Boston Children's Hospital

Until every child is well™

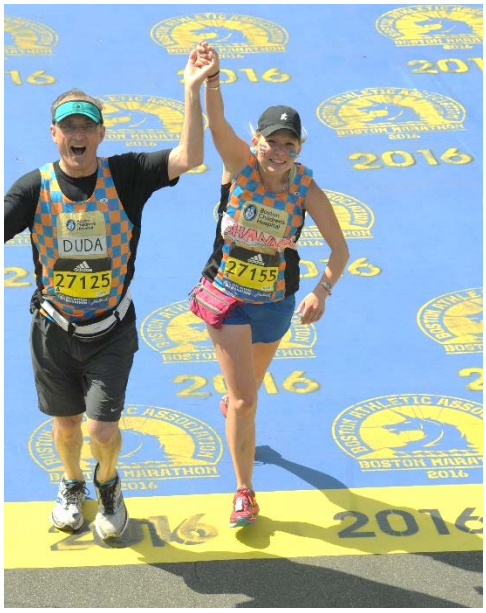
the future thanks you

To solve complex and rare medical disorders, such as abnormalities in blood vessel formation or pediatric brain tumors, cross-disciplinary collaborations are essential. Boston Children's—the world's largest pediatric research enterprise— has renowned oncologists, neurologists, neurobiologists, bio-statisticians, surgeons, vascular anomaly specialists, and radiologists among its pediatric experts. And—critically—we have exceptional philanthropic partners like the Credit Unions Kids at Heart Team.

Your wonderful generosity is vital to fueling discoveries and bringing us closer to novel diagnostic tools and treatments for children with moyamoya disease, cerebral palsy, malignant tumors, and Sturge-Weber Syndrome. On behalf of the patients and families who will benefit, our heartfelt thanks. Your team gives them hope!

Cleared to run—one patient's story

As Shannon Smith settled back in her dorm room after Thanksgiving break 2012, she suddenly noticed her right peripheral vision was blurry. Minutes later it cleared, but was replaced by a bad headache. A swift multi-institutional medical odyssey began as Shannon, with her parents soon at her side, went from a neighborhood urgent care center to a county hospital and then a neurologist in Pittsburgh, her hometown. A preliminary diagnosis of moyamoya disease sent her parents online. Their research led the family to Boston Children's Dr. Edward Smith.



"My brain was the only part of my body that didn't hurt," says Shannon after completing the 2016 Boston Marathon alongside Jim Duda, her Credit Unions Kids at Heart partner. It was Shannon's first marathon.

At Boston Children's, the angiogram both confirmed the diagnosis and showed the arteries were much more narrow and concerning than earlier scans had suggested. Dr. Smith recommended surgery, and it was scheduled for December 26—just a month after Shannon first noticed symptoms. "Dr. Smith told my parents I had a very boring brain and that that was very good," Shannon laughs. Three days after surgery she was discharged. And ten days after that, she was back in school. Not only did Shannon not fall behind as a result of her medical crisis, she graduated a semester early.

But before that day came, Shannon took on a daunting challenge. She got a call from Tracey Dickey of Credit Unions Kids at Heart—a long-standing supporter of Dr. Smith's work. Dr. Smith had suggested Tracey call Shannon to see if the cross-country runner might be interested in tackling the Boston Marathon as part of the Credit Unions Kids at Heart fundraising team. With the enthusiastic support of her college coach, Shannon began training. "To the best of our knowledge," Shannon says, "I'm the first person with moyamoya disease to run the Boston Marathon."

Shannon now shares her adventurous spirit with visitors to Disney World in Orlando, where she's a skipper on the Jungle Cruise. She returns to Boston once a year for her check-up. "Boston Children's and Dr. Smith are the reason I'm alive today. That's where indirect revascularization surgery was developed, and if it hadn't been…. Each year, my chance of a stroke would have continued to increase." Shannon pauses. "Boston Children's is a special place."

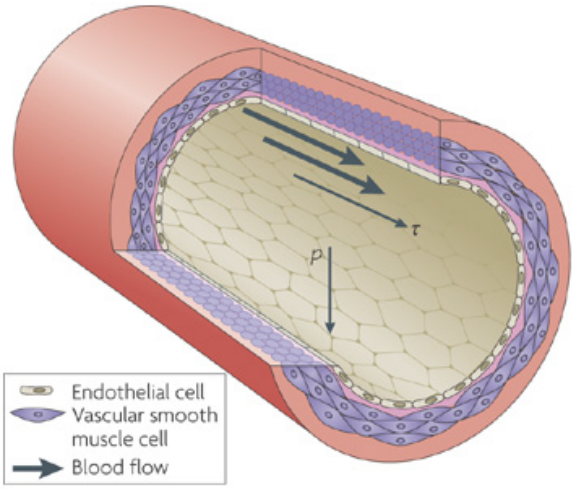
Brighter futures for children with cerebrovascular diseases

Edward R. Smith, MD
Director, Pediatric Cerebrovascular Neurosurgery
Co-Director, Cerebrovascular Surgery and Interventions Center

Cerebrovascular disease research

Differences among endothelial cells

Building on many years' research at Boston Children's Vascular Biology Program, neurosurgeon Edward Smith, MD, and this year's Warner Fellow David Penn, MD, are studying endothelial cells, which form the linings of blood vessels. They are comparing the biology of endothelial cells that line brain blood vessels to ones that line veins. Drs. Smith and Penn hypothesize that differences may be key to the development of cerebrovascular diseases like moyamoya, arteriovenous malformations (AVMs), and cerebral palsy (CP). Specifically, they examined a protein called netrin-1, which Dr. Smith has been studying for several years. They found that endothelial cells in AVMs and moyamoya disease respond very differently to netrin-1 than normal brain endothelial cells and vein endothelial cells.



Nature Reviews | Molecular Cell Biology

Dr. Penn presented his findings at the Joint Section for Pediatric Neurosurgery, Congress of Neurosurgeons and American Association of Neurosurgeons meeting in December 2016, where he received the prestigious Shulman Award for the best paper presented by a resident-in-training.

Drs. Smith and Penn hope to investigate how the altered responses to Netrin could be translated into treatment with a drug that would counter netrin-1's effect. Their ongoing research will further clarify the biology of multiple cerebrovascular diseases and cerebral palsy.

X-ray findings guide moyamoya treatment

Dr. Smith and his colleagues established for the first time that small blood vessels that grow through natural cracks in the skull from the outside in, serve as excellent radiographic biomarkers of moyamoya disease and predict which patients will be helped most by surgery. Their studies of pre-operative x-rays revealed more of these blood vessels—called transdural

collaterals—than they had anticipated. Moreover, they determined that the transdural collaterals are more common in advanced disease and directly correlate with perioperative complications. The discovery (published in *Journal of Neurosurgery Pediatrics*, March 2017) will enable surgeons to better screen patients, predict outcomes, and reduce the risk of surgery. At Boston Children's, the finding has already changed clinical practice and decreased perioperative complications by 30 percent.

New screening guidelines for familial moyamoya

Together with Kristopher Kahle, MD, PhD, former Boston Children's fellow now at Yale University Medical Center, Dr. Smith conducted the first ever familial study of pediatric moyamoya. Drs. Smith and Kahle determined that just 6 percent of moyamoya cases are familial. As a result of their research, families who are at higher risk are now being screened for alterations in two genes. The vast majority of families no longer have the added worry, wondering who else in the family should be screened. Drs. Smith's and Kahle's paper describing their findings and new guidelines has been accepted for publication by the *Journal of Neurosurgery Pediatrics*.

Studies in moyamoya and vein of Galen malformations

Drs. Smith and Kahle also partnered to conduct whole exome studies of patients with moyamoya disease as well as patients with vein of Galen malformations. They have completed the genetic screening and are now analyzing the results. They hope to share findings by the end of 2017.

Cross-over between moyamoya and cerebral palsy

With the generous ongoing support from Credit Unions Kids at Heart, Dr. Smith is applying his understanding of blood vessel biology to help children with CP. Since many cases of CP are the result of a stroke, Dr. Smith and his team are using their extensive knowledge of vascular endothelial cells to investigate ways to promote healing in the brain. As noted, the team has received national recognition for the pioneering research this year. This work represents a novel approach to understanding CP and hopefully will open new avenues of treatment in the future.

International partnership

As part of the ongoing partnership between the largest pediatric cerebrovascular disease research programs in the U.S. and the U.K., neurosurgeon Greg James, MD, PhD, from Great Ormond Street Hospital/Institute of Child Health in London spent several weeks with the team at Boston Children's observing surgical techniques. In 2017, the Boston Children's team will attend the international conference in London that the two institutions jointly launched to study outcomes and treatments for pediatric cerebrovascular disease.

Clinical innovation

Real-time imaging

Better instruments, advanced imaging, and rehearsing procedures in advance have reduced anesthesia time and made complex neurosurgical procedures less risky. But the Cerebrovascular Surgery and Interventions Center team is always striving to do even better. They have begun using intraoperative ultrasound and catheter-guided minimally invasive surgery. Immediately before the neurosurgeon begins an operation, s/he takes an ultrasound of the patient's brain and then inserts a tiny catheter into the target area. The surgeon can observe the catheter going in, which provides further helpful input. Most importantly, the catheter viewed in real time on the ultrasound serves as a navigation device even when the child's head is moved during surgery. This innovation enables shorter and ever-safer surgeries (published in *Pediatric Neurosurgery,* January 2017).

Patient family outreach

A full auditorium reflected great interest and attendance at the first Warner AVM & VOGM Family Symposium May 7, 2016. The program included talks on current research and clinical care initiatives for these disorders, along with recruitment for ongoing research initiatives. It was also live-streamed across the U.S. and around the world to maximize patient-family education and engagement. On May 6, 2017, Boston Children's hosted the second Moyamoya Day Family Symposium. The day featured presentations by Boston Children's faculty, including Drs. Smith and Orbach, and Michael Scott, MD. They were also joined by Cormac Maher, MD, of the University of Michigan.

With gratitude

On behalf of the Cerebrovascular Surgery and Interventions Center team, deepest thanks for the Credit Unions Kids at Heart Team's partnership and vision. Your philanthropic gifts continue to advance knowledge and successful treatment of cerebrovascular diseases in children. Your support saves lives.

Towards new treatments for Sturge-Weber Syndrome

Mustafa Sahin, MD, PhD
Director, Translational Neuroscience Center
Director, Sturge-Weber Program

Under the leadership of Mustafa Sahin, MD, PhD, the Translational Neuroscience Center facilitates the coming together of cross-disciplinary expertise, bridging the gap between basic science and new therapies to improve the lives of children with nervous system disorders, including Sturge-Weber Syndrome (SWS).

The pilot studies at Boston Children's that the Credit Unions Kids at Heart Team so generously funded built on the discovery that the *GNAQ* gene mutation causes Sturge-Weber Syndrome. Enabled by your support, Joyce Bischoff, PhD, a molecular biologist in the Vascular Biology Program and plastic surgeon Arin Greene, MD, MMSc, pinpointed endothelial cells, lining blood vessels as the cells harboring the *GNAQ* mutation and likely responsible for malformed capillaries.

This discovery catalyzed new collaborations among Drs. Bischoff, Greene and Dr. Sahin's group—neurologist Anna Pinto, MD, PhD, whose research focuses on SWS and epilepsy in very young children, and Robin Kleiman, PhD, head of Preclinical Research in the Translational Neuroscience Center.

Homing in on endothelial cells

The team's focus is on understanding how the *GNAQ* mutation in endothelial cells contributes to the development of SWS. As part of this effort, Dr. Bischoff and her colleagues hope to identify biomarkers that would predict which patients with port wine stains are at risk of SWS. Their discoveries could also lead to new therapies to prevent neurological impairment.

Mutation shows up in blood vessel and brain tissue endothelial cells

Dr. Bischoff's studies to date show that in patients with SWS, the *GNAQ* mutation is present in blood vessel endothelial cells in the brain and in port wine stains (published in *Pediatric Neurology,* February 2017). Most recently in a key finding, her lab isolated endothelial cells from SWS brain tissue, measured secreted proteins, and found a number of alterations.

Comparisons among endothelial cells

In another series of experiments, Dr. Bischoff's lab has investigated how SWS brain endothelial cells behave compared to normal endothelial cells. Her team found that both respond robustly to molecules that promote blood vessel growth. Her lab also determined that the SWS brain endothelial cells behave similarly to normal human endothelial cells that

have been engineered to include the *GNAQ* mutation. This helped confirm that the engineered cells will work well as a model. With these discoveries and her lab's ability to culture and grow SWS brain endothelial cells, the team is poised to address a key question: how does the mutation alter interactions between blood vessels and brain cells in patients with SWS?

The role of secreted proteins

Dr. Bischoff and her team have identified 20 proteins that were secreted at high or low levels by *GNAQ*-mutant endothelial cells. Together with Dr. Kleiman, Dr. Bischoff's team had hypothesized that the mutant endothelial cells may secrete a complement of proteins that are distinct from normal endothelial cells and that some of these secreted proteins may harm surrounding brain cells and cause seizures. To test the idea, they measured over 1,000 human proteins secreted from the mutant endothelial cells using a highly sensitive and specific technique. They took advantage of the two *GNAQ*-mutant endothelial cell models in hand from earlier experiments and SWS brain endothelial cells from a second patient to provide internal cross-checks for this analysis.

How do the secreted proteins effect brain cells?

The team is excited to follow up on their discovery of the 20 abnormally secreted proteins. In particular, they will study elevated proteins for which there are FDA-approved drugs that could target and tamp down their activity. Dr. Bischoff is working closely with Dr. Kleiman and neurobiologists in Dr. Sahin's lab to model the SWS endothelial–nerve cell interactions. They are testing the effect(s) of the proteins secreted by the SWS brain endothelial cells on normal cortical nerve cells.

In addition, as a part of the research that was funded by the Credit Unions Kids at Heart Team, Dr. Pinto is now leading a national consortium aimed at preventing epilepsy and developmental delay in children with SWS. The application will be submitted to the NIH soon. If funded, this will be the first prevention trial in SWS.

With gratitude

Each experiment is providing new insights into how mutant endothelial cells cause SWS. Thanks to the Credit Unions Kids at Heart Team's steadfast support, we know so much more today than just a few years ago.

New therapies for children with brain cancer

Mark Kieran, MD, PhD
Director, Pediatric Medical Neuro-Oncology

The support of the Credit Unions Kids at Heart Team has been critical to advances in treating brain cancer in children. Dr. Kieran and his colleagues are passionate in their quest for effective and less damaging approaches, and are deeply grateful for your partnership.

Targeted drugs for low-grade glioma

The clinical trial in which Dr. Kieran and his colleagues evaluated dabrafenib had encouraging results. Building on its success as well as what physician scientists are learning from adult cancer studies, Dr. Kieran and his colleagues have now opened a new international clinical trial in which they are testing dabrafenib in combination with a second targeted therapy—trametinib. The trial includes children with low-grade glioma and other less common cancers in which the cancer cells have the BRAF V600E mutation. The combined therapy has been very effective for adult patients with melanoma who have the same mutation. As an added benefit, the two drugs taken together actually have fewer side effects than when they're taken separately. If this two-drug approach proves as effective as they hope, the goal is to evaluate the treatment at the time of diagnosis for children with high-grade glioma, who have few therapy options available when they relapse.

Dr. Kieran and his colleagues continue to unravel how errant signals are relayed in low- and high-grade glioma cells, instructing them to divide incessantly. They are discovering new drugs to block the process, especially at important cellular junctures. These drugs bind with the targeted molecule, preventing the signal from traveling down the cellular pathway to the nucleus so the cancer cell stops dividing and the tumor stops growing. It's like putting a key in a lock and breaking it. The door cannot be unlocked.

Learning even more from our patients

Two promising targeted drugs (MEK-162 and TAK-580) will be evaluated in upcoming trials. These studies will include a step that is increasingly a part of adult cancer trials but is relatively new in pediatric trials. For children whose brain tumors are operable, physicians will first treat them with the targeted drug for up to three weeks. Then the neurosurgeon will remove the tumor. This approach will make it possible for scientists to examine the cancer cells to see what effect the drug has had. How much of the drug is in the tumor? Did it bind to the molecule we want to block? Has the cancer cell by-passed the block? They are likely to discover critical information that will further improve cancer therapy.

Progress in diffuse intrinsic pontine glioma

Diffuse intrinsic pontine gliomas (DIPG) are the most lethal of all pediatric cancers. But now that physician scientists are learning so much more about the underlying biology and the

mutations that drive the majority of DIPG tumors, they can finally begin to develop new treatments. In the coming year, Dr. Kieran hopes to begin a multi-institutional trial to test a new targeted therapy on a subgroup of patients with DIPG, who share one particular mutation.

In another dramatic development Dr. Kieran is partnering with a company to design vaccines against the mutations he and his colleagues have identified. The vaccines being created are made from small, simple proteins called peptides. They won't prevent a child from developing DIPG. Rather, matched to the mutations that are propelling the cancer, the vaccines will stimulate the patient's immune system to home in on the cancer cells and destroy them. Their goal is to begin to evaluate one of the vaccines in patients within a year.

With gratitude

This exciting progress against brains cancers is made possible by dedicated friends like you, who have done so much over the years to advance treatments for patients. On behalf of all who benefit from your kindness and generosity, our heartfelt thanks.