



Annual Report 2014

Technology & Innovation Development Office



Boston Children's Hospital
Until every child is well™



**Boston
Children's
Hospital**

Boston Children's Hospital is a 395-bed comprehensive center for pediatric health care. *U.S. News & World Report* has named Boston Children's the number one pediatric hospital in the United States for 2014–15. In addition, eight of our clinical specialties were deemed to be the best of their kind in the nation. Boston Children's is home to the world's largest research enterprise based at a pediatric hospital. More than 1,300 scientists comprise our research community, including seven members of the National Academy of Sciences, 12 members of the Institute of Medicine, 14 members of the Howard Hughes Medical Institute (HHMI) and 28 members of the American Society for Clinical Investigation. Our research facilities include more than 800,000 square feet of basic and translational research space and 50,000 square feet of clinical research space.

\$290M

Total Research Funding

\$7.3M

Gross Licensing Revenue

\$5.7M

Net Licensing Revenue

\$11.4M

Industry Sponsored
Research Funding

45

Industry Research Agreements
(up 55%)

33

License & Option Agreements

175

Invention Disclosures

3

Startups Created

Technology & Innovation Development Office (TIDO) facilitates the translation of Boston Children's laboratory research and clinical expertise into lifesaving biomedical products, devices, software and algorithms for the public benefit. TIDO is a team of experienced professionals in academic and biomedical research, technology licensing, startup formation, business and law. TIDO partners Boston Children's experts and intellectual property with biotechnology, pharmaceutical, diagnostic, IT and medical device companies at all stages and forms new companies around platform technologies to achieve its mission.

Fiscal Year 2014 was a year of change and improved performance in the Technology & Innovation Development Office at Boston Children's Hospital.

As we move into FY15, we are happy to welcome and introduce TIDO's new Senior Director, Irene Abrams. Irene comes to TIDO with over 19 years of experience working at academic licensing offices, starting her career as a Technology Licensing Officer at MIT and most recently serving as an Executive Director at Partners Healthcare Innovation, responsible for commercializing technology from Massachusetts General Hospital. We want to recognize and thank Jane Amara, PhD, who served as the Interim Director through the end of the fiscal year. Her leadership and guidance was instrumental in keeping TIDO's operations moving forward and upward.

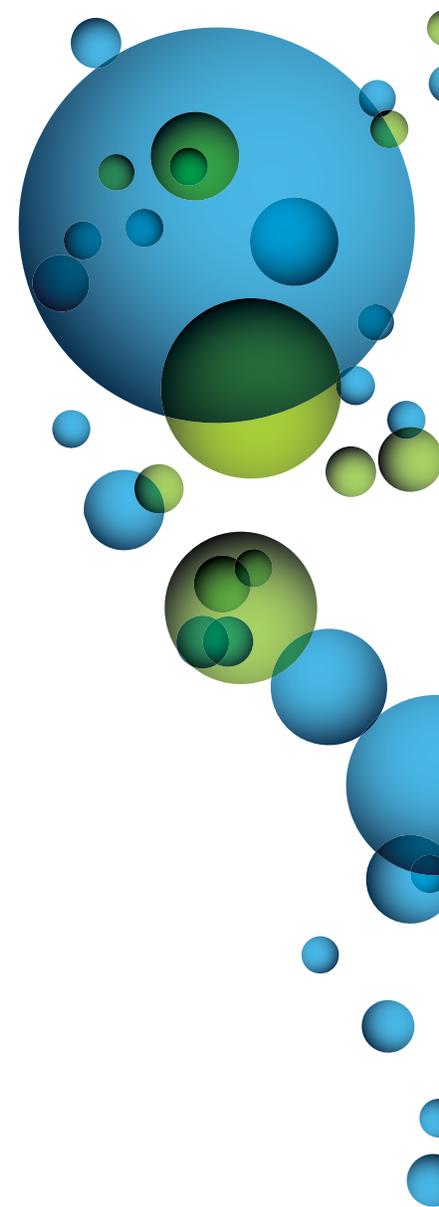
Boston Children's was recognized by *Nature Bioentrepreneur* in November 2014 as one of the top 10 biomedical research institutions in the country for our ability to execute technology licenses. This honor is a testament to TIDO's efforts to help translate Boston Children's technologies and laboratory research into lifesaving products.

A cornerstone of these efforts is the Technology Development Fund, a program to transform seed-stage academic technologies into later-stage, high-impact opportunities. In FY14, two Technology Development Fund projects hit commercial milestones: the MAPS vaccine platform developed by Richard Malley, MD, Infectious Diseases, was licensed to startup Affinivax (more on page 7) and Epidemico, an informatics startup company founded by John Brownstein, PhD, Boston Children's Hospital Informatics Program, was acquired by Booz Allen Hamilton.

Boston Children's collaboration and sponsored research agreements spiked to an all time high of 45 in FY14, a 55 percent increase over the prior year, while the number of negotiated and executed industry research agreements and licenses reached 78, an increase of 24 percent over the prior year.

TIDO's performance is measured by the impact Boston Children's technologies have on patients beyond our walls. To this end, we are proud that two Biogen Idec drugs based in part on Wayne Lencer's work in Gastroenterology received FDA approval for adults and children: ALPROLIX™ and ELOCTATE™ for treating hemophilia B and A, respectively. The drugs, longer-acting versions of the coagulation factors IX and VIII, will improve patient care by meaningfully reducing the frequency of infusions needed to treat these lifelong diseases.

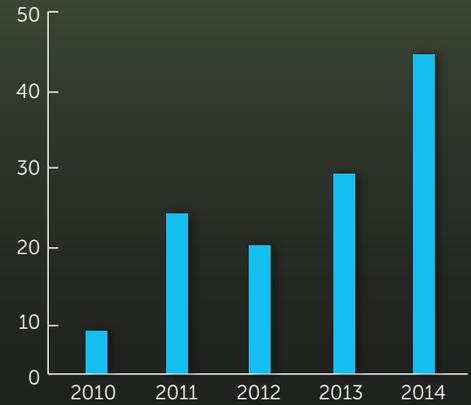
In FY15, TIDO will focus on continuing to build and facilitate new partnerships with industry to increase our chances of bringing our lifesaving products to market and helping patients worldwide.



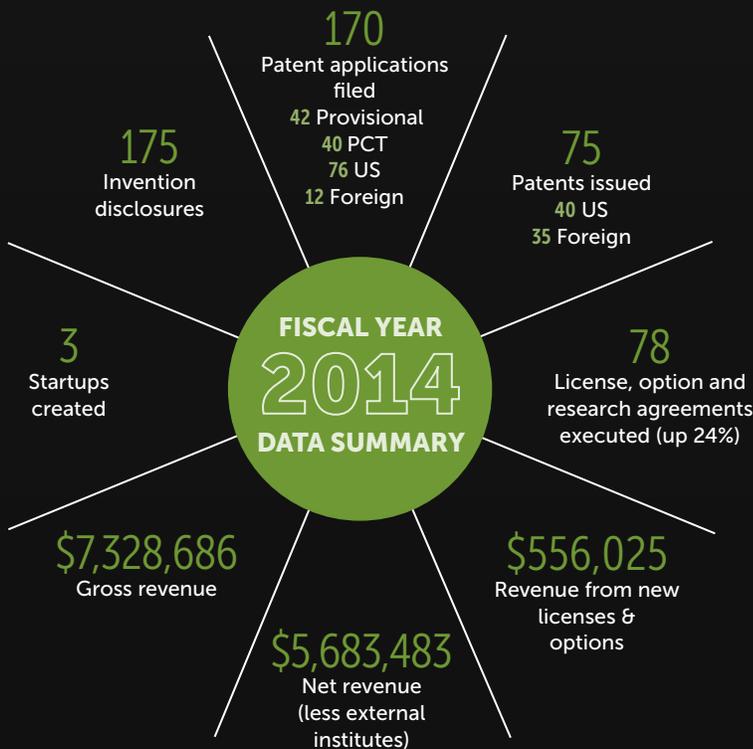
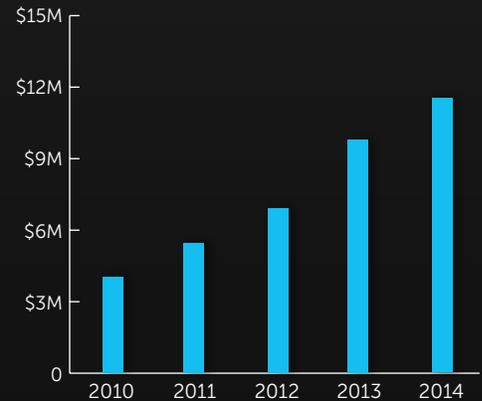
By the Numbers



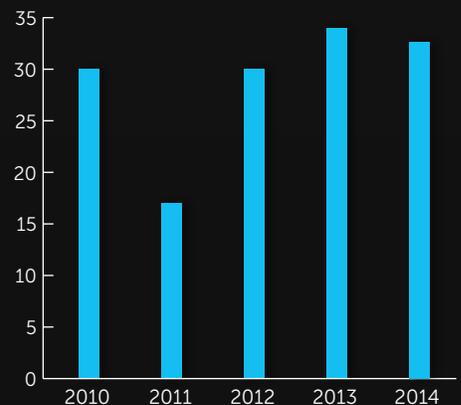
Sponsored Research and Collaboration Agreements



Corporate Sponsored Research Funding



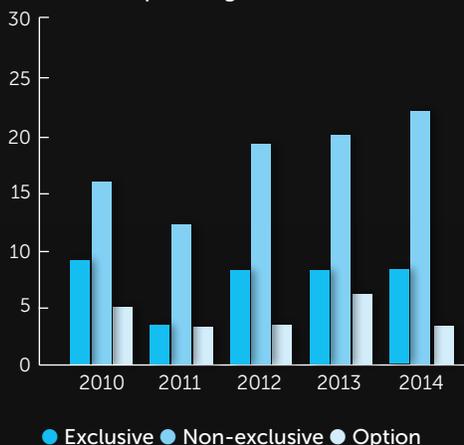
Licenses and Options Executed



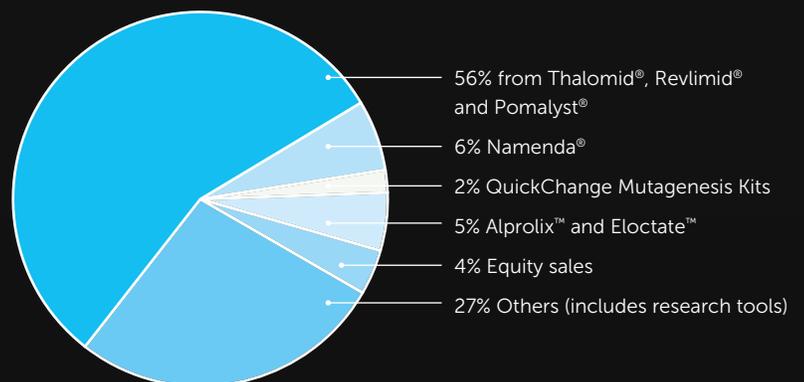
Issued US Patents

8,546,382	Daley, George Methods for enhancing hematopoietic progenitor cell engraftment	8,609,733	Kohane, Daniel Sensory-specific local anesthesia and prolonged duration local anesthesia	8,674,075	Williams, David Chimeric peptides for the regulation of GTPases
8,551,782	Zon, Leonard Methods for promoting HSC engraftment	8,642,735	Murray, Martha Biologic replacement for fibrin clot	8,679,029	Krauss, Baruch Automated interpretive medical care system and methodology
8,563,310	Zon, Leonard Methods for promoting hematopoietic reconstitution	8,647,861	Ingber, Donald Organ mimic device with microchannels and methods of use and manufacturing thereof	8,685,411	Harrison, Stephen Rotavirus antigens
8,569,280	von Andrian, Ulrich Methods for the treatment of multiple myeloma	8,652,508	Puder, Mark Dietary formulations and methods for treatment of inflammation and other disorders	8,685,659	Zetter, Bruce Method for diagnosis and prognosis of epithelial cancers
8,586,100	Mulligan, Richard Populations of hematopoietic stem cells	8,658,699	Kohane, Daniel Chemical permeation enhancers enhance nerve blockade by toxins	8,685,434	Teng, Yang (Ted) Methods and compositions for the treatment of open and closed wound spinal cord injuries
8,597,910	Orkin, Stuart DNA encoding von Willebrand Factor (vWF) and methods and cells for producing vWF, and vWF produced by the DNA, methods and cells	8,669,236	Zetter, Bruce Biotinylated compositions	8,697,072	Frank, Markus Targeting ABCB5 for cancer therapy
8,618,055	D'Amato, Robert Prominin-1 peptide fragments and uses thereof	8,673,552	Harrison, Stephen Druggable regions in the dengue virus envelope glycoprotein and methods of using the same	8,703,413	Daley, George Detection of human somatic cell reprogramming
				8,709,412	Umetsu, Dale Modulation of TIM receptor activity in combination with cyto-reductive therapy

Breakdown of License & Option Agreements



Sources of Licensing Revenue



8,716,465	Rossi, Derrick Kit for making induced pluripotent stem cells using modified RNAs	8,748,567	Narasimhaswamy, Manjunath Method for delivery across the blood brain barrier	8,802,438	Rossi, Derrick Compositions, kits, and methods for making induced pluripotent stem cells using synthetic modified RNAs
8,722,638	Ingber, Donald Methods for the modulation of angiogenesis	8,758,283	Rogers, Gary Orthotic device for preventing and/or correcting deformational posterior plagiocephaly	8,822,410	Kohane, Daniel Tympanic membrane permeating ear drops and uses thereof
8,729,248	Clapham, David Sperm-specific cation channel, CATSPER2, and uses therefor	8,772,471	Narasimhaswamy, Manjunath Targeted delivery of siRNA	8,822,539	Jensen, Frances Combination therapies: inhibitors of GABA transaminase and NKCC1
8,728,756	He, Zhigang Promoting axon regeneration in the adult CNS through control of protein translation	8,785,446	Jensen, Frances Treating post-seizure patients	8,835,105	Clapham, David Sperm-specific cation channel, CatSper4, and uses therefor
8,741,557	Schachter, Asher Predicting graft rejection	8,785,618	Lieberman, Judy Method of delivering RNA interference and uses thereof	8,842,333	Kohane, Daniel Particulate delivery vehicles for embryoid bodies
8,741,310	Harrison, Stephen Fusion-intermediate state of HIV-1 gp41 targeted by broadly neutralizing antibodies	8,790,634	D'Amato, Robert MetAP-2 inhibitor polymersomes for therapeutic administration	8,801,694	Dimitrakoff, Jordan Intravesical drug delivery device

Issued Foreign Patents

2060917	Moses, Marsha Non-invasive matrix metalloproteinase screen for prostate cancer	2007208243	Murray, Martha Methods and procedures for ligament repair	2012200909	Carroll, Michael Natural IgM antibodies and inhibitors thereof
2,361,334	Folkman, Judah Deglycosylated kringle 1-3 region fragments of plasminogen and methods of use	5480488	Klagsbrun, Michael Soluble inhibitors of vascular endothelial growth factor and use thereof	5557982	Carroll, Michael Natural IgM antibodies and inhibitors thereof
1154358	Atala, Anthony Augmentation of organ function	5513412	Corfas, Gabriel Treatments for neuropathy	5618852	Carroll, Michael Natural IgM antibodies and inhibitors thereof
2,552,882	Moses, Marsha Methods for diagnosis and prognosis of cancers of epithelial origin	2009255973	He, Zhigang Promoting axon regeneration in the adult CNS through control of protein translation	2,576,925	Lieberman, Judy Methods for delivering RNA interference and uses thereof
1931996	Moses, Marsha Free NGAL as a biomarker for cancer	5415538	Ingber, Donald Organ mimic device with microchannels and methods of use and manufacturing thereof	311504	von Andrian, Ulrich Vaccine nanotechnology
1931273	Imam, Farhad Light-guided transluminal catheter	321769	Orkin, Stuart Modulation of BCL11A for treatment of hemoglobinopathies	5559049	Feske, Stefan Stromal interacting molecule knockout mouse and uses thereof
5426389	Zon, Leonard Method to enhance tissue regeneration	597858	Malley, Richard Vaccines and antibodies against <i>Streptococcus pneumoniae</i>	5449134	Smith, Lois Method and product for treatment and/or prevention of complications of prematurity
319340	Zon, Leonard Method to enhance tissue regeneration	2035549	Frank, Markus ABCB5 positive mesenchymal stem cells as immunomodulators	2387579	Hensch, Takao Polypeptides for specific targeting to OTX2 target cells
1133394	Zon, Leonard Method to enhance tissue regeneration	2008239633	Frank, Markus Targeting ABCB5 for cancer therapy		

Technology Development Fund 2014 grant awardees and results

The Boston Children's Technology Development Fund (TDF) is pleased to announce the recipients of the 2014 Technology Development Fund awards.

The TDF was created in 2009 to advance Boston Children's clinicians' and researchers' promising technologies and support their translation into new devices, diagnostic tests and therapeutics to benefit our patients and the broader public. In addition to providing financial support for projects, the TDF provides access to an external advisory board of industry experts in product development who also serve as mentors for the selected projects. The TDF also offers access to a network of preferred contract research organizations (CROs) with the expertise necessary to execute specific project plans and generate the independent validation required by investors and life science partners to consider licenses and partnerships.

The 2014 grant awardees and projects—selected from 51 letters of intent submitted for consideration—include:

Judy Lieberman, MD, PhD—PCMM/Medicine: Pro-siRNAs for cost-effective RNAi

Derrick Rossi, PhD—PCMM/Medicine: Small molecules for *ex vivo* maintenance and expansion of hematopoietic stem cells

Frederick Alt, PhD—PCMM/Medicine: A high throughput mouse model for optimizing therapeutic antibody specificity and affinity

Michael Carroll, PhD—PCMM/Medicine: Therapeutic to reduce inflammation following severe burn injury

Richard Malley, MD—Infectious Diseases/Medicine: Use of MAPS platform for the development of a tuberculosis vaccine

Ofer Levy, MD, PhD, and Guzman Sanchez-Schmitz, PhD—Infectious Diseases/Medicine: Development of a microphysiologic tissue construct to accelerate age-specific human vaccine development

Gregory Priebe, MD—Anesthesiology: Optimization of *Pseudomonas aeruginosa* vaccines

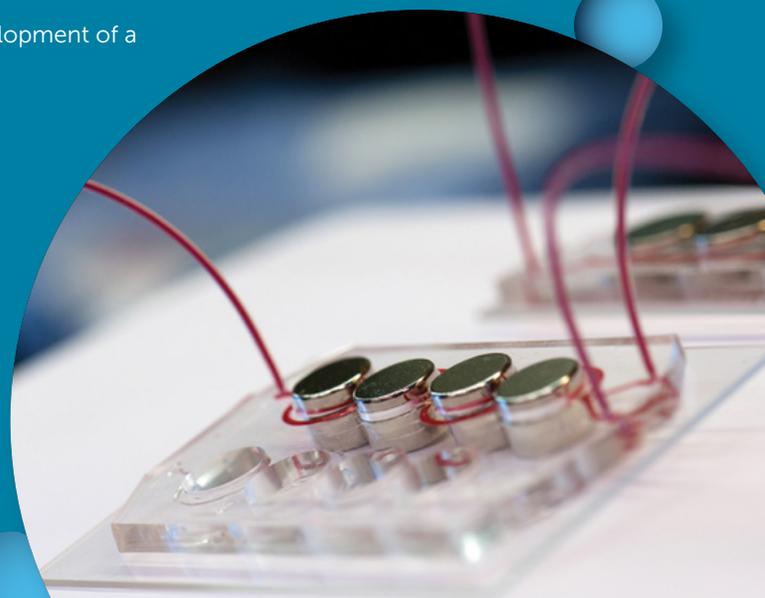
Brian McAlvin, MD, and Daniel Kohane, MD, PhD—Anesthesiology: Highly selective blood filtration with a novel circuit device to treat sepsis

Kaifeng Liu, MD, and Gary Visner, DO—Pulmonary/Medicine: Development of a novel magnetic needle for difficult surgeries

Joseph Madsen, MD, and Eun-Hyoung Park, PhD—Neurosurgery: Rapid visualization of epileptogenic networks in epilepsy surgery planning

Rudolph Pienaar, PhD—Radiology: Children's Research Integration System (ChRIS)—a Web-based medical image data and workflow platform

**Blood filtration device
to treat sepsis**



Technology Development Fund 2014 grant awardees and results

Since 2009, TDF awards have led to:

- » **4 STARTUP COMPANIES**, the most recent being Affinivax. The four new companies (medical device, vaccine and software) have collectively received \$13.6M in seed funding from various venture capitalists, the FDA, and foundations.
- » **10 NOVEL PARTNERSHIPS** with external academic programs and biomedical companies that expanded product development expertise, funding, resources and tools to accelerate the development of Boston Children's innovations.
- » **\$13.2M IN FOLLOW-ON FUNDING** for projects from external sources, including the National Institutes of Health, the Department of Defense, the American Heart Association and the Bill & Melinda Gates Foundation.
- » **9 NEW PATENT APPLICATIONS**
- » **20+ PUBLICATIONS AND MANUSCRIPTS**

"The strong support of the TDF by Boston Children's over its first five years has enabled real advancement of hospital technology," said Jane Amara, PhD, TIDO's associate director. "We are grateful for the continuing support, proud of the TDF's excellent track record of funded projects, and delighted by the high-caliber proposals this year."

Agreements

STARTUPS

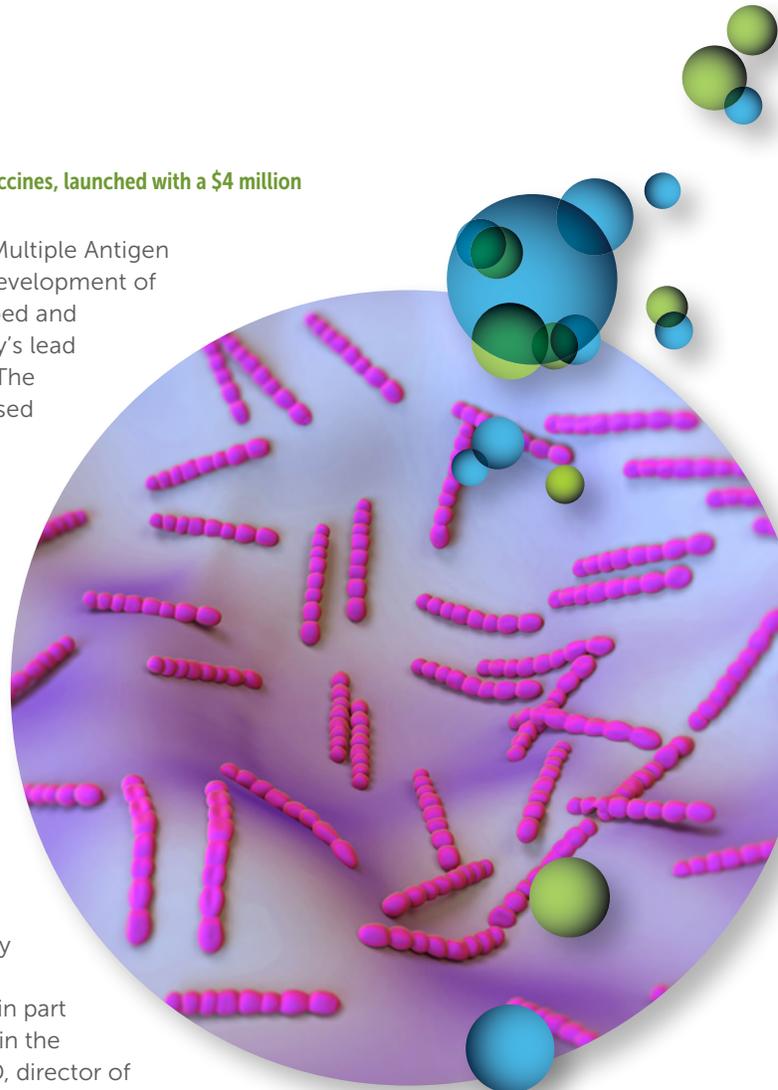
Affinivax, a biotechnology company dedicated to developing novel vaccines, launched with a \$4 million investment from the Bill & Melinda Gates Foundation

Announced in October 2014, Affinivax was formed to develop a Multiple Antigen Presenting System (MAPS) technology platform and enable the development of novel vaccines to protect children and adults in both the developed and developing worlds. The startup will initially focus on the company's lead drug program for *Streptococcus pneumoniae* (pneumococcus). The intellectual property related to the platform was exclusively licensed from Boston Children's Hospital.

The MAPS platform was developed at Boston Children's by three members of the Division of Infectious Diseases: Richard Malley, MD, professor of pediatrics and the Kenneth McIntosh chair in Pediatric Infectious Diseases; Fan Zhang, PhD, instructor; and Yingjie Lu, PhD, assistant professor at Harvard Medical School, who are all scientific founders of Affinivax. MAPS development was supported by Boston Children's Translational Research Program, Boston Children's Technology Development Fund, and the Bill & Melinda Gates Foundation.

Scholar Rock secures exclusive license to intellectual property around growth factor discoveries

In January 2014, startup Scholar Rock, Inc. secured an exclusive license from Boston Children's to fundamental intellectual property related to modulation of niche activators of growth factors for therapeutic applications. This intellectual property was developed in part by Scholar Rock co-founders, Timothy Springer, PhD, investigator in the Program in Cellular and Molecular Medicine, and Leonard Zon, MD, director of the Stem Cell Program. The company is discovering and developing a new class of biologic therapies, "niche modulators," that selectively target dysregulated growth factors in the disease microenvironment, resulting in therapeutic effects specifically at the source of disease. In September 2014, Scholar Rock raised \$20 million in Series A financing. Scholar Rock also established a corporate partnership with Janssen Biotech, a pharmaceutical division of Johnson & Johnson, that makes focused use of the niche modulator technology for the treatment of certain immune-mediated diseases.



Streptococcus pneumoniae

LICENSES

Etiometry exclusively licenses T3 patient-monitoring technology

Boston Children's has licensed the rights to commercialize its T3 (Tracking, Trajectory and Triggering) patient-monitoring software to Etiometry Inc., a Boston-based predictive analytics company that provides clinicians with a real-time, patient-specific assessment of clinical risks and their underlying causes. T3 was the brainchild of Peter Laussen, MD, former chief of Boston Children's Cardiovascular Intensive Care Division and now chief of the Department of Critical Care Medicine at the Hospital for Sick Children, Toronto, and Melvin C. Almodovar, MD, medical director of Boston Children's Cardiac Intensive Care Unit. The T3 software system captures and visualizes patients' physiologic data and tracks their clinical course. By channeling physiologic data into sophisticated mathematical models, T3 generates accurate risk predictions based on a patient's clinical state and enables clinicians to make better care decisions.

bluebird bio and Sangamo non-exclusively license BCL11A genetic target to treat sickle cell disease

Research in the lab of Stuart Orkin, MD, chair of Pediatric Oncology and associate chief of the Division of Hematology/Oncology, has shown that silencing the gene encoding the protein Bcl11a can reactivate fetal hemoglobin production in adult mice, effectively reversing sickle cell disease. This serious genetic disease, caused by defective hemoglobin production, affects as many as 100,000 people in the United States, starting in childhood. bluebird bio and Sangamo each separately licensed intellectual property related to Orkin's BCL11A gene research to develop gene editing therapeutics using their own proprietary platforms.

Raiing Medical Inc. licenses Thermia fever educational framework

Raiing Medical Inc. and Boston Children's Hospital entered into a license agreement for Boston Children's Thermia™ education platform, designed to assist parents in learning more about fever, illness and fever management. The online educational framework will be integrated with Raiing's iThermonitor device, a wearable thermometer with US FDA 510(k) clearance. Thermia co-inventors John Brownstein, PhD, director of the Computational Epidemiology Group within the Boston Children's Hospital Informatics Program and Jared Hawkins, PhD, research fellow in Boston Children's Hospital Informatics Program, will play key roles in the collaboration.

Under the agreement, Raiing Medical Inc. will incorporate the intellectual property from Boston Children's with the real-time body temperature information captured by iThermonitor and build an innovative solution to provide personalized education information regarding fever to users. The aim of this strategic collaboration is to better educate parents about fever management, with the goal of optimizing efficient use of health care resources and reducing medical costs.

Sickle cells

Agreements

SPONSORED RESEARCH

Lilly enters sponsored research to study gene expression profiles after gastric bypass surgery

Eli Lilly and Company and Boston Children's Hospital have entered into a sponsored research agreement to study the genomic, proteomic, and lipidomic signatures of diabetes resolution after bariatric weight loss surgery in preclinical models. In a July 2013 *Science* paper, Nicholas Stylopoulos, MD, of the Division of Endocrinology, observed that after gastric bypass surgery in rats, the way in which the small intestine processes glucose changes. His group showed that use and disposal of glucose by the intestine regulates blood glucose levels in the rest of the body, helping to resolve type 2 diabetes. The small intestine—widely believed to be a passive organ—is actually a major contributor to the body's metabolism. Led by Stylopoulos, the goals of this study are to characterize the physiological and biochemical changes associated with weight loss surgery and to identify new drug targets to develop treatments for obesity.

Merck sponsors research aimed at using social media to study sleep health

Merck and Boston Children's have entered into a research agreement to analyze social media platforms to better understand insomnia. Led by John Brownstein, PhD, director of the Computational Epidemiology Group in the Boston Children's Hospital Informatics Program, the study aims to gain meaningful insights into predictors of sleep deprivation based on social media activities and other social and demographic information. "This project is using new data sources to carry out basic epidemiology research on sleep disorders and better understand the patient experience of insomnia," Brownstein says. "The social media content people produce could teach us a great deal about factors driving sleep disorders and help uncover new populations of insomnia patients that haven't yet been described."

Pfizer CTI enters collaboration to develop an antibody therapeutic against autoimmune diseases

Through the 2014 Boston Children's/Pfizer's Centers for Therapeutic Innovation (CTI) large-molecule collaboration, researchers led by Michael Carroll, PhD, senior investigator in the Program in Cellular and Molecular Medicine, together with a team of Pfizer scientists, will conduct research to develop a monoclonal antibody intended for the treatment of autoimmune diseases such as lupus.

High throughput screening



Agreements

Pfizer and Boston Children's enter multiple sponsored research agreements

In FY14, Pfizer Inc. (Pfizer) and Boston Children's entered into research collaboration agreements with multiple principal investigators.

One research collaboration is with Stuart Orkin, MD, chair of Pediatric Oncology, associate chief of the Division of Hematology/Oncology, and a pioneer in hematologic research. In this collaboration, Pfizer and Boston Children's will collaborate on studies that aim to identify a lead compound that reduces the activity of BCL11A, thus increasing the expression of fetal γ -globin, for use in the development of a potential treatment for sickle cell disease.

Another research collaboration is with Louis Kunkel, PhD, director of the Genomics Program, and a Duchenne muscular dystrophy (DMD) research pioneer. In this collaboration, Pfizer and Boston Children's will collaborate on studies that aim to investigate, identify, de-risk, and confirm new targets for the potential treatment of DMD using various zebrafish and/or mouse models.

Novartis and Boston Children's enter in-kind collaboration to study FAM gene

Novartis and Boston Children's have entered into an in-kind research collaboration agreement to study the normal and pathologic functions of the FAM gene and its possible role in melanoma tumorigenesis. Published human gene expression studies suggest that the FAM gene may be overexpressed in B-cell tumors. The lab of Leonard Zon, MD, director of the Stem Cell Program, will study the biology underlying the pigment-containing, light-reflecting organelles (the chromatophores) in cells, while Novartis is providing the DNA constructs and transgenic fish. The study is designed to answer whether the overexpression of FAM induces chromatophore expansion and to determine the significance of FAM biology on human tumors and the development of melanoma.

Merck and Boston Children's enter in-kind collaboration to study genetic underpinnings of inflammatory bowel disease

Merck and Boston Children's have entered into an in-kind research collaboration to identify and validate genes involved in immune function related to inflammatory bowel disease through next-generation sequencing. This study is led by investigator Scott Snapper, MD, PhD, director, Inflammatory Bowel Disease Center. Mendelian disorders provide a way to understand pathways involved in immunology and to identify therapeutic targets. Through the Very Early Onset Inflammatory Bowel Disease (IBD) Initiative, a large number of infantile IBD patients were found to have Mendelian inheritance. Understanding these patients could lead to insights into the immunoregulatory pathways impacting IBD and an opportunity to identify new therapeutic targets.

Zebrafish breeding tank



Technologies

NeoSaxitoxin completes Phase I trials

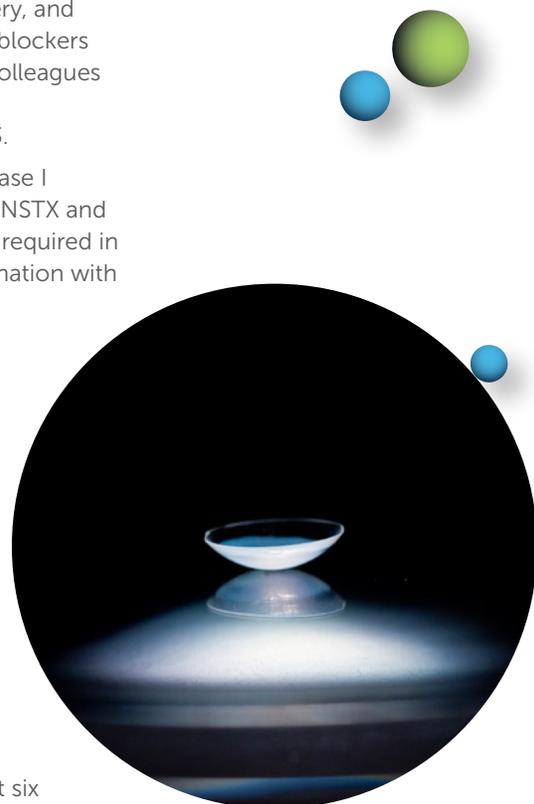
Boston Children's, through a collaboration with Proteus SA, is making strides on turning NeoSaxitoxin (NSTX) into a long-lasting local anesthetic for the management of postoperative pain. NSTX is a site-1 sodium channel blocker derived from cyanobacteria. Proteus has developed a proprietary technology to biosynthesize stable NSTX in a clean, inexpensive and environmentally friendly process. Charles Berde, MD, PhD, chief of the Division of Pain Medicine, Daniel Kohane, MD, PhD, director of the Laboratory for Biomaterials and Drug Delivery, and their colleagues conducted basic and translational studies of site-1 sodium channel blockers as promising candidates for safer and more prolonged local anesthesia. Berde and colleagues completed a preclinical development program that led to the FDA's approval of an investigator-initiated Phase I Investigational New Drug (IND) application in April 2013.

Joseph Cravero, MD, principal investigator at Boston Children's, has completed a Phase I clinical trial in the US. Cravero studied several cohorts of patients being treated with NSTX and bupivacaine, and another cohort also being treated with epinephrine, which may be required in certain clinical settings. The study of 66 patients indicated that NSTX given in combination with bupivacaine is more effective in producing blockade than bupivacaine alone as measured by mechanical pain detection and mechanical touch detection. In the 84 patient dose escalation study of NSTX alone or with bupivacaine, NSTX combinations did not produce adverse physiologic effects. The results were presented in October 2014 at the annual meeting of the American Society of Anesthesiologists and won the meeting's Best Clinical Science Abstract award. Based on these data, there are no systemic safety barriers to proceeding with Phase II clinical trials.

Stopping blindness: The drug-eluting contact lens

Glaucoma is the leading cause of irreversible blindness worldwide. While FDA-approved medications such as latanoprost can prevent vision loss by reducing pressure in the eye, their beneficial effects are limited by poor patient compliance: at six months of treatment, compliance is estimated to be little more than 50 percent. Even for compliant patients, administering the drops can be difficult.

Daniel Kohane, MD, PhD, director of the Laboratory for Biomaterials and Drug Delivery and Joseph Ciolino, MD, an ophthalmologist from Massachusetts Eye and Ear, have developed a possible solution. The two researchers, in collaboration with MIT, have spent several years developing a novel contact lens that dispenses latanoprost and other front-of-the-eye drugs gradually and steadily. In a recently published study, the researchers demonstrated prolonged delivery of latanoprost to treat glaucoma in rabbits—the first study of its kind to show that a contact lens-based system could release a drug for a full month in an animal model at clinically relevant levels. Kohane and Ciolino are now working toward a first-in-human clinical trial.



Drug-eluting
contact lens

Targeting Lin28/let-7 to fight cancer

Lin28 is a developmentally important microRNA-binding protein that acts by preventing maturation of regulatory let-7 microRNAs. If let-7 precursors in a cell do not mature, the cell can't differentiate fully; instead, it remains stem cell-like and can potentially become cancerous. Likewise, suppressing Lin28 with RNA interference has been shown to suppress tumor growth. As with transcription factors, Lin28 is likely to be very difficult to target with therapeutic compounds.

Research in the lab of Richard Gregory, PhD, principal investigator in the Stem Cell Program, has identified two other key enzymatic players that work in tandem with Lin28. Both are associated with the loss of mature let-7 and are found in some tumors. Because they are enzymes, they may prove to be more druggable therapeutic targets than Lin28. One enzyme target is TUTase, which adds a long "tail" of repeating uridine molecules to the immature precursor let-7. This UUU tail flags the pre-let-7 for degradation by yet another enzyme called Dis312. With National Cancer Institute funding, Gregory and colleagues have screened some 15,000 small molecule compounds to find those that block TUTase in hopes of finding new compounds to fight against cancer. Candidate inhibitors are being tested in human cancer cells and mouse models in collaboration with George Daley, MD, PhD, Samuel E. Lux IV professor of Hematology/Oncology and the director of the Stem Cell Transplantation Program, to identify the most promising cancer therapies.

Hub scrubbing device developed to wipe out central line infections

A handheld device that can clean and dry a central line hub with the push of a button was created in the labs of John Kheir, MD, assistant in Cardiology, and Pierre Dupont, PhD, chief of Pediatric Cardiac Engineering, to streamline and optimize the way we clean catheters and protect patients from central line infections. Doctors in the US see over 41,000 bloodstream infections per year, many of which are caused by unclean hubs, i.e., external connectors of central lines. There are guidelines on how to clean a hub but no way to enforce that these guidelines are followed correctly. This automated scrubbing device could bring uniformity to hub cleaning and reduce cleaning time. The hope is that its use will decrease the number of infections, thereby reducing costs incurred due to treating these infections and potentially saving thousands of lives.

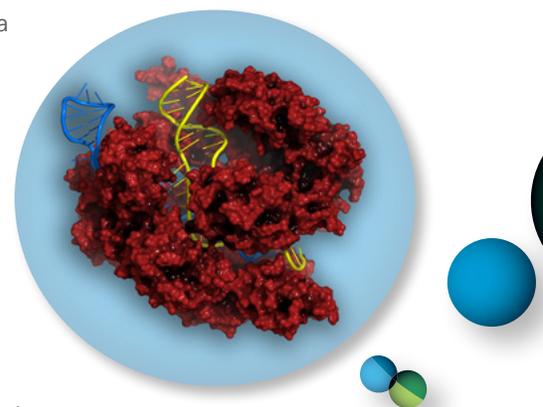


Hub scrubbing prototype

A first for CRISPR: Cutting genes in blood stem cells

A tool called CRISPR (for “clustered regularly interspaced short palindromic repeats”) is a gene editing technology that lets researchers make precise mutations, deletions and even replacements in genomic DNA. First discovered as a kind of genomic immune memory in bacteria, labs around the world are leveraging the technology.

In a recent *Cell Stem Cell* paper, a team led by Derrick Rossi, PhD, of the Program in Cellular and Molecular Medicine, and Chad Cowan, PhD, of Massachusetts General Hospital, reports a first for CRISPR: efficiently and precisely removing clinically relevant genes from cells collected directly from people. They applied CRISPR to human hematopoietic stem and progenitor cells (HSPCs) and T-cells. Rossi and Cowan showed they could edit the beta-2 microglobulin gene out of T-cells and CCR5 out of HSPCs efficiently, predictably and precisely. The edited HSPCs went on to produce the normal portfolio of blood and immune cells. The new gene editing technique could prove to be effective for blocking HIV from invading and destroying patients’ immune systems.

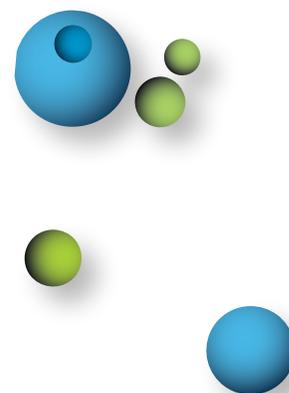


The CRISPR system

A rapid, high throughput mouse model for optimizing therapeutic antibody specificity and affinity

Humanized antibodies derived from phage display or immunization of mice that express humanized antibody genes are among the most successful therapeutic antibodies. However, many antibodies generated by these approaches do not achieve their maximum affinity and specificity. Biotech companies desire to generate variants of these antibodies with higher affinities or modified specificities. The lab of Frederick Alt, PhD, director, Program in Cellular and Molecular Medicine and an HHMI investigator, has developed a novel approach to generate high throughput antibody-producing mouse models to maximize affinity and specificity of therapeutic antibodies.

The Alt lab can rapidly generate mice in which the majority of antibody-producing B lymphocytes develop from progenitors that assemble the genetic components of a known antibody into both the original form and also into a myriad of slightly different variations. Following immunization with target antigens, the variant therapeutic antibody-producing B cells further diversify these antibodies and produce a broad range of variant therapeutic antibodies, including variants with higher affinities or greater specificity for the target antigen. This approach could complement existing methods of therapeutic antibody production and may improve existing therapeutic antibodies for clinical applications.



Boston Children's Hospital Simulator Program (SIMPeds) 3D print service for surgical preparation

Through the multidisciplinary in-house SIMPeds 3D printing program, clinicians are now able to produce on demand exact replicas of a specific patient's anatomy for surgical planning and simulation rehearsal, which is having a positive impact for unusual or difficult surgeries. Using the 3D replicas, physicians have experienced improved surgical efficiency, better outcomes and increased satisfaction and confidence with the surgical experience.

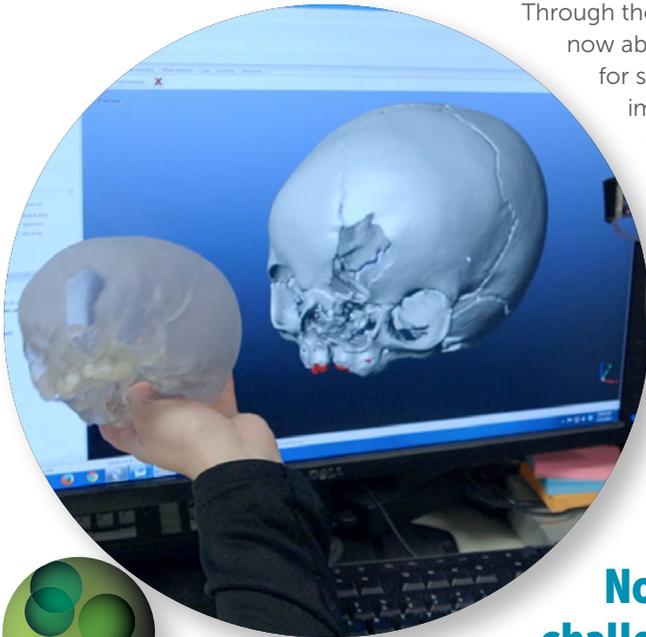
The printed models are also enhancing resident training and patient and family education. An additional focus of the printing program includes 3D printed patient-specific clinical and research devices to explore and develop personalized pediatric care. SIMPeds is directed by Peter Weinstock, MD, PhD, and the SIMPeds 3D service is co-directed by Sanjay Prabhu, MBBS, DCH, MRCPCH, FRCR. The growing team, comprised of 14 staff, includes radiologists, CAD designers, engineers and clinicians. "This could be a game changer in surgical preparedness," says Weinstock. To date, the program has printed over 180 replica body parts and demand is increasing.

Novel magnetic needle tackles suturing in challenging surgical fields

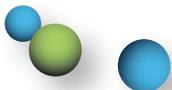
The current method of suturing used in surgery—stitching with a thread that is attached at the end of a curved needle and pulled forward—has been unchanged for generations. Kaifeng Liu, MD, a research fellow at Boston Children's, is reimagining this fundamental surgical technique. His work in animal microsurgery inspired him to create a new method of suturing for small and challenging surgical situations. Liu aims to reinvent the suturing system to make it simpler, faster and more efficient for researchers and clinicians alike.

Liu's new method employs a needle with a magnetic element. The needle and thread are separate from each other, allowing the needle to pierce the tissue independently, and the two parts interact via magnets. Once the magnet engages, the thread is pulled through the tissue by the needle system.

Currently, Liu has created needles as small as 1mm in diameter and 5mm in length. He aims to use the new device in confined surgical fields, such as in laparoscopic surgery. With his recent Technology Development Fund award, Liu plans to optimize the prototype and perform proof of concept studies to illustrate the functionality of the suturing system.



3D printed skull



Licensee Milestones



Two **Biogen Idec (BIIB)** drugs based in part on Wayne Lencer's work (Gastroenterology) received FDA approval for adults and children: ALPROLIX™ and ELOCTATE™, for treating hemophilia B and A, respectively. The drugs, longer-acting versions of the coagulation factors IX and VIII, are improving patient care by meaningfully reducing the number of infusions needed.



**CLARITAS
GENOMICS**

Claritas Genomics secured \$15 million in Series B financing with new investor WuXi NextCode Genomics joining Series A investors Boston Children's Hospital, Cincinnati Children's Hospital Medical Center, and Cerner. Claritas also released a next-generation sequencing assay that investigates 28 genes that represent single-gene causes of pediatric steroid-resistant nephrotic syndrome based on a discovery in the lab of Friedhelm Hildebrandt (Nephrology).



Baxter International Inc. (BAX) announced positive results from a Phase III clinical trial evaluating the safety, efficacy and pharmacokinetics of BAX 111, a recombinant von Willebrand factor (rvWF) based on Stuart Orkin's work (Hematology/Oncology). rvWF is under investigation for the treatment of bleeding episodes in patients with von Willebrand disease. Baxter submitted a Biologics License Application (BLA) to the FDA in December 2014.



Moderna Therapeutics, started in part around Derrick Rossi's mRNA technology (Program in Cellular and Molecular Medicine), raised \$450 million in new funding. Since the company's founding in 2011 by Flagship VentureLabs™, Moderna has secured more than \$950 million in funding through financing activities and commercial partnerships.



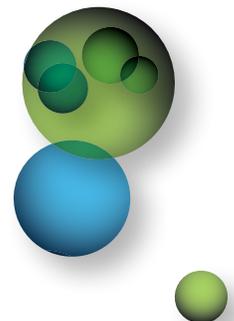
The Chamberlain Group launched Surgical Sam, the first breathing, bleeding, high-fidelity team trainer with a beating heart for pediatric surgery that was co-developed with Peter Weinstock (SIMPeds).



Zafgen, Inc. (ZFGN) went public on June 18 and raised \$96 million. Zafgen also initiated a Phase IIb clinical trial with its lead product candidate beloranib, based on Maria Rupnick's work (Vascular Biology Program), for the treatment of patients with both severe obesity and type 2 diabetes.



SpecialNeedsWare launched TeachMate365, a new cloud-based teaching platform and its language development game Puddingstone for iOS, both developed in collaboration with Howard Shane (Autism Language Program and the Center for Communication Enhancement). TeachMate365 will help educators, therapists, and parents collaborate to help kids.



Licensee Milestones



Genocea Biosciences, Inc. (GNCA), a clinical-stage biopharmaceutical company developing T cell-directed vaccines and immunotherapies, launched a Phase IIa trial for GEN-004, the company's universal vaccine candidate against pneumococcus based in part on Richard Malley's work (Infectious Diseases).



Novartis acquired CoStim Pharmaceuticals in February 2014. Prior to the acquisition, CoStim licensed Boston Children's intellectual property from Dale Umetsu and Rosemarie DeKruyff (both Immunology) for its goal of developing novel antibodies targeting immune checkpoint inhibitors for oncology indications.



DecImmune Therapeutics was awarded a \$3 million, three-year Phase II SBIR grant to support late preclinical studies and initial clinical trials of DeciMab™, its novel monoclonal therapeutic for the treatment of vascular inflammatory diseases based on the work of Michael Carroll (Program in Cellular and Molecular Medicine) and his collaborator Francis Moore, Jr. (Brigham and Women's Hospital).



SCHOLAR ROCK

Scholar Rock, founded by Timothy Springer (Program in Cellular and Molecular Medicine) and Leonard Zon (Stem Cell Program), raised \$20 million in Series A financing. Proceeds will be used to advance proprietary niche modulators from preclinical research toward clinical drug development.



InVIVO Therapeutics (NVIV) announced in January 2015 that a second subject has been enrolled in the pilot study of its Neuro-Spinal Scaffold based on Yang (Ted) Teng's work (Neurology) for the treatment of complete traumatic spinal cord injury.

Booz | Allen | Hamilton

Booze Allen Hamilton acquired Epidemico, an informatics company started around technologies out of John Brownstein's group (Boston Children's Hospital Informatics Program) that provide early insights, continuous monitoring and consumer engagement for varied aspects of population health, including disease outbreaks, drug safety, supply chain vulnerabilities and more.

Global Pediatric Innovation Summit wows the audience

The second annual Boston Children's Hospital Global Pediatric Innovation Summit + Awards was held October 30-31 at the Seaport Hotel in Boston.

At the center of the summit was Boston Children's first Innovation Tank event. Daymond John of ABC's "Shark Tank" and a five-judge panel of venture capitalists and physicians selected two winners from three company presentations. The judges awarded the fledgling companies—both of which have created products for central lines—\$12,500 each.

The two winners were:

- » CareAline, a company that is manufacturing and selling stretchable, washable cloth sleeves or wraps with a hole and pocket, which keeps PICC lines in place, off of the skin and away from external hazards.
- » Boston Children's automated central line hub scrubbing device to prevent central line-associated blood stream infections, caused by bacterial contamination of needleless connectors of central venous lines. The device is designed to streamline and standardize the 60-second manual decontamination and disinfection process.

Two innovation awards were handed out during the event: the Rising Star award to Catherine Rose, PhD, MBA, senior product manager for Philips Healthcare Applications, who launched LightAide, a teaching tool for children with low vision and cognitive disabilities; and the Lifetime Impact award to David G. Nathan, MD, president emeritus of Dana-Farber Cancer Institute and physician-in-chief emeritus of Boston Children's Hospital, for his leadership roles in developing successful thalassemia and sickle cell disease treatments and diagnostic tests.

Other highlights included keynote speeches from:

- » Bill Taylor, *Fast Company* co-founder
- » Zeke Emanuel, MD, PhD, bioethicist
- » Carlos Dominguez, senior vice president, Cisco

Join us next year for the third annual **Boston Children's Hospital Global Pediatric Innovation Summit + Awards** on November 9 & 10, 2015 at the Seaport Hotel in Boston.

Innovation Tank discussion





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