—and he was getting sicker. Even though the doctors at home were skeptical, the family decided to try Dr. Agarwal’s new marrow transplant process and flew the 3,000 miles to Boston Children’s. At that point, Katie says, Riley was so ill that “when I got on the airplane, I wasn’t sure if I would be bringing him home.”

After transplant, Katie describes Riley’s transformation as “amazing.” He is now healthy, muscular and growing. He runs track on his high school team. Riley is one of the seven patients who have undergone Dr. Agarwal’s new process. All are thriving.

In contrast, patients who receive the standard treatment have a mortality rate of 40 percent after two years. Now, Agarwal is expanding this study through an international multi-center trial.

15-year-old Riley celebrates a victory by his beloved Denver Broncos in January 2016—the game that got them to the SuperBowl.
Pushing the frontiers of gene therapy

Seven years ago, Sung-Yun Pai received the TRP’s Translational Investigator Service (TIS) award. This funding over five years gave her the freedom to pursue game-changing ideas in gene therapy. Since then, the gene therapy team has enjoyed spectacular results, producing cutting-edge gene therapy techniques that are now curing previously untreatable immune diseases. Today Boston Children’s is the undisputed world leader in gene therapy for children—we currently have five gene therapy clinical trials enrolling patients, with an additional two planned for 2016-2017.

Your exceptional, early-stage support for gene therapy has paid off in so many ways. Driven by the success of our pioneering program, Boston Children’s has become a founding institution of a new gene therapy company, Orchard Therapeutics, which brings Great Ormond Street Hospital for Children in London, UK, and the Mattel Children’s Hospital at the University of California Los Angeles, into a collaboration that will develop new treatments for rare genetic diseases, including immune and metabolic disorders.

Our TRP-funded gene therapy innovators are also seeing the fruits of their labors in an expanded gene therapy program at Boston Children’s, which is joining with colleagues at Dana Farber Cancer Institute to investigate diseases that affect the brain and liver, as well as vision and hearing disorders. Alessandra Biffi, MD, a world-renowned gene therapy expert, will lead this newly expanded initiative. Biffi recently applied experimental gene therapy techniques to create a new treatment paradigm for metachromatic leukodystrophy (MLD), a devastating neurodegenerative disorder.

On the horizon too are plans to establish a new biotechnology hub, which will optimize the unique expertise and technologies in the Longwood area and help bring promising new therapies to patients around the world. Your early partnership helped us set the standard and now Boston Children’s will continue to push the frontiers of gene therapy.

*Orchard Therapeutics is a new gene therapy company formed by Boston Children’s and other leading pediatric medical centers.*
Recreating heart disease in a dish

William Pu, MD, one of the earliest recipients of TIS support, was studying the biology of Barth syndrome—a rare mitochondrial disorder that affects both heart and skeletal muscle. But he was also aiming to create a system that can be broadly applied to study heart disease. And that’s exactly what happened.

To probe Barth syndrome more deeply, Pu took skin cells from two patients who suffer from the disorder, and using stem cell technology, coaxed them to become cardiomyocytes (heart muscle cells). With collaborator Kit Parker, PhD, at Harvard University’s Wyss Institute, Pu developed a unique two-dimensional system. This “heart-on-a-chip” enabled scientists to visualize and closely investigate (at the tissue level) how heart cells contract. That work, published in *Nature Medicine* in 2014, uncovered a surprising role for reactive oxygen species (ROS), chemically reactive molecules containing oxygen. Working with biotech and pharmaceutical companies, Pu is now exploring ROS as a potential therapy for Barth syndrome.

The heart-on-a-chip technology also paved the way for studies of other, more common forms of heart disease, such as inherited arrhythmias. With Dominic Abrams, MD, who heads Boston Children’s Inherited Cardiac Arrhythmia Program, Pu and Parker have collaboratively pioneered methods to reproduce and study arrhythmias in a dish. He and his colleagues received a multiyear grant from the NIH and an American Heart Associate grant to continue this innovative work. One of the big questions they seek to answer: Can doctors personalize patients’ treatment based on how their cells respond in the heart-on-a-chip tests?
Transforming knee surgery

Tears of the knee’s anterior cruciate ligament (ACL) are increasingly common among young athletes. Although current methods to surgically repair torn ACLs can work well in adults, they are not ideal for young children whose bones are still growing. Conventional ACL replacement requires long recovery and tedious rehabilitation—a challenge for even the most patient of adolescents. And up to 80 percent of teens and young patients develop arthritis within 15 years of the procedure. A better way to repair youngsters’ knees was needed.

That’s why Martha Murray, MD, has spent two decades devising an ingenious method to improve ACL repair. The first-in-human trials of her novel repair method, which began enrolling patients in January 2015, has completed a 20-patient safety trial. Instead of replacing the torn ACL with a tendon graft, Dr. Murray developed a special protein-enriched sponge to act as a bridge between the ligament’s frayed ends. The special scaffold stimulates natural healing and reconnection. Ten trial participants received the bridge-enhanced ACL repair (BEAR) and 10 underwent standard ACL reconstruction. BEAR did as well as the standard method in terms of overall knee function and stability—and better in terms of muscle recovery.

Murray’s results were widely publicized when they were reported this spring, appearing in the Boston Globe, New York Times, Washington Post and other publications. Although only time will tell whether BEAR will also reduce the risk of arthritis, preclinical studies in animal models suggest it will. To help support this work, Dr. Murray won a TRP seed grant in 2013 and became a TIS awardee in 2014. She is now launching a new Phase II trial, enrolling additional patients in a 100-patient study.
Program Highlights

The Mooney Family Initiative for New Therapies
Jim and Lisa Mooney, founding members of the VPN, have been steadfast TRP supporters. To help translate powerful ideas into clinical benefits for children, the Mooney family gave an additional generous gift to Boston Children’s to establish the Mooney Family Initiative for Translational and Clinical Studies in Rare Diseases (TCSRD). The award will help investigators by providing extraordinary needs support to patient families eligible to become subjects in early phase human trials.

The Mooney Initiative builds an important bridge from the TRP to the clinic. It helps children and families who often incur enormous costs to participate in clinical trials and thereby get the life-saving care only available at Boston Children’s. With visionary philanthropy like this, we can continue to bring groundbreaking new therapies to children who desperately need them.

Funds from the Mooney family’s gift were awarded to Janet Soul, whose search for a better medicine to treat newborn seizures is described in our opening Letter from the Director; Suneet Agarwal, who has developed an alternative bone marrow transplantation regimen (see page 6); and Jennifer Whangbo, MD, PhD, who studies graft-versus-host disease.

Activities
To fulfill its mission to advance promising research, the TRP hosts numerous activities including a lecture series, quarterly TIS meetings, workshops, symposiums, and retreats. The TRP brings together researchers, outside experts, and specialized representatives from government and industry. In addition, volunteers such as Phil Reilly, from the venture capital firm, Third Rock; and Lex Van der Ploeg, former Merck executive and current CSO of Rhythm Pharmaceuticals, offer advice and mentorship to our scientists. Together, we are finding new ways to enhance translational research.

Retreat
The annual TIS retreat is an opportunity for TIS members and invited guests to come together for two days to present problems and share solutions, think, and grow professionally as a result of the informal interactions with a diverse team of experts. This year’s retreat for TIS members, held in September 2015 in Chatham, MA,
Symposium focuses on brain injuries
As noted earlier in this report, the TRP is partnering with Boston Children’s Brain Injury Center to fund new awards in 2016-2017. Traumatic brain injuries took center stage at this year’s TRP symposium, held in March 2016. The event was open to the entire hospital community, and featured presentations by Rebekah Mannix, MD, MPH (Emergency Medicine), Alexander Rotenberg, MD, PhD (Neurology), Benoit Scherrer, PhD (Radiology), and Shenandoah Robinson, MD, FAAP, FACS (Neurosurgery). The keynote address was given by Alvaro Pascual-Leone, MD, PhD, Chief of the Division of Cognitive Neurology and Director of the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center.

Thank you
As the TRP approaches its ninth year, it grows stronger. More discoveries are advancing to clinical implementation. At the same time, we are maintaining a robust pipeline of early-stage research with the potential to transform pediatric health. All of this is possible through your generous support. Thank you for your steadfast commitment to fueling translational research. Together, we are forging a new world for children with debilitating diseases.
Metrics
How do we know whether the TRP is making a difference? Every year we ask TRP grantees about research milestones, scientific publications, and other key indicators of success in translational sciences. This year we revised the survey questions to more precisely gauge the TRP’s potential to improve patient health and health care. We also grouped the survey results by short-term, medium-term, and long-term impact. Figure 1 (next page) summarizes the survey results from 27 respondents who received seed project funding and TIS and TIA awards between 2009 and 2015. As you’ll read, we are now reaping the precious fruits of early, strategic investment in game-changing translational research.

Research findings presented
As the summary table shows, the vast majority of TRP researchers (93 percent) presented their data in an abstract, poster, or discussion at national and international scientific meetings; 78 percent of researchers contributed to the scientific literature in the last year or are preparing manuscripts for future publication. In a paper that appeared in *Science Translational Medicine* in September 2015, Pedro del Nido (recipient of seed grants in 2012 and 2013) described a catheter-based tool to deliver a light-activated adhesive patch to repair tissue defects. Suneet Agarwal’s paper about mutations linked to telomere diseases was published in *Nature Genetics* in October 2015.
### Impact of TRP Support: 2016 Survey Summary

#### Short-Term Effects
1. Data used at a professional presentation 93%
2. Articles published, or in the process of being published 78%
3. Data leveraged further funding to obtain external grants /funding 93%
4. Protocol approved for testing in humans (IRB approval) 33%

#### Medium-Term Effects
5. Led to human trials that accrued patients 19%
6. Resulted in a licensing or material transfer agreement (MTA) 15%
7. Resulted in a patent filing 30%
8. Resulted in a completed human trial 15%
9. Led to a subsequent phase II-IV trial or a multi-institutional or cooperative group trial 11%

#### Long-Term Effects
10. Research results led to changes in health care delivery 11%
11. Improved outcomes in a serious childhood illness and/or led to better understanding of disease 30%
12. Resulted in published work cited as a landmark or seminal study 4%
13. Enhanced patient/family satisfaction with care delivered 4%
14. Other impacts from TRP funding beyond specific project findings—for example, key skills gained, equipment purchases used in other projects, etc. 44%
Leveraged further funding
An impressive 93 percent of TRP researchers attracted additional funding from external sources like government agencies or foundations. Among them were Sung-Yun Pai, who received more than $5 million from the NIH to support gene therapy; Suneet Agarwal won about $1.1 million from the NIH; Roberto Chiarle received prestigious awards from Dana-Farber and the Koch Institute at MIT totaling $1.1 million and 2015 TIS awardee Arin Greene received multiple NIH awards totaling about $700,000.

Testing in humans
More than 15 clinical trials have emerged from TRP projects since the program’s inception. Investigators who are ready to test their innovation in humans start by getting the green light from the hospital’s Scientific Review Committee, an expert committee that reviews the scientific questions being investigated in humans, and the Institutional Review Board (IRB), an expert ethics panel that makes sure the work will be conducted in an appropriate manner, and, in some cases the U.S. Food and Drug Administration (FDA); 33 percent of TRP scientists in this year’s survey reported that they had a protocol approved by the IRB. Early-phase clinical trials focus on safety and lay the groundwork for subsequent mid- and late-stage trials that determine whether the new treatment being tested is better than or equivalent to the standard treatments. This year 19 percent of researchers reported enrolling patients in human trials and 15 percent reported completing their early-stage clinical trials. Late-stage and large-scale multicenter/ cooperative group clinical trials are essential to developing modern therapies. Among the researchers running late-stage or multicenter trials are Martha Murray, whose clinical trial is evaluating a novel method to repair knee injury; Rick Malley’s trial of a new vaccine; and Suneet Agarwal’s gentler bone marrow transplantation regimen.

Intellectual property milestones
Filing a patent is crucial to protect the researchers’ and the hospital’s intellectual property related to novel drugs, methods or devices. Patent filing helps assure that pharmaceutical or biotech companies can develop successful clinical interventions on a broad scale. In this year’s survey 30 percent of TRP investigators reported filing a patent. Among them was Rick Malley, for the modular technology he invented (called MAPS), which is being used to develop new vaccines. Licensing or material transfer agreements are needed when a pharmaceutical or biotechnology company
or another external organization indicates an interest in contributing to the development of a treatment or device; such companies have the expertise and resources to develop FDA-approved therapies that could become successful clinical interventions. One innovation that led to a licensing agreement this year was Roberto Chiarle’s way to engineer immune cells that can recognize and attack an individual patient’s tumor.

Wide impact on medicine and health care delivery

The whole point of translational research is to improve health care. As we reach our ninth year, we can point to research that has enhanced understanding of disease or improved health in patients. Sung-Yun Pai’s two 2014 publications in the New England Journal of Medicine (noted in prior annual reports) are now considered seminal works on the treatment of primary immune deficiencies. Another potential breakthrough described in prior annual reports was Rick Malley’s work in vaccine development, which could in the future be used to fashion vaccines that protect the health of children and adults all over the world. From this year’s survey: Martha Murray’s Bridge-Enhanced ACL repair (BEAR) method—two decades in the making—could transform knee surgery. And Bill Pu’s studies, which produced insight into a rare mitochondrial disorder, have been cited as a blueprint for how to use stem-cell-derived heart cells to probe the biology of heart disease.
Moreover, the transformative work being carried out by TRP researchers can extend into or advance other projects and fields; 44 percent of researchers report that their TRP-funded projects led them to cultivate skills and technologies applicable to additional scientific problems. For example, Kristin Moffit used her seed grant to develop a novel way to study the bacterium Staph aureus in samples taken from pediatric skin and soft tissues; today, she is applying these methods to samples collected from other parts of the body (such as tracheal aspirates) and to study different pathogens.

**Figure 2**

TRP Innovation categories 2011-2014 (33 projects)

- Novel Diagnostic/Screening Test (31%)
- Novel Uses of Approved Drugs (17%)
- Innovative Disease Treatments (14%)
- Innovative Drugs and Therapeutics (11%)
- Novel Devices (11%)
- Innovative Disease Prevention (8%)
- Enabling Platforms (6%)
- Clinical Trials (3%)
Investments
Through the types of awards described below, the TRP has distributed more than $16 million in funding to support researchers.

• **Seed grants** of up to $100,000 fund a one-year effort to pursue and validate innovative ideas. The beauty of seed grants is that they jumpstart promising studies with relatively modest outlays of funds. In 2015, the TRP awarded five new seed grants supporting studies in cardiac surgery, neurology, radiology, pediatric oncology and immunology.

• **Core grants** fuel a two-year effort to build up the research infrastructures—and the tools critical to translational research. Core grants support fundamental enabling platforms and aim to increase the entire hospital’s ability to shape research.

• **Translational Investigator Service (TIS) awards**, which total a minimum of $600,000, are distributed over five years to support remarkable researchers as they conduct translational studies. TIS awards go to a small cadre of exceptional physician-scientists. The support is much more than monetary, with regularly scheduled updates on the progress of research projects, special lectures, provision of outside expert consultants (including venture capital and business advisors), an annual symposium and an annual off-campus retreat.

• **Translational Innovator Awards (TIA)**, two-year grants that total $400,000, are intended to support the kind of game-changing projects nearly impossible to fund by any other mechanism. The inaugural TIA grants (2014-2016) were selected jointly with The Manton Center for Orphan Disease Research. This year’s new TIA grant will be awarded jointly with Boston Children’s Brain Injury Center to push traumatic brain injury research to a whole new level.

• **Senior TIS grants** give past TIS awardees up to 20 percent of their NIH maximum salary for three years. This lets them stay involved in the TIS program as mentors to the current TIS team. This award, established in 2014, lets current TRP researchers take advantage of the mentors’ skills and experience, and to develop their own mentoring skills by serving as resources and reviewers for more junior investigators in the program.
Figure 3
TRP Awards 2008-2016 (as of July 2016)

<table>
<thead>
<tr>
<th>Year</th>
<th>Seed Grants (1 year $50,000-$100,000)</th>
<th>Core Grants (2 years - $50K/yr)</th>
<th>TIS Awards (5 year Awards)</th>
<th>TIA Grants (2-year Awards)</th>
<th>Senior Investigator</th>
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<tr>
<td>2008</td>
<td>$625,000</td>
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<tr>
<td>2009</td>
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<td>$200,000</td>
<td>$1,180,000</td>
<td>-</td>
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<tr>
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<td>$99,918</td>
<td>$0</td>
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<tr>
<td>2011</td>
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<td>$200,000</td>
<td>$959,000</td>
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<td>2012</td>
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<td>$1,231,250</td>
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<tr>
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<td>2014</td>
<td>$500,000</td>
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<td>$1,200,000</td>
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<tr>
<td>2015</td>
<td>$500,000</td>
<td>-</td>
<td>$838,490</td>
<td>-</td>
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<tr>
<td>2016</td>
<td>$700,000</td>
<td>-</td>
<td>-</td>
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<tr>
<td>TOTALS</td>
<td>$5.83M</td>
<td>700K</td>
<td>$8.34M</td>
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<td>500K</td>
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</table>

Thanks to the VPN’s philanthropic partnership, the TRP awarded $6.5M in seed and core grants; $8.3M to the Translational Investigator Service (TIS); $800K in Translational Innovator awards (TIA); and $500K to Senior Investigators since 2008—a total of more than $16 million.

Far reaching
Thanks to your support, Boston Children’s Translational Research Program is changing the world. Our scientists’ creativity, innovation, and power to move the needle on pediatric and adult health all stem from your VPN investment. When government and industry support for research has faltered, you have stepped in. Philanthropy is an essential ingredient for pioneering translational research. The financial backing of the VPN enables us to carry out a life-saving mission—to accelerate clinical innovation from the bench to the bedside and back to the bench. We are grateful for your support.
Rett Syndrome (RTT) is the most common form of intellectual disability in girls. It is caused by mutations in the MeCP2 gene and currently, there are no treatments to stop or slow the progression of the disease; nor are there established biomarkers to help monitor and predict its course. Neurological abnormalities are subtle at first and then progressively worsen with age.

Dr. Fagiolini won seed grants in 2013 and 2014 to support her work in developing new therapeutic interventions and establish reliable and quantitative biomarkers in RTT. Her latest work capitalizes on the rapid insights provided by RTT mouse models. Her team has tested the hypothesis that administration of NMDA receptor antagonists, which block NMDA receptors (NMDARs) found on neurons, may prevent or delay regression of cortical function. The researchers have begun to establish the Visual Evoked Potential (VEP) as a non-invasive, reliable and quantitative biomarker of developmental regression in RTT patients. Now, Dr. Fagiolini is evaluating the feasibility and efficacy of chronic NMDAR antagonist treatment in halting and/or reversing regression in a more realistic mouse model, MeCP2 deficient female mice. In parallel, she is following a cohort of RTT subjects and testing them one year later using VEP in combination with in-depth clinical evaluation.

**Impact/Progress**
- Launched pre-clinical tests of a possible drug to halt or slow disease progression.
- Testing VEP as a noninvasive biomarker suitable for quantifying disease progression.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DISEASE TARGET</th>
<th>GRANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel Uses of Approved Drugs</td>
<td>Rett syndrome</td>
<td>$100K Seed</td>
</tr>
</tbody>
</table>
Advanced genetic methods to identify potential vaccine antigens for Staphylococcus aureus

Principal Investigator: Kristin Moffitt, MD
Associate Physician, Infectious Disease
Boston Children’s Hospital
Assistant Professor of Pediatrics
Harvard Medical School

Bacterial skin and soft tissue infections are usually caused by Staphylococcus aureus, and are a frequent cause of emergency room visits. S. aureus can also cause more serious infections including pneumonia, bone and joint, and bloodstream infections. Staph strains with increased resistance to antibiotic treatment, such as methicillin-resistant S. aureus (known as MRSA), are a serious worldwide threat to both healthy individuals and those with complex medical issues. Vaccine development against this pathogen has thus far been unsuccessful; multiple clinical trials have failed.

Instead of working with animal models of disease, Dr. Moffitt’s research seeks to gain an understanding of the bacterial factors elaborated specifically during human infection. She has collected and isolated samples from the abscesses of patients treated for S. aureus infection at Boston Children’s and is searching for bacterial RNA transcripts that are increased during human infection; proteins encoded by these up-regulated transcripts may serve as targets for vaccines. If Dr. Moffitt’s study identifies and validates genetic targets in animal models of staph infection, her work could lay the foundation for effective vaccines to prevent S. aureus infections in humans.

Impact/Progress
• An effective vaccine against MRSA is urgently needed to reduce morbidity and mortality and lower health care costs.
• Methods optimized in this study are now being applied to other clinical infection samples (e.g., respiratory aspirates from patients with S. aureus pneumonia), allowing generation of S. aureus transcriptome signatures that are specific to the different types of infections it causes. Similar techniques also applied to clinical samples of other bacterial pathogens.
• Project attracted additional funding.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DISEASE TARGET</th>
<th>GRANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovative Disease</td>
<td>Staphylococcal infection</td>
<td>$100K Seed</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
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</tbody>
</table>
Design, fabrication, and modeling of a direct cardiac compression device

Principal Investigator: Frank Pigula, MD
Director of Neonatal Cardiac Surgery
Boston Children’s Hospital
Associate Professor of Surgery
Harvard Medical School

Boosting heart function during surgery, particularly in the setting of heart failure, could improve outcomes for children and adults alike. Available assistive devices to support failing hearts have limited effectiveness.

This project seeks to better recapitulate normal cardiac contraction patterns. Researchers have modeled, designed, and fabricated a soft robotic sleeve that mimics the muscular organization and contractions of a healthy heart. This biologically inspired approach relies on a series of balloon-like elements that can be surgically implanted around a diseased heart. It will not come into contact with a patient’s blood supply, which obviates the need for anticoagulation therapy and reduces the risk of thromboembolic and infectious complications.

The invention promises to provide superior mechanical assistance to the failing heart through improved augmentation of both systolic and diastolic function. Following the initial design and fabrication phase, the team will assess the device’s efficacy in studies of both a healthy and acute heart failure animal model, comparing relevant measures of cardiac function and blood flow.

Impact/Progress
• The invention promises to provide better mechanical assistance to the failing heart than existing devices, without coming into contact with the blood.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DISEASE TARGET</th>
<th>GRANT</th>
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<tbody>
<tr>
<td>Novel Device</td>
<td>Heart disease</td>
<td>$100K Seed</td>
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Biomarkers to predict the need for EPO treatment in preterm infants

Principal Investigator: Shenandoah Robinson, MD
Associate Physician, Neurosurgery
Boston Children’s Hospital
Associate Professor of Neurosurgery
Harvard Medical School

A child who is born prematurely is exquisitely vulnerable to brain injuries as a result of impaired blood flow, decreased oxygen levels, and infection. Such injuries often require lifelong care. Currently there are no safe, reliable tests to identify which preterm infants are at risk for neurological problems and to guide therapy.

This project aims to develop a first-of-its-kind blood test to identify babies in need of treatment following preterm birth. Using a rat model of extreme preterm birth, the team has shown that post-injury neonatal treatment with erythropoietin (EPO) can prevent the molecular events that lead to impaired neural cell function—a process likely mediated by the enzyme calpain. Serum levels of calpain following brain injury could predict future neurological deficits and serve as a clinical biomarker to inform treatment following preterm birth. Researchers are studying the calpain pathway and how it changes in response to prenatal injury. The team has developed in vitro assays, a key step toward evaluating the correlation between EPO treatment, outcomes, and serum calpain levels. Together, these studies will inform the use of neuroprotective treatments to optimize neurodevelopment following preterm birth.

Impact/Progress
• Twelve percent of U.S. children are born preterm, and a significant proportion suffer from chronic neurological deficits, including learning and walking difficulties as well as seizures.
• A serum biomarker could help identify patients at risk of neurodevelopmental problems and guide therapy.
• Study results published in Developmental Neuroscience (November 2015).
• This project secured additional support from Harvard Medical School.
• Findings have been extended to traumatic brain injury (TBI) in infants, a common cause of cerebral palsy.

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<td>Novel Diagnostic/Screening Test</td>
<td>Neurological deficits in preterm infants</td>
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Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide, with 8.6 million cases of active TB and 1.3 million TB-related deaths annually. Children account for approximately 10% of TB globally. Unlike adult TB, pediatric TB is characterized by a low bacterial burden, which means that conventional TB tests are not suitable for diagnosing TB in children. This lack of robust diagnostic modalities for TB in children has led the World Health Organization to list diagnostics as the top research priority in pediatric TB.

Dr. Steen addresses this need by exploring the possibility of urine-based diagnostic modalities for childhood TB. Using mass spectrometry-based proteomics, he and his colleagues are mapping the urinary proteome in children with confirmed TB, with and without HIV co-infection, and in appropriate controls (10 children per group) to identify disease-specific differences in host and/or bacterial proteins. Urine specimens are drawn from a sample repository for a study underway in Kenya that is led by Boston Children’s Hospital investigators, the CDC, and the Kenya Medical Research Institute. Dr. Steen’s research aims to spur development of a diagnostic for childhood TB that could be deployed in resource-limited settings.

**Impact/Progress**

- A robust diagnostic test for pediatric TB could have a major impact on global health: Children account for approximately 10 percent of active cases, nearly 1 million worldwide.
- Data presented at 14th Human Proteome Organization World Conference, Vancouver.
- Researchers generated pilot data to support their hypothesis and their efforts to compete for longer term follow-up funding.
## 2015 Projects

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Project</th>
<th>Disease Target</th>
<th>Summary</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank Pigula, MD</td>
<td>A biometric direct cardiac compression device</td>
<td>Heart disease</td>
<td>Continue ongoing work to develop and test a biomimetic device that mechanically assists the failing heart without contacting the blood.</td>
<td>Novel Device</td>
</tr>
<tr>
<td>Yana Pikman, MD</td>
<td>CDK4/6 inhibition in T-cell acute lymphoblastic leukemia (T-ALL)</td>
<td>Leukemia</td>
<td>Develop potential combination therapies for T-ALL by evaluating the use of CDK4/6 inhibitors in combination with chemotherapy.</td>
<td>Novel Uses of Approved Drugs</td>
</tr>
<tr>
<td>Rima Rachid, MD</td>
<td>Fecal microbiota transplant in peanut allergy patients</td>
<td>Food allergies</td>
<td>Evaluate the safety and efficacy of fecal microbiota transplantation for peanut allergic patients.</td>
<td>Innovative Disease Treatments</td>
</tr>
<tr>
<td>Alex Rotenberg, MD, PhD</td>
<td>Measuring oxidative stress and its impact on cortical inhibition following traumatic brain injury</td>
<td>Traumatic brain injury</td>
<td>Develop a noninvasive method to measure post-TBI oxidative stress and as a way to diagnose traumatic brain injury and monitor response to treatment.</td>
<td>Novel Diagnostic/Screening Test</td>
</tr>
</tbody>
</table>
From Theory to Therapy

In medical research, the path from “Aha!” moment to realization of a new tool or therapy is hardly assured. That’s why our Translational Investigator Service (TIS) and Translational Innovator Awards (TIA) awards are so crucial in bringing science from a researcher’s lab bench to a child’s bedside. These awards supply our brightest scientific and clinical minds with the funding, support and infrastructures they need to turn dreams into reality for sick children and their families.

Translational Investigator Service Awards: Community
The Translational Investigator Service (TIS) is a unique five-year award providing outstanding physician-scientists with stable funding to move their best science into new human therapies. The TIS purposely brings together a multidisciplinary group of investigators to foster an exchange of ideas and insights.

Opportunities for sharing include regular research project progress updates, special lectures, advice from outside experts (including from the venture capital and pharmaceutical biotech sectors), a yearly symposium and an annual off-campus retreat. Such gatherings spark ideas and innovations that will save lives. On the following pages, we offer brief profiles of the TIS winners from 2011 to 2015: Suneet Agarwal, Arin Greene, Alejandro Gutierrez, John Kheir, Rick Malley, Martha Murray, Ann Poduri, Rachel Rosen, Alex Rotenberg, Scott Snapper; and past TIS awardees who continue to be involved with the TIS as mentors—Sung-Yun Pai, Bill Pu, and Mustafa Sahin.

Translational Innovator Awards: Trailblazers
The two-year Translational Innovator Awards (TIA) are reserved for scientists with innovative and potentially transformative scientific ideas. The first two TIA grants, which were awarded in collaboration with The Manton Center for Rare Disease Research at Boston Children’s Hospital in 2014, helped fund Pierre Dupont’s robotic implant for inducing growth of disconnected esophageal segments; and Wayne Lencer’s novel enzyme-replacement therapies aimed at rare but deadly genetic disorders. The 2016 TIA award went to Benoit Scherrer, PhD, of Radiology, whose profile will appear in next year’s report.
Plastic surgeon Dr. Greene focuses his research on the most severe and disfiguring kind of vascular anomalies – arteriovenous malformations (AVMs). Surgery is often only a temporary solution, as AVM lesions can regrow and no drug exists to counter the abnormal growth. Patients need better options. TIS funding has enabled Dr. Greene to take essential steps toward new treatments. He is working with molecular scientist Matt Warman, MD, and vascular biologist, Joyce Bischoff, PhD, to unravel the genetic mutations that trigger AVM growth and identifying compounds that can curb the malformation.

Alejandro Gutierrez has spent his career trying to improve outcomes for children with cancer. Knowing that certain tumor characteristics make cancer cells resistant to conventional chemotherapy, Dr. Gutierrez set out to discover alternate treatments for T-cell acute lymphoblastic leukemia (ALL), an aggressive blood cancer that strikes adolescents and young adults. Since effective treatment will likely require a combination of drugs, research in Dr. Gutierrez’s lab is multipronged. He is studying the cancer-promoting effects of mutations in the Hedgehog signaling pathway; and the role of proteins that halt uncontrollable cell growth and improve the effectiveness of chemotherapy.
John N. Kheir, MD  
*Assistant in Cardiology*  
*Boston Children’s Hospital*  
*Assistant Professor of Pediatrics*  
*Harvard Medical School*

Dr. Kheir is leading an effort to invent an injectable form of oxygen that can go directly and safely into the bloodstream of people who can’t breathe on their own. His invention is a composite of microparticles, each ferrying oxygen. The mixture could open a life-saving 30-minute window for victims of heart attacks, drowning, severe head trauma and many other critical conditions. The oxygen solution, which is now in animal trials, could become an indispensable tool in ERs and ICUs, ambulances and transport helicopters, and even beachfront lifeguard stands.

Martha Murray, MD  
*Orthopedic Surgeon*  
*Boston Children’s Hospital*  
*Associate Professor in Orthopedic Surgery*  
*Harvard Medical School*

An anterior cruciate ligament (ACL) tear can be a devastating sports injury. Every year, 400,000 people, many of them teen athletes, sustain ACL injuries or tears. The current standard of care, surgical ACL reconstruction, is not an adequate solution for young patients, since children and adolescents face a high risk of developing premature osteoarthritis after conventional knee surgery. Martha Murray has worked for more than two decades to find a better way to fix ACL injuries—and to create a new procedure known as bridge-enhanced ACL repair (BEAR) that encourages natural healing. Instead of removing the torn ACL and replacing it with a tendon graft, the BEAR technique uses a special protein-enriched sponge to encourage the torn ends to reconnect and heal. Dr. Murray’s team recently completed the first clinical trial to evaluate the safety of bridge-enhanced ACL repair and now her team is enrolling additional patients in a 100-patient clinical study.
TIS 2013 Awardees

**Annapurna Poduri, MD, MPH**  
*Director, Epilepsy Genetics Program*  
*Boston Children’s Hospital*  
*Assistant Professor of Neurology*  
*Harvard Medical School*

Ann Poduri is seeking new ways to treat epilepsy. An expert in the genetics of seizure disorders, Dr. Poduri and her team established a patient registry and created a zebrafish model of PCDH19—a “female-only” epilepsy gene. A recent avenue of her research involves working with fellow TIS investigator, Alex Rotenberg, to examine the effects of PCDH19-related epilepsy on electrical brain activity in these fish; she will also use these animal models to test drug compounds for potential therapeutic effects. Dr. Poduri’s overall goal is to initiate a new wave of gene-targeted epilepsy therapies that will dramatically improve the health and quality of life for many children and families.

**Scott Snapper, MD, PhD**  
*Wolpow Family Chair in IBD Treatment and Research*  
*Director, Center for Inflammatory Bowel Disease*  
*Boston Children’s Hospital*  
*Associate Professor of Medicine*  
*Harvard Medical School*

Scott Snapper is partnering with colleagues around the world to determine the genetic, immunological, microbial, and environmental influences that contribute to a little-understood and devastating illness, very early onset inflammatory bowel disease (VEO-IBD). Children under age six may become sick with a form of IBD that does not respond to conventional therapies. It can be fatal. New treatments are thus badly needed. Studying the disease as it presents in the youngest patients is also a unique opportunity to identify the genetic factors that play a role in IBD’s pathogenesis.
Suneet Agarwal, MD, PhD
Attending Physician in Hematopoietic Stem Cell Transplantation, Hematology/Oncology
Assistant Professor of Pediatrics
Harvard Medical School

Suneet Agarwal is a compassionate physician-scientist who has developed novel methods to reduce the harshness and improve the safety of bone marrow transplantation. He uses “direct reprogramming” to create stem cells from the skin cells of patients with blood disorders in order to understand disease mechanisms and develop new therapies. And he also studies how mutations in epigenetic pathways lead to blood stem cell failure and cancer. Dr. Agarwal applies his clinical perspective, scientific training and innovative research tools to improve understanding and treatment of blood diseases.

Rachel Rosen, MD
Director, Aerodigestive Center
Attending Physician in Gastroenterology, Hepatology + Nutrition
Assistant Professor of Pediatrics
Harvard Medical School

Rachel Rosen is a clinical investigator who has studied the impact of non-acid reflux on gastrointestinal and pulmonary diseases. She cares for patients with complex motility disorders, patients with intractable gastroesophageal reflux, and children with reflux-related chronic lung disease. Her research has focused on the impact of non-acid reflux on respiratory disease. She is also identifying biomarkers for reflux-related lung disease. Dr. Rosen has called her TIS award “invaluable and life-changing.” The same could be said for her patients, since Dr. Rosen’s research has resulted in new treatment guidelines for children with combined gastrointestinal and respiratory disease.
TIS 2011 Awardees

Richard Malley, MD,
Kenneth Macintosh Chair in Pediatric Infectious Diseases
Director, Travel and Geographic Medicine Clinic
Boston Children’s Hospital
Professor of Pediatrics
Harvard Medical School

Rick Malley is a world leader in the quest to develop more effective and less expensive vaccines against diseases that claim the lives of millions of children. His alternative pneumococcal vaccine has shown promise in clinical trials. And he has invented a new modular technology (Multiple Antigen Presenting System or MAPS) which offers the possibility of producing novel vaccines that protect against health threats to children and adults. With colleagues and support from funders including the Bill & Melinda Gates Foundation, he has formed a biotech company, Affinivax, which will apply MAPS to bring new vaccines to market. To further his highly translational research, Dr. Malley was awarded TRP seed grants in 2008, 2012, and 2013. He became a TIS member in 2011.

Alexander Rotenberg, MD, PhD
Research Associate in Neurology
Director, Neuromodulation Program
Associate Professor of Neurology
Harvard Medical School

Alex Rotenberg won TRP seed grants in 2009 and 2010 that allowed him to show that a direct electrical current could help subvert traumatic brain conditions like severe epileptic seizures. Support from his 2011 TIS grant allows him to design simple systems that can deliver just the right amount of current to the brain no matter who the patient or the severity of the incident. He is currently working to develop his devices with commercial partners. Dr. Rotenberg is also now working with fellow TIS awardee Ann Poduri to detect and measure seizures in zebrafish models of a genetic form of epilepsy, using novel electrophysiological tools developed and perfected in his lab.
Senior TIS Investigators

Three TIS “graduates” will continue their involvement in the TIS program as mentors to the current TIS team. This award, established in 2014, is aimed at building up the skills and knowledge base of the TIS group.

Sung-Yun Pai, MD
Associate Director Gene Therapy Program
Attending Physician, Hematology/Oncology
Assistant Professor of Pediatrics
Harvard Medical School

Sung-Yun Pai is one of the nation’s most promising researchers in the fields of bone marrow transplantation and gene therapy. Her studies of T cell development helped advance both conventional bone marrow transplants and innovative trials of gene therapy. Among her achievements are two New England Journal of Medicine articles, published in 2014, that give hope to patients with immune disorders previously thought to be incurable. Her TIS grant, which funded her work from 2010-2015, helped Boston Children’s develop its novel gene therapy approaches that led to clinical trials for rare immune disorders including X-linked severe combined immunodeficiency (X-SCID).

William Pu, MD
Assistant in Cardiology
Associate Professor of Pediatrics
Harvard Medical School

To help children with congenital heart disease, Bill Pu studies the regulation of gene expression. Awarded a TIS grant in 2010, his work has focused primarily on how transcription factors affect gene expression to guide heart development and control function. Dr. Pu has been systematically collecting heart muscle samples from patients with genetic forms of congenital heart disease and using stem cell technology to model their disease. He led a team in 2014 that used stem cell techniques and a new technology called organs-on-a-chip to grow for the first time functioning heart tissue affected by a cardiac condition called Barth syndrome. Dr. Pu is a past winner of the E. Meade Johnson award for research in pediatrics. He focuses on new approaches that promise to provide insights into the pathogenesis of heart disease.
Dr. Sahin is both a leading expert on the molecular structure of the brain and a pioneer in an exciting wave of translational studies testing drugs that may improve cognitive outcomes in genetically based neurodevelopmental disorders. A foremost expert on tuberous sclerosis complex (TSC)—a disease whose complications include autism and epilepsy—Dr. Sahin’s team investigates mutations implicated in neurodevelopmental disorders. He leads 10-center NIH-funded study of three rare genetic syndromes that often cause autism spectrum disorder (ASD) and intellectual disability (ID). The study’s ultimate goal is to launch clinical trials of new treatments and develop reliable biomarkers that can be used to monitor treatment effectiveness—for three rare syndromes and possibly for broader groups of ASD/ID patients. His 2009-2014 TIS award enabled him to make significant progress at the crossroads of discovery and treatment.
With a 2014 TIA grant, Dr. Pierre Dupont is leading a project aimed at dramatically improving the care of babies born without a fully formed esophagus. Long-gap esophageal atresia is an orphan disease in which a portion of the esophagus is missing at birth. The gap is too large to be bridged by conventional surgical approaches so the method now in use applies traction forces to the segments, causing them to lengthen and allow the two ends to join. But this approach requires the baby to be immobilized—a procedure that is difficult for the patient and costly. Dr. DuPont has created an implantable robotic device that can precisely apply traction forces to two segments of the esophagus in animal models. They are extending these animal studies and are also designing a miniaturized version suitable for babies—a revolutionary device that could stimulate the child’s body to grow a new esophagus over a period of several weeks and avoid immobilization.

Dr. Wayne Lenceral is working to harness molecular carriers for enzyme replacement therapies. Such therapies hold promise for a group of rare and lethal genetic disorders called lysosomal storage disorders in which the enzymes responsible for clearing certain fats are defective, resulting in toxic buildup in cells and early cell death. Funding from The Manton Center and other philanthropic sources enabled Dr. Lenceral and his team to generate results that led to significant industry support. They are now testing their techniques for creating protein-lipid fusions—a method for hooking the replacement enzyme to a carrier molecule that facilitates its transport through the bloodstream to target cells and tissues. Dr. Lenceral’s group is applying these methods in animal models of Hunter’s disease, setting the stage for enzyme replacement in humans.
Bridging the gap between research and clinical care

Boston Children’s Hospital’s Translational Research Program was created in 2008 to bridge the gap between research and clinical care. The TRP’s mission is to stimulate and facilitate preclinical, and ultimately, human translational studies to improve the care of children with serious diseases. To do this, the TRP provides support for faculty-initiated research, along with funding for infrastructure to get the projects completed efficiently.

Established with $5 million in seed money from Boston Children’s and further supported by the Venture Philanthropy Network (VPN), the TRP provides five forms of monetary support to researchers:

• **Seed grants** of up to $100,000 fund a one-year effort to pursue and validate innovative ideas.

• **Core grants** fuel a two-year effort to build up the research infrastructures—and the tools critical to translational research.

• **Translational Investigator Service (TIS) awards**, which total a minimum of $600,000, are distributed over five years to support remarkable researchers as they conduct translational studies.

• **Translational Innovator Awards (TIA)**, two-year grants that total $400,000, are intended to support the kind of game-changing projects nearly impossible to fund by any other mechanism.

• **Senior TIS grants** give past TIS awardees up to 20 percent of their NIH maximum salary for three years.

**Cycle of Translational Research**

A new treatment goes through a series of steps as it progresses from the basic “discovery” phase to the point where it is picked up by a biotechnology or pharmaceutical company. The TRP shepherds promising new treatments through the cycle of translational research.
TRP Leadership

David A. Williams, MD
Chief of the Division of Hematology/Oncology, Boston Children’s Hospital
Director of Clinical and Translational Research, Boston Children’s Hospital
Associate Chairman, Department of Pediatric Oncology, Dana Farber Cancer Institute
Leland Fikes Professor of Pediatrics, Harvard Medical School
President, Dana-Farber/Boston Children’s Cancer and Blood Disorders Center

An internationally renowned researcher, Dr. Williams’ work focuses on blood stem cell biology, leukemia, and gene therapy to correct genetic blood disorders. He has won numerous prestigious awards for his research, including: The E. Mead Johnson Award for Research in Pediatrics; the William Dameshek Award of the American Society of Hematology; the Samuel Rosenthal Prize for Excellence in Pediatrics; the Frank Oski Award of the American Society of Pediatric Hematology/Oncology; the Donald Metcalf Award from the International Society of Experimental Hematology. He is the recipient of the American Society of Gene Therapy’s Outstanding Achievement Award for his work in gene therapy. He serves on the NIH Loan Repayment Program Study Section and has served as faculty and on the Joint Oversight Committee of the Translational Research Training in Hematology program of the European Hematology Association and American Society of Hematology. He is immediate past-President of the American Society of Hematology, the world’s largest professional society concerned with the causes and treatment of blood disorders. Dr. Williams was a Howard Hughes Medical Institute investigator for 16 years, is currently a member of the National Academy of Sciences Institute of Medicine, and is a Fellow of the American Association for the Advancement of Science.

Dr. Williams originally trained in hematology/oncology at Boston Children’s Hospital and Dana-Farber Cancer Institute. During his fellowship research at the MIT Cancer Center and the Whitehead Institute, he developed techniques to use retroviruses for introducing genes into murine and human hematopoietic cells that are still commonplace today and utilized in many human gene therapy trials. Dr. Williams has multiple patents, several of which have been licensed to pharmaceutical and biotechnology firms. He has an active research laboratory that has been continuously NIH funded since 1986. In addition to ongoing clinical work in pediatric hematology, he leads multiple human gene therapy clinical trials.
Trained as a cell and molecular biologist, Dr. Fleming did her undergraduate studies at Bryn Mawr College, and her dissertation work on protein transport in platelets and endothelial cells at the nonprofit research and educational organization formerly called the Immune Disease Institute, which became affiliated with Boston Children’s Hospital in 2009. (It’s now called the Program in Cellular and Molecular Medicine or PCMM.) After receiving her PhD from Tufts Medical School, Dr. Fleming spent seven years as a post-doctoral fellow at Children’s in the Division of Hematology/Oncology. There, she defined the biochemical and genetic defects in the rare inherited disease thiamine-responsive megaloblastic anemia with diabetes and deafness (TRMA).

Leaving Children’s in 2004, Dr. Fleming went to Merck & Co. as a Senior Research Biologist in the Cancer Biology and Therapeutics group, where she provided scientific support for late-phase clinical trials that led to FDA approval of Zolinza (vorinistat), the first compound licensed for clinical use in a new class of drugs—histone deacetylase (HDAC) inhibitors. Thereafter, her efforts were focused on pre-clinical investigation and validation of other HDAC inhibitors as well as additional novel anticancer drug targets. In May 2008, Dr. Fleming returned to Children’s to help Dr. Williams establish and grow the TRP. She is now the Associate Director for Clinical and Translational Research.
To select the best ideas and programs with the highest chances of success, the TRP applies an extremely rigorous review process for seed and core grants, comparable to that of the National Institutes of Health (NIH). The TRP has enlisted 21 world-class researchers, each a star in his or her field of expertise, to evaluate grant submissions received from Boston Children’s elite candidate pool.

Jane Amara, Ph.D.
Associate Director, Technology & Innovation Development Office, Boston Children’s Hospital

Dr. Amara joined the Technology & Innovation Development Office at Boston Children’s in October of 2012. Prior to joining TIDO, whose mission is to maximize the impact of Boston Children’s innovations on patient health while enhancing research, she worked in venture capital, overseeing investments into university spin-out companies in the UK. Before that, she worked in biotech business development, including five years identifying, evaluating, and executing transactions at Biogen Idec. Her industry experience also includes research and project management responsibilities at start-up and established companies, including Genzyme and ARIAD Pharmaceuticals. Jane earned a B.A. in Biology from the University of California, San Diego, and a Ph.D. in Pharmacology from Yale University. She was a postdoctoral fellow in the laboratory of Dr. Harvey F. Lodish at the Whitehead Institute.

Roberto Chiarle, MD
Research Associate, Boston Children’s Hospital
Associate Professor, Harvard Medical School

Dr. Chiarle focuses his work on chromosomal translocations in lymphomas and other cancer. He focuses on chromosomal translocations that involve the Anaplastic Lymphoma Kinase gene, which is involved in the pathogenesis of Anaplastic Large Cell Lymphoma (ALCL), Non-Small Cell Lung Cancer (NSCLC) and other tumors. In 2008, he joined Dr. Fred Alt (Children’s Hospital Boston, HHMI) lab as a Visiting Professor to develop a high-throughput genome-wide translocation sequencing (HTGTS) method that allows the cloning of thousands of chromosomal translocations genome-wide and can be used to generate genomic maps of translocation in any cell type. He came to Boston Children’s Hospital in February 2012 to expand his research interests in the mechanisms of chromosomal translocations formation and in the molecular pathogenesis and therapy of lymphoma and solid tumors.
Michela Fagiolini, PhD
Associate in Neurology, Boston Children’s Hospital
Assistant Professor of Neurology, Harvard Medical School
Dr. Fagiolini research aims at understanding how neuronal cortical circuits are sculpted by sensory experience in early postnatal life, identifying the mechanisms underlying cortical plasticity in neurodevelopmental disorders and developing new treatments that can be rapidly translated in a clinical setting. Recently she has discovered a clear visual cortical phenotype in mouse models of Rett syndrome and demonstrated its rescue by environmental and genetic manipulation using behavioral, electrophysiological and molecular techniques. These results reveal a specific role for Mecp2 in the experience-dependent refinement of cortical circuits by regulating the excitation of pivotal inhibitory neurons. The identification of a particular receptor pathway within a specific cortical circuit has offered an accessible membrane target for drug intervention strategies that do not rely on the re-expression of Mecp2 itself. These findings have launched a very fruitful collaboration with the Rett Clinic and the Laboratory of Cognitive Neuroscience at BCH to assess the vision in young girls with Rett syndrome and discovered significant atypical visual processing using Visual Evoked Potential technique (VEP). Importantly, we can now use VEP as a robust biomarker of both cortical status and its response to therapy.

Mark Fleming, MD, D.Phil
Pathologist-in-Chief, Department of Pathology, Boston Children’s Hospital
S. Burt Wolbach Professor of Pathology, Harvard Medical School
Dr. Fleming is an expert hematopathologist specializing in the diagnosis of cancers of the blood and lymph systems. His research has provided new insight into iron deficiency. Dr. Fleming earned his undergraduate degree in molecular biology from Princeton University in 1987, his doctor of philosophy in organic chemistry from the University of Oxford in England in 1990 and his medical degree from Harvard Medical School in 1993. He received the prestigious Pew Fellowship in Biomedical Research in 2000.

Rani George, MD, PhD
Attending Physician, Department of Pediatric Hematology and Oncology, Dana-Farber Cancer Institute and Boston Children’s Hospital
Associate Professor of Pediatrics, Harvard Medical School
Dr. George is a physician-scientist whose laboratory focuses on two aspects of the pediatric solid tumor neuroblastoma, identifying molecular targets that can be translated into novel therapies and understanding the perturbations that occur during development to drive neuroblastoma initiation and progression. She led the effort that resulted in the discovery of inhibitor-sensitive mutations in the ALK tyrosine kinase receptor in neuroblastoma tumors, establishing this receptor as a tractable therapeutic target in this disease. Additionally, her laboratory has characterized the enhancer landscape of MYCN-amplified neuroblastoma and has identified novel strategies to target the oncogenic effects
of amplified MYCN through inhibition of cyclin-dependent kinases involved in the regulation of transcription. Dr. George received an MD from the University of Liberia and a PhD from the University of Newcastle-upon-Tyne. She completed her pediatrics residency and pediatric hematology/oncology fellowship at Children’s Hospital Boston/Dana-Farber Cancer Institute. Her honors include a Medical Research Council (UK) Research Award, the Schweisguth Prize of the International Society of Pediatric Oncology (SIOP), a Young Investigator Award from the American Society of Clinical Oncology, and a Sidney Kimmel Cancer Foundation Award. Research in her laboratory is supported by the Friends for Life Neuroblastoma Foundation, Alex’s Lemonade Stand Foundation, National Institutes of Health, the American Cancer Society and the Department of Defense.

P. Ellen Grant, MD. MSc.
Director, Fetal-Neonatal Neuroimaging & Developmental Science Center, Boston Children’s Hospital
Professor of Radiology, Harvard Medical School
One of the world’s foremost pediatric neuroradiologists, Dr. Grant is the Founding Director of Boston Children’s Fetal-Neonatal Neuroimaging and Developmental Science Center (FNNDSC) and the first incumbent of Boston Children’s Hospital Chair in Neonatology. The FNNDSC is focused on developing and optimizing tools and analysis streams to better understand normal and abnormal brain development with the goal of improving cognitive and neurological outcomes. The three modalities involved in the center are Magnetic Resonance Imaging (MRI), Magnetoencephalography (MEG) and Near Infrared Spectroscopy (NIRS). In addition, FNNDSC has a computational core that provides access to imaging analysis pipelines through web-based tools and a high performance computing backbone developed and managed by the FNNDSC.

Dr. Grant headed the Division of Pediatric Radiology at Massachusetts General Hospital for five years before moving to Boston Children’s Hospital. She has won a number of awards for her research as well as recognition for her clinical excellence. She holds a Master of Science degree in Physics and an MD from the University of Toronto. She did her Radiology residency at Vancouver General Hospital in British Columbia, Canada, and her fellowship in Adult and Pediatric Neuroradiology at the University of California, San Francisco.

Joel Hirschhorn, MD
Director, Center for Basic and Translational Obesity Research, Boston Children’s Hospital
Attending in Endocrinology, Boston Children’s Hospital
Concordia Professor of Pediatrics and Professor of Genetics, Harvard Medical School
Dr. Hirschhorn’s research focuses on using human genetics and genomics to identify genes that influence common diseases and quantitative traits, including obesity and height. He leads the GIANT consortium, which has discovered nearly all of the common variants known to be associated with anthropometric traits. His laboratory uses genetic data and novel computational methods to uncover underlying biology of obesity, skeletal growth, diabetic kidney disease, and other polygenic diseases and traits. The lab also uses sequencing to understand the role of rare variation in short stature and
other endocrine disorders. A winner of the E. Mead Johnson Award from the Society for Pediatrics Research, Dr. Hirschhorn has published over 200 papers and has received many other awards.

Dr. Hirschhorn received his A.B. summa cum laude in biochemistry from Harvard College and later earned his M.D. and Ph.D. in genetics from Harvard Medical School. He completed a fellowship in pediatric endocrinology at Boston Children’s Hospital and postdoctoral training with Eric Lander at the Whitehead Institute/MIT Center for Genome Research. In 2001, he started as a faculty member at Boston Children’s Hospital and Harvard Medical School, and has been a member of the Broad Institute since its founding. Dr. Hirschhorn is currently the Concordia Professor of Pediatrics and Professor of Genetics at Children’s Hospital/Harvard Medical School and an Institute Member of the Broad Institute.

John Kheir, MD  
Staff Physician, Cardiac Intensive Care Unit  
Department of Cardiology, Boston Children’s Hospital  
Assistant Professor, Harvard Medical School  
Dr. Kheir is a Principal Investigator in the Department of Cardiology at the Boston Children’s Hospital Heart Center whose lab studies the measurement and optimization of oxygen delivery. Because much of the organ damage that happens in patients with heart disease occurs due to oxygen deprivation (either as a result of heart disease or during the process of repairing it), the lab is developing techniques to measure the energy states of the work horse of the cell, the mitochondria, to give a clear picture of when oxygen-related organ injury is occurring. He has also developed a clinical protocol to examine the amount of oxygen being delivered and consumed by infants undergoing repair of complex congenital heart disease. Finally, over the past 8 years, he and his team have been working to create an injectable form of oxygen gas which may be used to rescue patients from severe oxygen deprivation due to choking, anesthetic procedures, lung disease or heart attacks (see his talk at TEDMED 2013).

Jordan Kreidberg, MD, PhD  
Director, Development and Stem Cell Research, Boston Children’s Hospital  
Professor of Pediatrics, Harvard Medical School  
Dr. Kreidberg is widely recognized for his innovative research in organ formation and malfunction. His discovery that the Wilms’ tumor gene controls kidney development was a major breakthrough in renal cancer research. A leader among his peers, Dr. Kreidberg served on the NIH’s Study Section that reviews all grant applications for the study of kidney development. He is a member of the Children’s Hospital Stem Cell Program executive committee and chairs the Membership Committee for the Harvard Stem Cell Institute. Dr. Kreidberg also directs Children’s Office of Fellowship Training, offering research and career development seminars to fellows and faculty.
Richard Lee, MD
Department of Urology, Boston Children’s Hospital
Assistant Professor of Surgery (Urology), Harvard Medical School
Dr. Lee is a Surgeon-Scientist who spends half of his time as a Pediatric Urologist and half in translational research. His clinical work focuses on the management and treatment of renal damage from urologic associated pathology. His clinical concentration translates well to his basic research which focuses on identifying urinary biomarkers of renal damage. He has developed one of the largest pediatric urine, plasma and tissue banks available (PUPPI – Pediatric Urinary Proteome Program Initiative). He is also leading the Department’s Translational Urinary Proteomic Initiative. As a by-product of his research, it has lead to the development of three novel and unique research techniques that in collaboration with the Technology and Innovation and Development Office are moving towards commercial development.

Rick Malley, MD
Kenneth McIntosh Chair in Pediatric Infectious Diseases, Boston Children’s Hospital
Director, Travel and Geographic Medicine Clinic, Division of Infectious Diseases,
Boston Children’s Hospital
Professor of Pediatrics, Harvard Medical School
Dr. Malley is a world leader in the quest to develop more effective and less expensive vaccines against diseases. He has authored dozens of important publications on pneumococcal pathogenesis and prevention, acquired and innate immunity, correlates of protection and mechanisms of infection. He has also worked on developing predictive models of meningococcal disease and models to distinguish bacterial from viral meningitis. With the support of PATH, a nonprofit organization based in Seattle, Dr. Malley headed up a group of researchers from Boston Children’s Hospital, Instituto Butantan in Brazil, and the University of Goteborg in Sweden to manufacture a novel pneumococcal vaccine suitable for developing countries. This work has entered its clinical phase, with a Phase I trial of this novel vaccine having been successfully completed in December 2012, and a Phase II trial currently ongoing in Kenya. Dr. Malley’s group also received funding from the Bill and Melinda Gates Foundation to develop a vaccine against typhoid fever and pneumococcus; in addition he has received NIH funding for over a decade. His group has also recently discovered a novel technology, so called Multiple Antigen Presentation System (MAPS) for the development of highly effective vaccines that target multiple pathogens. This work has led to the creation of a biotechnology company in Cambridge, funded by the Bill and Melinda Gates Foundation and which will focus on the development of novel vaccine based on the MAPS technology. The lead program at Affinivax is the development of a universal pneumococcal vaccine, with planned clinical trials to begin in 2017.
Benjamin Matthews, MD
Staff Physician, Division of Medicine Critical Care, Boston Children’s Hospital
Assistant Professor of Pediatrics, Harvard Medical School

The unifying themes in Dr. Matthews’ research are 1) to understand the molecular basis of mechanotransduction (a process whereby cells sense and convert mechanical forces into biochemical signaling) and 2) to design mechanotransduction based treatment strategies to prevent ventilator induced lung injury (VILI), an acute inflammatory process that contributes to mortality in adult and pediatric aged patients with respiratory failure. Dr. Matthews developed novel in vitro micromanipulation techniques to apply large scale (nN) forces to cells through ligand coated micron sized magnetic beads. This work led to the discovery that force applied to certain cells induces near instantaneous (<5 ms) localized calcium influx through the stretch activated membrane ion channel TRPV4, which has subsequently been found to mediate lung edema in VILI. Dr. Matthews also helped design and characterize an in vitro ‘lung-on-a-chip’ micro-fluidic device that recapitulates physiological functions of the human alveolus including oxygenation, pulmonary fluid barriers, and inflammatory responses, and permits analysis of lung physiology and pathophysiology by real-time, high-resolution imaging, microfluorimetry and fluorescence microscopy. In also establishing ex vivo and in-vivo murine lung models to complement the in-vitro models, Dr. Matthews is now focused on developing inhalation based drug delivery strategies that target TRPV to prevent VILI and other forms of lung edema.

Martha Murray, MD
Orthopedic Surgeon, Boston Children’s Hospital
Associate Professor of Orthopedic Surgery, Harvard Medical School

Dr. Murray is working on novel methods to treat injuries of tissues within joints. Tissues that live within joints (the ACL, rotator cuff, meniscus, articular cartilage, hip labrum, etc.) all have difficulty healing after injury and after enough damage, these tissues are typically excised rather than repaired. Her lab focuses on defining why these tissue don’t heal when others do, and overcoming that problem using a novel tissue-engineered scaffold to enhance healing of joint tissues. Her lab’s first target tissue is the ACL and preclinical studies of a bridge-enhanced ACL repair (BEARTM) technique are promising. With the help of the TRP, her team has recently completed enrollment for a first in human study of this ACL technology and obtained FDA approval for a 100 patient pivotal trial at Boston Children’s Hospital. Dr. Murray received her MD from the University of Pennsylvania. She completed a residency in orthopedic surgery at Harvard Medical School and fellowships in pediatric orthopedics and sports medicine at Boston Children’s Hospital.
**Sung-Yun Pai, MD**

*Division of Hematology/Oncology, Boston Children’s Hospital*
*Associate Professor of Pediatrics, Harvard Medical School*

Dr. Pai is a physician scientist and Associate Professor at Boston Children’s Hospital and Dana-Farber Cancer Institute. A graduate of Harvard Medical School, she completed pediatrics residency at Boston Children’s Hospital and fellowship in pediatric hematology-oncology at Dana-Farber Cancer Institute. Her research focuses on the development of better treatments for children with primary immunodeficiency, including allogeneic hematopoietic stem cell transplantation and gene therapy. Her laboratory investigates immune reconstitution and biomarkers of successful immune function after cellular therapy.

**William Pu, MD**

*Department of Cardiology, Boston Children’s Hospital*
*Professor of Pediatrics, Harvard Medical School*
*Principal Faculty, Harvard Stem Cell Institute*

Dr. Pu’s lab studies heart development and heart regeneration. The lab is interested in transcriptional regulation of cardiac development, and in applying lessons learned from heart development to heart regeneration. TRP-funded research is directed at developing induced pluripotent stem cell models of heart disease and using those models to advance heart disease treatment. Dr. Pu received his MD summa cum laude from the Harvard-MIT program in Health, Sciences, and Technology. After completing pediatrics residency and pediatric cardiology fellowship at Boston Children’s Hospital, Dr. Pu received research training at Harvard Medical School. He is an Established Investigator of the American Heart Association and received the 2013 E Mead Johnson Award for Pediatric Research.

**Rachel Rosen, MD**

*Division of GI/Nutrition, Boston Children’s Hospital*
*Assistant Professor of Pediatrics, Harvard Medical School*

Dr. Rosen has been studying the impact of acid and non-acid reflux on respiratory symptoms in children and discovering biomarkers of reflux related lung disease. Dr. Rosen’s research interest grew out of a clinical observation that many children continue to have symptoms of gastroesophageal reflux despite normal reflux testing. She hypothesized that patients experience persistent reflux undetected by standard testing, and that this reflux is weakly or non-acidic with a pH>4. Using multichannel intraluminal impedance technology, she discovered that non-acidic, full-column reflux events were more likely than acid events to trigger pulmonary symptoms and to impact clinical outcome. Since all prior pediatric research focused on the diagnosis and treatment of acid reflux, this was a paradigm-shifting discovery. She then asked, “by what mechanism can non-acid reflux influence disease?” Again, a clinical observation shaped scientific inquiry as more than 30% of patients at BCH have positive bronchoscopy cultures. Dr. Rosen hypothesized that these positive cultures resulted from microaspiration of refluxed, non-acidic, bacterial laden gastric contents into
the airways. Dr. Rosen showed that, in children with chronic cough or with cystic fibrosis, lung culture positive patients have significantly more full-column, nonacid reflux than culture negative patients do. Her current research is focused now on the impact of a nonacidic gastric milieu (seen in children taking antacids) on gastric, lung, saliva and stool microflora and the resultant risk for clinical infection. Dr. Rosen has close collaborations with the Broad Institute and the MIT Center for Microbiome Informatics and Therapeutics.

**Alexander Rotenberg, MD, PhD**  
*Director, Neuromodulation Program, Department of Neurology, Boston Children’s Hospital*  
*Associate Professor of Neurology, Harvard Medical School*

Dr. Rotenberg’s translational research is focused on noninvasive electrical brain stimulation, a rapidly evolving field in neurotechnology. In recent years, he developed both a clinical program for noninvasive brain stimulation for children, and a laboratory for preclinical development and testing of novel brain stimulation protocols in animal disease models. Most of Dr. Rotenberg’s experimental work has been dedicated to the development of diagnostic and therapeutic applications for transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in epilepsy and in related syndromes. With support form the Translational Research Program, Dr. Rotenberg has established the first Neuromodulation Program in a children’s hospital where, beyond epilepsy, he anticipates to provide noninvasive brain stimulation treatment options for children with major depression, stroke, chronic pain, and other neuropsychiatric disorders for which conventional drug therapies are incompletely effective. His research is otherwise supported by the NIH, Department of Defense, industry grants, and other sources.

**Mustafa Sahin, MD, PhD**  
*Director of the Multi-Disciplinary Tuberous Sclerosis Program, Boston Children’s Hospital*  
*Professor of Neurology, Harvard Medical School*

Dr. Sahin is one of the world’s foremost experts in tuberous sclerosis complex (TSC). He established and directs Children’s Multidisciplinary Tuberous Sclerosis Program. Dr. Sahin’s research on nerve fiber connections has improved our understanding of nerve function and new treatment approaches to epilepsy and autism. He has received numerous awards, including the 2005 Young Investigator Award from the Child Neurology Society and a 2009 John Merck Scholar Award. He is the PI of a multi-center Autism Center of Excellence (ACE) Network grant and a multi-center Rare Diseases Clinical Research Network from the NIH.
Scott B. Snapper, MD, PhD
Wolpow Family Chair in IBD Treatment and Research
Director, Inflammatory Bowel Disease Center
Director of Basic and Translational Research
Associate Professor of Medicine, Harvard Medical School

Dr. Snapper’s translational research is focused on understanding the genetic, immunological, microbial, and environmental influences that lead to very early onset inflammatory bowel disease (VEO-IBD). Inflammatory Bowel Disease is a chronic intestinal inflammatory condition that can afflict all individuals; VEO-IBD is defined as affecting children less than six years of age. Dr. Snapper’s team has begun an international effort (www.veoidb.org) to understand the basis of the disease in young children. Although the work is international in scope, his effort is centered at Boston Children’s with involvement of basic and translational scientists, clinicians, and research coordinators spanning several departments. Dr. Snapper’s research is a true marriage between basic and translational science, and has already led to the identification of a number of new genetic causes of VEO-IBD and the development of at least one new novel therapeutic approach.

Martha Sola-Visner, MD
Attending Neonatologist, Division of Newborn Medicine, Boston Children’s Hospital
Associate Professor of Pediatrics, Harvard Medical School

Dr. Sola-Visner’s research focuses on identifying the mechanisms underlying the predisposition of newborn infants to develop low platelet counts and bleeding, and the best therapeutic options for these problems. Her research program has been nearly continuously funded by the NIH, and she has served as a permanent and ad hoc member of multiple NIH Study Sections. Dr. Sola-Visner was also part of the National Heart, Lung and Blood Institute Pediatric Transfusion Medicine Task Force, served as chair of the American Society of Hematology Scientific Committee on Platelets, and is currently a member of the NIH/NHLBI Program Project Grant Parent Committee.

Lucinda Williams, DNP, MSN, RN, PNP
Program Director, Research Nursing, Boston Children’s Hospital
Nursing Director, Clinical and Translational Study Unit (CTSU), Boston Children’s Hospital

Ms. Williams is the Nursing Director for the CTSU at Boston Children’s hospital where she and the staff of the CTSU aid investigators in operationalizing clinical research studies with children. Ms. Williams has worked in pediatric hematology/oncology/stem cell transplant and clinical research for more than two decades and has focused on improving outcomes for pediatric Hematology/Oncology patients, who continue to face sepsis and other acute events that cause serious illness. When she and colleagues implemented a pediatric early warning scoring tool (PEWS) with an associated multi-disciplinary action algorithm in a pediatric/oncology unit, they were able to remove barriers to timely referral of children who are clinically deteriorating and need immediate help. Their work also enhanced multi-disciplinary team communication, and led to a more than three-fold increase in days between codes on the Hematology/Oncology unit.
Boston Children’s receives more NIH awards than any other pediatric hospital. We rank third among all 5,000+ independent hospitals.